PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	LAparoscopic Versus Abdominal hysterectomy (LAVA): Protocol of a randomised controlled trial
AUTHORS	Antoun, Lina; Middleton, Lee; Smith, Paul; Saridogan, Ertan; Cooper, Kevin; Brocklehurst, Peter; McKinnon, William; Bevan, Sheriden; Woolley, Rebecca; Jones, Laura; Fullard, Jayne; Morgan, Monique; Roberts, Tracy; Clark, T

VERSION 1 – REVIEW

REVIEWER	Luchristt, Douglas Duke University School of Medicine
REVIEW RETURNED	26-Dec-2022

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. I applaud the team for tackling a fundamental consideration in the surgical management of benign gynecologic disease. Introduction The framing of the introduction is good and discussion of the Cochrane review is appropriate. I would note that there are other considerations that influence the decision to perform an open vs laparoscopic approach beyond intraoperative complications. This includes provider and patient preference (including considerations of cosmesis), patient health status and anatomical considerations, and surgical resources. Methods and Analysis This is a well formulated study protocol. I overall feel that the methods are appropriate and well described, though I do have some recommended clarifications and considerations that could inform further protocol development. • I feel that there needs to be greater clarification of how the third inclusion criterion (“This hysterectomy can be undertaken by either a laparoscopic or open abdominal routes”) was to be assessed. Is this the determination of the operating surgeon? Is there external review of the appropriateness of the candidate for either approach? How would generalizability be assured or was a pragmatic approach taken? • The inclusion criteria state benign disease. Are patients with pelvic organ prolapse or stress urinary incontinence who may undergo concomitant abdominal procedures being included in this group? • Could you provide justification for the selection of 12 procedures per year as the threshold for expertise? What proportion of surgeons would this include/exclude within the participating NHS hospitals?

	• While I recognize that the trial may not be powered for these outcomes, there are procedure specific outcomes that would likely be of interest to the readers of this trail (e.g. bladder injury or bowel injury). Could you please clarify if the nature of the complication would be recorded or simply the Clavien Dindo Grade? • I would recommend further clarification of the design of the study. My understanding, though it is not entirely clear in the manuscript, is that is designed as a non-inferiority trial, not an equivalency trial, for a major surgical complication. Moreover, it appears that a 3% non-inferior margin was developed based on expert opinion and run by patients in some of the focus groups. • Please clarify what the assumed recovery time is for laparoscopic hysterectomy as compared to abdominal that was used in the power analysis for the key secondary outcome. • The manuscript states “For the trial to declare non-inferiority of the laparoscopic approach, the lower margin of the absolute risk difference confidence interval must not exceed 3%.” To ensure clarity of the one sided nature of this non-inferiority design, I believe that this should state “upper” margin or “-3%”? • Why was there a plan for analgesia use to be summarized but not formally analyzed? It would be helpful to provide rationale for a lack of analysis for this secondary outcome compared to others.

REVIEWER	Gkrozou, Fani University of Ioannina
REVIEW RETURNED	29-Jan-2023

GENERAL COMMENTS	It is a very well written article about a very well planned trial. I am looking forward to see the full work published.

VERSION 1 – AUTHOR RESPONSE

	Reviewer’s comments	Our response
Reviewer 1	I applaud the team for tackling a fundamental consideration in the surgical management of benign gynaecologic disease.	-
1.	Introduction The framing of the introduction is good and discussion of the Cochrane review is appropriate. I would note that there are other considerations that influence the decision to perform an open vs laparoscopic approach beyond intraoperative complications. This includes provider and patient preference (including considerations of cosmesis), patient health status and	We have taken reviewers’ comments on-board, and revised our introduction by adding; “The uptake of laparoscopic hysterectomy is increasing with greater familiarity and increased proficiency in the technique aided by improved training and better surgical equipment [16,17,18]. Patient’s values and preferences, especially around speed of recovery may also be driving this trend.

	anatomical considerations, and surgical resources.	." It should be noted that "cosmesis" (part of patient preference) is captured in the study protocol as a "body image" questionnaire at 12 months is included Ref 16. Lee SH, Oh SR, Cho YJ, Han M, Park JW, Kim SJ*, et al.* Comparison of vaginal hysterectomy and laparoscopic hysterectomy: a systematic review and meta-analysis. *BMC Womens Health* 2019;**19**:83. https://doi.org/10.1186/s12905-019-0784-4. 17. Madhvani K, Curnow T, Carpenter T. Route of hysterectomy: a retrospective, cohort study in English NHS Hospitals from 2011 to 2017. *BJOG* 2019;**126**:795-802. https://doi.org/10.1111/1471-0528.15539 18. Cook JA, Elders A, Boachie C, Bassinga T, Fraser C, Altman DG*, et al.* A systematic review of the use of an expertise-based randomised controlled trial design. *Trials* 2015;**16**:241. https://doi.org/10.1186/s13063-015-0739-5 The change can be found on lines (116-119) in the revised manuscript
	Methods and Analysis This is a well formulated study protocol. I overall feel that the methods are appropriate and well described, though I do have some recommended clarifications and considerations that could inform further protocol development.	-

