

BMJ Open Excisional treatment in women with cervical adenocarcinoma in situ (AIS): a prospective randomised controlled non-inferiority trial to compare AIS persistence/recurrence after loop electrosurgical excision procedure with cold knife cone biopsy: protocol for a pilot study

Paul A Cohen,^{1,2,3} Alison Brand,⁴ Peter Sykes,^{5,6} David C H Wrede,^{7,8,9} Orla McNally,^{10,11} Lois Eva,^{12,13} Archana Rao,^{14,15} Michael Campion,^{16,17} Martin Stockler,^{18,19} Aime Powell,²⁰ Jim Codde,²¹ Max K Bulsara,²² Lyndal Anderson,^{23,24} Yee Leung,^{25,26,27,28} Louise Farrell,²⁹ Pennie Stoyles³⁰

To cite: Cohen PA, Brand A, Sykes P, *et al*. Excisional treatment in women with cervical adenocarcinoma in situ (AIS): a prospective randomised controlled non-inferiority trial to compare AIS persistence/recurrence after loop electrosurgical excision procedure with cold knife cone biopsy: protocol for a pilot study. *BMJ Open* 2017;**7**:e017576. doi:10.1136/bmjopen-2017-017576

► Prepublication history and additional material for this paper are available online. To view please visit the journal (<http://dx.doi.org/10.1136/bmjopen-2017-017576>).

Received 2 May 2017
Revised 10 June 2017
Accepted 14 July 2017



CrossMark

For numbered affiliations see end of article.

Correspondence to

Dr Paul A Cohen;
paul.cohen@sjog.org.au

ABSTRACT

Introduction Adenocarcinoma in situ (AIS) of the uterine cervix is the precursor to invasive endocervical adenocarcinoma. An excisional biopsy such as a cold knife cone biopsy (CKC) should be performed to exclude invasive adenocarcinoma. Loop electrosurgical excision procedure (LEEP) is an alternative modality to CKC but is controversial in AIS. There is a perception that there is a greater likelihood of incomplete excision of AIS with LEEP because the depth of excised tissue tends to be smaller and the tissue margins may show thermal artefact which can interfere with pathology assessment. In the USA, guidelines recommend that any treatment modality can be used to excise AIS, provided that the specimen remains intact with interpretable margins. However, there are no high-quality studies comparing LEEP with CKC and well-designed prospective studies are needed. If such a study were to show that LEEP was non-inferior to CKC for the outcomes of post-treatment persistence, recurrence and adenocarcinoma, LEEP could be recommended as an appropriate treatment option for AIS in selected patients. This would benefit women because, unlike CKC, LEEP does not require general anaesthesia and may be associated with reduced morbidity.

Methods and analysis The proposed exploratory study is a parallel group trial with an allocation ratio of 2:1 in favour of the intervention (LEEP: CKC). Participants are women aged ≥ 18 to ≤ 45 years diagnosed with AIS on cervical screening and/or colposcopically directed biopsy in Australia and New Zealand, who are to receive excisional treatment in a tertiary level centre.

Ethics and dissemination Ethical approval for the study has been granted by the St John of God Healthcare Human Research Ethics Committee (reference number #1137).

Strengths and limitations of the study

► Strengths of this pilot study include its prospective, randomised design, allocation concealment and strategies to minimise surgical performance bias. Should the pilot study demonstrate safety and feasibility, potential limitations of a subsequent phase III study include those pertaining to non-inferiority trials which lack a placebo group, can only provide an indirect assessment of the efficacy of the treatment compared with an existing standard and where the choice of non-inferiority margin can be subjective.

Results from the study will be presented at conferences and published in a peer-reviewed scientific journal.

Registration ANZCTR registration number ACTRN12617000132347 <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=372173&isReview=true>

INTRODUCTION

Adenocarcinoma in situ (AIS) of the uterine cervix is the precursor to, and may coexist with, invasive endocervical adenocarcinoma.¹ Current guidelines recommend that women in whom AIS is reported on screening cytology are referred to a gynaecologist with expertise in the colposcopic evaluation of suspected malignancies or a gynaecologic oncologist, and if invasive disease is not identified at colposcopy, a cold knife cone biopsy

