COVER PAGE

Mind over Cervix: Using Virtual Reality to reduce Colposcopy Anxiety

VR as a distraction technique for management of acute anxiety and pain during outpatient colposcopy procedures – a single centre randomised control trial

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Data Category	Information
Sources of monetary or material support	Ulster University Queen Elizabeth Hospital, Gateshead
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Public title	**Mind over Cervix:** Using Virtual Reality to reduce Colposcopy Anxiety
Scientific title	Virtual Reality as a distraction technique for management of acute anxiety and pain during outpatient colposcopy procedures – a single centre randomised control trial
Countries of recruitment	England
Health condition(s) or problem(s) studied	Anxiety, pain reduction, colposcopy
Intervention	Virtual reality headsets to reduce anxiety. Comparator – standard care in colposcopy
Key inclusion and exclusion criteria	Inclusion Criteria (Patients) - Patients: biological females of >18 years of age who attend for outpatient colposcopy and provide informed written consent Exclusion criteria (Patients) - Significant hearing or visual impairments that would impair communication during the procedure

	- Any known characteristics that may make the office procedure more difficult (>1previous LLETZ, previous cervical conisation, uterine didelphis) - Inability to provide consent. - Denial or withdrawal of informed oral consent Inclusion Criteria (Staff) – Have completed colposcopy training and be a registered member of the British Society of Colposcopy and Cervical Pathology (BSCCP) – Informed written consent to take part in the trial. Exclusion criteria (Staff) – The denial or withdrawal of informed consent. – Trainee colposcopist performing clinic.
Study type	Interventional Allocation: randomized Intervention model: parallel assignment Masking: non blinded Primary purpose: anxiety reduction Phase I
Date of first enrolment	TBC
Target sample size	141
Recruitment status	Awaiting ethical approval
Primary outcome(s)	Reduction in anxiety experienced by biological females attending for outpatient colposcopy as measured by STAI (state trait anxiety index)

Key secondary outcomes	Reduction in pain experienced by biological females attending for outpatient colposcopy as measured by numerical rating scores (NRS) Understanding the acceptability and effectiveness in terms of reducing anxiety of VR interventions within the procedural groups and how these might vary as a function of different patient demographics. Feasibility and acceptance of intervention from clinicians' perspective Does the introduction of VR have an impact on patients' attendance to follow up appointments

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Study Management: Ulster University

Study Coordination Centre: Queen Elizabeth Hospital, Gateshead.

Funding: This study is part of a research fellowship. The medical devices company Rescape have provided the headsets for use in research free of charge but have had no role in the design of the study and will not have a role during its execution, analyses, interpretation of data or decision to submit results. It will have no access to or ownership over any patient data collected during this study.

General and clinical queries, supply of study documents and collection of data please contact Dr Victoria Braden (Clinical Research Fellow, Chief Investigator) (Victoria.braden@nhs.net) or Ms Nithya Ratnavelu (Consultant Gynaeoncologist, Study Supervisor) (Nithya.ratnavelu@nhs.net)

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Abstract

- **Background**: Colposcopy is an important aspect of biological females's health. Due to cervical screening and early treatment of abnormal results with colposcopy, the incidence of cervical cancer has greatly reduced. However, due to its intimate nature and association with cancer, colposcopy has been shown to be a time of very high anxiety for patients. As healthcare gets more patient centred it becomes imperative that we try to improve the patient experience. Virtual reality (VR) is increasingly used throughout healthcare as a method of reducing anxiety and pain for patients. We believe this could be of great benefit to patients attending for outpatient colposcopy as a form of non-pharmacological digital distraction.
- **Methods**: We will perform a single centre, non-blinded, parallel, randomised control trial to measure the reduction in state trait anxiety (STAI) scores and numerical rating scores (NRS) for pain in participants allocated to the intervention arm (addition of VR headsets during their colposcopy appointment) compared to the control arm (standard colposcopy care). All biological females attending Queen Elizabeth Hospital, Gateshead, for their colposcopy appointment will be offered enrolment to the trial dependant on inclusion/exclusion criteria.
- **Discussion**: We believe the addition of the VR headsets will have a significant impact in reducing patients's anxiety and pain and improving their overall satisfaction scores. This has potential to translate to other outpatient procedures within the hospital.
- **Trial registration**:

