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

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Manuscripts

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5 2 **randomised controlled trial**
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1
2
3 45 **Abstract**
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5 46

6
7 47 Introduction
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10 48 There is uncertainty about the advantages and disadvantages of laparoscopic hysterectomy
11
12 49 compared with abdominal hysterectomy, particularly the relative rate of complications of the
13
14 50 two procedures. Whilst uptake of laparoscopic hysterectomy has been slow, the situation is
15
16 51 changing with greater familiarity, better training, better equipment and increased proficiency
17
18 52 in the technique. Thus, a large, robust, multi-centre randomised controlled trial (RCT) is
19
20 53 needed to compare contemporary laparoscopic hysterectomy with abdominal hysterectomy
21
22 54 to determine the safest and most cost-effective technique.
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25
26 55 Methods and analysis
27

28 56 A parallel, open, non-inferiority, multicentre, randomised controlled, expertise-based surgery
29
30 57 trial with integrated health economic evaluation and an internal pilot with an embedded
31
32 58 qualitative process evaluation. A within trial-based economic evaluation will explore the cost-
33
34 59 effectiveness of laparoscopic hysterectomy compared to open abdominal hysterectomy. We
35
36 60 will aim to recruit 3250 women requiring a hysterectomy for a benign gynaecological
37
38 61 condition and who were suitable for either laparoscopic or open techniques. The primary
39
40 62 outcome is major complications up to six completed weeks post-surgery and the key
41
42 63 secondary outcome is time from surgery to resumption of usual activities using the
43
44 64 personalised PROMIS-SF (Patient-Reported Outcomes Measurement Information System
45
46 65 Physical Function) questionnaire. The principal outcome for the economic evaluation is to
47
48 66 be cost per QALY at 12 months' post-surgery. A secondary analysis is to be undertaken to
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50 67 generate costs per major surgical complication avoided and costs per return to normal
51
52 68 activities.
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56 69 Ethics and dissemination
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3 70 The study was approved by the West Midlands-Edgbaston Research Ethics Committee, 18th
4
5 71 February-2021 (Ethics ref: 21/WM/0019). We will present the findings in national and
6
7 72 international conferences. We will also aim to publish the findings in high impact peer
8
9 73 reviewed journals. We will disseminate the completed paper to the Department of Health,
10
11 74 the Scientific Advisory Committees of the RCOG, the Royal College of Nurses (RCN) and
12
13 75 the BSGE.
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16 76 Trial registration: University of Birmingham, ISRCTN14566195.
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3 78 **Strengths and limitations of this study**
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- 5 79 • The LAVA trial is larger than all the previous 25 RCTs evaluating laparoscopic and
6
7 80 open hysterectomy and of higher quality, addressing the methodological deficiencies
8
9 81 of previous trials; namely their power to show a meaningful difference, accounting for
10
11 82 surgical expertise bias and the ensuring the validity of outcomes assessments,
12
13 83 especially the key secondary outcome of personalised recovery
14
15
16 84 • In the LAVA trial a novel, validated, personalised recovery tool is used via SMS and
17
18 85 an expertise-based design to mitigate against surgical expertise bias employed.
19
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21 86 • Third part randomisation is to be performed balancing important prognostic variables.
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24 87 • Due to the differing natures of the intervention it is impossible to blind either the care
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26 88 providers, investigators or participants to their allocated group.
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92 Introduction

93
94 Hysterectomy is common, with one in ten women undergoing the procedure in their lifetime,
95 mostly for benign conditions [1,2,3]. 30,000 women undergo a hysterectomy every year in
96 the UK for benign indications such as abnormal uterine bleeding and pelvic pain [1,2,3]. The
97 procedure is associated with high rates of patient satisfaction and improvement in quality of
98 life (QoL) but serious complications can arise [4, 5]. The morbidity arising from hysterectomy
99 imposes a burden on women and the ubiquity of the procedure utilises a substantial amount
100 of scarce health care resources [6,7,8,9]. Currently, most hysterectomies are performed by
101 laparotomy, through a vertical or transverse incision because this traditional method is
102 thought to minimise intra-operative complications but the increased trauma of an abdominal
103 incision can prolong recovery [5]. This may be especially true in overweight and obese
104 women, where morbidity is greater from mobility restrictions and wound infection [10].

105
106 Several RCTs, mostly small and of low or moderate quality, have compared the surgical
107 approach to hysterectomy for benign disease. The 2015 Cochrane review identified 25 trials
108 (2983 women) comparing laparoscopic and abdominal hysterectomy [5]. Laparoscopic
109 hysterectomy was found to have significantly more urinary tract injuries (bladder or ureter)
110 but the available evidence was of low quality. The largest RCT included in this review was
111 conducted over 15 years ago, when laparoscopic hysterectomy was in its infancy [11].
112 Smaller, but more recent trials of laparoscopic hysterectomy, have shown a trend towards a
113 lower major complication rate [12,13,14,15]. The Cochrane review [5] identified no
114 differences in the costs or outcomes apart from return to normal activities, which was shorter
115 in the laparoscopic hysterectomy group by 14 days on average.

116
117 A systematic review of cost-effectiveness studies of hysterectomy, found laparoscopic
118 hysterectomy to be the least cost-effective but the authors felt that conclusions were difficult
119 to draw due to variation in study design, follow up times, and the QoL measurement used

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2
3 120 [16]. Thus, we designed a large RCT to determine the clinical and cost-effectiveness of
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5 121 laparoscopic hysterectomy compared to open abdominal hysterectomy for women with a
6
7 122 benign gynaecological condition.
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10 124

11 125 **Methods and analysis**

12 126

13 127 ***Aims and objectives***

14 128 *Main clinical objectives:* To compare laparoscopic hysterectomy with open abdominal
15 129 hysterectomy in terms of major intra-operative and post-operative surgical complications (up
16 130 to six weeks). Post-operative recovery will also be evaluated by measuring the time from
17 131 surgery to resumption of usual activities.
18

19 132

20 133 *Economic objectives:* To compare the relative cost effectiveness of laparoscopic
21 134 hysterectomy with open abdominal hysterectomy in terms of cost per quality adjusted life
22 135 year. Additional cost-effectiveness analyses will explore cost per major surgical complication
23 136 avoided and cost per return to normal activities.
24

25 137

26 138 ***Study design and setting***

27 139 The study is designed as a parallel, open, non-inferiority, multicentre, randomised controlled,
28 140 expertise-based surgery trial with integrated health economic evaluation and an internal pilot
29 141 with an embedded qualitative process evaluation to assess the ability of the study to recruit
30 142 and randomise.

31 143 Recruitment to the LAVA study will take place in gynaecology departments (general and
32 144 relevant specialist clinics including menstrual disorders and pelvic pain clinics, hysteroscopy
33 145 and colposcopy services) in up to 50 NHS Hospitals within the UK.
34

35 146

36 147 ***Patient and Public Involvement (PPI)***

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2
3 148 Our research has been developed with involvement of members of the RCOG Women's
4
5 149 Voices group, the Hysterectomy Association, and the Birmingham Women's Hospital
6
7 150 Hysterectomy Focus Group. A total of 945 women responded to our PPI survey. Major
8
9 151 complications were ranked as the most important outcome for the trial to assess, with return
10
11 152 to usual activities considered the second most important outcome (ranked in the top three
12
13 153 most important outcomes in the BSGE survey). A measure of the speed and quality of
14
15 154 recovery was also considered one of the most important outcomes to measure after major
16
17 155 complications and improvement in QoL in the PPI survey.
18
19 156 Two focus groups felt the burden placed upon women from administering outcome
20
21 157 questionnaires at 24 hours' post-surgery and the frequency of dissemination post-
22
23 158 operatively proposed was acceptable. Indeed, the consensus view was that measuring
24
25 159 recovery against pre-set targets was a good thing (with tools already available on the
26
27 160 internet). This frequency of contact was also supported by the PPI survey; 6 weeks 485/945
28
29 161 (51%) and 12 months 514/945 (54%) were the most popular time points.
30
31 162 Overall almost 50% (462/945) of PPI survey respondents were willing to consider taking part
32
33 163 in the proposed trial. Excluding the 483 women declining to participate because they had
34
35 164 already undergone a hysterectomy revealed that 63% (292/462) of respondents were willing
36
37 165 to take part, with the remainder being "not sure".
38
39 166 Results of the study will be shared with study participants, staff members at research sites
40
41 167 and investigators of other studies related to hysterectomy and benign gynaecological
42
43 168 surgery. A formal notification to the ethics committee, Department of Health, key partners
44
45 169 and sponsors will be made. Outreach to other key stakeholders (trial networks, health
46
47 170 advocates) involved in related trials is planned. The trial team has key individuals to optimise
48
49 171 the dissemination of results. With our PPI co-applicants and contacts we will produce
50
51 172 effective, contemporary formats for dissemination e.g. the use of video podcasts and social
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53 173 media outlets.
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5 176 **Participants**6
7 177 Women are eligible for recruitment to the LAVA trial if they meet the following inclusion
8
9 178 criteria and do not have any of the exclusion criteria set out below:10
11 179 *Inclusion Criteria*

- 12
-
- 13 180
- 14 • Aged between 18-55 years of age and able to give informed consent to participate
 - 15 181 • Have a benign gynaecological condition that is being treated with a hysterectomy
 - 16 182 • This hysterectomy can be undertaken by either a laparoscopic or open abdominal
 - 17 183 routes

18
19 184 *Exclusion Criteria*

- 20
-
- 21 185
- 22 • Women with suspected malignant disease of the genital tract
 - 23 186 • Women who require concomitant gynaecological surgery for bladder or other pelvic
 - 24 187 support
 - 25 188 • Women who require concomitant gynaecological surgery for excision of deep
 - 26 189 endometriosis that requires dissection of the para-rectal space

27
28 19029
30 191 **Choice of intervention**31 192 The LAVA trial will compare laparoscopic with conventional abdominal
32 193 hysterectomy. Vaginal hysterectomy has been shown to be beneficial in terms of
33 194 complications and recovery but this technique is largely confined to women with prolapse
34 195 and where the uterus is not enlarged [17]. Whilst the uptake of laparoscopic hysterectomy
35 196 has been slow [18], the situation is changing with greater familiarity, better training, better
36 197 equipment and increased proficiency in the technique, such that nearly as many
37 198 hysterectomies for benign disease are now being done laparoscopically as abdominally [18].
38 19939 200 Contemporary gynaecological practice has developed rapidly in response to technological
40 201 advances facilitating less invasive surgical techniques for common operations aligned with
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3 202 innovations in pre, peri- and post-operative care designed to 'enhance' recovery [20]. The
4
5 203 results of this trial will have a significant impact on day-to-day clinical practice in women's
6
7 204 health care.
8

9 205

11 206 **Recruitment and randomisation**

13 207 Women with benign gynaecological conditions requiring a hysterectomy and who are
14
15 208 suitable for either surgical technique are eligible for inclusion in the LAVA trial. Potential
16
17 209 participants will be provided with a REC approved Study Participant Information Sheet (PIS)
18
19 210 and given time to consider their involvement.
20
21

22
23 211 After participant eligibility is confirmed and informed consent received, the baseline
24
25 212 questionnaires are to be completed and then the participant randomised into the trial.

