BMJ Open

Comparing the efficacy and safety of three surgical approaches for total hysterectomy (TSATH): protocol for a multicentre, single-blind, parallel-group, randomised controlled trial

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To cite: Zhang W, Deng L, Yang F, *et al*. Comparing the efficacy and safety of three surgical approaches for total hysterectomy (TSATH): protocol for a multicentre, single-blind, parallel-group, randomised controlled trial. *BMJ Open* 2024;**14**:e074478. doi:10.1136/bmjopen-2023-074478

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-074478).

Received 07 April 2023
Accepted 16 November 2023

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ABSTRACT

Introduction Hysterectomy is the most common surgical procedure in the field of gynaecology. The traditional multiport laparoscopy, transumbilical laparoendoscopic single-site surgery (TU-LESS) and transvaginal natural orifice transluminal endoscopic surgery (vNOTES) hysterectomy approaches have been implemented to varying degrees in clinical practice. At present, although their feasibility has been proven, there are no large randomised controlled studies on postoperative rehabilitation. This study aims to evaluate postoperative recovery and assess the safety and effectiveness of these three surgical approaches for total laparoscopic hysterectomy.

Method and analysis This is a multicentre, randomised, single-blind, three-arm, parallel-group, interventional clinical trial. Recruitment will be carried out in five tertiary hospitals in China. Patients diagnosed with benign uterine disease or precancerous lesions will be assigned to the vNOTES group, TU-LESS group and conventional laparoscopy group at a 1:1:1 ratio. The achievement rate of comprehensive indices of enhanced recovery after surgery (ERAS) within 24 hours postoperatively will be considered the primary outcome (the comprehensive indicators of ERAS include fluid intake, passing flatus, urination after catheter removal, ambulation and a Visual Analogue Scale score ≤3.) This study will use a non-inferiority test, with a power (1−ß) of 80% and a margin of −0.15, at a one-sided α of 0.0125. The sample size will be 480 patients (including an assumed 15% dropout rate), calculated according to the primary outcome.

Ethics and dissemination This study was approved on 25 April 2022 by the Medical Ethics Committee of West China Second University Hospital (2022(057)), Sichuan University, Chengdu, China. All participants will be required to provide informed consent before their participation in the study. The results of the trial will be submitted for publication in a peer-reviewed journal and presented at international conferences.

Protocol version V.3.0, 31 August 2023.

Trial registration number ChiCTR2200057405.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a large, multicentre, randomised controlled trial for the three main laparoscopic approaches to hysterectomy.
⇒ The comprehensive index of enhanced recovery after surgery is the primary outcome.
⇒ We carried out a pretest to verify the feasibility and calculate the sample size.
⇒ The participating centres are limited to those with surgeons certificated in all three treatment approaches.

INTRODUCTION

Hysterectomy is one of the most common and basic operations in gynaecology.[1] There are over 6 million hysterectomies carried out annually worldwide.[2] The laparoscopic technique is the most important innovation in modern surgery. It minimises surgical trauma and promotes postoperative recovery. At present, most hysterectomies are performed by conventional multiport laparoscopy, which was first reported in 1989.[3 4] Compared with traditional open surgery, laparoscopic surgery is safe, effective and less invasive.[5]

With the rapid evolution of laparoscopic techniques and the emergence of enhanced recovery after surgery (ERAS), which is another crucial innovation, higher demands are being placed on surgical practices. As a large amount of evidence has proven that minimally invasive techniques minimise surgical trauma, which is beneficial to postoperative recovery, clinicians are exploring various minimally invasive approaches in addition to traditional laparoscopy.[6 7] In the past decade, transumbilical laparoendoscopic single-site surgery (TU-LESS) has

emerged rapidly. Compared with traditional multiport laparoscopic surgery, TU-LESS not only minimises the incision count for cosmetic benefits but also appears to be more minimally invasive, thereby enhancing postoperative rehabilitation. However, several publications have demonstrated that this approach prolongs the operation time, which seems to be not conducive to surgical rehabilitation.[8 9]

Transvaginal natural orifice transluminal endoscopic surgery (vNOTES), which has emerged in recent years, is a combination of laparoscopic and transvaginal surgery. Transvaginal surgery has been shown to be the most minimally invasive procedure, and its effectiveness in postoperative recovery has been confirmed by a large body of literature, but its use is limited due to the difficulty of abdominal exploration.[10] Reportedly, the vNOTES hysterectomy offers not only the benefits from vaginal surgery—minimal abdominal scarring, reduced analgesic consumption and quicker recovery to normal activity—but also laparoscopic advantages such as facilitating adnexal surgery, promoting effective learning and adhering to the latest recommendation of prophylactic salpingectomy during hysterectomy to prevent ovarian cancer.[11–14] One single-centre randomised controlled trial (RCT) proved the feasibility of vNOTES compared with traditional multiport laparoscopy, and another preliminary single-centre randomised pilot study demonstrated seemingly higher pain intensity compared with TU-LESS hysterectomy.[15 16]

The three approaches have been implemented to varying degrees in clinical practice. At present, although research has proven the feasibility of these approaches and that a certain surgical approach has advantages in the face of a single evaluation indicator, there is no large randomised controlled study on postoperative rehabilitation.[4 9] This study is a large, multicentre RCT under the latest ERAS guidelines to mainly evaluate postoperative recovery after the use of vNOTES, TU-LESS and traditional laparoscopic surgery in patients undergoing hysterectomy to provide a basis for clinicians in the selection of surgical approaches.