Keywords

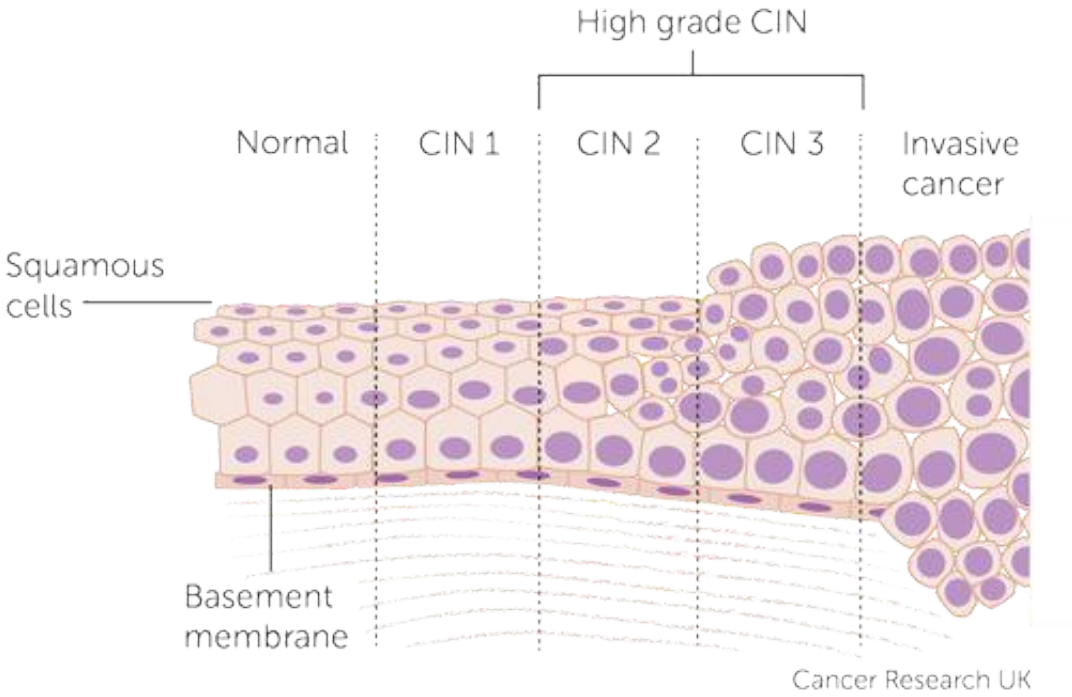
Colposcopy
Cervical Screening
Virtual Reality
Anxiety reduction
Pain reduction

Introduction

Background and rationale

Colposcopy

There are approximately 3200 new cases of cervical cancer diagnosed annually in the UK, with around 690 biological females dying from the disease. However, 99.8% of these cases are preventable. The numbers of cancer are consistently dropping, largely due to the advances in cervical screening and colposcopy, however screening attendance is at a 20 year low with one in four people with a cervix not participating. (1) More than 95% of cervical cancers are due to the human papilloma virus (HPV), particularly type 16 and 18. HPV is a common viral infection of the reproductive tract that most sexually active men and women will be infected by at some point of their lives. 90% of people will clear the infection themselves without any symptoms or treatment required, however HPV infection is a well-known risk factor for many types of cancer. If HPV does infect cervical epithelial cells, it changes the way cells interact with one another, causing the infected cells to multiply in an uncontrolled manner. (2) These can form the precancerous cells known as cervical intra-epithelial neoplasia (CIN). These changes, especially in young biological females, often revert to normal cells due to an appropriate immune response and the rapid proliferation of cells of the cervix. 60% of CIN-1 will regress to normal after 1 year. People with CIN-2 and CIN-3 are at higher risk for developing cervical cancer and so should receive treatment. Regular cervical smears enable early detection of cervical changes to CIN cascade and prompt referral to colposcopy for further investigation. (2,3)



Colposcopy is the process of visualizing the cervix, specifically the transformation zone, using a binocular microscope called a colposcope. The transformation zone is where the ectocervical columnar cells are continuously converting into squamous cells in the endocervix. This is the most common site for cervical cancer to arise. 235,223 biological females are year are referred to colposcopy following an abnormal smear. (1) After inserting a speculum, acetic acid or schillers iodine is applied to the cervix by the clinician. Normal cervical tissue appears pale after application of acetic acid, while areas of abnormal tissue, such as those with dysplasia or precancerous changes, turn white due to increased protein coagulation - known as the "acetowhite" effect. Iodine works by staining glycogen-rich cells brown, which helps in differentiating between normal and abnormal tissue. Normal cervical squamous epithelium is rich in glycogen and stains dark brown, while areas lacking glycogen, such as those with dysplasia or abnormal changes, remain unstained. If these show concerns about the cells in the cervix, they can either be biopsied if unsure of the diagnosis or treated in the form of a large loop excision of the transformation zone (LLETZ). A LLETZ is when the colposcopist uses a thin looped wire with electrical current passing through it is used to take a biopsy of the cervix, including the transformation zone. This can be painful for patients, so local anesthetic is used to provide some pain relief. The cervix is innervated with parasympathetic nerve fibers from S2-S4 which travel through the broad ligament to enter the cervix at 3o’clock and 9 o’clock. This is where the clinician will inject local anesthetic to minimize pain for the patient. Despite the use of local anesthetic, there can still be an element of discomfort for the patients. (4) The specimen is then sent to the histopathology lab for examination to investigate the extent of any abnormalities. The aim is that any precancerous changes are excised

with clear margins. Various outcomes from the examination and procedure can mean many patients are invited to reattend for a further colposcopy in a few weeks or months – such as follow up following a biopsy, unclear margins, mismatch between clinical findings and histopathological findings or the specimen being upgraded to a cancer. (5) Hence, colposcopy is often not a one stop clinic for service users so anxiety may be increasingly heightened as time progresses.