26
27 213 Baseline data collected includes demographic and medical data (age ethnicity, BMI
28
29 214 (≤ 29.9 , $30-34.9$, ≥ 35 Kg/m²), previous caesarean section (yes / no), uterine size ≤ 12
30
31 215 weeks, >12 weeks, planned retention of cervix yes / no); Patient-Reported Outcomes
32
33 216 Measurement Information System Physical Function (PROMIS-PF) item bank v1.2 [16] (see
34
35 217 "key secondary outcome"); quality of life, symptom and physical functioning questionnaires,
36
37 218 EuroQoL EQ-5D-5L and EQ VAS [15], Urogenital Distress Inventory (UDI) [28], Pelvic organ
38
39 219 prolapse symptom score (POP-SS) [28], Defecatory Distress Inventory (DDI) [31], Sexual
40
41 220 Activity Questionnaire (SAQ) [32].
42
43

44 221
45
46 222 Randomisation is provided by a secure online randomisation system at the Birmingham
47
48 223 Clinical Trials Unit (BCTU) (available at <http://www.trials.bham.ac.uk/lava>). Participants will
49
50 224 be randomised at the level of the individual in a 1:1 ratio to undergo their hysterectomy by
51
52 225 either a laparoscopic or open abdominal route. A minimisation algorithm will be used within
53
54 226 the online randomisation system to ensure balance in the treatment allocation over the
55
56 227 following variables:

- 58 228 • Previous caesarean section (yes / no)
- 59
60

- 229 • BMI (≤ 29.9 , 30-34.9, ≥ 35 Kg/m²)
- 230 • Uterine Size (≤ 12 weeks, > 12 weeks)
- 231 • Planned retention of cervix (yes / no)
- 232 • Recruiting centre

234 ***Interventions and expertise-based surgery***

235 Hysterectomy is undertaken by either a laparoscopic or an open abdominal route, by a
236 surgeon who had self-declared as having expertise in laparoscopic hysterectomy, abdominal
237 hysterectomy or both approaches to hysterectomy. Satisfactory experience requires
238 surgeons to have performed a minimum of 30 cases and to have a current caseload of at
239 least 12 cases per year. For surgeons to conduct both procedures, these criteria will need to
240 be met for both procedures. The decision to remove or retain cervix (total or sub-total) or
241 remove and retain ovaries was left to the discretion of the participant in consultation with her
242 gynaecologist. The expertise design process for eligible centres is depicted in (Figure 1)

245 ***Outcome Measures***

246 Women who give consent in a face to face setting will subsequently complete their baselines
247 questionnaires and then proceed to randomisation. The baseline questionnaires are self-
248 explanatory but help to complete them will be provided by the local or central medical
249 research teams on request using remote means (telephone / VOIP /video consultation)
250 where feasible. Participants will be made aware of this resource by the local research teams.
251 It is anticipated that some participants may need help to select their 8 personalised recovery
252 targets from 29 options PROMIS-PF (Patient-Reported Outcomes Measurement Information
253 System Physical Function) item bank v1.2 [16], [21,22,23]. Local research teams will offer
254 remote (telephone, VOIP or video) contact, or exceptionally face to face appointments, to
255 provide explanation.

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3 2564
5 **257 Trial Outcomes**6
7 **258 Primary Outcome**8
9 259 Major surgical complications. These will be objectively ascribed and largely in accordance10
11 260 with the validated and widely used Clavien-Dindo classification of surgical complications12
13 261 [24]. They will be defined as any of the following up to and including six full weeks' post-14
15 262 surgery: i) all Clavien-Dindo grade III-V complications ii) Clavien-Dindo grade II16
17 263 complications of pulmonary embolus or blood transfusion or; iii) haemorrhage \geq 1L or; iv)18
19 264 major adverse anaesthetic event.20
21 265 However, other less common major surgical or anaesthetic complications may arise and22
23 266 these will be ascribed in accordance with the appropriate Clavien-Dindo classification shown24
25 267 in (Table 1)26
27 26828
29 269 TABLE 130
31 270 DEFINITION OF MAJOR SURGICAL COMPLICATIONS IN THE LAVA TRIAL32
33 271

Major haemorrhage	Haemorrhage \geq 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)

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35 27236
37 273 *Non-life threatening elective or precautionary admission to an HDU (e.g. because of medical co-morbidities)38
39 274 post-operatively will not be considered a grade IV complication.40
41 275

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3 276 Complication data occurring during and up to 6 weeks following hysterectomy will be
4
5 277 collected from the relevant case report forms completed by the local research team:
6

7 278

9 279 *Key secondary outcome*

11 280 Time from surgery to resumption of usual activities. To increase accuracy and to minimise
12
13 281 recall bias, the validated, personalised PROMIS-PF (Patient-Reported Outcomes
14
15 282 Measurement Information System Physical Function) item bank v1.2 will be used [16]. 29
16
17 283 items covering relevant activities for our study population will be used from the entire 121
18
19 284 item bank [21]. Every item contains five response categories.

22 285 At baseline participants were asked to select 8 activities from this list of 29 that, in their view,
23
24 286 would most reflect their day-to-day activities. In this way participants created their
25
26 287 personalised physical function short form. Participants will record when each activity is
27
28 288 resumed, with full recovery being achieved once all 8 personalised activities have been
29
30 289 resumed. Until all personalised activities have resumed participants will be asked to
31
32 290 complete this weekly for the first 12 weeks, then fortnightly from week 13 to week 26 after
33
34 291 which requests will cease.

36 292

39 293 *Other secondary outcomes*

41 294 1- Surgical outcomes:

43 295 ○ Duration of operation, (minutes)

45 296 ○ Estimated blood loss, (ml)

47 297 2- In hospital stay:

49 298 ○ In hospital post-operative pain using a Numerical rating scale (NRS) (with 0
51 299 indicating no pain to 10 indicating maximum pain)*, measured daily

53 300 ○ Total analgesia use*

55 301 ○ Overall quality of recovery score taken from the Quality of Recovery 15 (QoR-
57 302 15) questionnaire [25] (with 0 indicating worst recovery and 10 indicating best
58 303 recovery), measured at approximately 24 hours post-operation*

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2
3 304 ○ Time from operation to discharge in days
4
5 305 3- Up to 14 days after surgery:
6
7 306 ○ Post-operative pain using a Numerical rating scale (NRS) (with 0 indicating
8
9 307 no pain to 10 indicating maximum pain), measured daily
10
11 308 ○ Total analgesia use
12
13 309 ○ Overall quality of recovery score taken from the Quality of Recovery 15 (QoR-
14
15 310 15) questionnaire²⁵ (with 0 indicating worst recovery and 10 indicating best
16
17 311 recovery), measured at approximately 24 hours post-operation*
18
19 312 ○ Time from operation to discharge in days
20
21
22 313 4- Up to 6 weeks post-surgery:
23
24 314 ○ Minor complications (Haemorrhage 500mL to \leq 1 L; pyrexia [presumed
25
26 315 infection] requiring antibiotics; pain uncontrolled with usual analgesic
27
28 316 management; urinary retention requiring re-catheterization; catheterisation for
29
30 317 longer than 72 hrs; pelvic haematoma NOT requiring radiological or surgical
31
32 318 intervention; pelvic abscess NOT requiring radiological or surgical
33
34 319 intervention; wound infections/complications managed at the bedside or on
35
36 320 the ward)
37
38 321 ○ Representation to hospital
39
40 322 ○ Readmission to hospital
41
42 323 ○ Use of health services
43
44 324 ○ Time away from normal activities
45
46
47 325 5- 6 weeks post-surgery:
48
49 326 ○ Quality of life score using EuroQol-5D-5L questionnaire [26] (with -0.285
50
51 327 indicating worst possible value and 1.0 as best possible value)
52
53 328 ○ Quality of life score using EuroQol-5D-5L visual analogue scale (with 0
54
55 329 indicating worst possible score and 100 as best possible score)
56
57
58 330 6- 12 weeks post-surgery:
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2
3 331 ○ Quality of life score using EuroQol-5D-5L questionnaire [26] (with -0.285
4
5 332 indicating worst possible value and 1.0 as best possible value)
6
7 333 ○ Quality of life score using EuroQol-5D-5L visual analogue scale
8
9 334 ○ Time from surgery to work (if working) in days
10
11 335 ○ Work productivity and activity impairment scores using WPAI-GH questionnaire
12
13 336 [27] (absenteeism score; presenteeism score; work productivity loss score;
14
15 337 activity impairment score – all scored 0 good to 100 bad) at 12 weeks only
16
17
18 338 7- 12/24/36 months post-surgery:**
19
20
21 339 ○ Satisfaction with hysterectomy
22
23 340 ○ Symptoms of urogenital prolapse using the Pelvic Organ Prolapse Symptom
24
25 341 Score (POP-SS) questionnaire [28]
26
27 342 ○ Bladder function using Urogenital Distress Inventory (UDI) [29,30] questionnaire
28
29 343 ○ Bowel function using Defecatory Distress Inventory (DDI) [31] questionnaire
30
31 344 ○ Sexual function using the Sexual Activity (SAQ) questionnaire [32]
32
33 345 ○ Quality of life score using EuroQol-5D-5L questionnaire
34
35 346 ○ Quality of life score using EuroQol-5D-5L visual analogue scale
36
37 347 ○ Body image using the Body Image Scale (BIS) questionnaire [33]
38
39 348 ○ New gynaecological symptoms (abdominal pain [cyclical, non-cyclical and
40
41 349 dyspareunia] and vaginal bleeding; yes/no)
42
43
44 350 ○ Contact with Community Social and Clinical Care Services i.e. outpatients or
45
46 351 emergency visits, and hospital services e.g. re-presentations, re-admissions,
47
48 352 outpatient appointments and further medical treatment, time away from normal
49
50 353 activities.