METHODS AND ANALYSIS

Trial design

This is a multicentre, single-blind, three-arm, parallel-group, randomised clinical trial and will be conducted in five tertiary hospitals across China. The patients will be assigned to the vNOTES group, TU-LESS group and conventional laparoscopy group at a 1:1:1 ratio. An outline of the study is shown in figure 1.

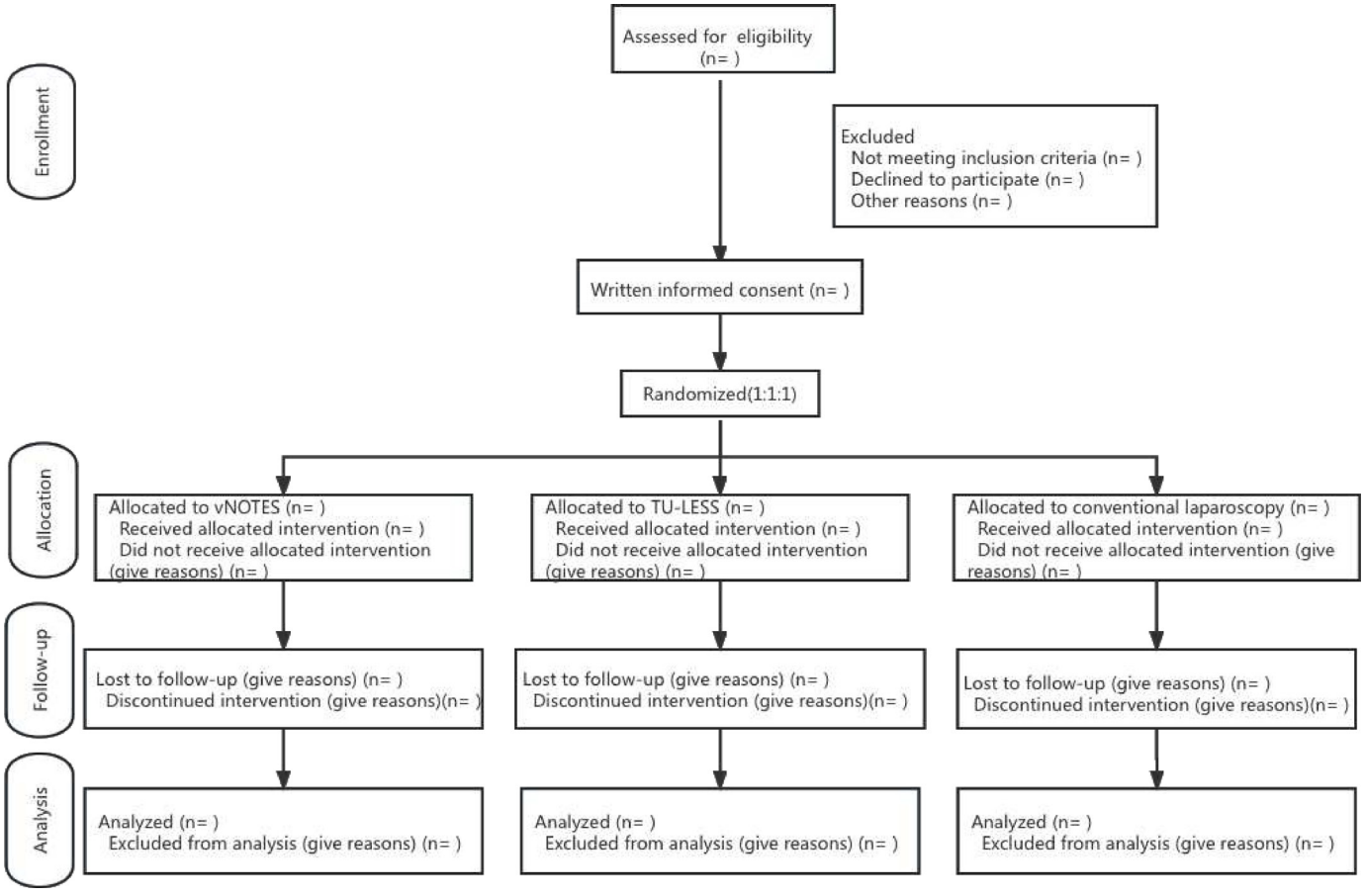

Figure 1 Trial flow diagram. TU-LESS, transumbilical laparoendoscopic single-site surgery; vNOTES, transvaginal natural orifice transluminal endoscopic surgery.

