Does Virtual Reality Technology Reduce Pain and Anxiety During Outpatient Hysteroscopy? A Randomised Controlled Trial

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Name & Role	**Date**	**Signature**

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Clinical Queries

Clinical queries should be directed to Mr Thomas Sewell who will direct the query to the appropriate person

Sponsor

Imperial College Healthcare NHS Trust is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
Imperial College London & Imperial College Healthcare NHS Trust
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Imperial College – Research Governance and Integrity Team (RGIT) Website

Funder: N/A

No funding required (VR headset loaned by Sync VR Medical).

This protocol describes the virtual reality technology during outpatient hysteroscopy study and provides information about procedures for entering participants. . Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

3D US	Three dimensional Ultrasound
VR	Virtual reality
OPH	Outpatient Hysteroscopy
NHS	National Health Service

KEYWORDS

Virtual reality technology, outpatient hysteroscopy, pain, anxiety. Endometrial receptivity; endometrial receptivity array; mRNA expression; uterine fibroids; uterine septum; recurrent miscarriage; subfertility; implantation; window of implantation; metroplasty; myomectomy

STUDY SUMMARY

TITLE Does Virtual Reality Technology Reduce Pain and Anxiety During Outpatient Hysteroscopy? A Randomised Controlled Trial

DESIGN Randomised controlled trial

AIMS To evaluate whether the use of virtual reality technology can reduce pain and anxiety during outpatient hysteroscopy procedures.

OUTCOME MEASURES Primary outcome measures are patient reported NRS (numeric rating score) for pain and anxiety.
Secondary outcome measures will be length of procedure, complication rate, reported side effects, procedure completion or if stopped, hysteroscopy findings and type of procedure performed.

POPULATION Women aged referred from general gynaecology clinics for outpatient hysteroscopy procedures.

ELIGIBILITY Inclusion criteria are age 18-70, capacity to give informed consent and cognitive and linguistic ability sufficient to understand and fill out the NRS questionnaire. Exclusion criteria are epilepsy or severe vertigo, blindness or significant hearing impairment and recent facial injury/burn

DURATION 1 year

1. INTRODUCTION

1.1 BACKGROUND

Hysteroscopy is a very common gynaecological procedure where a camera attached to a thin scope is passed into the uterus via the vagina and cervix in order to obtain views of the inside of the uterus. Hysteroscopy is used for the diagnosis and management of a variety of benign and conditions as well as the diagnosis of uterine cancer. It can be performed under general anaesthetic or in an outpatient setting without formal anaesthetic. The latter has several advantages when compared to hysteroscopy with general anaesthesia as it avoids the additional risk of general anaesthesia, has a quicker recovery time, shorter hospital stay and reduced cost. Outpatient hysteroscopy (OPH) is generally well tolerated although some women will experience significant pain and pain is one of the most common reasons for failure to complete the procedure.

As pain is one of the leading reasons for procedure failure, finding ways to reduce pain and anxiety is of critical importance. The optimal method of controlling pain and anxiety during outpatient hysteroscopy is poorly understood and hotly debated. Options include sedation, local anaesthetic, analgesics including paracetamol, non-steroidal anti-inflammatory medication, opioids, Entonox and various distraction techniques. There is a wide variation of clinical practice between different units within the UK due to a paucity of good quality evidence informing best practice. Conventional therapy, as recommended by the Royal College of Obstetricians and Gynaecologists, involves the use of simple pain killers taken prior to the procedure and sometimes local anaesthetic during the procedure if dilatation of the cervix is required (RCOG 2011).

Virtual reality (VR) technology is a relatively new and promising technology which if used as a distraction technique, may be able to reduce pain and anxiety experienced from a wide range of medical procedures. Virtual reality (VR) is a human–computer interface that provides users with various physical sensations (e.g., visual, haptic, auditory) to increase realism in the virtual world (Seth et al. 2011). This heightened sense of realism produces a phenomenon known as “presence,” which refers to the user’s authentic experience of being in the virtual world as a result of visual or auditory displays generated by a computer (Barfield and Hendrix 1995). VR’s ability to provide users with highly realistic immersive experiences can be used to for a variety of medical indications including distraction from uncomfortable or painful procedures.

To date VR has been used in a wide variety of inpatient and outpatient clinical scenarios to reduce pain and anxiety including simple blood tests, ENT procedures and minor gynaecological procedures such as hysterosalpingograms (Chan et al 2018, Wang et al 2020 and Ahmadpoura et al 2019). However, currently, to the best of our knowledge, there is only one relatively small-scale trial investigating the use of VR in an outpatient hysteroscopy setting (Deo et al 2020) meaning further studies are urgently needed to clarify the situation.