52 354 8- Throughout: Serious adverse events

55 355 * Questionnaire may be completed at home if patient discharged on the same day as
56
57 356 surgery

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

359
 360 A SUMMARY OF THE SCHEDULE OF ASSESSMENTS IS SHOWN IN (TABLE 2) AND THE TRIAL
 361 FLOW DIAGRAM SHOWN IN (FIGURE 2)

362
 363 TABLE 2
 364 SUMMARY OF SCHEDULE OF ASSESSMENTS

365

Visit	Pre-randomisation		Rand	Surgery	Post-surgery							
	Screening and recruitment	Baseline			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				

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3 Work questionnaire 4 / Work Productivity 5 and Activity 6 Impairment 7 Questionnaire 8 (WPAI-GH)									x			
9 Six week post- 10 surgery 11 complication and 12 representation form								x				
13 Satisfaction with 14 hysterectomy												x
15 New gynae 16 symptoms												x
17 Pelvic organ 18 prolapse 19 quantifications – 20 POP-SS		x										x
21 Body Image Scale 22 (BIS)												x
23 Contact with 24 Community Social 25 and Clinical Care 26 Services form												x
27 Serious Adverse 28 Events				x	x	x	x	x	x	x	x	x

29 366

30 367 Rand = randomisation

31 368 * If patient discharged as a day-case then they should be instructed to complete at home at 24 hours post-

32 369 surgery

33 370 ** The same 12-month post-surgery questionnaires will be sent to all participants reaching 24 and 36 months of

34 371 follow up post-surgery, prior to close of the LAVA study; defined as when the last randomised patient reaches 12

35 372 months follow up post-surgery

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37 374

38 374 **Statistical consideration**39 375 **Sample size**

40 376 To enable 90% power to test the non-inferiority hypothesis at a one-sided 2.5% significance

41 377 level (two-sided 5% level) assuming a 3% margin of non-inferiority and a major surgical

42 378 complication rate of 6% in the abdominal (control) group requires 2634 participants. The

43 379 estimate of 6% is taken from a similar previous comparative study [11]. A 3% margin is

44 380 justifiable because of the trade-off of potentially swifter recovery with laparoscopic surgery; a

45 381 view shared by our patient focus group and is substantially less than the 5% difference

46 382 observed in the previous major trial [11] which led to the continued use of open abdominal

47 383 hysterectomy.

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3 385 An extra consideration is the potential for clustering by surgeon due to the expertise based
4
5 386 design [19,34] Under the assumption that each of the 50 centres will utilise 6 surgeons
6
7 387 (operating on approximately 9 patients on average during the study), along with an intra-
8
9 388 cluster correlation (ICC) estimate of 0.02, the sample size has been increased by 16% to
10
11 389 3055. This ICC estimate used - in the absence of precise estimates - is considered
12
13 390 conservative given the outcome is clinical and of low prevalence, both of which are factors
14
15 391 associated with low ICC [35, 36]. However, even varying these factors up to an ICC of 0.07
16
17 392 or average cluster size of 29, shows we will have at least 80% power to establish non-
18
19 393 inferiority in these situations. Assuming the median recovery time in the abdominal group is
20
21 394 between 6 and 9 weeks [37] we will have high levels of power (>90%) to detect reductions of
22
23 395 1 week in all cases.
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397 ***Analysis of outcome measures***

30 398 A separate Statistical Analysis Plan will be produced and will provide a more comprehensive
31
32 399 description of the planned statistical analyses. For the primary outcome, given the nature of
33
34 400 the non-inferiority design, supportive per-protocol and CACE analyses [38] will be
35
36 401 considered alongside the intention-to-treat population. All outcomes will be adjusted for the
37
38 402 minimisation variables where possible.
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43 404 For all major outcome measures, summary statistics and differences between groups, e.g.
44
45 405 relative risks, will be presented with 95% confidence intervals. For the primary outcome, this
46
47 406 is equivalent to a one-sided 97.5% confidence interval and hence conservative in terms of
48
49 407 the non-inferiority margin. For the trial to declare non-inferiority of the laparoscopic
50
51 408 approach, the lower margin of the absolute risk difference confidence interval must not
52
53 409 exceed 3%.
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3 411 For the key secondary outcome of time from surgery to resumption of usual activities, we will
4
5 412 incorporate a conditional hierarchical approach to interpretation of the 95% confidence
6
7 413 interval to ensure we appropriately control for the overall rate of type I error [39].
8

9 414

11 415 *Primary Outcome Measure*

13 416 We will use a mixed effect binomial regression model to estimate the absolute risk difference
14
15 417 and 95% confidence interval (primary method). Relative risks will be calculated in a similar
16
17 418 fashion. Parameters for treatment group as well as the minimisation variables will be
18
19 419 included in the model as fixed effects. We will explore methods to most appropriate account
20
21 420 for both centre and surgeon variation; these elements will also be included in the model as
22
23 421 random effect.
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28 423 *Secondary Outcome Measures*

30 424 The key secondary outcome of time from surgery to resumption of normal activities will be
31
32 425 analysed using a mixed effects ('frailty') Cox Proportional Hazard model [40], allowing the
33
34 426 same minimisation variables and incorporating parameters for both centre and surgeon.
35
36 427 Linear regression models will be used to analyse response from continuous outcome
37
38 428 measures such as, e.g. participant reported questionnaires, duration of surgery and pain via
39
40 429 NRS; mean differences and 95% confidence intervals will be produced. Other binary and
41
42 430 time-to-event analyses will be considered in the same fashion as the primary and key
43
44 431 secondary outcomes. Satisfaction responses will be analysed using ordinal logistic
45
46 432 regression. Serious adverse events will be summarised and analysed using a chi-squared
47
48 433 test. Analgesia use will be summarised but not formally analysed. Appropriate summary
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50 434 statistics split by group will be presented for each outcome (e.g. proportions/percentages,
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52 435 mean/standard deviation or median/interquartile range).
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58 437 *Subgroup Analyses*

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3 438 Subgroup analyses will be limited to the same variables used in the minimisation algorithm,
4
5 439 and performed on the primary and key secondary outcomes. Given they will have low power
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7 440 to assess non-inferiority on the primary outcome variable they will be treated as exploratory.
8
9 441 Tests for statistical heterogeneity (e.g. by including the treatment group by subgroup
10
11 442 interaction parameter in the regression model) will be undertaken.
12
13
14 443

15 444 *Missing Data and Sensitivity Analyses*

17 445 Every attempt will be made to collect full follow-up data on all study participants; it is thus
18
19 446 anticipated that missing data will be minimal. Participants with missing primary outcome data
20
21 447 will not be included in the primary analysis in the first instance. This presents a risk of bias,
22
23 448 and sensitivity analyses will be undertaken to assess the possible impact of the risk.
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27 450 *Planned Interim Analysis*

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29 451 Interim analyses of safety and efficacy for presentation to the independent DMC will take
30
31 452 place during the study. The committee will meet prior to study commencement to agree the
32
33 453 manner and timing of such analyses but this is likely to include the analysis of the primary
34
35 454 and key secondary outcome and full assessment of safety (SAEs) at least at annual
36
37 455 intervals. Criteria for stopping or modifying the study based on this information will be ratified
38
39 456 by the DMC. Details of the agreed plan will be written into the Statistical Analysis Plan.
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43 458 *Planned Final Analyses*

44
45 459 The primary analysis for the study will occur once all participants have completed the
46
47 460 assessments at 12 months post-surgery and corresponding outcome data has been entered
48
49 461 onto the study database and validated as being ready for analysis. This analysis will include
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51 462 data items up to and including this time-point only. The longer term data collected at 24
52
53 463 months and 36 months post-surgery will be restricted to the subgroup of patients who have
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55 464 reached these assessment points prior to study close and reported at a later date (see Trial
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57 465 Schema) (Figure 2)
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5 467 **Sub-studies**6
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8 468 Full details of these sub-studies are available from the authors on request9
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11 469 *Qualitative process evaluation*12
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14 470 A qualitative process evaluation was undertaken in parallel to the pilot phase. The primary
15
16 471 aim of the qualitative study was to explore the feasibility, acceptability and appropriateness
17
18 472 of the trial and intervention for women and healthcare professionals (HCPs). The results
19
20 473 were to inform decision-making around progression to a full trial, including study design and
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22 474 processes.23
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28 476 *Health economic evaluation*29
30 477 An economic evaluation was designed to assess the cost-effectiveness of laparoscopic
31
32 478 hysterectomy compared to open abdominal hysterectomy in the management of benign
33
34 479 gynaecological conditions. A within trial-based economic evaluation was to explore the cost-
35
36 480 effectiveness of laparoscopic hysterectomy compared to open abdominal hysterectomy. The
37
38 481 principal outcomes for the economic evaluation was cost per QALY at 12 months post-
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40 482 surgery. A secondary analyses was planned
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42 483 to generate costs per major surgical complication avoided and costs per return to normal
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44 484 activities.45
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51 487 **Discussion**52
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54 488 The LAVA trial protocol was designed in 2019 and amended during 2020 before funding and
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56 489 ethical approval was granted. The trial commenced recruitment in September 2021 but failed
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58 490 to meet its RAG ('red; amber; green) criteria for site set up and recruitment rate and so for
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3 491 this reason and the recognition by the funder (The NIHR HTA Programme) of insufficient
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5 492 NHS clinical and Research & Development capacity post the Covid-19 pandemic, the trial
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7 493 was closed. The research question remains relevant, given that almost 30,000
8
9 494 hysterectomies are undertaken per year [7,18] and especially now that the laparoscopic
10
11 495 approach to hysterectomy is being facilitated further by advances in instrumentation
12
13 496 including robotic surgery [41,42]. Our research group plans to analyse qualitative and
14
15 497 quantitative data acquired from the commencement of the trial to inform future surgical trials
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17 498 and aid future researchers wishing to undertake comparative trials in hysterectomy. We
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19 499 believe that our carefully considered protocol will be of value to future researchers working in
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21
22 500 the field of optimising clinical outcomes for women undergoing hysterectomy.
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Strengths and limitations

29
30 503 The LAVA trial was larger than all the previous 25 RCTs evaluating laparoscopic and open
31
32 504 hysterectomy and of higher quality, addressing the methodological deficiencies of previous
33
34 505 trials; namely their power to show a meaningful difference, the validity of outcomes
35
36 506 assessment, especially the key outcome of recovery and a failure to account for surgical
37
38 507 expertise. In the LAVA trial we used a novel, validated, personalised recovery tool
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40 508 [17,21,22], and employed an expertise-based design to mitigate against surgical expertise
41
42 509 bias [19,34]. Third part randomisation was performed balancing important prognostic
43
44 510 variables. Due to the differing natures of the intervention it is impossible to blind either the
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46 511 care providers, investigators or participants to their allocated group.
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Potential impact and implications

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56 514 Hysterectomy is common, with one in ten women undergoing the procedure in their lifetime,
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58 515 mostly for
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3 516 benign conditions [12,13,14]. The operation imposes substantial morbidity upon women,
4
5 517 disrupts families and impacts upon wider society through utilisation of scarce health care
6
7 518 resources and lost productivity [3,4,5,6] [15]. These burdens could potentially be reduced
8
9 519 with safe, less invasive surgery allowing quicker recovery. Currently, most hysterectomies
10
11 520 are performed abdominally because this traditional method is thought to minimise intra-
12
13 521 operative complications but the increased trauma of an abdominal incision can prolong
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15 522 recovery [2]. This may be especially true in overweight and obese women, where morbidity
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17 523 is greater from mobility restrictions and wound infection [16].
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21
22 525 Laparoscopic hysterectomy avoids the need for a large surgical incision speeding recovery
23
24 526 for most women but has been associated with serious complications and specialist surgical
25
26 527 skills. However, scientific advances in imaging and equipment, has made laparoscopic
27
28 528 surgery easier as well as more accessible to general gynaecologists [11] [17,18].
29
30 529 Furthermore, laparoscopic surgery forms an integral part of modern packages of nursing,
31
32 530 anaesthetic and surgical care designed to enhance recovery and allow 24 hour hospital
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34 531 discharge [20].
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39 533 The wider adoption of contemporary laparoscopic hysterectomy has the potential to
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41 534 minimise morbidity, expedite recovery and improve clinical outcomes for women in the short-
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43 535 term and longer-term. Furthermore, enhanced recovery has the potential to be economically
44
45 536 advantageous to the NHS through resource efficiencies and wider society via increased
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47 537 productivity.
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51 52 539 ***Ethics and dissemination*** 53