Despite colposcopy having undeniable significance in biological female's healthcare, the entire process is associated with high levels of stress and anxiety for patients. Colposcopy is a unique circumstance due to the intimate nature of the examination and the association with cancer. It is associated with fear, stress and loss of control. Many studies show that patients experience a "very high" level of anxiety when attending for colposcopy. (6) In comparison to other medical procedures, biological female patients experience a higher level of anxiety when attending colposcopy than when they are attending for cardiac surgery. (6,7) Anxiety can negatively impact a person's cognitive abilities and decreases the ability to recall and act on advice, leading to patients being less likely to comply with any information given. (8) Higher pre-procedural anxiety is predictive of post operative pain reported by patients in gynecological settings. Thus, by addressing these feelings, clinicians can reduce pain perception, however reducing this during a procedure without pharmacological agents remains a difficult task. (9)
Research has shown that heightened anxiety and pain during colposcopy can also negatively impact patients willingness to comply with recommended follow up appointments and screening procedures. (10) Although the absolute value varies widely from region to region, it shown that people with a cervix who do not attend for regular cervical screening have a higher risk of developing cervical cancer compared to people who do not attend for screening. (11) Additionally, the discomfort associated with the procedure can lead to increased muscle tension and resistance, activating the cycle of pain, and potentially affecting the accuracy and ability to complete the investigation. (12) If an examination or treatment is unable to be completed, these patients are often added to a theatre list for a general anesthetic to allow the clinician the ability to complete the process. Although this will always be a necessity for some patients, it puts them at risk of a general anesthetic, as well as taking valuable theatre time that could be used for other cases, so it is preferable to do as many patients as possible in the outpatient setting
As healthcare is becoming more holistic and patient centered, it is imperative that we aim to create as positive an experience as possible for both patients and healthcare providers.

Virtual Reality

A 2007 Cochrane review looked at the various randomized controlled trials that investigated ways to reduce anxiety levels during colposcopy. (13) Of the

randomized controlled trials included, playing music or video colposcopy as distraction techniques appeared to have good effect. (13,14)
Advanced technologies are increasingly being used throughout health care to alleviate the feelings of anxiety and stress felt by many patients. Virtual Reality (VR) is an immersive technology that transports users to computer generated environments. It is increasingly being used as an alternative form of analgesia in medical procedures as well as being effective in managing phobias, PTSD and other behavioral healthcare. (15 – 18) It works by combining clinical hypnotherapy and integrative therapeutic techniques, delivered via a virtual reality headset with accompanied sound modules to distract patients. By providing a controlled and engaging sensory experience, it diverts patients' attention aware from the procedure itself, reducing anticipatory anxiety and enhancing overall relaxation. (15, 19, 25)

There are multifaceted benefits from using VR as a form of digital distraction. Firstly, it is nonpharmacological. This circumvents potential side effects associated with sedatives or anxiolytic medications. (20) Secondly, its versatility allows tailoring of experiences to individual preferences, accommodating various ages groups and clinical scenarios. Moreover, the interactive and customisable nature of VR allows healthcare workers to engage patients in the decision-making process, fostering a collaborative approach. (21) Ambulatory procedures should use multimodal forms of pain relief including pharmacological as well as non-pharmacological. By giving the patient options, this will increase the number of successful procedures. (22)

A 2023 systematic review looking at the use of VR in pain management shows it as a feasible option, with a reduction in pain perceived and anxiety levels in surgical patients. (23) Other recent studies in gynecological outpatient settings such as brachytherapy rod removal have shown it to be an effective adjunct to improve pain and anxiety score with a similar efficacy to nitrous oxide. (20) Moreover, it has also been shown to increase emotional detachment from the procedure in patients, aiding relaxation, reducing unnecessary movement and allowing the healthcare professionals to focus on the treatment. (24) This dual effect should both increase clinic efficiency as well as decrease the frequency of procedure abandonment.
The use of virtual reality during colposcopy procedures has not yet been published, therefore, it is important to establish if this improves patient anxiety, pain and overall satisfaction.

Patient and Public Involvement

A scoping exercise was carried out in the outpatient colposcopy clinic prior to initiation of the intervention to assess the people attending attitudes in relation to colposcopy and the introduction of VR headsets. Biological females attending clinic were interviewed by the lead researcher and given questionnaires to assess their attitudes to colposcopy and acceptability of using the headset. Most participants reported feeling "nervous" and "jittery" as "very much so," on the modified STAI

score. 87% of participants interviewed (N=15) stated they would be accepting to use the VR headset during their consultation and thought it would be of benefit.
Biological females attending colposcopy will be invited to take part a focus group to review our patient information leaflets, questionnaires and consent forms to ensure they are easily understandable by service users. We will use the focus groups to ensure the study runs in a way that the local patient population feel is beneficial to them.
The study has been presented at the regional colposcopy business meeting with a very strong consensus from clinical staff that this will be a worthwhile study to perform for patients attending colposcopy.
The research proposal was presented to the colposcopy staff at the monthly business meeting and to the gynaecological oncology team at an inaugurate annual research meeting. The proposal was met with enthusiasm from the team and everyone presented to was willing to take part. Feedback regarding logistics was given and incorporated into the proposal.
The study is aligned to current government aims of transforming the NHS for the future. We are living in an increasingly digitalised environment and further research and investment is needed in these advancing technologies. Use of VR is highly transferrable into other outpatient procedural settings which could improve patient experience globally. NICE guidance in 2018 has recommended that further studies be performed to investigate methods to reduce anxiety in biological females undergoing colposcopy in order to improve patient experience and reduce the number of patients lost to follow up.