Table 1 Patient characteristics and data collection

	Study period					
Data collection	Screening stage	Surgery	POD1	Hospital discharge	3 months	6 months
Informed consent	✔					
Demographic characteristics	✔					
Pelvic examination	✔					
Medical history	✔					
Surgical information		✔				
VAS score		✔	✔			
Intraoperative complications		✔				
Comprehensive indicators of ERAS		✔	✔	✔		
Postoperative complications				✔	✔	
Total amount of analgesics used in 24 hours postoperatively				✔		
Readmission within 3 months					✔	
Postoperative pathology			✔	✔	✔	
Postoperative diagnosis		✔	✔	✔	✔	
POSAS					✔	✔
FSFI	✔					✔

ERAS, enhanced recovery after surgery; FSFI, Female Sexual Function Index; POD1, postoperative day 1; POSAS, Patient and Observer Scar Assessment Scale; VAS, Visual Analogue Scale.

This protocol will follow the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting guidelines, which are reported in the SPIRIT checklist.[17]

Randomisation and data management

This study will adopt a block randomisation method stratified by centre. Eligible patients will be randomly assigned to a treatment group at a 1:1:1 ratio. The random file will be randomly generated by the statistical department using the PLAN process of SAS (V.9.4 or later). Given the number of seeds, an appropriate block length will be selected to generate a random arrangement for 480 subjects, that is, the random code table. The block sizes will not be disclosed to ensure concealment.

All protocol-needed data will be entered in the electronic case report form (eCRF), which is an online system that is provided by Beijing LNKMED Pharmaceutical Technology Co, by the investigators at each centre. Table 1 shows patient characteristics and data collection.

Blinding

After each patient's baseline characteristics are entered, the system will automatically provide a random code. The research assistant, who is independent of the trial, will check the random code table and inform the surgeon of the approach. Patients will remain blinded to their allocations for a period of 24 hours following the surgery. To achieve this, wound pads will be applied to each patient's abdomen, simulating the wounds typically seen in traditional laparoscopy procedures, irrespective of whether actual wounds exist. These pads will only be replaced if they become soaked before the 24-hour mark. An independent investigator, who is not involved in the surgical process, will gather postoperative data and enter these into the eCRF system.

Surgeon certification and surgery centre certification

All surgeons participating in the study should be qualified or certified in gynaecological vaginal surgery or laparoscopy. Surgeons involved in the study will be required to have completed at least 25 surgeries using the corresponding surgical approach, with a minimum of five cases completed in the past year, and to have read the description of the surgical method in this study.[18 19] The surgeons must perform the operation according to the protocol. Each centre must have surgeons certified in three surgical pathways. Certification standards will ensure that all procedures in the study are performed by well-trained surgeons to ensure the validity of the study and establish standards for the trial so that the results can be generalised to other surgeons.

Eligibility criteria

Women with a diagnosis of benign uterine diseases or precancerous lesions scheduled to undergo total hysterectomy with or without salpingectomy/adnexectomy will be recruited.

Inclusion criteria

Patients eligible for the trial must meet all the following criteria:

1. Eligible women aged 18–70 years.
2. Women with indications for total hysterectomy (uterine leiomyoma, adenomyosis, cervical intraepithelial neoplasia, endometrial atypical hyperplasia, cervical adenocarcinoma in situ), who are planning to undergo total hysterectomy.
3. Patients who approve of the three surgical approaches and are willing to be randomly assigned to undergo any of them.
4. Patients who are willing to sign the informed consent form.
5. Patients with a performance status of 0 or 1 on the Eastern Cooperative Oncology Group Scale.

Exclusion criteria

Patients will be excluded for any of the following reasons:

1. Virginity.
2. Requiring simultaneous surgical intervention for concomitant cysts of ovaries or lesions of vulva, vagina, appendix and so on.
3. Malignancy or highly suspected malignancy that may change the planned surgical method.
4. Twice or more pelvic surgical histories or considering severe pelvic adhesions (rectovaginal examination suspected rectovaginal endometriosis, or poor uterine mobility).
5. History of peritoneal dialysis, pelvic radiation therapy and previous pelvic laparoscopic tuberculosis.
6. The size of uterus is over 3 months of pregnancy (ultrasound indicates that the maximum uterine diameter line is greater than 12 cm).
7. Diabetes mellitus with poor blood glucose control.
8. Body mass index >30 kg/m^2.
9. Patients with poor compliance or living far away for adequate follow-up.

Interventions

Preoperative preparation

No dairy products or starch solid food (patients should fast from fried, fatty and meaty foods for more than 8 hours) should be consumed 6 hours before anaesthesia. Additionally, clear fluid intake (total amount <300 mL) should be avoided within 2 hours of anaesthesia. No bowel preparation will be needed. Prophylactic antibiotics will be administered before surgery, and surgery will be performed under general anaesthesia. Indwelling catheterisation and preventive measures for deep vein thrombosis will be implemented according to clinical pathways. Additionally, a pre-emptive oral dose of paracetamol (0.5 g) will be administered for prophylactic analgesia 2 hours before surgery.