54
55 540 The study was approved by the West Midlands-Edgbaston Research Ethics Committee. All
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57 541 participants gave informed consent before participation. The trial was being conducted in
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59 542 accordance with the Research Governance Framework for Health and Social Care, the
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3 543 applicable UK Statutory Instruments, (which include the Data Protection Act 1998) and the
4
5 544 Principles of GCP. The protocol will be submitted to and approved by the main REC prior to
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7 545 circulation.
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11 547 The findings will be presented and disseminated via the BSGE, RCOG and other national
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13 548 and international conferences. We will also aim to publish the findings in high impact peer
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15 549 reviewed journals. We will disseminate the completed paper to the Department of Health,
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17 550 the Scientific Advisory Committees of the RCOG, the Royal College of Nurses (RCN) and
18
19 551 the BSGE.
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23 24 25 553 **Acknowledgments**

26
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28
29 555 trial.
30

31 556

32 33 34 557 **Statements**

35
36
37 558 **Author's contribution:** TJC, LM, PB, JF, MM, KC, ES, LJ, PS, TR, WM were involved in
38
39
40 559 conception and trial design. TJC, LA and were involved in drafting of the article. TJC
41
42 560 reviewed and critiqued the article for intellectual content. All the authors were involved in
43
44 561 final approval of the article.
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46 562

47
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49
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56 566 **Competing interests statement:** None declared.
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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 expertise²
- (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 expertise² within the participating centre

- Expert surgeon LAPAROSCOPIC
- Expert surgeon OPEN

Randomisation by local research team

Eligibility confirmed by a surgeon willing to randomise to LAVA³

Laparoscopic hysterectomy
Allocated LAPAROSCOPIC expert surgeon⁴

Open hysterectomy
Allocated OPEN expert surgeon⁴

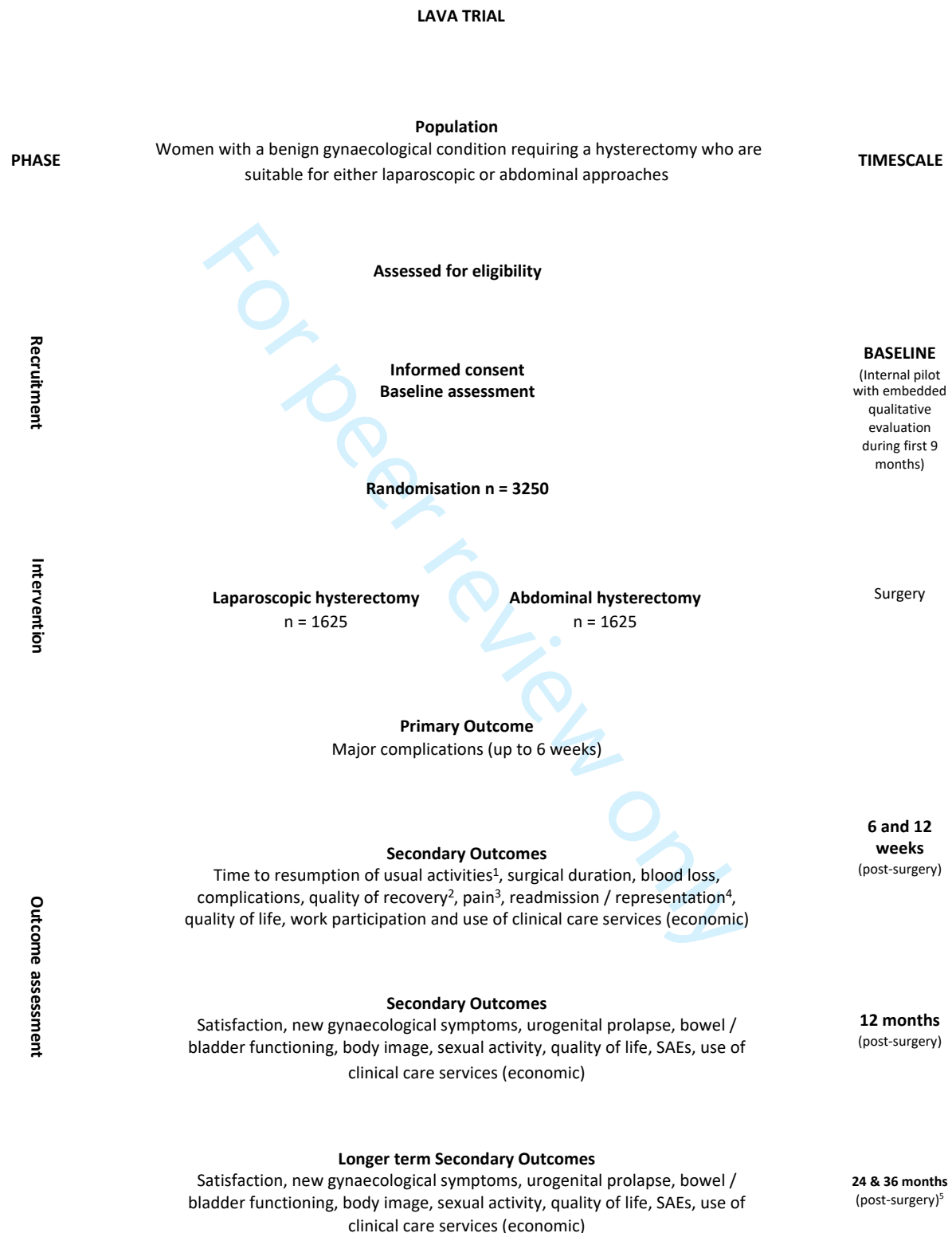
1 Collective group of surgeons within a centre willing to operate on patients recruited into the LAVA trial. Not all surgeons within the LSU need to be willing to randomise but they should be prepared to perform a hysterectomy, according to their expertise, on patients following randomisation.

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

BMJ Open

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

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Manuscripts

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3 1 **Laparoscopic Versus Abdominal hysterectomy (LAVA): Protocol of a randomised controlled**
4 **trial**
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50 43 **Trial Protocol Version Number: 3.0**
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53 44 **Trial Protocol Version Date: 7th July 2021**
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3 46 **Abstract**
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9 48 Introduction
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12 49 There is uncertainty about the advantages and disadvantages of laparoscopic hysterectomy
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14 50 compared with abdominal hysterectomy, particularly the relative rate of complications of the
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16 51 two procedures. Whilst uptake of laparoscopic hysterectomy has been slow, the situation is
17
18 52 changing with greater familiarity, better training, better equipment and increased proficiency
19
20 53 in the technique. Thus, a large, robust, multi-centre randomised controlled trial (RCT) is
21
22 54 needed to compare contemporary laparoscopic hysterectomy with abdominal hysterectomy
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24 55 to determine the safest and most cost-effective technique.
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27 56 Methods and analysis
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30 57 A parallel, open, non-inferiority, multicentre, randomised controlled, expertise-based surgery
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32 58 trial with integrated health economic evaluation and an internal pilot with an embedded
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34 59 qualitative process evaluation. A within trial-based economic evaluation will explore the cost-
35
36 60 effectiveness of laparoscopic hysterectomy compared to open abdominal hysterectomy. We
37
38 61 will aim to recruit 3250 women requiring a hysterectomy for a benign gynaecological condition
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40 62 and who were suitable for either laparoscopic or open techniques. The primary outcome is
41
42 63 major complications up to six completed weeks post-surgery and the key secondary outcome
43
44 64 is time from surgery to resumption of usual activities using the personalised PROMIS-SF
45
46 65 (Patient-Reported Outcomes Measurement Information System Physical Function)
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48 66 questionnaire. The principal outcome for the economic evaluation is to be cost per QALY at
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50 67 12 months' post-surgery. A secondary analysis is to be undertaken to generate costs per
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52 68 major surgical complication avoided and costs per return to normal activities.
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56 69 Ethics and dissemination
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3 70 The study was approved by the West Midlands-Edgbaston Research Ethics Committee, 18th
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5 71 February-2021 (Ethics ref: 21/WM/0019). REC approval for the protocol version 2.0 dated
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7 72 02nd February 2021 was issued on 18th February 2021.
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10 73 We will present the findings in national and international conferences. We will also aim to
11
12 74 publish the findings in high impact peer reviewed journals. We will disseminate the completed
13
14 75 paper to the Department of Health, the Scientific Advisory Committees of the RCOG, the Royal
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16 76 College of Nurses (RCN) and the BSGE.
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19 77 Trial registration
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22 78 University of Birmingham, ISRCTN14566195.
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3 80 **STRENGTHS AND LIMITATIONS OF THIS STUDY**
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- 5 81 • The LAVA trial is larger than all the previous 25 RCTs evaluating laparoscopic and
6
7 82 open hysterectomy and of higher quality, addressing the methodological deficiencies
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9 83 of previous trials; namely their power to show a meaningful difference, accounting for
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11 84 surgical expertise bias and the ensuring the validity of outcomes assessments,
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13 85 especially the key secondary outcome of personalised recovery
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16 86 • In the LAVA trial a novel, validated, personalised recovery tool is used via SMS and
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18 87 an expertise-based design to mitigate against surgical expertise bias employed.
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21 88 • Third part randomisation is to be performed balancing important prognostic variables.
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24 89 • Due to the differing natures of the intervention it is impossible to blind either the care
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26 90 providers, investigators or participants to their allocated group.
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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.

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3 118 The uptake of laparoscopic hysterectomy is increasing with greater familiarity and increased
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5 119 proficiency in the technique aided by improved training and better surgical equipment [16,
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7 120 17,18]. Patient's values and preferences, especially around speed of recovery may also be
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9
10 121 driving this trend.