2.	I feel that there needs to be greater clarification of how the third inclusion criterion ("This hysterectomy can be undertaken by either a laparoscopic or open abdominal routes") was to be assessed. Is this the determination of the operating surgeon? Is there external review of the appropriateness of the candidate for either approach? How would generalizability be assured or was a pragmatic approach taken?	We have revised the manuscript by adding to the third bullet of the inclusion criteria "The feasibility, and appropriateness of both routes of hysterectomy for women were to be decided pragmatically, the operating surgeon deciding where their equipoise was taking into consideration factors such as the size of the uterus, likelihood of pelvic adhesions and anticipated surgical complexity for either approach" The change can be found on lines (214-217) in the revised manuscript
3.	The inclusion criteria state benign disease. Are patients with pelvic organ prolapse or stress urinary incontinence who may undergo concomitant abdominal procedures being included in this group?	Patients undergoing a concomitant abdominal procedure for pelvic organ prolapse or stress urinary incontinence were excluded from this trial (please find our exclusion criteria) - lines (220-221)
4.	Could you provide justification for the selection of 12 procedures per year as the threshold for expertise? What proportion of surgeons would this include/exclude within the participating NHS hospitals?	Surgeons will self-declare as having expertise in laparoscopic hysterectomy, abdominal hysterectomy or both approaches to hysterectomy. However, to participate in the LAVA trial, these gynaecological surgeons will have to meet minimum standards, regarding experience and caseload, to be considered competent in a particular type of hysterectomy. Satisfactory experience will require surgeons to have performed a minimum of 30 cases [24] and to have a current caseload of at least 12 cases per year [25-27]. For surgeons to conduct both procedures, these criteria will need to be met for both procedures. These thresholds are evidence-based. In a series of over 10,000 laparoscopic hysterectomies, surgeons who had performed more than 30 laparoscopic hysterectomies had a significantly lower incidence of ureteric and bladder injuries (0.5% and 0.8% respectively) compared with those performing 30 operations or fewer (2.2% and 2.0% respectively) [24].

		The importance of surgical experience as a predictor of successful surgical outcome has been shown in other studies [25]. Surgical volume is well recognised to correlate with safety in hysterectomy [26]. A systematic review and meta-analysis of studies including 741,760 patients reported complication rates according to surgical volume. High volume surgeons were defined as performing at least one of a particular type of hysterectomy per month on average (i.e. a minimum of 12 per year). Low volume surgeons performed fewer than 12 hysterectomies per year and had higher major complication rates (total complications (odds ratio [OR] 1.3, 95% CI 1.2- 1.5%), intraoperative complications (OR 1.6, 95% CI, 1.2%-2.1%) and postoperative complications (OR 1.4 95% CI 1.3%-1.4%) [27]. Ref 24. Mäkinen J, Johansson J, Tomás C, Tomás E, Heinonen PK, Laatikainen T, Kauko M, Heikkinen A, Sjöberg J. Morbidity of 10110 hysterectomies by type approach, Human Reprod 2001;16 :1473-1478. 25. Twijnstra AR, Blikkendall MD, von Zwet EW, van Kersteren PJ, deKroon CD, Jansen FW. Predictors of successful surgical outcome in laparoscopic hysterectomy. Obstet Gynecol. 2012;119:700–7 26. Glaser LM, Brennan L, King LP, Milad MP. Surgeon Volume in Benign Gynecologic Surgery: Review of Outcomes, Impact on Training, and Ethical Contexts. J Minim Invasive Gynecol. 2019;26:279-287. doi: 10.1016/j.jmig.2018.09.775 27. Mowat A, Maher C, Ballard E. Surgical outcomes for low-volume vs high-volume surgeons in gynecology surgery: a systematic review and meta-analysis. Am J Obstet Gynecol 2016;215:21-33.

		Change can be found on lines (309-324) in the revised manuscript
5.	While I recognize that the trial may not be powered for these outcomes, there are procedure specific outcomes that would likely be of interest to the readers of this trail (e.g. bladder injury or bowel injury). Could you please clarify if the nature of the complication would be recorded or simply the Clavien Dindo Grade?	We have provided this clarity in the revised manuscript “The specific type of major complication will be presented in addition to the Clavien-Dindo grade III-V classification.” The change can be found on lines (346-347) in the revised manuscript
6.	I would recommend further clarification of the design of the study. My understanding, though it is not entirely clear in the manuscript, is that is designed as a non-inferiority trial, not an equivalency trial, for a major surgical complication. Moreover, it appears that a 3% non-inferior margin was developed based on expert opinion and run by patients in some of the focus groups.	We think the non-inferiority design, the rationale and the power calculations are clear. See section 7 of the Methods No change
7.	Please clarify what the assumed recovery time is for laparoscopic hysterectomy as compared to abdominal that was used in the power analysis for the key secondary outcome.	We have not speculated upon an assumed recovery time for laparoscopic hysterectomy. Rather our large sample size (for a surgical trial) powered on the primary outcome of major surgical complications would also be powered to detect a reduction in recovery time of one week or more. See section 7 of the results “Assuming the median recovery time in the abdominal group is between 6 and 9 weeks [37] we will have high levels of power (>90%) to detect reductions of 1 week in all cases.” No change needed

8.	The manuscript states “For the trial to declare non-inferiority of the laparoscopic approach, the lower margin of the absolute risk difference confidence interval must not exceed 3%.” To ensure clarity of the one sided nature of this non-inferiority design, I believe that this should state “upper” margin or “-3%”?	We have taken reviewer’s comment on board and changed the wording of the sentence from 'lower margin' to 'upper margin' The change can be found on line (491) in the revised manuscript
9.	Why was there a plan for analgesia use to be summarized but not formally analyzed? It would be helpful to provide rationale for a lack of analysis for this secondary outcome compared to others.	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. The change can be found on lines (516-523) in the revised manuscript
Reviewer: 2	It is a very well written article about a very well planned trial. I am looking forward to see the full work published	-

VERSION 2 – REVIEW

REVIEWER	Luchristt, Douglas Duke University School of Medicine
REVIEW RETURNED	10-Apr-2023

GENERAL COMMENTS	I appreciate the author's attention to the recommended changes, and while not all recommendations were addressed, I feel this is appropriate for publication.

VERSION 2 – AUTHOR RESPONSE