Procedures

The patients will be placed in the lithotomy position. A 30° rigid endoscope will be used for all groups. The manufacturer and the type of port used in the vNOTES group and the TU-LESS group will be recorded.

vNOTES group

The colpotomy can be made through either the anterior or posterior vaginal fornix. The port protective sleeve will be inserted into the pelvic cavity and then tightened and connected to the upper sealing cover, setting up the carbon dioxide (CO_2) pneumoperitoneum. The surgeon and assistants will position themselves at the patient's caudal side. The laparoscope will be inserted into one of the holes of the multiport, held by an assistant. The surgeon will insert the instruments (grasping forceps, bipolar electrocoagulation, scissors, ultrasonic scalpel, needle holder and so on) and perform total hysterectomy retrograde from the caudal to cephalic sides. Bilateral adnexectomy or bilateral salpingectomy will be carried out as previously discussed. Following hysterectomy, the vaginal stump will be sutured through the vagina.

TU-LESS group

A 2–2.5 cm longitudinal incision will be made at the umbilicus, and the abdominal cavity will be entered layer by layer. The port protective sleeve will be inserted into the abdominal cavity and then tightened and connected to the upper sealing cover, setting up the CO_2 pneumoperitoneum. The surgeon and an assistant will be positioned at the patient's head or body. Given the multiple operating holes on the port, the surgeon will have the flexibility to select any hole for placing the laparoscope, which will be held by the assistant. A uterine manipulator can be placed through the vagina and operated by another assistant, depending on the situation. The surgeon will insert the instruments (grasping forceps, bipolar coagulation, scissors, ultrasonic scalpel, needle holder, etc) through other holes of the port and perform antegrade hysterectomy from the cephalad to caudal sides. Bilateral

adnexectomy or bilateral salpingectomy will be carried out in line with preoperative discussions. The uterus can be removed through the vagina or the umbilicus. Suturing of the vaginal stump will be performed through the abdomen. The abdominal incision will be sutured in layers with absorbable sutures, and the skin will be sutured for cosmetic purposes. If an auxiliary hole needs to be established after the evaluation of experts in each centre during the operation, the surgery will be converted to conventional laparoscopy.

Conventional laparoscopy group

The surgeon will make a 1 cm incision at the umbilicus to insert a 10 mm trocar and position the laparoscope. CO_2 pneumoperitoneum will be established with a pneumoperitoneum pressure over 12 mm Hg. A uterine manipulator can be placed through the vagina and managed by another assistant. The surgeon will be positioned on the left (or right) side of the patient and can create two incisions for trocar placement. Trocars (5 mm or 10 mm) can be selected by the surgeon, and the instruments (grasping forceps, bipolar coagulation, scissors, ultrasonic scalpel, needle holder and so on) can be inserted through the trocars on both sides. Anterograde hysterectomy will be performed from the cephalad to caudal sides. Bilateral adnexectomy or bilateral salpingectomy will be carried out as discussed preoperatively. The uterus will be removed through the vagina. Suturing of the vaginal stump will be performed through the abdomen. The surgeon has the discretion to decide whether to include an assistant on the opposite side and incorporate one to two additional incisions based on the case. The 10 mm incisions will be sutured by absorbable suture layer by layer, and the skin will be sutured for cosmetic purposes.

Postoperative care

We recommend avoiding the placement of drainage tubes. If drainage is necessary, it will be recorded and can be placed through the vagina. Following the principle of blinding, all patients' abdomens should be routinely covered with three to five dressings, which should not be changed within 24 hours unless they become soaked.

After waking up from anaesthesia, the patient can receive fluids and move freely. The urinary catheter will be removed at 6 hours postoperatively, unless contraindicated due to operation-related factors.

The patient will be discharged according to the local hospital's criteria at each centre. They will be followed up until 6 months postoperatively.

Outcomes

Primary outcome

While Asian patients typically experience longer hospital stays than patients in Western countries, the discharge criteria under the ERAS guidelines are similar.[14] By reviewing ERAS guidelines and related articles, we collected the comprehensive criteria as follows: resuming a semiliquid diet, ceasing intravenous fluids, functional recovery of intestinal activity or exhaust, relieving pain well with oral analgesics, well-functioning organs and free mobilisation.[20–23] Therefore, we will use the corresponding enhanced recovery comprehensive indicators instead of the mean hospital stay as the primary outcomes to compare the effectiveness of the three surgical approaches. These indicators are as follows: (1) postoperative liquid diet, (2) passing flatus, (3) self-urination after catheter removal, (4) ambulation and (5) a Visual Analogue Scale (VAS) score ≤3. We named these indicators comprehensive indices of ERAS.