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13 122 A systematic review of cost-effectiveness studies of hysterectomy, found laparoscopic
14
15 123 hysterectomy to be the least cost-effective but the authors felt that conclusions were difficult
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17 124 to draw due to variation in study design, follow up times, and the QoL measurement used
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19 125 [19,20]. Thus, we designed a large RCT to determine the clinical and cost-effectiveness of
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21 126 laparoscopic hysterectomy compared to open abdominal hysterectomy for women with a
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23 127 benign gynaecological condition.
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31 32 130 **2. Aims and objectives**

33 34 131 35 132 **2.1. Main clinical objective**

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37 133 To compare laparoscopic hysterectomy with open abdominal hysterectomy in terms of
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39 134 major intra-operative and post-operative surgical complications (up to six weeks). Post-
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41 135 operative recovery will also be evaluated by measuring the time from surgery to
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43 136 resumption of usual activities.
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50 51 138 **2.2. Economic objectives**

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54 139 To compare the relative cost effectiveness of laparoscopic hysterectomy with open
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56 140 abdominal hysterectomy in terms of cost per quality adjusted life year. Additional cost-
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3 141 effectiveness analyses will explore cost per major surgical complication avoided and cost
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5 142 per return to normal activities.
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11 144 **3. Study design and setting**

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15 146 **3.1. Trial design**

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18 147 The study is designed as a parallel, open, non-inferiority, multicentre, randomised controlled,
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20 148 expertise-based surgery trial with integrated health economic evaluation and an internal pilot
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22 149 with an embedded qualitative process evaluation to assess the ability of the study to recruit
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24 150 and randomise.
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30 152 **3.2. Trial setting**

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33 153 Recruitment to the LAVA study will take place in gynaecology departments (general and
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35 154 relevant specialist clinics including menstrual disorders and pelvic pain clinics, hysteroscopy
36
37 155 and colposcopy services) in up to 50 NHS Hospitals within the UK.
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43 157 **3.3. Identification of participants**

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46 158 Eligible women will be identified by a member of the clinical team responsible for the direct
47
48 159 care of the potential participant in outpatient gynaecology clinics and pre-operative
49
50 160 assessment clinics in each recruiting centre. The LAVA study will be introduced by a member
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52 161 of the clinical or research team, with full counselling about the trial (including provision of
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54 162 information about the qualitative process evaluation).
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3 164 **3.4. Sub-studies**
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6 165 **3.4.1. Qualitative evaluation**
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9 166 A qualitative process evaluation will be undertaken in parallel to the pilot phase. The primary
10 167 aim of the qualitative study is to explore the feasibility, acceptability and appropriateness of
11 168 the trial and intervention for women and healthcare professionals (HCPs). The results will
12 169 inform decision-making around progression to a full trial, including study design and
13 170 processes.
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23 172 **3.4.2. Health Economic evaluation**
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26 173 An economic evaluation alongside the RCT will explore the cost-effectiveness of laparoscopic
27 174 hysterectomy compared to open abdominal hysterectomy based on a primary outcome of
28 175 quality-adjusted life years and secondary outcomes such as major surgical complications
29 176 avoided. The analysis will adopt the perspective of the health service. All resource use will be
30 177 collected prospectively and unit costs attached. Deterministic and probabilistic sensitivity
31 178 analysis will be carried out.
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43 180 **3.5. Patient and Public Involvement (PPI)**
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46 181 Our research has been developed with involvement of members of the RCOG Women's
47 182 Voices group, the Hysterectomy Association, and the Birmingham Women's Hospital
48 183 Hysterectomy Focus Group. A total of 945 women responded to our PPI survey. Major
49 184 complications were ranked as the most important outcome for the trial to assess, with return
50 185 to usual activities considered the second most important outcome (ranked in the top three
51 186 most important outcomes in the BSGE survey). A measure of the speed and quality of
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3 187 recovery was also considered one of the most important outcomes to measure after major
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5 188 complications and improvement in QoL in the PPI survey.
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8 189 Two focus groups felt the burden placed upon women from administering outcome
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10 190 questionnaires at 24 hours' post-surgery and the frequency of dissemination post- operatively
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12 191 proposed was acceptable. Indeed, the consensus view was that measuring recovery against
13
14 192 pre-set targets was a good thing (with tools already available on the internet). This frequency
15
16 193 of contact was also supported by the PPI survey; 6 weeks 485/945 (51%) and 12 months
17
18 194 514/945 (54%) were the most popular time points.
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20

21 195 Overall almost 50% (462/945) of PPI survey respondents were willing to consider taking part
22
23 196 in the proposed trial. Excluding the 483 women declining to participate because they had
24
25 197 already undergone a hysterectomy revealed that 63% (292/462) of respondents were willing
26
27 198 to take part, with the remainder being "not sure".
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31 199 Results of the study will be shared with study participants, staff members at research sites
32
33 200 and investigators of other studies related to hysterectomy and benign gynaecological surgery.
34
35 201 A formal notification to the ethics committee, Department of Health, key partners and sponsors
36
37 202 will be made. Outreach to other key stakeholders (trial networks, health advocates) involved
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39 203 in related trials is planned. The trial team has key individuals to optimise the dissemination of
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41 204 results. With our PPI co-applicants and contacts we will produce effective, contemporary
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43 205 formats for dissemination e.g. the use of video podcasts and social media outlets.
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52 208 **4. Participants**

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57 210 Women are eligible for recruitment to the LAVA trial if they meet the following inclusion criteria
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59 211 and do not have any of the exclusion criteria set out below:
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3 212 *Inclusion Criteria*
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5

- 6 213 • Aged between 18-55 years of age and able to give informed consent to participate
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8
9 214 • Have a benign gynaecological condition that is being treated with a hysterectomy
10
11 215 • This hysterectomy can be undertaken by either a laparoscopic or open abdominal
12
13 216 routes. The feasibility, and appropriateness of both routes of hysterectomy for
14
15 217 women were to be decided pragmatically, the operating surgeon deciding where their
16
17 218 equipoise was taking into consideration factors such as the size of the uterus,
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19 219 likelihood of pelvic adhesions and anticipated surgical complexity for either approach.
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22 220 *Exclusion Criteria*
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- 25 221 • Women with suspected malignant disease of the genital tract
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27 222 • Women who require concomitant gynaecological surgery for bladder or other pelvic
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29 223 support
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31 224 • Women who require concomitant gynaecological surgery for excision of deep
32
33 225 endometriosis that requires dissection of the para-rectal space
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39 227 **4.1. Choice of intervention**
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42 228 The LAVA trial will compare laparoscopic with conventional abdominal hysterectomy. Vaginal
43
44 229 hysterectomy has been shown to be beneficial in terms of complications and recovery but this
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46 230 technique is largely confined to women with prolapse and where the uterus is not enlarged
47
48 231 [16]. Whilst the uptake of laparoscopic hysterectomy has been slow [17], the situation is
49
50 232 changing with greater familiarity, better training, better equipment and increased proficiency
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52 233 in the technique, such that nearly as many hysterectomies for benign disease are now being
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54 234 done laparoscopically as abdominally [18,19].
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3 236 Contemporary gynaecological practice has developed rapidly in response to technological
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5 237 advances facilitating less invasive surgical techniques for common operations aligned with
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7 238 innovations in pre, peri- and post-operative care designed to 'enhance' recovery [20]. The
8
9 239 results of this trial will have a significant impact on day-to-day clinical practice in women's
10
11 240 health care.

12 241

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14 243 **5. Consent**

15 244

16 245 It will be the responsibility of the Investigator to obtain informed consent (paper or
17 246 electronic) for each participant prior to performing any trial related procedure
18 247 (Supplementary file). A research nurse, research midwife or clinician is able to take
19 248 consent providing that local practice allows this and responsibility has been delegated by
20 249 the Principal Investigator as captured on the Site Signature and Delegation Log.

21 250

22 251

23 252 **6. Recruitment, enrolment and randomisation**

24 253

25 254 **6.1. Recruitment**

26 255 Potential participants will be identified and approached by medical staff who are responsible
27 256 for the direct care of the potential participant in participating centres after having received
28 257 appropriate training relating to the trial and who are delegated this task on the site
29 258 delegation log. Recruitment will take place in gynaecology clinics in gynaecologist lead
30 259 centres located across the United Kingdom. Research Ethics Committee (REC) approved

1
2
3 260 posters making potential participants aware of the study may be displayed in areas that will
4
5 261 be accessed by them, such as waiting areas, clinics and consulting rooms
6

7 262

9 263 **6.2. Enrolment**

11
12 264 Women with benign gynaecological conditions requiring a hysterectomy and who are suitable
13
14 265 for either surgical technique are eligible for inclusion in the LAVA trial.
15

16
17 266 Prior to clinical consultations, the medical records of potential participants may be screened
18
19 267 for eligibility by clinic doctors, nurses, and research nurses, after having received appropriate
20
21 268 training relating to the trial.
22

23
24 269 Potential participants will be provided with a REC approved Study Participant Information
25
26 270 Sheet (PIS) and given time to consider their involvement. Clinic doctors will confirm eligibility
27
28 271 for the trial. After participant eligibility is confirmed and informed consent received, the
29
30 272 baseline questionnaires are to be completed and then the participant randomised into the trial.
31
32 273 Baseline data collected includes demographic and medical data (age ethnicity, BMI (≤ 29.9 ,
33
34 274 $30-34.9$, ≥ 35 Kg/m²), previous caesarean section (yes / no), uterine size ≤ 12 weeks, >12
35
36 275 weeks, planned retention of cervix yes / no); Patient-Reported Outcomes Measurement
37
38 276 Information System Physical Function (PROMIS-PF) item bank v1.2 [19] (see "key secondary
39
40 277 outcome"); quality of life, symptom and physical functioning questionnaires, EuroQoL EQ-5D-
41
42 278 5L and EQ VAS [15], Urogenital Distress Inventory (UDI) [21], Pelvic organ prolapse symptom
43
44 279 score (POP-SS) [21], Defecatory Distress Inventory (DDI) [22], Sexual Activity Questionnaire
45
46 280 (SAQ) [23].
47

48
49
50 281 Participants should be aware at the beginning that they can freely withdraw (discontinue
51
52 282 participation) from the trial (or part of) at any time. LAVA has adopted an analysis based on a
53
54 283 modified intention to treat principle, i.e. all participants will be followed up and analysed in the
55
56 284 treatment group to which they were randomised provided a hysterectomy (of any type) was
57
58 285 undertaken unless they withdraw from the study
59
60

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4
56 287 **6.3. Randomisation**

8
9 288 Randomisation is provided by a secure online randomisation system at the Birmingham
10
11 289 Clinical Trials Unit (BCTU) (available at <http://www.trials.bham.ac.uk/lava>). Participants will
12
13 290 be randomised at the level of the individual in a 1:1 ratio to undergo their hysterectomy by
14
15 291 either a laparoscopic or open abdominal route. A minimisation algorithm will be used within
16
17 292 the online randomisation system to ensure balance in the treatment allocation over the
18
19 293 following variables:

- 22 294 • Previous caesarean section (yes / no)
- 23 295 • BMI (≤ 29.9 , 30-34.9, ≥ 35 Kg/m²)
- 24 296 • Uterine Size (≤ 12 weeks, > 12 weeks)
- 25 297 • Planned retention of cervix (yes / no)
- 26 298 • Recruiting centre

27 299
28
29 300 **6.4. Blinding**

30
31 301 Due to the differing natures of the intervention it is impossible to blind either the care
32
33 302 providers, investigators or participants to their allocated group.
34

35 303
36 304 **6.5. Interventions and expertise-based surgery**

37
38 305 Hysterectomy is undertaken by either a laparoscopic or an open abdominal route, by a
39
40 306 surgeon who had self-declared as having expertise in laparoscopic hysterectomy,
41
42 307 abdominal hysterectomy or both approaches to hysterectomy
43