(CKC) should be performed to exclude invasive adenocarcinoma.^{2,3}

The role of alternative excision modalities to CKC in the investigation and management of AIS has been the subject of extensive debate. Single-specimen excision biopsies with minimal thermal damage or disruption of resection margins are essential for accurate histopathological assessment. A comprehensive review of the Australian 2005 National Cervical Screening Programme (NCSP) guidelines² has recommended that 'cold-knife cone biopsy should be considered the "gold standard" for the diagnostic assessment of glandular lesions. However, a diathermy excisional procedure may be appropriate in some circumstances and could provide an appropriate surgical specimen when performed by a gynaecologist with appropriate training, experience and expertise'.⁴ There is a perception that there is a greater likelihood of incomplete excision with loop electrosurgical excision procedure (LEEP) because the depth of excised tissue and the overall dimensions of the specimen tend to be smaller in comparison to CKC. It is also argued that the tissue margins in a LEEP biopsy may show significant thermal artefact, which can interfere with the pathological assessment of biopsy margins.^{5,6} Some studies have shown a greater risk of a positive endocervical margin with LEEP but these have included cases in which AIS was not suspected prior to the excisional procedure.⁷⁻⁹ However, current American Society for Colposcopy and Cervical Pathology consensus guidelines recommend that any treatment modality can be used for diagnostic excision, provided that the specimen remains intact with interpretable margins and that there is no fragmentation, including 'top-hat' serial endocervical excisions.³

Conservative treatment of women with AIS by CKC or LEEP is also controversial because AIS may co-exist with cervical adenocarcinoma¹⁰ and hence total hysterectomy has been regarded as definitive management.³ However, CKC and LEEP present fertility-preserving alternatives to hysterectomy in women of reproductive age in whom AIS is prevalent.^{11,12}

Positive or close histopathological margins have been associated with an increased risk of AIS persistence and recurrence.¹³ A 2014 systematic review¹⁴ reported higher rates of incomplete excision with LEEP (51%) than with CKC (30%) or laser cone (28%) using pooled data and reported rates of recurrence of AIS ranging from 9% to 29% after LEEP and from 6% to 11% after CKC. This review concluded that LEEP had acceptable safety and was comparable to CKC when negative margins were achieved, and is associated with better obstetric outcomes.¹⁴ Furthermore, recent evidence suggests that CKC and LEEP are associated with similar rates of positive margins and recurrent AIS.¹⁵ Advantages of LEEP compared with CKC include the ability to perform the procedure under local anaesthesia in an outpatient setting and lower morbidity, including adverse obstetric outcomes.^{16,17}

There are no prospective randomised studies of AIS treatment to inform clinical practice. More recent retrospective studies have found similar recurrence and persistence rates for LEEP and CKC.^{18,19} The absence of prospective randomised studies has recently been highlighted by Cancer Council Australia's working party draft clinical management guidelines for the prevention of cervical cancer.⁴ There is a clear need for prospective randomised clinical trials to determine whether LEEP is associated with similar histopathological and clinical outcomes when compared with CKC in the investigation and management of cervical AIS.

The Cancer Council Australia Cervical Cancer Screening Guidelines Working Party argued that 'Well-designed prospective research studies are needed to compare the use of cold knife cone biopsy with diathermy loop excision (LEEP or LLETZ) in the diagnosis and treatment of AIS. If such a study were to show that loop excision was non-inferior to cold-knife cone biopsy for the outcomes of post-treatment persistence and recurrence, and adenocarcinoma, loop excision could be recommended as an appropriate treatment option for AIS in selected patients. This would benefit women because, unlike cold-knife cone procedures, loop excision does not require hospital admission and general anaesthesia. Studies evaluating endocervical curettage would provide useful evidence to determine its role in clinical practice. Long-term data from the National Cervical Screening Program should be analysed to determine the minimal effective surveillance period for women undergoing annual Test of Cure for post-treatment AIS before returning to routine 5-yearly screening'.⁴

The aim of the proposed pilot study is to demonstrate the feasibility and safety of LEEP versus CKC for the treatment of cervical AIS prior to conducting a phase III prospective multicentre randomised non-inferiority trial.

The specific objectives of the proposed phase I study are

1. to compare LEEP with CKC in terms of margin status and specimen dimensions
2. to compare rates of early complications at 6 weeks, for example, pain, infection, primary and secondary haemorrhage, readmission to hospital, return to the operating theatre after the two treatment modalities
3. to assess patient satisfaction following LEEP and CKC
4. to determine the costs of treatment.

If feasibility and safety are demonstrated, the objective of the subsequent phase III trial would be to determine if the treatment of cervical AIS by LEEP is non-inferior to CKC in terms of disease persistence at 12 months and recurrence at 5 years in women managed conservatively, when treatment is performed in tertiary level dysplasia and gynaecologic oncology centres.

METHODS AND ANALYSIS

The protocol conforms to the SPIRIT (Standard Protocol Items for Randomised Trials) statement.

Trial design

The proposed exploratory study is a parallel group trial with an allocation ratio of 2:1 in favour of the intervention (LEEP: CKC).

Study setting

Academic tertiary level hospitals in Australia and New Zealand.

Study sites are listed in the ANZCTR registration number ACTRN12617000132347.

Web address: <http://www.ANZCTR.org.au/ACTRN12617000132347.aspx>

Eligibility criteria

Women aged ≥ 18 to ≤ 45 years diagnosed with AIS on cervical screening and/or colposcopically directed biopsy in Australia and New Zealand, who are to receive excisional treatment in a tertiary level centre.