We will count the achievement rate of comprehensive indices of ERAS within 24 hours postoperatively, which is a dichotomous variable. The comprehensive indicators of ERAS include fluid intake, passing flatus, urination after catheter removal, ambulation and a VAS score ≤3. The completion time of the above indicators will be recorded, and all the above indicators should be achieved within 24 hours. If any indicator exceeds the duration of 24 hours, it is not achieved.

Secondary outcomes

1. The duration of operation will be measured in minutes, starting from the initiation of the skin (or vaginal) incision and concluding upon the completion of the skin (or vaginal) suturing. If a frozen biopsy is needed during the operation, the increased time for the frozen biopsy should be subtracted. However, patients for whom the surgical method is changed due to the result of the frozen biopsy should be excluded.
2. Estimated intraoperative blood loss (through an intraoperative suction device and usage of gauze).
3. Surgical convention rate (the conversation of the vNOTES approach or TU-LESS approach to conventional laparoscopy or laparotomy; the conversion of conventional laparoscopy to laparotomy).
4. Postoperative pain measured by the VAS score. The VAS scores at 12 hours and 24 hours postoperatively will be recorded.
5. Intraoperative complications and postoperative complications within 3 months will be categorised according to the Clavien-Dindo classification.
6. The total dosage of analgesics taken during the first 24 hours following surgery.
7. The hospital readmission rate within 3 months after surgery.
8. The Patient and Observer Scar Assessment Scale (POSAS) will be used to assess abdominal scars at 3 and 6 months after the surgery during follow-up visits.
9. The Female Sexual Function Index (FSFI) will be self-reported by patients both at baseline and 6 months after surgery using either a paper sheet or online questionnaire.

The duration of the operation, estimated intraoperative blood loss, VAS scores, total dosage of analgesics taken, POSAS score and FSFI score will be considered continuous variables. On the other hand, the surgical convention rate, intraoperative and postoperative complications,

and hospital readmission rate will be classified as discrete variables.

Participant timeline

The surgeons at each centre will enrol the patient candidates based on the eligibility criteria before surgery. Then, the patients will be given explanations of the trial and sign the informed consent form (see online supplemental file 1). The data will be collected at baseline, during the perioperative period, and at 3 months and 6 months after surgery.

Pretest

Since there was no evidence in the literature on ERAS as a primary outcome, we conducted a small pilot pretest to evaluate achievement rate of comprehensive indices of ERAS within 24 hours post-surgery for the three approaches. It was conducted with 10 patients in each group, totalling 30 patients. The pretest was assessed. In the vNOTES group, eight patients achieved the ERAS index, but one had delayed catheterisation and urination beyond 24 hours, while another began fluid intake at 24.7 hours. In the TU-LESS group, six patients achieved the ERAS index, while one needed recatheterisation for urinary retention, one passed flatus at 24.6 hours and two did not have their catheters removed promptly, leading to urination beyond 24 hours postoperatively. In the traditional laparoscopy group, eight patients achieved the ERAS index, but one experienced delayed flatus (36.7 hours) and did not have post-catheter urination, and another had delayed flatus (24.6 hours). For sample size estimation, to moderate expectations for the experimental vNOTES group, we treated the two patients for whom the ERAS index was not achieved in the TU-LESS group due to delayed catheter removal as completed cases. Each group had eight completed cases, yielding an 80% completion rate.

Sample size

The calculation of the sample size was based on the primary outcome of the pretest, which is an achievement rate of the comprehensive ERAS index within 24 hours post-surgery. The overall type I error rate of this study was 0.025, generated by a one-sided test with a randomisation ratio of 1:1:1. The type I error rate (α) was calculated under the following two hypotheses: (1) vNOTES is not inferior to traditional laparoscopy (0.0125) and (2) vNOTES is not inferior to TU-LESS (0.0125). The fulfilment of either of these hypotheses will denote the trial's success. The largest sample size was selected for pairwise comparison. For the first hypothesis, both the vNOTES group and the conventional laparoscopy group exhibited an 80% completion rate. With a one-sided test and a detection level of α=0.0125, the test efficiency (1−β) was 80% and the margin was 0.15. The required sample size for each group was estimated to be 136 patients by using the statistical analysis software PASS V.15. Regarding the second hypothesis, since the completion rate of each group in the pretest was the same, the sample size was calculated as 136 with reference to the above calculation. Considering a 15% dropout rate, we need to include 160 patients in each group, totalling 480.

Recruitment and eligibility

We have advertised the trial on peer meetings of China. The hospitals that can perform the three approaches for total laparoscopic hysterectomy will receive invitations. We will access the centres based on the surgeon certification and surgery centre certification. The centres will enrol patients based on the eligibility criteria. Since hysterectomy is the most common gynaecological surgery, we estimated that recruitment will last 1 and a half years with a 6-month follow-up. The whole process will last approximately 2 years.