44
45 308 The decision to remove or retain cervix (total or sub-total) or remove and retain ovaries was
46
47 309 left to the discretion of the participant in consultation with her gynaecologist. The expertise
48
49 310 design process for eligible centres is depicted in (Figure 1).
50
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1
2
3 311 Satisfactory experience requires surgeons to have performed a minimum of 30 cases [24]
4
5 312 and to have a current caseload of at least 12 cases per year [25,26,27]. For surgeons to
6
7 313 conduct both procedures, these criteria will need to be met for both procedures. These
8
9 314 thresholds are evidence-based. In a series of over 10,000 laparoscopic hysterectomies,
10
11 315 surgeons who had performed more than 30 laparoscopic hysterectomies had a significantly
12
13 316 lower incidence of ureteric and bladder injuries (0.5% and 0.8% respectively) compared with
14
15 317 those performing 30 operations or fewer (2.2% and 2.0% respectively) [24].
16
17
18

19 318 The importance of surgical experience as a predictor of successful surgical outcome has
20
21 319 been shown in other studies [25]. Surgical volume is well recognised to correlate with safety
22
23 320 in hysterectomy [26]. A systematic review and meta-analysis of studies including 741,760
24
25 321 patients reported complication rates according to surgical volume. High volume surgeons
26
27 322 were defined as performing at least one of a particular type of hysterectomy per month on
28
29 323 average (i.e. a minimum of 12 per year). Low volume surgeons performed fewer than 12
30
31 324 hysterectomies per year and had higher major complication rates (total complications (odds
32
33 325 ratio [OR] 1.3, 95% CI 1.2- 1.5%), intraoperative complications (OR 1.6, 95% CI, 1.2%-
34
35 326 2.1%) and postoperative complications (OR 1.4 95% CI 1.3%-1.4%) [27].
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44 329 **7. Outcome Measures**

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50 331 Women who give consent in a face to face setting will subsequently complete their baselines
51
52 332 questionnaires and then proceed to randomisation. The baseline questionnaires are self-
53
54 333 explanatory but help to complete them will be provided by the local or central medical research
55
56 334 teams on request using remote means (telephone / VOIP /video consultation) where feasible.
57
58 335 Participants will be made aware of this resource by the local research teams. It is anticipated
59
60 336 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.

340

341 **7.1. Trial Outcomes**

342 **7.1.1. Primary Outcome**

343 Major surgical complications. These will be objectively ascribed and largely in accordance with
 344 the validated and widely used Clavien-Dindo classification of surgical complications [28]. They
 345 will be defined as any of the following up to and including six full weeks' post-surgery: i) all
 346 Clavien-Dindo grade III-V complications ii) Clavien-Dindo grade II complications of pulmonary
 347 embolus or blood transfusion or; iii) haemorrhage \geq 1L or; iv) major adverse anaesthetic
 348 event. The specific type of major complication will be presented in addition to the Clavien-
 349 Dindo grade III-V classification.

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

353

354 **TABLE 1**

355 **DEFINITION OF MAJOR SURGICAL COMPLICATIONS IN THE LAVA TRIAL**

356

Major haemorrhage	Haemorrhage \geq 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)

357

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

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

- 362 • Day of Surgery CRF
 - 363 ○ Detailing the type of major peri-operative complications
- 364 • Post-operative inpatient CRF
 - 365 ○ Detailing the type and timing of major surgical complications occurring during
 366 inpatient stay up until hospital discharge)
- 367 • 6 week post-surgery complication and representation CRF
 - 368 ○ Detailing the type and timing of major post-operative complications, as well as any
 369 reattendance and / or readmissions to hospital up to 6 weeks post-surgery, will be
 370 recorded. The data will be acquired by the local research team from scrutiny of the
 371 hospital case-notes and / or follow up consultation (if conducted routinely at
 372 approximately 6 weeks post-hysterectomy).

373

374 **7.1.2. Key secondary outcome**

375 Time from surgery to resumption of usual activities. To increase accuracy and to minimise
 376 recall bias, the validated, personalised PROMIS-PF (Patient-Reported Outcomes
 377 Measurement Information System Physical Function) item bank v1.2 will be used [19]. 29

1
2
3 378 items covering relevant activities for our study population will be used from the entire 121 item
4
5 379 bank [21]. Every item contains five response categories.
6
7

8 380 At baseline participants were asked to select 8 activities from this list of 29 that, in their view,
9
10 381 would most reflect their day-to-day activities. In this way participants created their
11
12 382 personalised physical function short form. Participants will record when each activity is
13
14 383 resumed, with full recovery being achieved once all 8 personalised activities have been
15
16 384 resumed. Until all personalised activities have resumed participants will be asked to complete
17
18 385 this weekly for the first 12 weeks, then fortnightly from week 13 to week 26 after which requests
19
20
21 386 will cease.
22
23

24 387

26 388 **7.1.3. Other secondary outcomes**

28 389 • Surgical outcomes:

- 30 390 ○ Duration of operation, (minutes)
- 31 391 ○ Estimated blood loss, (ml)

33 392 • In hospital stay:

- 34 393 ○ In hospital post-operative pain using a Numerical rating scale (NRS) (with 0
35 394 indicating no pain to 10 indicating maximum pain)*, measured daily
- 36 395 ○ Total analgesia use*
- 37 396 ○ Overall quality of recovery score taken from the Quality of Recovery 15 (QoR-
38 397 15) questionnaire [25] (with 0 indicating worst recovery and 10 indicating best
39 398 recovery), measured at approximately 24 hours post-operation*
- 40 399 ○ Time from operation to discharge in days

41 400 • Up to 14 days after surgery:

- 42 401 ○ Post-operative pain using a Numerical rating scale (NRS) (with 0 indicating no
43 402 pain to 10 indicating maximum pain), measured daily
- 44 403 ○ Total analgesia use

- 1
2
3 404 ○ Overall quality of recovery score taken from the Quality of Recovery 15 (QoR-
4
5 405 15) questionnaire [25] (with 0 indicating worst recovery and 10 indicating best
6
7 406 recovery), measured at approximately 24 hours post-operation*
- 8
9 407 ○ Time from operation to discharge in days
- 10
11 408 • Up to 6 weeks post-surgery:
- 12
13 ○ Minor complications (Haemorrhage 500mL to ≤ 1 L; pyrexia [presumed
14 409 infection] requiring antibiotics; pain uncontrolled with usual analgesic
15 410 management; urinary retention requiring re-catheterization; catheterisation for
16 411 longer than 72 hrs; pelvic haematoma NOT requiring radiological or surgical
17 412 intervention; pelvic abscess NOT requiring radiological or surgical intervention;
18 413 wound infections/complications managed at the bedside or on the ward)
- 19
20 414 ○ Representation to hospital
- 21
22 415 ○ Readmission to hospital
- 23
24 416 ○ Use of health services
- 25
26 417 ○ Time away from normal activities
- 27
28 418 • 6 weeks post-surgery:
- 29
30 419 ○ Quality of life score using EuroQol-5D-5L questionnaire [29] (with -0.285
31 420 indicating worst possible value and 1.0 as best possible value)
- 32
33 421 ○ Quality of life score using EuroQol-5D-5L visual analogue scale (with 0
34 422 indicating worst possible score and 100 as best possible score)
- 35
36 423 • 12 weeks post-surgery:
- 37
38 424 ○ Quality of life score using EuroQol-5D-5L questionnaire [29] (with -0.285 indicating
39 425 worst possible value and 1.0 as best possible value)
- 40
41 426 ○ Quality of life score using EuroQol-5D-5L visual analogue scale
- 42
43 427 ○ Time from surgery to work (if working) in days
- 44
45 428 ○ Work productivity and activity impairment scores using WPAI-GH questionnaire
46 429 [30] (absenteeism score; presenteeism score; work productivity loss score; activity
47 430 impairment score – all scored 0 good to 100 bad) at 12 weeks only
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3 432 • 12/24/36 months post-surgery:**
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6 433 ○ Satisfaction with hysterectomy
7
8 434 ○ Symptoms of urogenital prolapse using the Pelvic Organ Prolapse Symptom Score
9
10 435 (POP-SS) questionnaire [31,32]
11
12 436 ○ Bladder function using Urogenital Distress Inventory (UDI) [33,34] questionnaire
13
14 437 ○ Bowel function using Defecatory Distress Inventory (DDI) [35] questionnaire
15
16 438 ○ Sexual function using the Sexual Activity (SAQ) questionnaire [36]
17
18 439 ○ Quality of life score using EuroQol-5D-5L questionnaire
19
20 440 ○ Quality of life score using EuroQol-5D-5L visual analogue scale
21
22 441 ○ Body image using the Body Image Scale (BIS) questionnaire [37]
23
24 442 ○ New gynaecological symptoms (abdominal pain [cyclical, non-cyclical and
25
26 443 dyspareunia] and vaginal bleeding; yes/no)
27
28 444 ○ Contact with Community Social and Clinical Care Services i.e. outpatients or
29
30 445 emergency visits, and hospital services e.g. re-presentations, re-admissions,
31
32 446 outpatient appointments and further medical treatment, time away from normal
33
34 447 activities.
35
36 448 • Throughout: Serious adverse events
37
38
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40

41 449 * Questionnaire may be completed at home if patient discharged on the same day as surgery
42
43

44 450 **The latter two time-points will only be collected for participants who reach these times prior
45
46 451 to the study closes after all patients have been followed up for 12 months.
47
48

49 452 A summary of the schedule of assessments is shown in (Supplementary Table 1) and the trial
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51 453 flow diagram shown is (Figure 2)
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8. Statistical consideration

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3 457
45 458 **8.1. Sample size**
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8 459 To enable 90% power to test the non-inferiority hypothesis at a one-sided 2.5% significance
9
10 460 level (two-sided 5% level) assuming a 3% margin of non-inferiority and a major surgical
11
12 461 complication rate of 6% in the abdominal (control) group requires 2634 participants. The
13
14 462 estimate of 6% is taken from a similar previous comparative study [11]. A 3% margin is
15
16 463 justifiable because of the trade-off of potentially swifter recovery with laparoscopic surgery; a
17
18 464 view shared by our patient focus group and is substantially less than the 5% difference
19
20 465 observed in the previous major trial [11] which led to the continued use of open abdominal
21
22 466 hysterectomy.
23
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29 468 An extra consideration is the potential for clustering by surgeon due to the expertise based
30
31 469 design [19,34] Under the assumption that each of the 50 centres will utilise 6 surgeons
32
33 470 (operating on approximately 9 patients on average during the study), along with an intra-
34
35 471 cluster correlation (ICC) estimate of 0.02, the sample size has been increased by 16% to 3055.
36
37 472 This ICC estimate used - in the absence of precise estimates - is considered conservative
38
39 473 given the outcome is clinical and of low prevalence, both of which are factors associated with
40
41 474 low ICC [35, 36]. However, even varying these factors up to an ICC of 0.07 or average cluster
42
43 475 size of 29, shows we will have at least 80% power to establish non-inferiority in these
44
45 476 situations. A final inflation of 6% to account for loss to follow-up brings the final sample size
46
47 477 total to 3250 participants. This size of sample would give the ability to detect meaningful
48
49 478 differences between groups in our key secondary outcome of time from surgery to resumption
50
51 479 of usual activities. Assuming the median recovery time in the abdominal group is between 6
52
53 480 and 9 weeks [37] we will have high levels of power (>90%) to detect reductions of 1 week in
54
55 481 all cases.
56
57
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59 482
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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