Inclusion criteria

- ▶ Aged between ≥ 18 and 45 years of age at time of study enrolment
- ▶ Documentation of AIS on cervical cytology and/or cervical biopsy test results
- ▶ Lesion amenable to single-pass excision (serial endocervical excisions including 'top-hat' will not be permitted in accordance with American Society for Colposcopy and Cervical Pathology Recommendations)⁷
- ▶ Proficient in English.

Exclusion criteria

- ▶ High-grade cervical abnormality prior to current AIS diagnosis
- ▶ Previous excisional or ablative treatment (LEEP, CKC, Fisher cone biopsy, laser cone, laser ablation, radical diathermy)
- ▶ Previous history of cervical cancer treated by radiation or chemoradiation
- ▶ Cytology suspicious of invasion
- ▶ Clinical/colposcopic suspicion of invasion
- ▶ Presence of a concurrent gynaecological cancer
- ▶ Patients unable to comply with follow-up evaluations
- ▶ Immunosuppression
- ▶ Pregnancy
- ▶ Lesion considered unsuitable for single-pass excision by treating specialist.

Interventions

Eligible participants will be randomised to undergo either LEEP or CKC. LEEP is the standard procedure performed for the more common high-grade squamous cervical dysplasia and the technique is described in detail in online supplementary appendix A. In Australia, CKC has been the preferred technique to excise cervical AIS and the technique is outlined in online supplementary appendix A. The interventions will be administered within the usual clinical time frames as per local practice.

Patient management will follow the National Health and Medical Research Council's 2005 Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen-detected abnormalities and the revised 2016 guidelines. Participants randomised to the LEEP arm of the study will have their procedure performed either under local or general anaesthesia in an outpatient setting or operating theatre at the discretion of the treating specialist as per local routine practice. All participants will undergo endocervical curettage at the time of their LEEP or CKC.

Following treatment, all patients will undergo the 'Test of Cure' management pathway:

1. colposcopy and cervical cytology at 6 months' postexcisional treatment
2. cervical cytology and oncogenic human papilloma virus (HPV) typing at 12 months' post-treatment and then annually in accordance with the revised 2017 NCSP guidelines.⁴

Methods for protecting against sources of bias

A potential issue in surgical trials is performance bias. The study setting will be tertiary level dysplasia/gynaecologic oncology units and only the named study investigators will be performing the excisional procedures which will mitigate this bias to some extent. All clinical investigators are highly experienced providers and are certified under the Colposcopy Quality Improvement Programme in accordance with the requirements of the Royal Australia and New Zealand College of Obstetrics and Gynaecology. The requirement for a single-pass specimen will also limit surgical performance bias.

Strategies to improve adherence to intervention protocols and any procedures for monitoring adherence

It is anticipated that participants will attend for treatment and those who do not attend will be recalled as per routine clinical practice. Participants will be encouraged to complete the patient satisfaction questionnaire at 6 weeks' post-treatment by a phone call and/or email from the site trial co-ordinators.

Outcomes

Primary outcomes: Histopathological margin status and status of the excised specimen (single specimen or more than one piece).

Rationale: Margin status has consistently been shown to predict persistence and recurrence of cervical AIS.¹³ Disruption to the excision specimen can make orientation and interpretation of tissue margins impossible. If there are significantly more LEEP specimens with positive margins compared with those excised by CKC, or if there are a greater number of specimens excised in more than one piece compared with CKC, then it may not be appropriate to conduct a larger phase III study.

Key secondary outcomes: Frequency of early complications (pain, infection, primary and delayed haemorrhage, readmission to hospital, return to the operating theatre),