Statistical analysis

Statistical analysis will be performed using SPSS V.26.0 software. All primary data will be analysed according to the principle of intention-to-treat analysis. Per-protocol (PP) analysis will also be considered. Patients for whom the surgical approach is converted from vNOTES or TU-LESS to traditional laparoscopy or laparotomy will not be included in the PP analysis. Continuous variables will be expressed as the mean±SD, while discrete variables will be expressed as medians, ranges and IQRs. After the normal distribution test is performed on the continuous variables, the independent t-test will be used to compare the normally distributed data between groups, and the rank-sum test will be used to compare the non-normally distributed data between groups. The count data will be expressed in the form of frequencies (percentages), and the X^2 test will be used for comparisons between groups. $P<0.05$ will be considered statistically significant.

Data monitoring

After each patient's information is input, the eCRF will assign a random number for allocation. All the online data will be monitored simultaneously by the system itself, the clinical research associates at each centre and the clinical research associates at the core centre. Modifications of the original data will be available via electronic logs and audit trails. An interim analysis will be carried out by an independent statistician to evaluate the safety and feasibility of the three surgical approaches. If the analysis demonstrates that the 3-month morbidity rate in the vNOTES group is significantly higher than that in the other two groups, suspension of the study will be considered.

Harms

Additional harms for the participants beyond those of laparoscopic surgery are not expected, especially because surgeons can convert the approach to traditional laparoscopy or laparotomy at any time during the operation. Data on adverse events will be collected from the date patients sign the informed consent until 12 months after surgery.

Serious adverse events must be reported to the Ethics Committee within 24 hours of detection. The compensation for harm related to the study will be provided in accordance with the relevant laws.

Modification of the protocol

After the initial approval of the protocol by the Ethics Committee, if any modification is made, a 'protocol modification description' must be written, signed by the principal investigator and approved by the Ethics Committee before it can be implemented. The modified protocol must be approved and signed by the principal investigator. Anyone participating in the trial must not violate the protocol. The modified protocol will be updated in the registry record and modifications reported when reporting the primary results of the study.

Patient and public involvement

Patients and/or the public were involved in the reporting plans of this research. Specifically, patients will participate in reporting the outcomes. However, they were not involved in the design, conduct, or dissemination of the study.

ETHICS AND DISSEMINATION

This study was approved on 25 April 2022 by the Medical Ethics Committee of West China Second University Hospital (2022(057)), Sichuan University, Chengdu, China. Ethics approval for each centre will be obtained in accordance with the regulations of each respective centre prior to enrolling the first patient. All participants will be required to provide informed consent before participating in the study. The results of the trial will be submitted for publication in a peer-reviewed journal and presented at international conferences.

DISCUSSION

This will be the first multicentre RCT of the three main laparoscopic approaches.

When comparing the open approach with minimally invasive surgery, the most significant advantage offered by minimally invasive surgery is the improved recovery of patients.[24] This is achieved through shortened hospital stays, reduced hospital costs and decreased perioperative morbidity.[24–26] However, the mean hospital stay varies according to the country and culture, which causes large bias and is hard to compare.[14 27] We reviewed the ERAS guidelines and chose the comprehensive ERAS index.

The index indicators consist of either patients' symptoms or functional status. This approach circumvents observer bias, enhances patient engagement and provides a more objective basis for comparison, thus allowing for easier generalisation.[28] A large body of research has verified the safety and feasibility of the conventional and TU-LESS approaches, so we set the two approaches as the control groups.[9 29] We carried out a pretest to determine the sample size and preliminary viability, as there are no previous references.

In clinical practice, not all doctors need to master every approach to excel. Hence, our study's surgeon certification focuses on experienced practitioners who have surpassed the learning curve and recently performed a specific procedure. These surgeons, with their relative experience, are better positioned to provide a comprehensive evaluation of the pros and cons of different surgical methods, thereby enhancing the overall applicability of our findings.

To establish a patient evaluation baseline, participating centres must have surgeons certified in all three pathways. However, it is worth noting that many centres excel in just one or two approaches. Due to potential bias in patient distribution across these centres, we have chosen not to include them in our study. This exclusion may raise concerns about limited generalisability, as participation will be restricted to centres offering all three techniques.

We excluded women with large uteri, as we believe that dealing with large uteri presents challenges across various surgical approaches. This condition can lead to higher blood loss, extended surgical duration and an elevated risk of complications. We also believe that trials may prioritise patient safety by concentrating on cases where the procedure is more achievable with lower risk. Additionally, the vNOTES approach is a relatively new technique. For most qualified surgeons, there are not enough cases for them to become confident in performing surgeries for women with large uteri. In particular, our trial will be a multicentre study, and we must consider its ubiquity. We would consider this a limitation of our study.

Study status

The study started the recruitment in September 2022. Three centres were actively recruiting patients at the time this protocol was submitted for publication. The recruitment is slower than expected due to the COVID-19 pandemic.