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2
3 532 to assess non-inferiority on the primary outcome variable they will be treated as exploratory.
4
5 533 Tests for statistical heterogeneity (e.g. by including the treatment group by subgroup
6
7 534 interaction parameter in the regression model) will be undertaken.
8
9

10 535

13 536 **8.6. Missing Data and Sensitivity Analyses**

16 537 Every attempt will be made to collect full follow-up data on all study participants; it is thus
17
18 538 anticipated that missing data will be minimal. Participants with missing primary outcome data
19
20 539 will not be included in the primary analysis in the first instance. This presents a risk of bias,
21
22 540 and sensitivity analyses will be undertaken to assess the possible impact of the risk.
23
24

25 541

28 542 **8.7. Planned Interim Analysis**

31 543 Interim analyses of safety and efficacy for presentation to the independent DMC will take place
32
33 544 during the study. The committee will meet prior to study commencement to agree the manner
34
35 545 and timing of such analyses but this is likely to include the analysis of the primary and key
36
37 546 secondary outcome and full assessment of safety (SAEs) at least at annual intervals. Criteria
38
39 547 for stopping or modifying the study based on this information will be ratified by the DMC.
40
41 548 Details of the agreed plan will be written into the Statistical Analysis Plan.
42
43

44 549

47 550 **8.8. Planned Final Analyses**

51 551 The primary analysis for the study will occur once all participants have completed the
52
53 552 assessments at 12 months post-surgery and corresponding outcome data has been entered
54
55 553 onto the study database and validated as being ready for analysis. This analysis will include
56
57 554 data items up to and including this time-point only. The longer term data collected at 24 months
58
59 555 and 36 months post-surgery will be restricted to the subgroup of patients who have reached
60

1
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3 556 these assessment points prior to study close and reported at a later date (see Trial Schema)
4
5 557 (Figure 2)
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9 558

11 559 **9. Sub-studies**

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14 560

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16
17 561 Full details of these sub-studies are available from the authors on request
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19

20 562 **9.1. Qualitative process evaluation**

21
22
23 563 A qualitative process evaluation was undertaken in parallel to the pilot phase. The primary aim
24
25 564 of the qualitative study was to explore the feasibility, acceptability and appropriateness of the
26
27 565 trial and intervention for women and healthcare professionals (HCPs). The results were to
28
29 566 inform decision-making around progression to a full trial, including study design and
30
31 567 processes.
32
33

34 568

36 569 **9.2. Health economic evaluation**

37
38
39
40 570 An economic evaluation was designed to assess the cost-effectiveness of laparoscopic
41
42 571 hysterectomy compared to open abdominal hysterectomy in the management of benign
43
44 572 gynaecological conditions. A within trial-based economic evaluation was to explore the cost-
45
46 573 effectiveness of laparoscopic hysterectomy compared to open abdominal hysterectomy. The
47
48 574 principal outcomes for the economic evaluation was cost per QALY at 12 months post-surgery.
49
50 575 A secondary analyses was planned
51
52
53 576 to generate costs per major surgical complication avoided and costs per return to normal
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55 577 activities.
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3 579 **9.3. Data collection**
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6 580 In the first instance, participants will be invited to participate in an interview via
7
8 581 telephone/video conference (e.g. Zoom, Skype or WhatsApp). To ensure inclusivity, where
9
10 582 participants are unable to participate virtually, we may consider face to face interviews in the
11
12 583 clinic where they were treated/work, at the University of Birmingham (if local to Birmingham),
13
14 584 in the participant's home or in an appropriate public space

15
16 585 For women, we will aim to conduct interviews within four to six weeks of them being
17
18 586 approached to participate (decliners) or being randomised (women who consent to
19
20 587 randomisation). This will however remain flexible to accommodate the needs of the women.
21
22

23 588

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25
26 589 **9.4. Management of risk**
27

28
29 590 If a participant raises issues about their care that the qualitative research team deem as
30
31 591 potentially harmful to them (or others) then the researcher will advise them to contact their
32
33 592 local Patient Advice and Liaison Service (PALS) (or equivalent) whose contact details are
34
35 593 provided in the PIS. The lead for the qualitative sub-study will also inform the CI. The CI,
36
37 594 where appropriate, will ensure that the local unit PI is aware of the woman and potential
38
39 595 concerns so that follow-up can be arranged if required. Should a participant have questions
40
41 596 about their clinical care then the qualitative research team will advise the woman to contact
42
43 597 her clinical team and/or her GP.
44

45 598

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49 599

50
51 600 **10. Data management**
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53 601

54
55
56 602 Data Protection Registration: The University of Birmingham has Data Protection Registration
57
58 603 to cover the purposes of analysis and for the classes of data requested. The University's
59
60 604 Data Protection Registration number is Z6195856.

605 Coding and validation will be agreed between the trial's coordinator, statistician and
 606 programmer and the trial database will be signed off once the implementation of these has
 607 been assured.

608 Data can be entered onto the bespoke trial database by staff at BCTU, delegated staff at site
 609 or, in the case of participant completed questionnaires, the participant themselves if an on-
 610 line option is available.

611 DATA SOURCE CAN BE FOUND IN (TABLE 2)

612 TABLE 2

613 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.

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615

616 11. Discussion

617

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

1
2
3 621 reason and the recognition by the funder (The NIHR HTA Programme) of insufficient NHS
4
5 622 clinical and Research & Development capacity post the Covid-19 pandemic, the trial was
6
7 623 closed. The research question remains relevant, given that almost 30,000 hysterectomies are
8
9 624 undertaken per year [7,18] and especially now that the laparoscopic approach to hysterectomy
10
11 625 is being facilitated further by advances in instrumentation including robotic surgery [40,41].
12
13 626 Our research group plans to analyse qualitative and quantitative data acquired from the
14
15 627 commencement of the trial to inform future surgical trials and aid future researchers wishing
16
17 628 to undertake comparative trials in hysterectomy. We believe that our carefully considered
18
19 629 protocol will be of value to future researchers working in the field of optimising clinical
20
21 630 outcomes for women undergoing hysterectomy.
22
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30
31 633 **12. Strengths and limitations**
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34 634
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36 635 The LAVA trial was larger than all the previous 25 RCTs evaluating laparoscopic and open
37
38 636 hysterectomy and of higher quality, addressing the methodological deficiencies of previous
39
40 637 trials; namely their power to show a meaningful difference, the validity of outcomes
41
42 638 assessment, especially the key outcome of recovery and a failure to account for surgical
43
44 639 expertise. In the LAVA trial we used a novel, validated, personalised recovery tool [16,21,22],
45
46 640 and employed an expertise-based design to mitigate against surgical expertise bias [18,34].
47
48 641 Third part randomisation was performed balancing important prognostic variables. Due to the
49
50 642 differing natures of the intervention it is impossible to blind either the care providers,
51
52 643 investigators or participants to their allocated group.
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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.

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3 671 **14. Ethics and dissemination**
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8
9 673 The study was approved by the West Midlands-Edgbaston Research Ethics Committee. REC
10 674 approval for the protocol was issued on 18th February 2021. All participants gave informed
11
12 675 consent before participation. The trial was being conducted in accordance with the Research
13
14 676 Governance Framework for Health and Social Care, the applicable UK Statutory Instruments,
15
16 677 (which include the Data Protection Act 1998) and the Principles of GCP.
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23 679 The findings will be presented and disseminated via the BSGE, RCOG and other national and
24
25 680 international conferences. We will also aim to publish the findings in high impact peer reviewed
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27 681 journals. We will disseminate the completed paper to the Department of Health, the Scientific
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29 682 Advisory Committees of the RCOG, the Royal College of Nurses (RCN) and the BSGE.
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38 685 **15. Confidentiality**
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44 687 Personal data recorded on all documents will be regarded as strictly confidential and will be
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46 688 handled and stored in accordance with the Data Protection Act 1998.

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48 689 Participants will always be identified using their unique trial identification number and partial
49
50 690 date of birth (month / year) on the Case Report Form and correspondence between BCTU
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52 691 and local centres.

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54 692 The Investigator must maintain documents not for submission to BCTU (e.g. Participant
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56 693 Identification Logs) in strict confidence.
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3 694 BCTU will maintain the confidentiality of all participant's data and will not disclose
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5 695 information by which participants may be identified to any third party other than those
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7 696 directly involved in the treatment of the participant and organisations for which the
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9 697 participant has given explicit consent for data transfer (e.g. laboratory staff, competent
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11 698 authority, sponsor).
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15 16 17 18 19 701 **16. Trial organisational structure**

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21 22 23 24 25 703 **16.1. Sponsor**

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27
28 704 University of Birmingham.

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31 705 Contact Details: Research Governance, University of Birmingham, Edgbaston, Birmingham,
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33 706 B15 2TT. Email: researchgovernance@contacts.bham.ac.uk

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35 36 37 38 708 **16.2. Coordinating Centre**

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40
41 709 The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit, based at the
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43 710 University of Birmingham.

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45 46 47 712 **16.3. Trial Management Group**

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49 713 The Trial Management Group will take responsibility for the day-to-day management of the
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51 714 trial, and will include (but is not limited to) the CI, co-applicants, statistician, team leader and
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53 715 trial manager. The role of the group is to monitor all aspects of the conduct and progress of
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55 716 the trial, ensure that the protocol is adhered to and take appropriate action to safeguard
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57 717 participants and the quality of the trial itself.