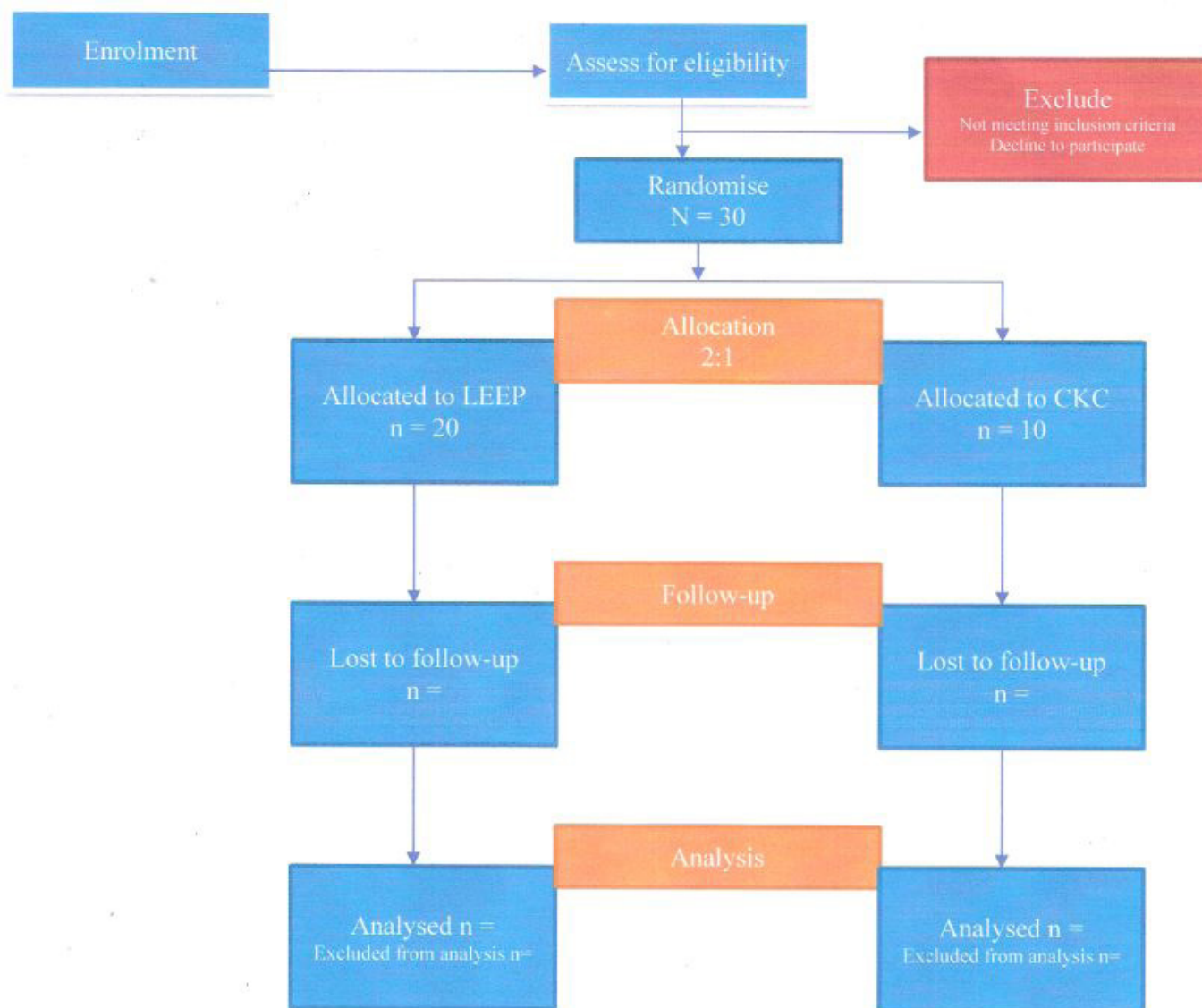


Figure 1 Consolidated standards of reporting trials (CONSORT) flow diagram of EXCISE study. CKC, cold knife cone biopsy; LEEP, loop electro-surgical excision procedure.

patient satisfaction at 6 weeks' postprocedure and costs of treatment.

Rationale: Retrospective studies have suggested that LEEP is associated with fewer early complications.^{16 17} Although the proposed study is underpowered to detect differences in these outcomes, the purpose of their inclusion is to determine the feasibility of data collection.

Participant timelines

Figure 1 shows a consolidated standards of reporting trials (CONSORT) flow diagram of the EXcisional treatment Comparison for In Situ Endocervical adenocarcinoma (EXCISE) study. The schedule of enrolment, interventions and assessments is presented in figure 2. Following randomisation, participants will undergo the treatment to which they are allocated (LEEP or CKC). LEEP and CKC are usually day-case procedures. Participants will have one follow-up visit with a local study

co-ordinator at 6 weeks' postprocedure. This visit may be conducted face to face or via telephone and will involve collection of information regarding complications post-procedure, return to hospital, general practitioner (GP) visits and a request to complete and return the patient satisfaction questionnaire.

We are aiming to recruit 35–40 participants for the proposed phase I study. This sample size was determined on a pragmatic basis (five patients recruited at each of seven participating sites).

Sample size

The sample size for the pilot study is pragmatic. The sample size for the potential subsequent phase III study was estimated using a two-group test of non-inferiority of proportions, where the primary end point is the AIS recurrence rate at 5 years and the comparison will be between CKC and LEEP, based on a one-sided test for

	STUDY PERIOD			
	Enrolment	Allocation	Intervention	Close-out
TIMEPOINT	$-t_1$	0 Within 7 days (+4) (Day 0-11)	t_1 Within 8 weeks of allocation (Day 0-56)	t_x 6 weeks' post intervention (+14 days)
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
<i>[List other procedures]</i>				
Allocation		X		
INTERVENTIONS:				
<i>[Intervention A]</i>			LEEP	
<i>[Intervention B]</i>			CKC	
<i>[List other study groups]</i>				
ASSESSMENTS:		t_1	t_2	t_x
Baseline variables	Age Parity BMI Smoking status HPV vaccine status STIs Family history Comorbidities AIS on Pap AIS on biopsy Colposcopy findings			
Outcome variables				Histopathology Report Complications Patient Satisfaction Questionnaire Hospital costs of treatment