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Acknowledgements We thank the team of Professor Yan Hou from Beijing LNKMED Pharmaceutical Technology Co, for the data monitoring and statistical support.

Contributors WZ and SC drafted the first version of this manuscript. YZ, YW, LD and WZ participated in the study design and critically revised the manuscript. FY and XY helped in ethical approval. DZ, YL, XQ, JL and JG helped with the implementation of the trial. YZ and YW initiated the trial. YZ is the principal

investigator. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

Funding This study was supported by the Science and Technology Bureau of Chengdu City (grant number 2019-YF05-00473-SN) and National Key Research and Development Program of China (grant number 2022YFC2704103).

Competing interests None declared.

Patient and public involvement
Patients and/or the public were involved in the reporting plans of this research. Specifically, patients will participate in reporting the outcomes. However, they were not involved in the design, conduct, or dissemination of the study.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Informed Consent

Study title: A multicenter, randomized, single-blind, parallel controlled trial to compare the efficacy and safety of three surgical approaches for laparoscopic total hysterectomy (TSALTH)

Participant: Identity Card Number:

Address:

Your current diagnose is ; We sincerely invite you to participant in this multicenter, randomized, single-blind, parallel controlled trial to compare the efficacy and safety of three surgical approaches for laparoscopic total hysterectomy (TSALTH) .The principal investigator of this study was Chief Physician Zheng Ying. This clinical trial is undertaken by the Department of Obstetrics and Gynecology of the West China Second Hospital of Sichuan University, granted by Science and Technology Department of Sichuan Province, and is approved by the Medical Ethics Committee of the West China Second Hospital of Sichuan University. This notice provides you with information to help you decide whether to participate in this clinical trial. Please read it carefully, and if you have any questions, please ask the person in charge of the clinical treatment research and the clinical doctor in charge.

1. Why we invite you to this clinical trial?

Background: Hysterectomy is the most common gynecological surgery. For the choice of surgical approach, laparoscopy is a mature gynecological technique, which has the advantages of less trauma, faster recovery, shorter hospital stays, less pain, less cost, and less scarring. In the past 5-6 years, single-port laparoscopic technology has risen rapidly. Literature reports at have confirmed that trans-umbilical laparoendoscopic single site surgery (TU-LESS) for total hysterectomy is safe and effective. The trans-vaginal natural orifice transluminal endoscopic surgery (vNOTES), emerged in recent years, is a combination of laparoscopic and transvaginal surgery. The effectiveness and safety of vNOTES hysterectomy have been reported in the literature at home and abroad. At present, the three laparoscopic surgical approaches are widely carried out in China, and they are all relatively mature technologies, but there is no parallel randomized controlled study on them.

Research purpose: This study will compare the safety and effectiveness of three different approaches of total hysterectomy through traditional multi-hole laparoscopy, TU-LESS and vNOTES.

2. What do you need to do if you take part in this research?

After screening you to be included in this clinical study, the professional clinical supervisor will fully inform you of the specific process and related risks of this clinical study. After you fully understand and voluntarily join this clinical research and sign the

informed consent, we will randomly assign you to each treatment group according to the way of drawing envelopes. A total of 480 patients were included in this study design.

During the treatment period, you are required to provide relevant information completely and truthfully, strictly follow the doctor's advice to improve relevant inspections and medications, give timely feedback on your health status and conduct regular outpatient follow-up visits.

3. What are other treatment options available?

Laparotomy for hysterectomy is the oldest surgical approach. All minimally invasive approaches can be completed through laparotomy, and there is also the possibility of conversion to laparotomy. You can also choose laparotomy. directly.

4、What are the responsibilities and obligations?

1) You need to provide complete and truthful information about your medical history and current physical condition.

2) Tell the clinician truthfully about your health problems, other medicines you take and other treatment options you have received during treatment.

3) Actively cooperate with clinicians, strictly follow the doctor's advice for medication, regular follow-up, and improve relevant inspections, with good compliance.

4) If you need to take additional medications during the treatment, you need to consult your doctor in charge.

5) You cannot participate in other medical research while in the period of clinical observation and treatment of this trial.

6) IF you have anything unclear, you can consult the clinical subject group leader or member.

5. Who will be invited to participate in this clinical study?

Eligibility Criteria

Women with the diagnosis of benign uterine disease or precancerous lesions, will be proposed to undergo total hysterectomy with or without salpingectomy/adnexectomy.

Inclusion Criteria

Patients eligible for the trial must meet all the followings.

1)Eligible women aged 18–70 years.

2)Indications for total hysterectomy (hysteromyoma, adenomyosis, cervical intraepithelial neoplasia, endometrial atypical hyperplasia, cervical adenocarcinoma in situ), planning for total hysterectomy.

3)Patients in the study approve the three surgical approaches and are willing to be randomly assigned to any of them.

4)Patients are willing to sign the informed consent.

5)Performance status of 0 or one on the ECOG (Eastern Cooperative Oncology Group) scale.

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction

1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Exclusion Criteria

patients will be excluded for any of following reason.