Aim

The aim of this study is to assess the effectiveness of utilising Virtual Reality technology as a non-pharmacological intervention to alleviate anxiety, reduce pain perception, and enhance overall satisfaction for people with a cervix undergoing colposcopy procedures.

Nul hypothesis

The addition of virtual reality headsets to outpatient colposcopy as a form of digital digital has no effect on biological females measured anxiety or pain scores.

Objectives

Primary objective

- To determine if the addition of virtual reality headsets during outpatient colposcopy appointments has an impact on patients' anxiety perception compared to standard management.

Secondary objectives

- To determine if the addition of virtual reality headsets during outpatient colposcopy appointments has an impact on patients' pain perception compared to standard management

- Understanding the acceptability and effectiveness regarding anxiety reduction of VR interventions within the procedural groups and how these might vary as a function of different patient demographics.
- Feasibility and acceptance of intervention from clinicians' perspective
- To investigate if the introduction of VR have an impact on patients' attendance to follow up appointments

Study Design

Trial design

The "Mind over Cervix" trial is designed as a single centre, prospective, non-blinded, randomised control trial with two parallel groups to determine the superiority of VR headsets in patients' anxiety reduction and pain reduction during outpatient colposcopy compared to standard care.

Study setting

The study will be carried out in the colposcopy outpatient clinic in Queen Elizabeth Hospital (QEH), Gateshead, Gateshead Health Trust.
QEH is a large tertiary referral centre for gynaeoncology and colposcopy in the north-east of England. Over 1700 patients attend the department for colposcopy annually. (24) Colposcopy is provided by consultant gynaeoncologists, consultant gynaecologists and nurse colposcopists.

Withdrawal Criteria

Patients can withdraw from the study at any time and without giving a reason. Deciding to withdraw or not take partake in the study will not have any effect on the standard of care they receive. In addition, any staff member may withdraw their consent at any time without giving a reason.

Recruitment

Queen Elizabeth Hospital in Gateshead is a large tertiary referral centre for Gynaeoncology and colposcopy in the northeast of England. Over 1700 patients attend the department for colposcopy annually. (24)
Following prospective ethical and trust approval via IRAS, all patients who attend for outpatient colposcopy will be informed of the study prior to their arrival to the department. They will be sent a patient invitation leaflet (Appendix 1) to their home through the post 2-4 weeks prior to their appointment to inform them of the study and the fact they may be approached. On arrival to the department, a poster will be displayed in the department to remind attendees of the study and the potential for their participation (Appendix 1a). They will be given information again via the PIL (Appendix 1b) which will be provided by the clerical staff when they attend reception to check in for their appointment.

A member of the research team comprising of the PI (V.B) and other research and colposcopy staff (L.P) will approach the patients once they have arrived at their colposcopy appointment. Patients will be asked if they have had a chance to read the PIL, explain the process further and if they have any initial questions. Each patient will then be asked if they would be interested in taking part in the study. If the service user declines, colposcopy care will proceed as normal. If the patient agrees to take part, they will be taken to a free clinic room to allow the consent process to be completed confidentially. (Appendix 2a) The right of the patient to withdraw consent at any time without reason will be respected. Following consent, the form will be copied in triplicate with one copy added to the clinical research file, one to the patients' notes and one to the patient. The patients' colposcopist will be notified of the involvement in the study. Patients will be identified by their unique study number only. Number of cases which declined and number not suitable for inclusion will be noted prospectively and anonymously in a screening log of patient age and ethnicity. Previous PPI work performed in the department indicated that the majority (87%, n=15) patients approached would be accepting to take part in the study. Virtual reality has been studied extensively in clinical trials with high uptakes in patient populations reported. (6,15,17,18,19,20)
All colposcopy staff who work in the clinic will be invited to take part in the study. The trial has already been presented and proposed to the team at a unit monthly business meeting. It was met with enthusiasm and all trained colposcopists present where agreeable to participation. They will be enrolled by a staff participant information leaflet (Appendix 1c) and consented by a member of the research team (Appendix 2b)

Eligibility criteria

Inclusion Criteria (Patients)

- Patients: biological females of over 18 years of age who attend for outpatient colposcopy
- Be able to complete informed consent.

Exclusion criteria (Patients)

- Significant hearing or visual impairments that would interfere with communication during the procedure.
- Any known characteristics that may make the office procedure more difficult (>1previous LLETZ, previous cervical conisation, uterine didelphis)
- Inability to provide consent.
- Denial or withdrawal of informed oral consent
- There are no addition exclusion criteria as per the manufacturers instructions

Inclusion Criteria (Staff)

- Have completed colposcopy training and be a registered member of the British Society of Colposcopy and Cervical Pathology (BSCCP)
- Have completed informed consent.