Figure 2 Schedule of enrolment, interventions and assessments. AIS, adenocarcinoma in situ; BMI, body mass index; CKC, cold knife cone biopsy; HPV, human papilloma virus; LEEP, loop electrosurgical excision procedure; STI, sexually transmitted infection.

non-inferiority. If we assume for patients in the standard treatment arm an 8% rate of AIS recurrence at 5 years, and a 5% non-inferiority margin (so an upper 95% confidence rate of AIS recurrence of 13% is still within the non-inferiority margin), the total sample size needed is 730 (365 per group). Assuming a 10% drop-out rate, a total sample size of 810 participants (405 per group) would need to be randomised. The one-sided type I error

is set at 5% with 80% power. Kaplan-Meier and log-rank tests will be used to test for non-inferiority at median follow-up of 5 years (with patient recruitment between 4 and 5 years, assuming 160–200 patients are successfully randomised per annum). Proportional hazard models will be used to test for differences between the two treatment groups controlling for confounding variables. All statistical analysis will be carried out as per CONSORT

recommendations for non-inferiority randomised controlled trials using intent-to-treat as well as per-protocol populations.

Recruitment: strategies for achieving adequate participant enrolment to reach target sample size

Several of the investigators are the clinical leads of their local dysplasia units and triage patient referrals to their centres. They will be ideally placed to identify potential eligible participants. The investigators believe that it is feasible to recruit the number of participants needed for this phase I study based on the local incidence of cervical AIS and enrolment rates in previous research studies.

Assignment of interventions

Allocation: Participants will be randomised to undergo LEEP or CKC (2:1 ratio).

Generation of the allocation sequence will be by computer-generated random numbers. The allocation sequence will be implemented by central telephone (interactive voice response system) and will be generated by the National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney.

Participants will be enrolled by the treating specialist who will be one of the named investigators. Following randomisation, participants will be assigned to LEEP or CKC by a study co-ordinator at each site.

Blinding

All study investigators and participants will not be blinded to the intervention.

Data collection, management and analysis

A case report form (CRF) will be used to record data for each participant. The primary outcomes will be assessed as part of routine clinical care by the reporting consultant anatomical pathologists at each site. All participating sites will be required to complete synoptic/standardised histopathology reports for each study participant. All specimens will undergo centralised pathology review at Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia, by Dr Lyndal Anderson, Consultant Pathologist and Study Investigator. Data regarding early complications will be obtained via patient medical records and at patient follow-up visits and recorded on the CRF by the site study co-ordinator. Patient satisfaction will be assessed by using those aspects of the European Organization for Research and Treatment of Cancer in-patient satisfaction (EORTC IN-PATSAT32) which are pertinent to outpatient care, as well as additional questions on the ease of making appointments, clinic accessibility and waiting times.^{20 21} The intervention is a surgical procedure so once performed it will not be possible for participants to deviate from the intervention protocol. Should a participant withdraw from the study postintervention then it may not be possible to obtain data regarding secondary outcomes (early complications and patient satisfaction).

Data will only be collected with the signed permission of the participant. All questionnaires/data CRFs will be given a unique identity number (de-identified data) and will not include information that would allow identification of the participant. Unique patient identification number will be generated by the interactive voice response system (IVRS) and identified patient data will only be available to the principal investigators at each participating institution. Only de-identified clinical information will be used for statistical analysis and reporting.

The original study participant CRFs will be stored securely by the relevant study site investigators. Copies of the completed CRFs accompanied with de-identified supporting source documents will be scanned by the study site researchers, saved in a PDF format and these version files will be emailed to the lead site for data entry.

The study standard operating procedures (SOP) will be used to ensure the collection of accurate, consistent, complete and reliable data. In addition, prior to the study initiation at each site, an investigator meeting and training session will be held via teleconference to prepare both the investigators and other trial staff involved and to standardise performance.

Safety reporting will be conducted according to trial specific procedures. Data management will be performed by the lead site. Accurate and reliable data collection will be assured by 100% verification and crosscheck of CRFs against the investigator's records by the St John of God (SJOG) Gynaecological Cancer Research Group.

All data will be stored in locked offices, password-protected computer files and password-protected database, accessible only by site staff. A FileMaker Pro database will be used for the data management, and data from the CRFs will be entered into the database by the SJOG Gynaecological Cancer Research Group.

Safety monitoring

An independent medical monitor (IMM) will undertake ongoing safety monitoring throughout the trials duration assessing serious adverse events (SAE) and suspected, unexpected adverse reactions (SUSARs) reported by research sites to the Trial Steering Committee (TSC). The IMM will provide recommendations whether the study should continue as planned or that changes should be made to the protocol to improve safety. If matters of major safety are identified, for example, a higher than expected SUSARs/SAEs being reported, the IMM can recommend that the study be postponed until matters are clarified and resolved. Otherwise, if study participant safety is compromised, the study must be terminated.