1.2 RATIONALE FOR CURRENT STUDY

The purpose of this study would be to determine if the use of VR technology can reduce pain and anxiety experienced by patients during outpatient hysteroscopy procedures when compared to standard pain management.

The optimal method of controlling pain and anxiety during outpatient hysteroscopy is poorly understood and there is a wide variation in clinical practice. This study aims to test whether VR technology could reduce pain and anxiety as a relatively simple and safe adjunct to conventional pain management. Although VR has been used in a variety of clinical settings to date, there is only one previous study investigating the use of VR in an outpatient hysteroscopy setting (Deo et al 2020). This existing trial established that the use of VR is feasible in the OPH setting and that it was effective with significant improvements in patient reported anxiety and pain scores compared to conventional pain management. However, as the authors themselves acknowledge, it involved relatively small numbers (20 patients in control and intervention group respectively). The rationale of this study would be to build upon this evidence by performing the first large scale adequately powered randomised control trial of the use of VR technology in this setting.

We hypothesise that the use of VR technology will significantly improve pain and anxiety when compared to conventional pain management. Finding additional low risk ways of improving pain and anxiety during OPH is of critical importance in order to improve patient experience and the success rate of the procedure as pain is a major reason for unsuccessful OPH procedures.

2. STUDY OBJECTIVES

The primary objectives of this study are to determine if:

1) VR technology can reduce pain during outpatient hysteroscopy?
2) VR technology can reduce anxiety during outpatient hysteroscopy?

The secondary objectives of this study are to determine if:

1) The use of VR technology feasible during outpatient hysteroscopy?

2) The use of VR during outpatient hysteroscopy reduces the procedure failure rate?

3) The use of VR increases the outpatient hysteroscopy appointment time?

3. STUDY DESIGN

The study design is an unblinded randomised controlled trial. This study design was chosen as it will provide the best quality of evidence with reduced bias compared to other study designs. A randomised controlled trial is also very feasible in this scenario. Neither the researchers nor the participants will be blinded as to which study arm they are in, as it would be impractical to do so with a VR headset used in the intervention group. The study will be adequately powered with a power calculation based upon findings from previous studies, meaning at least 40 patients will be included in each arm (at least 80 patients in total).

Patients will be randomly allocated by computer allocation to either the intervention or the control group. The intervention group will undergo OPH with standard care plus the use of VR technology administered through a headset with the option of wearing headphones (at the patient's discretion) or having the accompanying sound played aloud. The control group will undergo outpatient hysteroscopy with standard care. Standard care in this unit is in line with the RGCOG guidelines and involves advising patients to take ibuprofen and/or paracetamol one hour prior to their procedure unless there are contraindications. Local anaesthetic intracervical block is used at the discretion of the operator and is usually used if dilatation of the cervix is required.

The primary outcome measure will be the reported NRS (numeric rating score) score which is validated score to assess pain and anxiety levels with values from 0-11. The patient will be asked to fill out the NRS score prior to the hysteroscopy and following the hysteroscopy prior to leaving the clinic.

Secondary outcome measures will be length of procedure, complication rate, reported side effects, procedure completion, hysteroscopy findings and type of procedure performed (for example if purely diagnostic or if any operative procedures are performed).

Participants will be recruited from the general gynaecology clinics. Only patients who have already opted to undergo outpatient hysteroscopy will be invited to take part in the study and they will be made aware of the study at the time of the clinic appointment or shortly after. Interested parties will then be contacted by the research team to discuss the study in more detail at a time which is convenient for the patient. Written consent to enter the study will be sought from the participant in advance of their procedure and only after a full explanation has been given. The patient will be offered a study information leaflet. Whilst waiting for their hysteroscopy procedure, the patient will be offered a face-to-face appointment with a member of the research team to discuss the study and sign the written consent form if they wish to participate in the study. If it is more convenient for the patient, and to avoid unnecessary additional appointments for the patient, they may prefer to discuss the study and go through the consent by phone before confirming consent on the day of the procedure. Patients will have time to consider whether to take part in the study prior to their procedure day and will be informed that they can withdraw consent for participation in the study at any time. Participating or not participating in the study will have no effect on the timing of the outpatient hysteroscopy or the type of procedure performed. Patients will have the opportunity to choose which virtual reality scenario they wish to experience during the procedure (choice of 4 scenarios from beach, space, underwater and zen four seasons).