Exclusion Criteria (Staff)

- The denial or withdrawal of informed consent.
- Trainee colposcopist performing clinic.

Interventions

Explanation for the choice of comparators

Biological females are offered a colposcopy appointment depending on the results of their routine cervical screening. Screening occurs every 3 years from age 25 until 49, and then 5 yearly from age 50 to 64. Cervical screening looks for HPV initially, and if this is found then cytology is performed on the specimen. If abnormal cells are found, patients are referred to colposcopy for further investigation. Here, the cervix is examined in great detail for any concerning changes. If there are areas of concern, it may require a LLETZ treatment to remove part of the cervix to prevent it from developing into cancer.

Despite the undeniable importance of colposcopy in women's' health, it is known to be a time of very high anxiety. In line with NHS values, we need to try to improve patients experience of colposcopy and try novel methods of reducing their anxiety. VR has been shown to be an effective and safe intervention in other outpatient procedures to reduce anxiety, it has not yet been investigated during outpatient colposcopy procedures. (15,18,19,20)

Intervention description

Once consented and enrolled in the trial, participants will then be asked to complete the study questionnaire (Appendix 4) which will be a paper-based format. This will allow measurement of baseline and state anxiety and anticipated pain. We will collect this data prior to randomisation of the participant into either arm of the trial. Patients will then be randomly allocated to either the VR intervention arm or the standard procedure arm. The clinician taking consent will ask the service to choose from two opaque, blank envelopes that will contain inside if they are to be enrolled in the intervention or control arm. The envelopes will be blinded to both the clinician and the patient prior to selection.

The patient will be brought into the colposcopy consultation room, where the clinic will proceed as normal. The doctor/nurse providing the treatment will explain the process of colposcopy to the patient so that they know what to expect from the procedure as per standard practice. This involves undressing, sitting on the colposcopy couch, insertion of a speculum, application of acetic acid/iodine, inspection of the cervix using a colposcopy and treatment or biopsy if indicated.

Once the patient has been informed about both the colposcopy procedure and the VR intervention, they will be invited to prepare for their examination. There is always one assistant present in the room during any routine colposcopy appointment. The main role of the assistant is to provide support to the patient. If in the intervention arm, once the patient is prepared and seated in the colposcopy chair, the assistant will place the VR headset on the patient and begin the immersive therapy. The participant will be shown an immersive video specifically designed by Rescape Innovation Ltd, Cardiff, UK to reduce anxiety that will encourage them to focus on their breathing throughout. Rescape have been delivering VR therapies for over 3 years. DR.VR™ a pain and anxiety product, has been licensed and deployed into over 100 healthcare environments across the UK. The device and software are CE marked and is a class one medical device with content informed by cognitive behavioural therapy and dialectical behavioural therapy. The system which consists of a headset, earphones and tablet smart device is designed to work from its container without the need for local internet connection. It has a rigorous decontamination protocol between patients. DR.VR™ has been used successfully in the NHS in a range of specialisms such as A&E (32), phlebotomy (33), burns (34), and paediatrics (33).

A routine colposcopy appointment will normally take on average 5 minutes, or if treatment is being performed may take 10-15minutes. The VR videos developed by Rescape last approximately 7 minutes each. There are 3 videos available that we can play back-to-back to ensure immersion in the VR intervention with no break. The videos have been specifically chosen to aid feelings of relaxation and include, walking through a forest while David Attenborough narrates and an under the sea diving experience through a shipwreck. Participants will still be able to hear the clinician throughout the colposcopy to allow them to stay informed of any procedural elements taking place. No other aspects of the participants care in colposcopy will be changed apart from the addition of the headset. All other forms of pain relief will be provided as required in normal colposcopy. This includes local anaesthetic to provide a cervical block and nitrous oxide for inhalation. The participant will be free at her own will to remove the headset at any stage, and this will be recorded as part of the assessment.

Once the colposcopy treatment is complete the participant will be assisted to remove the headset and informed the results of the colposcopy the routine manner. Participants who are part of the control arm of the study will have colposcopy performed as per standard practice with no VR headset application at the time.

Following the completion of the colposcopy, participants will then be asked by the research team to complete another short paper questionnaire (Appendix 5) to quantify their perceived pain and actual anxiety score during the procedure. This will be kept anonymised and blinded from the clinician who has carried out consultation.

Participants who were allocated to be in the control arm of the study will be offered the opportunity to trial a headset following completion of their enrolment in the study.

Following completion of patient interaction, the clinician who has carried out the procedure will be asked to fill out a paper questionnaire (Appendix 6) provided by the PI/CRN regarding the ease and timing of the procedure, and if any difficulties were encountered with the equipment or communication with the patient.

Staff Training

All clinicians and clinic staff who will be involved in application of the headset to participants have had training from Rescape or PI on how to use to the system. The training video is available to all staff if they feel they need to renew their training. The training log has been recorded and will be added to the standard operating procedure file. (SOP).