Data monitoring

A systematic, prioritised risk-based monitoring schedule will be implemented by the study sponsor in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) (5.18 Monitoring) guidelines. It will encompass both on-site monitoring and centralised remote monitoring modalities. On-site

monitoring will verify that study participants have given their consent to participate voluntarily, have been fully informed of the research trial and that their rights, safety and well-being are assured. Additionally, the monitoring will verify that the data collected are accurate, complete and verifiable from source documents and that the site research personnel are conducting the trial in accordance with the Human Research Ethics Committee (HREC) approved study protocol and its 'conditions of approval'.

Centralised monitoring will complement and reduce on-site monitoring whereby reliable data and potentially unreliable data can be distinguished, that is, omissions, inconsistencies, incongruous or anomalous data entries will be identified and queries can be clarified and where applicable, corrected and resolved in a timely manner with the relevant study sites in accordance with GCP guidelines.

Harms

The investigator is responsible for reporting all AEs and SAEs that are observed during the study, regardless of their relationship to treatment or their clinical significance. All AEs and SAEs that occur after surgery during the study must be recorded in the patient's chart and the CRFs and followed to a satisfactory resolution or until the local Investigator deems the patient to be stable or the AE/SAE to have resolved. The description of the AE/SAE will include the onset date, duration, date of resolution, severity, seriousness, aetiology and the likelihood of relationship of the AE to study treatment. Severity of AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (CTC- AE v4.0).

If an AE occurs which is not contained in the CTC-AE v4.0, the following five-point scale will be used:

1. mild: discomfort noticed but no disruption of normal daily activity
2. moderate: discomfort sufficient to reduce or affect daily activity
3. severe: inability to work or perform normal daily activity
4. life threatening: represents an immediate threat to life
5. death.

Any AE considered serious by the local Investigator or which meets the previous criteria must be reported to the TSC. A CRF and SOP for SAE reporting will be provided by the lead site. If the patient is hospitalised because of, or during, an SAE, then a copy of the hospital discharge summary and any other reports/results should be emailed to the lead site (SJOG Subiaco) as soon as they are available.

Once an investigator becomes aware that an SAE has occurred in a study participant, they will immediately notify the lead site via email. The SAE form must be completed by site personnel as thoroughly as possible with all available details of the event, signed by the investigator

(or appropriately qualified designee) and emailed to the lead site within 24 hours of first becoming aware of the event. The investigator will always provide an assessment of causality at the time of the initial report.

All sites are required to submit locally occurring SAEs to their reviewing ethics committee or site governance office within 24 hours of first notification of SAE occurrence or according to local HREC policy.

At every study visit, patients will be asked a standard non-leading question to obtain any medically related changes in their well-being. They will also be asked if they have been hospitalised, had any accidents, used any new medications or changed concomitant medication regimens (prescription, over-the-counter medications and herbal supplements). In addition to patient or investigator observations, AEs will be documented from any data collected (eg, laboratory values, physical examination findings), or other documents that are relevant to patient safety.

The investigator's assessment of an AE's relationship to treatment is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

All AEs and SAEs will be followed until resolution, until the condition stabilises, until the event is otherwise explained, until the participant is lost to follow-up or up to close out visit.

Once resolved, the appropriate AE/SAE CRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other healthcare professionals.

New or updated information for SAEs will be recorded on the originally completed SAE form, with all changes signed and dated by the investigator or designee. The updated SAE form should be resent to the SJOG Gynaecological Cancer Research Group.

AUDITING

Participating sites will be audited at least once during the pilot phase by a study monitor who is an employee of the sponsor but independent of the investigators.

ETHICS AND DISSEMINATION

Ethical approval for the study has been granted by the St John of God Healthcare Human Research Ethics Committee (reference number #1137). Important protocol modifications will be submitted to the St John of God Subiaco Hospital HREC as requests to amend the approved study protocol. Informed consent will be obtained by the participant's treating specialist. Only the investigators, data manager and trial co-ordinator at St John of God Subiaco Hospital will have access to the final

trial dataset. Participants will undergo post-trial care in accordance with NHMRC guidelines for the follow-up of women after treatment for cervical AIS. There are no provisions for those who suffer harm from trial participation as any harm would be regarded as having arisen because of routine treatment and not specifically due to trial participation.

The investigators and sponsor do not intend to communicate results directly to participants. Results from the study will be presented at national and international conferences and published in a peer-reviewed scientific journal. The authorship guidelines largely follow the rules established by the International Committee of Medical Journal Editors.²² The investigators do not intend to use professional writers.