At the time of their hysteroscopy. The patient will fill out the pre-procedure NRS score prior to entering the hysteroscopy room. The patient will then enter the outpatient hysteroscopy room where there will be the hysteroscopy team consisting of the lead hysteroscopist and the assistant, and also a single member of the research team who will have taken the study consent from the patient prior to their procedure. Following discussion with the hysteroscopist as usual, the patient will prepare for the procedure and position themselves on the procedure couch. Once comfortable, the member of the research team will help the patient to put on the VR headset (See appendix 1), and if the patient wishes, headphones. The virtual reality software will then start running and is controlled by the research team member, the software will run for the length of the procedure. The hysteroscopy team will be preparing the equipment as the virtual reality software is running. The member of the research team will remain in the room throughout the procedure to troubleshoot any issues with the headset or software and if necessary to stop the VR program. Following completion of the procedure the patient will fill out a NRS score prior to going home.

The VR software involves breathing exercises, relaxing music and a distracting immersive walk through a virtual environment. The scenario will be started and subsequently controlled by a member of the research team operating a tablet device. The hysteroscopy team will perform the procedure in exactly the same way as they would normally and any clinical decisions regarding potential procedures such as polypectomy, discontinuing or proceeding with the hysteroscopy will be made by the hysteroscopy team along with the patient in the usual way without any input from the research team member.

Maintaining appropriate clinical hygiene is of critical importance as the same headset will be used for different patients. The headset can be easily and effectively cleaned between use and the manufacturer (VR medical) provides a recommended cleaning regimen which we will use for the trial. After use, the VR device and controller should be cleaned with a damp microfibre cloth and disinfectant wipe, both the parts that have been in contact with the skin and the headbands.

The timetable for the project is expected to run as follows. Three months for preparation and obtaining ethical approval. Recruitment is expected to start following this and we would expect to obtain the required number of participants by 3 months based on the average referral rate for outpatient hysteroscopy in the unit being 150 patients per month and a 20% study participation rate. Data analysis and preparing the final report would take a further 3 months.

Results will be recorded onto a pseudoanonymised database. Information will be collected from patients notes and imaging reports. Each patient will be allocated a study number and for each the following will be recorded:
Age
Parity
Symptoms and duration
Past medical history and co-morbidities
BMI
Previous surgery
Current medication and medication used within the last 6 months
Pain NRS (numeric rating score)
Anxiety NRS

Length of hysteroscopy procedure
Time in Outpatient Procedure room
Procedure successfully completed (or not) and reason for failure if appropriate
Complications
Hysteroscopy findings
Type of hysteroscopic procedure performed

3.1 STUDY OUTCOME MEASURES

The primary outcome measure will be the reported NRS (numeric rating score) score which is validated score to assess pain and anxiety levels with values from 0-11. The patient will be asked to fill out the NRS score prior to the hysteroscopy and following the hysteroscopy prior to leaving the clinic.

Secondary outcome measures will be length of procedure, complication rate, reported side effects, procedure completion, hysteroscopy findings and type of procedure performed (for example if purely diagnostic or if any operative procedures are performed).

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

Women opting to undergo outpatient hysteroscopy

4.2 INCLUSION CRITERIA

1. Age 18-70
2. Patients undergoing outpatient hysteroscopy for any indication
3. Capacity to give informed consent
4. Cognitive and linguistic ability sufficient to understand and fill out the NRS questionnaire.

4.3 EXCLUSION CRITERIA

1. Epilepsy
2. Severe vertigo
3. Significant hearing impairment
4. Blindness
5. Current facial injury /burn
6. Patients who have not given informed consent
7. Patients aged less than 18 or more than 70.

4.4 WITHDRAWAL CRITERIA

Participant request

5. ADVERSE EVENTS

5.1 DEFINITIONS

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

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

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

- **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 should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.3 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded.

5.3.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours.

All SAEs should be reported to the Greater Manchester East Research Ethics Committee 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 related and unexpected SAEs.

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

Contact details for reporting SAEs
RGIT@imperial.ac.uk
CI email (and contact details below)

6. ASSESSMENT AND FOLLOW-UP

Definition of end of study: when final participant has been recruited within 1 year study period and has had filled out their post procedure NRS questionnaire. Incidental findings are not expected in this study. Any clinically relevant incidental findings that do occur during this study will be reported to the GP for ongoing care as necessary.

7. STATISTICS AND DATA ANALYSIS

Normally distributed data will be analysed using IBM SPSS software. Comparisons will be done with between intervention group and controls with a p value less than 0.05 used to indicate statistical significance.
Means NRS scores will be compared between the 2 groups using the unpaired student's T test.
Data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the Greater Manchester East Research Ethics Committee Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Data will be psuedoanonymised.