Criteria for discontinuing or modifying allocated interventions

Participants are free to remove the VR headset at any point in the intervention. They will be informed of this prior to its application. Participants will be free withdraw consent and leave the trial at any point during the process. They do not have to give prior warning or any explanation. This will not change the clinical procedure being conducted. If participant becomes upset or display signs of anxiety during the procedure the distress protocol will be followed (Appendix 3)
There is a risk of cybersickness during the application of the headset. Patients will be informed of this during the consent process and informed to remove the headset should this occur. This is included in the distress protocol and the deviation log (Appendix 7).

Strategies to improve adherence to interventions

Potential participants will be shown photographs of the VR headset prior to enrolment in the trial via the PIL provided to ensure understanding of its involvement. If they are in the VR intervention arm, they will be given the opportunity to see the VR device prior to beginning the therapy. They will be given the opportunity to try the headset on prior to beginning the colposcopy consultation to ensure they are amenable to having it placed prior to the procedure.

Relevant concomitant care permitted or prohibited during the trial
Some patients attending colposcopy will only have an inspection performed of the cervix, other patients will have a biopsy or a LLETZ procedure performed. If a biopsy or LLETZ procedure is performed, the entire colposcopy experience will take longer and may be more painful than if only inspection is performed. If a patient needs a biopsy or LLETZ performed, this will not be known until the colposcopy inspection

has taken place, so it is not possible to stratify the study group arms prior to enrolment in the trial.

Provisions for post-trial care Patients that are enrolled into the study are covered by indemnity for negligent harm through the standard NHS Indemnity arrangements from Gateshead health trust. Following the procedure participants will be offered the opportunity to ask the team any questions. They will be provided with contact details for the study team if they have any concerns when they have left following the procedure.
Additional patient follow up will not routinely be performed as part of the study. Any follow up will be as per standard colposcopy practice.

Outcomes

Primary outcome

- To determine any change in anxiety experienced by people with a cervix attending for outpatient colposcopy as measured by STAI (state trait anxiety index) in both the intervention arm and the control arm. Pre procedure paper questionnaires will be conducted to establish a baseline anxiety measure for patients. The comparison will be performed from the post procedure paper questionnaires from both arms of the study.

Secondary outcomes

- To determine any change in pain experience by people with a cervix attending for outpatient colposcopy as measured by a numerical rating scale (NRS) in both the intervention arm and control arm via paper questionnaires.
- Understanding the acceptability and effectiveness of VR interventions within the procedural groups and how these might vary as a function of different patient demographics.
- Feasibility and acceptance of intervention from clinicians' perspective
- Does the introduction of VR have an impact on patients' attendance to follow up appointments?

Participant timeline

Sample size

The sample size calculation was run using the packages pwr and pwrss within R. For the calculation the significance level of 0.05 and power of 0.8 where used along with a Cohen's d of 0.5. Two different types of outcome variables will be used so the calculations used are based on ANCOVA (continuous) and the Mann-Whitney test (ordinal). Both results suggest a sample size of 64 participants in each group (128 in total) We have added on a 10% drop out rate which brings the total sample size to 141.

Assignment of interventions

Sequence generation and concealment mechanism

Participants will be randomly assigned to either control or VR intervention group by patient selection of a choice of two opaque envelopes. One envelope will instruct participant to be part of the control arm, one envelope will instruct the participant to be part of the intervention arm. The envelopes will be blinded to the researcher who provides the envelopes for the patient to choose.

Concealment mechanism Potential patients will be invited to take part in the trial prior to knowledge of what arm they will be involved in. They will be asked to complete the initial questionnaire to get a baseline STAI score before randomisation. They will be randomly allocated by patient choice of an opaque sealed envelope that will contain if they are to join the intervention or control arm. These envelopes will be blinded to the research team until after the patient selection.

Implementation All patients who consent for participation and meet the inclusion criteria will be randomized. Randomization will occur following the consent process and initial questionnaire. A member of the research team will be responsible for providing the sealed opaque envelopes for randomisation. Sealed identical opaque envelopes will be made ahead of time by the research team on a 1:1 ratio.

Assignment of interventions: Blinding

Who will be blinded?

Due to the nature of the intervention, the study team felt it is not possible to blind participants or assessors once the study arm has been allocated. Participant questionnaire results will be concealed from the assessor at point of contact.

Data collection and management

Plans for assessment and collection of outcomes

<u>Primary outcome</u>

Anxiety reduction: Anxiety will be measured using the state trait anxiety index (STAI) STAI was chosen as it is a well-known measure of trait and state anxiety. It is considered the “gold standard” of measuring preoperative anxiety and its reliability and validity have been well reported in literature. (33,34) State items include “I feel upset,” “I feel frightened, “I feel nervous,” “I am jittery” and I feel confused.” Patients respond with a numerical value of 1 to 4 with 1 meaning “not at all” and 4 meaning “very much so”. (27,28)

Participants will complete a questionnaire (Appendix 6a) with STAI questions prior to randomisation to get a baseline anxiety level. This will be compared to the post procedural questionnaire (Appendix 6b) with the same questions to compare the actual anxiety levels during the procedure. Comparison will be made between the two arms.