DISCUSSION

In contrast to cervical squamous dysplasia, the incidence of AIS is increasing in relative and absolute terms. There is a clear need for prospective randomised clinical trials to determine whether LEEP is associated with similar histopathological and clinical outcomes when compared with CKC in the investigation and management of cervical AIS. This is the first prospective randomised study to investigate this clinical question. Limitations of the pilot study are its relatively short follow-up period (6 weeks) and small sample size, which are pragmatic. The objective of the pilot study is to demonstrate the feasibility and safety of the intervention as defined by pathological margin status, and hence long-term outcomes of interest including rates of cervical AIS recurrence and obstetric complications will be endpoints in a subsequent phase III trial. Limitations of a phase III study include those of non-inferiority trials such as defining the acceptable margin of AEs that would render the interventional treatment inferior, lack of a placebo group and allowing only an indirect assessment of the efficacy of the intervention compared with an accepted standard.

Strengths of the study include its randomised design and attempts to minimise surgical performance bias. If LEEP was found to be non-inferior to CKC for the outcomes of post-treatment persistence and recurrence, and adenocarcinoma, it could be recommended as an appropriate treatment option for AIS in selected patients. This would benefit women because, unlike cold knife cone procedures, loop excision does not require hospital admission and general anaesthesia.

Author affiliations

¹Division of Women's and Infants' Health, School of Medicine, University of Western Australia, Crawley, Western Australia, Australia

²Department of Gynaecological Oncology, King Edward Memorial Hospital for Women, Subiaco, Western Australia, Australia

³Department of Gynaecological Oncology, St John of God Hospital Bendat Family Comprehensive Cancer Centre, Subiaco, Western Australia, Australia

⁴Department of Gynaecological Oncology, University of Sydney, Sydney, New South Wales, Australia

⁵Department of Obstetrics and Gynaecology, Christchurch Women's Hospital, Christchurch, Otago, New Zealand

⁶Department of Obstetrics and Gynaecology, University of Otago, Christchurch, New Zealand

⁷Department of Obstetrics and Gynaecology, Obstetrics and Gynaecology Consulting Group, Melbourne, Victoria, Australia

⁸Gynaecological Cancer Centre, The Royal Women's Hospital, Melbourne, Victoria, Australia

⁹Department of Obstetrics and Gynaecology, University of Melbourne, Melbourne, Victoria, Australia

¹⁰Department of Gynaecological Oncology, Victorian Comprehensive Cancer Centre, Melbourne, Victoria, Australia

¹¹Department of Obstetrics and Gynaecology, University of Melbourne, Melbourne, Victoria, Australia

¹²Department of Gynaecological Oncology, National Women's Health, Auckland City Hospital, Auckland, New Zealand

¹³Department of Gynaecological Oncology, University of Auckland, Auckland, New Zealand

¹⁴Department of Gynaecological Oncology, Royal Hospital for Women, Randwick, New South Wales, Australia

¹⁵Department of Obstetrics and Gynaecology, University of New South Wales, Sydney, New South Wales, Australia

¹⁶Department of Obstetrics and Gynaecology, Royal Hospital for Women, Randwick, New South Wales, Australia

¹⁷School of Women's and Children's Health, University of New South Wales, Sydney, New South Wales, Australia

¹⁸NHMRC Clinical Trials Centre, Camperdown, New South Wales, Australia

¹⁹Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia

²⁰Institute for Health Research, University of Notre Dame Australia, Fremantle, Western Australia, Australia

²¹Institute for Health Research, University of Notre Dame Australia, Fremantle, Western Australia, Australia

²²Institute for Health Research, University of Notre Dame Australia, Fremantle, Western Australia, Australia

²³Anatomical Pathology Department, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia

²⁴School of Medicine, Western Sydney University, Sydney, New South Wales, Australia

²⁵Department of Gynaecological Oncologist, King Edward Memorial Hospital for Women, Subiaco, Western Australia, Australia

²⁶Division of Women's and Infants' Health, School of Medicine, University of Western Australia, Crawley, Western Australia, Australia

²⁷Western Australia Gynaecologic Cancer Service, Perth, Western Australia, Australia

²⁸Department of Surgical Education, King Edward Memorial Hospital for Women, Subiaco, Western Australia, Australia

²⁹Department of Obstetrics and Gynaecology, King Edward Memorial Hospital for Women, Subiaco, Western Australia, Australia

³⁰Consumer and Community Committee, Australia and New Zealand Gynaecological Oncology Group, Camperdown, New South Wales, Australia

Contributors PAC is the principal investigator, conceived the study and wrote the protocol. AB, PS, DCHW, OM, LE, AR, MC, MS, AM, JC, LA, YL, LF and PS assisted in the design of the study and drafting of the protocol. MKB participated in the statistical design of the study and helped draft the protocol. All authors read and approved the final manuscript.

Funding This work has been supported by the Australia and New Zealand Gynaecological Oncology Group (ANZGOG) Fund for New Research grant number FNR 2016/03'.