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3 719 **16.4. Trial Steering Committee (TSC)**
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5 720 The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial.
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7 721 Ideally, the TSC should include members who are independent of the investigators, their
8
9 722 employing organisations, funders and sponsors. The TSC should monitor trial progress and
10
11 723 conduct and advise on scientific credibility. The TSC will consider and act, as appropriate,
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13 724 upon the recommendations of the Data Monitoring Committee (DMC) or equivalent and
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15 725 ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds
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17 726 of safety or efficacy.
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23 728 **16.5. Data monitoring committee**
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25 729 Data analyses will be supplied in confidence to an independent Data Monitoring Committee
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27 730 (DMC), which will be asked to give advice on whether the accumulated data from the trial,
28
29 731 together with the results from other relevant research, justifies the continuing recruitment of
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31 732 further participants. The DMC will operate in accordance with a trial specific charter based
32
33 733 upon the template created by the Damocles Group. The DMC will meet at regular intervals
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35 734 that will allow them to effectively monitor the trial unless there is a specific reason (e.g.
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37 735 safety phase) to amend the schedule.
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46 738 **17. Amendments**
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52 740 As sponsor, The University of Birmingham will be responsible for deciding whether an
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54 741 amendment is substantial or non-substantial. Substantive changes will be submitted to
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56 742 REC for approval. Once this has been received, R&D departments will be notified of the
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58 743 amendment and requested to provide their approval. If no response is received within 35
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3 744 days, an assumption will be made that the site has no objection to the amendment and it
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5 745 will be implemented at the site.
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13 748 **18. Access to the final trial dataset**
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17 750 During the period of the study only the trial steering group will have access to the full trial
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19 751 dataset. Following publication of the findings, the final trial dataset will be made available to
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21 752 external researchers upon approval from the trial management group and the BCTU data
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23 753 sharing committee in line with standard data sharing practices for clinical trial data sets.
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30 756 **19. Post-trial care**
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35 758 All patients will continue to receive standard medical care following participation in the
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37 759 clinical trial. There are no interventions that participant's will be prevented from accessing
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39 760 after their participation in the trial has been completed.
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47 763 **20. Publication policy**
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52 765 Authors must acknowledge that the trial was performed with the support of the University
53
54 766 of Birmingham and Birmingham Clinical Trials Unit. Intellectual property rights will be
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56 767 addressed in the Clinical Study Site Agreement between Sponsor and site.
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3 769 Results of the study will be shared with study participants, staff members at research
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5 770 sites and investigators of other studies related to hysterectomy and benign
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7 771 gynaecological surgery.
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15 774 **21. Auditing**

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20 776 The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory
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22 777 inspection(s) at their site, providing direct access to source data/documents.
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30 780 **Acknowledgments**

31
32 781 The authors thank Dr Zeyah Sairally, and Dr Lynsey Matthews for their help in the LAVA trial.
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41 784 **Statements**

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47 786 **Author's contribution:** TJC, LM, PB, JF, MM, KC, ES, LJ, PS, TR, WM, SB, RW were
48
49
50 787 involved in conception and trial design. TJC, LA and were involved in drafting of the article.
51
52 788 TJC reviewed and critiqued the article for intellectual content. All the authors were involved in
53
54 789 final approval of the article.
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60 791 **Competing interests statement:** None declared.

792

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For peer review only

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 expertise²
- (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 expertise² within the participating centre

- Expert surgeon LAPAROSCOPIC
- Expert surgeon OPEN

Randomisation by local research team

Eligibility confirmed by a surgeon willing to randomise to LAVA³

Laparoscopic hysterectomy
Allocated LAPAROSCOPIC expert surgeon⁴

Open hysterectomy
Allocated OPEN expert surgeon⁴

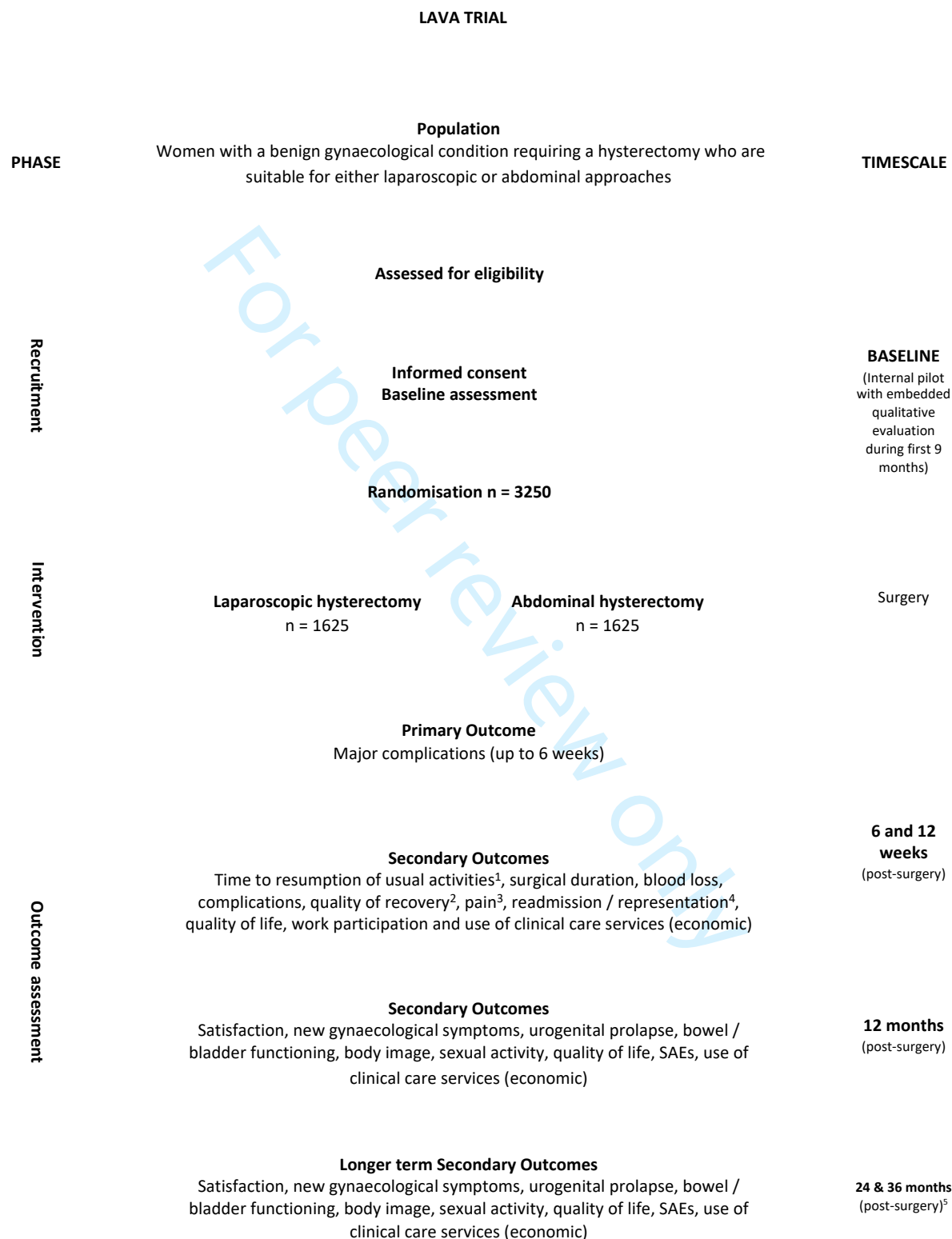
1 Collective group of surgeons within a centre willing to operate on patients recruited into the LAVA trial. Not all surgeons within the LSU need to be willing to randomise but they should be prepared to perform a hysterectomy, according to their expertise, on patients following randomisation.

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

Visit	Pre-randomisation		Rand	Surgery	Post-surgery						
	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)
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						

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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

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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.	



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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	<p>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.</p> <p>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.</p> <p>I understand that Textlocal will securely delete all the information they hold on me at the end of the LAVA study.</p>	
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 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

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2 5d Composition, roles, and responsibilities of the coordinating centre,
3 steering committee, endpoint adjudication committee, data
4 management team, and other individuals or groups overseeing the
5 trial, if applicable (see Item 21a for data monitoring committee)
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8 Pages (31,32), lines (708-725)
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11 Introduction

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13 Background and 6a Description of research question and justification for undertaking the
14 rationale trial, including summary of relevant studies (published and
15 unpublished) examining benefits and harms for each intervention
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18 Page 6, lines (92-125)
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20 6b Explanation for choice of comparators
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23 Pages 11, lines (225-232)
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25 Objectives 7 Specific objectives or hypotheses
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28 Page 7, lines (130-134)
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30 Trial design 8 Description of trial design including type of trial (eg, parallel group,
31 crossover, factorial, single group), allocation ratio, and framework (eg,
32 superiority, equivalence, noninferiority, exploratory)
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35 Page 8, lines (144-176)
36

37 Methods: Participants, interventions, and outcomes

38 Study setting 9 Description of study settings (eg, community clinic, academic hospital)
39 and list of countries where data will be collected. Reference to where
40 list of study sites can be obtained
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43 Page 8, lines (150-153)
44

45 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility
46 criteria for study centres and individuals who will perform the
47 interventions (eg, surgeons, psychotherapists)
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50 Pages (10-11), lines (206-223)
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52 Page (14), lines (303-308)
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54 The expertise design process for eligible centres is depicted in (Figure
55 1)
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2	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
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5			Page 14, lines (302-311)
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7		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)
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10			Page 12, lines (279-283)
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13		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
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15			Page 13, lines (264-278)
16			Page 31, lines (712-716)
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22		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
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26			Page 11, lines (218-223)
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28	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
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37			Pages (15-20), lines (327-446)
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40	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)
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45			Trial schema (Figure 2)
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47	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
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52			Pages (21-22), lines (449-472)
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54	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
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58			Page 13, lines (262-266)
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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)

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- 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)

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2 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and
3 spontaneously reported adverse events and other unintended effects
4 of trial interventions or trial conduct

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7 Page 26, lines (587-595)

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9 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and
10 whether the process will be independent from investigators and the
11 sponsor

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14 Page 34, lines (773-776)

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16 **Ethics and dissemination**

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18 Research ethics 24 Plans for seeking research ethics committee/institutional review board
19 approval (REC/IRB) approval

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22 Page 30, lines (669-676)

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24 Protocol 25 Plans for communicating important protocol modifications (eg,
25 amendments changes to eligibility criteria, outcomes, analyses) to relevant parties
26 (eg, investigators, REC/IRBs, trial participants, trial registries, journals,
27 regulators)

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30 Pages (32-33), lines (737-744)

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32 Consent or assent 26a Who will obtain informed consent or assent from potential trial
33 participants or authorised surrogates, and how (see Item 32)

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36 Page 12, lines (241-247)

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38 26b Additional consent provisions for collection and use of participant data
39 and biological specimens in ancillary studies, if applicable

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44 Confidentiality 27 How personal information about potential and enrolled participants will
45 be collected, shared, and maintained in order to protect confidentiality
46 before, during, and after the trial

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49 Pages (30-31), lines (684-697)

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51 Declaration of 28 Financial and other competing interests for principal investigators for
52 interests the overall trial and each study site

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55 Page 34, line 790

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2	Access to data	29	Statement of who will have access to the final trial dataset, and
3			disclosure of contractual agreements that limit such access for
4			investigators
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7			Page 33, lines (747-752)
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9	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
10	post-trial care		compensation to those who suffer harm from trial participation
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12			Page 33, lines (755-759)
13			
14	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
15	policy		participants, healthcare professionals, the public, and other relevant
16			groups (eg, via publication, reporting in results databases, or other
17			data sharing arrangements), including any publication restrictions
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20			Page 30, lines (678-681)
21			Page 34, lines (768-770)
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24		31b	Authorship eligibility guidelines and any intended use of professional
25			writers
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27			Page 34, lines (785-788)
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30		31c	Plans, if any, for granting public access to the full protocol, participant-
31			level dataset, and statistical code
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33			Page 33, lines (749-752)
34			Page 34, lines (768-770)
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37	Appendices		
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39	Informed consent	32	Model consent form and other related documentation given to
40	materials		participants and authorised surrogates
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42			Please see supplementary file
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44	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
45	specimens		specimens for genetic or molecular analysis in the current trial and for
46			future use in ancillary studies, if applicable
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49			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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.