Secondary Outcome

Pain reduction: Pain scores will be measured by a Numeric Rating Scale (NRS) from 0 through to 10. 0 represents “no pain” and 10 represents “worst pain imaginable”. This will be shown alongside a visual analogue scale (VAS) of pain on animated faces. This is a validated measure for pain, is easy to use, has high compliance rates and detects meaningful change. (29,30,31) Participants will be asked to state the “maximum pain felt, if only for one moment,” and also state the “average pain experienced,” throughout the procedure. Respondents will select the single number that best represents their pain intensity. Results from participants in the intervention arm will be compared to participants in the control arm.

Understanding the acceptability and effectiveness of VR in variations of patient demographics: Participants will be asked to state the following demographics – age, ethnicity, parity, menopausal status, previous attendances to colposcopy and previous treatments in colposcopy. Acceptability will be monitored by participants ongoing consent of using the VR headset. If a patient removes the headset before the colposcopy assessment is completed, this will be noted in the post procedural questionnaire and be noted that the patient did not find it acceptable. The demographics of this patient cohort will be reviewed to see how VR effects different patient demographics.

Feasibility and acceptance of intervention from clinicians’ perspective: Following completion of the colposcopy assessment, the clinician will be asked to complete a short survey of their experience using VR. (Appendix 6c) These will be questions on a Likert scale from “strongly disagree” to “strongly agree”. Clinicians will be asked did they find it easy to use the VR in their clinic, did they find it beneficial to the consultation, did they find it easy to communicate with the patient during the consultation.

Does the introduction of VR have an impact on patients attendance to follow up appointments: Following completion of the trial intervention period, a retrospective analysis of patients who are enrolled in the trial and require a further attendance, adherence to their follow-up appointments will be monitored. This will be completed using the department’s electronic booking system to monitor attendance. This will be compared to the department’s previous 6-month non-attendance. Data will be compared to see if enrolment on the trial and the addition of VR had any benefit in patient compliance to follow-up.

Plans to promote participant retention and complete follow-up

Participants are free to withdraw from the trial at any stage without explanation. This will be explained to them.

As participation in the trial is a relatively short amount of time, lasting only as long as their clinic appointment, we do not anticipate retention and follow-up being a significant factor in our study.

Data management

Research team members CMcF, NR, WM and LP have longstanding experience with data collection and storage. All study records and the Investigator Site File will be kept at site in a locked filing cabinet with restricted access. The Trial Master File will be held at Queen Elizabeth Hospital, Gateshead NHS trust in a locked filing cabinet with restricted access.

Data linkage will require use of NHS number which will be done securely with the IT network of Gateshead NHS Trust by a researcher with an NHS contract. The identifiable data will be stored with access restricted to the research team and will be protected by passwords. Computers will be protected by passwords and stored securely. The research team will follow guidance to ensure that personal data cannot be seen on screens or any other media by those outside the research team. Documentation including personal data will be minimal and if possible avoided and will be stored in locked cabinets in locked offices and destroyed in line with confidentiality requirements of the Trust as soon as it is no longer needed.

A pseudo-anonymised database will be prepared for analysis within the Trust for transfer for analysis at Queens University Belfast. The data for use outside the NHS will be prepared in a manner that will not allow the potential identification of individuals by combinations of data, for example, by using appropriate and ethnic group grouping that do not risk identification of individuals and anonymising all but the highest-level geographical data. Team members carrying out test accuracy and analysis will have no access to personal identifiable data.

Data generated from the research project will be stored for 10 years on NHS and/or University computers in an anonymised manner and after any patient identifiable information is removed. Access to these computers will be password protected and only by members of the research team.

Confidentiality

Confidentiality will be maintained at all times and be under the supervision of the primary investigator (VB). Members of the local site research team will have NHS

contracts with the obligation to follow all relevant NHS codes of practice and guidance. They will maintain required relevant training including NHS information governance, data security and GCP.

All participants will allocated a number from 1-141 on their enrolment into the trial. The PI will have a separate data log to enable correlation between clinical data and study data. No other members of the team will have access to it and it will be stored on a password protected trust computer.
Questionnaires collected for analysis will be anonymous and results will be added to a password encrypted Excel, retaining the anonymity of the patients. This anonymous data will be sent via a secure link to the statisticians for analysis. No identifiable patient information will leave the hospital trust information system.

Statistical methods
Demographic characteristics will be explored for missing data and distribution abnormalities. Means and standard deviations will be used to characterise the sample. Analysis of covariance (ANCOVA) and non-parametric tests (Mann – Whitney) will be used to determine whether the VR intervention lead to a significant difference between baseline and follow up anxiety between control VR and control arm. Descriptive statistics (i.e. age, gender, ethnicity, previous attendance to colposcopy, menopausal status and parity) for the baseline values will be presented within each randomized controlled arm. P values will be used to estimate statistical significance for all analysis.

End of Study Definition
The end of study will be upon completion of the final visit of the last participant/volunteer enrolled in the trial.