Competing interests None declared.

Ethics approval St John of God Healthcare Human Research Ethics Committee, Subiaco, Perth, Western Australia 6008, Australia.

Provenance and peer review Not commissioned; externally peer reviewed.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

1. Wilbur DC, Chieng DC, Guidos B, *et al.* Epithelial abnormalities: glandular. In: Nayar R, Wilbur DC, eds. *The Bethesda system for reporting cervical cytology. Definitions, criteria and exploratory notes.* 3rd ed: Springer, 2015.
2. National Cervical Screening Program. *Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen detected abnormalities.* Canberra: National Cervical Screening Program, 2005.
3. Massad LS, Einstein MH, Huh WK, *et al.* American Society for Colposcopy and Cervical Pathology Consensus Guidelines Conference. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis* 2013;17:S1–S27.
4. Anderson L, Hammond I, Pather S, *et al.* Cancer Council Australia Cervical Cancer Screening Guidelines Working Party. In: *Cancer Council Australia Cervical Cancer Screening Guidelines Working Party National Cervical Screening Program: Guidelines for the management of screen-detected abnormalities, screening in specific populations and investigation of abnormal vaginal bleeding.* Sydney: Cancer Council Australia. http://wiki.cancer.org.au/australia/Guidelines:Cervical_cancer/Screening/Management_of_glandular_abnormalities. (accessed 7 Jan 2017).
5. Krebs HB, Pastore L, Helmkamp BF. Loop electrosurgical excision procedures for cervical dysplasia: experience in a community hospital. *Am J Obstet Gynecol* 1993;169:289–95.
6. Mathevet P, Dargent D, Roy M, *et al.* A randomized prospective study comparing three techniques of conization: cold knife, laser, and LEEP. *Gynecol Oncol* 1994;54:175–9.
7. Azodi M, Chambers SK, Rutherford TJ, *et al.* Adenocarcinoma in situ of the cervix: management and outcome. *Gynecol Oncol* 1999;73:348–53.
8. Denehy TR, Gregori CA, Breen JL, Thad R. Endocervical curettage, cone margins, and residual adenocarcinoma in situ of the cervix. *Obstet Gynecol* 1997;90:1–6.
9. Kennedy AW, Biscotti CV. Further study of the management of cervical adenocarcinoma in situ. *Gynecol Oncol* 2002;86:361–4.
10. Costa S, Venturoli S, Negri G, *et al.* Factors predicting the outcome of conservatively treated adenocarcinoma in situ of the uterine cervix: an analysis of 166 cases. *Gynecol Oncol* 2012;124:490–5.
11. Bull-Phelps SL, Garner EI, Walsh CS, *et al.* Fertility-sparing surgery in 101 women with adenocarcinoma in situ of the cervix. *Gynecol Oncol* 2007;107:316–9.
12. van Hanegem N, Barroilhet LM, Nucci MR, *et al.* Fertility-sparing treatment in younger women with adenocarcinoma in situ of the cervix. *Gynecol Oncol* 2012;124:72–7.
13. Kietpeerakool C, Khunamornpong S, Srisomboon J, *et al.* Predictive value of negative cone margin status for risk of residual disease among women with cervical adenocarcinoma in situ. *Int J Gynaecol Obstet* 2012;119:266–9.
14. Baalbergen A, Helmerhorst TJ. Adenocarcinoma in situ of the uterine cervix—a systematic review. *Int J Gynecol Cancer* 2014;24:1543–8.
15. Latif NA, Neubauer NL, Helenowski IB, *et al.* Management of adenocarcinoma in situ of the uterine cervix: a comparison of loop electrosurgical excision procedure and cold knife conization. *J Low Genit Tract Dis* 2015;19:97–102.
16. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, *et al.* Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet* 2006;367:489–98.
17. Arbyn M, Kyrgiou M, Simoons C, *et al.* Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. *BMJ* 2008;337:a1284.
18. Munro A, Leung Y, Spilsbury K, *et al.* Comparison of cold knife cone biopsy and loop electrosurgical excision procedure in the management of cervical adenocarcinoma in situ: What is the gold standard? *Gynecol Oncol* 2015;137:258–63.
19. Dalrymple C, Valmadre S, Cook A, *et al.* Cold knife versus laser cone biopsy for adenocarcinoma in situ of the cervix—a comparison of management and outcome. *Int J Gynecol Cancer* 2008;18:116–20.
20. Brédart A, Bottomley A, Blazeby JM, *et al.* An international prospective study of the EORTC cancer in-patient satisfaction with care measure (EORTC IN-PATSAT32). *Eur J Cancer* 2005;41:2120–31.
21. Pather S, Tai D, Philp S, *et al.* A prospective study assessing patient satisfaction at a large tertiary gynecologic oncology/dysplasia unit. *Patient Relat Outcome Meas* 2010;1:149–52.
22. <http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html>