1)Virginity.

2)Requiring simultaneous surgical intervention for concomitant cysts of ovaries or lesions of vulva, vagina, appendix, and so on.

3)Malignancy or highly suspected malignancy and may change the planning surgical method.

4)Twice or more pelvic surgical histories or considering severe pelvic adhesions (Rectal-Vaginal-examination suspected rectovaginal endometriosis, or poor uterine mobility).

5)History of peritoneal dialysis, pelvic radiation therapy, and previous pelvic laparoscopic tuberculosis.

6)The size of uterus is over 3 months of pregnancy (ultrasound indicates that the maximum uterine diameter line is greater than 12cm).

7)Diabetes mellitus with poor blood glucose control.

8)BMI > 30Kg/m2.

9)Patients with poor compliance or living far away for adequate follow-up.

6.How is your safety guaranteed?

This clinical trial will be carried out in West China Second Hospital of Sichuan University. The stuff of this trial have received relevant training and have sufficient ability to undertake this study. For the clinical monitoring of this research, we will dynamically monitor and evaluate the changes of your condition and decide the next treatment plan according to the situation.

7. Possible related risks and impacts?

1) Laparoscopic total hysterectomy can be accomplished by three surgical approaches, all of which are visualized laparoscopic surgery. There are complications in surgery, such as infection, bleeding, thrombus, poor incision healing, intestinal tube and ureter injury and so on. The current research of the three surgical approaches believes that the complications should be equivalent.

2) The TU-LESS and vNOTES approaches both can convert to traditional laparoscopy and all the three approaches can convert to laparotomy.

3) If malignant lesions are accidentally discovered during the operation, including but not limited to malignant transformation of uterine fibroids, endometrial atypical hyperplasia confirmed as endometrial cancer or cervical precancerous lesions in the intraoperative frozen pathology report as malignant tumors, interoperative changes or additional surgical methods are required , or the postoperative pathological examination confirmed that it was a malignant tumor and needed to be re-operated and withdraw from this study.

4) When you decide to participate in this clinical treatment research, please carefully consider the possible impact of long-term follow-up on your daily work, family life, and economic situation. The regular follow-up visits are required to ensure your safety.

5) For other unexpected related risks, we will provide you with clinical guidance when necessary.

8. What's your benefit?

During the clinical treatment research period, your condition may be improved; you can report the discomfort and adverse reactions during the research period to the relevant clinicians of this research group timely and obtain reliable clinical guidance; Related problems such as difficulty in registration and difficulty in seeing a doctor will be reduced.

Meanwhile, participating in this clinical treatment study can evaluate the safety and effectiveness of the three surgical approaches in total laparoscopic hysterectomy. This result will help you and other similar patients.

The examination and treatment expenses related to this treatment study will be borne by you personally (reimbursement by medical insurance is still applicable during hospitalization). Since each surgical approach is widely carried out clinically, this study will not increase your additional expenses.

9.Is personal information confidential?

Your research data will be kept in West China Hospital of Sichuan University, and researchers, research authorities, and ethics review committees can check your medical records. Any public reporting of the results of this research will not reveal your personal identity. We will make every effort to protect the privacy of your personal medical data and personal information within the law.

10.Do I have to take part in this trial?

Participation in this study is completely voluntary. You can refuse to participate in the study or withdraw from the study at any time at any stage of the trial without discrimination and retaliation, and your medical treatment and rights will not be affected. If you decide to withdraw from this study, please contact your doctor so that the disease can be properly diagnosed and treated.

Participant Declaration: I have read the above introduction about this study. My researchers have fully explained the purpose of this study, the operation process, the

possible risks and potential benefits of participating in this study and answered all my relevant questions. I voluntarily participate in this study.

I agree□ or refuse□ to the use of my research materials and biological specimens for research other than this one.

Print name of participant: _____

Signature of participant: _____

Date: _ _ _ _Year _ _ Month _ _ Day

Telephone number of participant: _____

Mobile number of participant: _____

_

Print name of legal representative: _____ (if applicable)

Relationship with participant: _____

Signature of legal representative: _____

Date: _ _ _ _ Year _ _ Month _ _ Day

Reason for signature of legal representative: _____

Print name of witness: _____ (if applicable)

Signature of witness : _____

Date: _ _ _ _ Year _ _ Month _ _ Day

Reason for signature of witness: _____

Doctor's statement: I have explained the relevant details of the study to the above-mentioned volunteer participating in this study and provided him/her with an original signed informed consent form. I confirm that I have explained the situation of this study to the subject in detail, especially the ethical principles and requirements such as risks and benefits, free and compensation, damage and compensation, voluntariness and confidentiality that may arise from participating in this study.

Signature of doctor: _____

Date: _ _ _ _ Year _ _ Month _ _ Day

Doctor's phone number: _____

The Medical Ethics Committee of West China Second University Hospital
Phone number: 028-85422654, 028-85423237