Project Management Plan

PROJECT MANAGEMENT PLAN (with project milestones)			
Action	Timescale	Responsibility	Indicator / Outcome / Evidence
Develop protocol	*Aug 23- Dec 23*	*Fellow and Supervisors*	*Creation of protocol to ensure robust methodology and outcome measures*
Scoping exercise amongst service users	*Oct 23- Dec 23*	*Fellow*	*Ensure in keeping with service users focus*
Train staff on VR equipment	*Oct 23 - ongoing*	*Fellow, Rescape*	*Train staff alongside Rescape to use equipment*
Recruitment PPI work for patient information leaflets, questionnaires	*Oct 23 - ongoing*	*Fellow, Research nurses*	*Approaching service users for feedback to ensure legibility*
Begin recruitment of service users	*March 24 – August 24*	*Fellow, Research nurses*	*Consenting and awareness*
Begin trial and data collection	*March 24 – August 24*	*Fellow, Research team, supervisors*	*Comparison of VR to standard care*
Completion of data collection and writing up	*Aug 24 – Dec 24*	*Fellow, Supervisors*	*Writing up analysis*
Dissemination of information	*Jan 25 – Aug 25*	*Fellow, supervisors*	*Conference presentations, publications*

Oversight and monitoring

Composition of the coordinating centre

Dr Victoria Braden (Principal investigator) *Clinical Research Fellow Gynaecological Oncology*

- Design and conduct of “Mind over Cervix”.
- Preparation of protocol and revisions
- Chair of steering group

- Overall responsibility for study milestones
- Preparation of case report forms (CRFs)
- Managing, monitoring and ensuring integrity of collaborative relationships
- Direct and oversee day to day practicalities of study.
- Consent patients for participation in trial
- Intellectual contribution to preparation of reports, presentations and publications

Ms Claire McFeeters (Chief Investigator)

- Co – applicant
- Expert in clinical trial research and virtual reality headsets
- Advisor on preparation of protocol and revisions
- Member of project management group
- Intellectual contribution to preparation of reports, presentations and publications

Ms Nithya Ratnavelu (Study Supervisor) *Consultant Gynaecological Oncologist*

- Co – applicant
- Member of project management group
- Advisor on preparation of protocol and revisions
- Intellectual contribution to preparation of reports, presentations and publications

Ms Lorraine Pearce *Clinical Research Nurse Gynaecological Oncology*

- Extensive experience in daily management of clinical trials
- Recruitment and consent of patients
- Distribution of patient information leaflets
- Data collection and storage

Ms Wendy McCormick *Research Data Co-ordinator Gynaecological Oncology*

- Extensive experience in daily management of clinical trials
- Recruitment and consent of patients
- Distribution of patient information leaflets
- Data collection and storage

Dr Hannah Mitchell *Statistician* Member of project management group

- Sample size calculation and analysis of data
- Contribution to interpretation of results
- Intellectual contribution to preparation of reports, presentations and publications

Dr Lisa McFetridge *Statistician*

- Member of project management group
- Sample size calculation and analysis of data
- Contribution to interpretation of results
- Intellectual contribution to preparation of reports, presentations and publications

Adverse event reporting and harms

Definitions

Adverse Event (AE): any untoward medical occurrence in a patient of clinical study subject

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that

- Results in death
- Is life threatening
- Requires hospitalisation or prolongation of existing inpatients hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement may be exercised in deciding with an AE is serious in other situations. E.g., Patient distress, injury.

All adverse events will be reported. Depending on the nature of the adverse event the reporting procedures below will be followed. Any questions concerning adverse event reporting will be directed to the Primary Investigator (VB) in the first instance.

All SAEs will then be reported to Claire McFeeters (CI)where in the opinion of the Chief Investigator, the event was:

- 'related', i.e., resulted from the administration of any of the research procedures; and
- 'unexpected', i.e., an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators will report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees)

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendments will be agreed by the steering group and be approved by the ethics committee. All changes will be disseminated to the necessary clinicians via the research team and emails. Patients will be informed of any chances upon their arrival.

Dissemination plans

We would intend to publish our research protocol and then subsequent findings will be disseminated by publication in a high impact peer reviewed scientific journal of a gynaecological nature. E.g., British Journal of Obstetrics and Gynaecology (BJOG). Our objective is to complete a high quality randomised controlled trial that will be informative to various healthcare professionals – primarily gynaecologists and nurse colposcopists. We believe that this has the potential to change and develop future guidelines for other areas of medicine that frequently use outpatient procedures, such as colonoscopy, ENT, tissue viability nurses.

Results will also be disseminated via national and international presentations (e.g. British Gynaecological Cancer Society, for which Ms Ratnavelu, Co-PI is a committee member and British Society for Colposcopy and Cervical pathology meeting). This will ensure that data reaches the gynaecologists and policy makers who are responsible for these patients and have a direct impact on patient care.

We will approach charities who are involved in women's health promotion such as “the Eve appeal” or “Well Being of Women” to aid us in publicising our results online to raise awareness amongst service users.

Abbreviations

VR Virtual Reality
STAI State Trait Anxiety Index
NRS Numerical Rating Score
PI Primary Investigator
CI Chief Investigator
HPV Human Papilloma Virus
CIN Cervical Intraepithelial Neoplasia
LLETZ Large loop excision of transformation zone
QEH Queen Elizabeth Hospital
BSCCP British Society for Colposcopy and Cervical Pathology
CRF Case Report Form

AE Adverse Event
SAE Serious adverse event
SOP Standard operating procedure

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