8.4 INDEMNITY

Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Resolution for NHS Trusts in England, which apply to this study.

8.5 SPONSOR

Imperial College Healthcare NHS Trust will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING

No additional funding is necessary for this study. The VR device is being loaned by Sync VR Medical (Padualaan 8, 3584CH Utrecht Inc).

8.7 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Mr Thomas Sewell.

10. PUBLICATION POLICY

Data from the study will be published in peer-reviewed publications as well as presented at national and international conferences. All data will be anonymised.

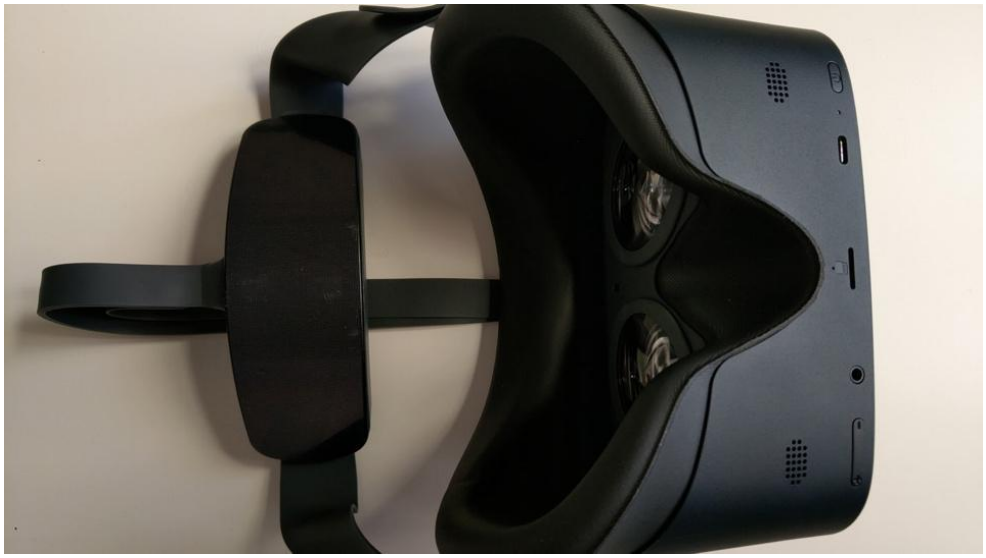
11. REFERENCES

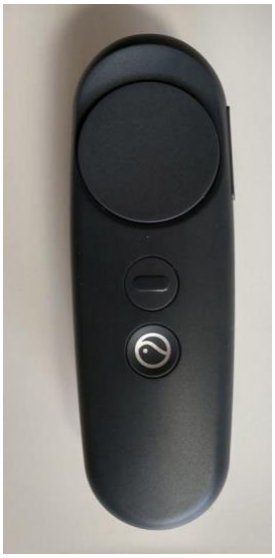
1. Royal College of Obstetricians and Gynaecologists. Green Top Guideline No. 59: Best Practice in Outpatient Hysteroscopy.London: Royal College of Obstetricians and Gynaecologists; 2011.
2. Seth, A., Vance, J.M. & Oliver, J.H. Virtual reality for assembly methods prototyping: a review. Virtual Reality **15,** 5–20 (2011). https://doi.org/10.1007/s10055-009-0153-y
3. Barfield, W., Hendrix, C. The effect of update rate on the sense of presence within virtual environments. Virtual Reality **1,** 3–15 (1995). https://doi.org/10.1007/BF02009709
4. Chan E, Foster S, Sambell R, Leong P. Clinical efficacy of virtual reality for acute procedural pain management: A systematic review and meta-analysis. PLoS One. 2018 Jul 27;13(7): e0200987. doi: 10.1371/journal.pone.0200987. PMID: 30052655; PMCID: PMC6063420.
5. Wang Y-L, Gao H-X, Wang J-S, Wang J-H, Bo L, Zhang T-T, et al. Immersive virtual reality as analgesia for women during hysterosalpingography: study protocol for a randomized controlled trial. Trials 2020;21:102.
6. Ahmadpour N, Randall H, Choksi H, Gao A, Vaughan C, Poronnik P. Virtual Reality interventions for acute and chronic pain management. Int J Biochem Cell Biol. 2019 Sep;114:105568. doi: 10.1016/j.biocel.2019.105568. Epub 2019 Jul 12. PMID: 31306747.
7. Deo N, Khan KS, Mak J, Allotey J, Gonzalez Carreras FJ, Fusari G, Benn J. Virtual reality for acute pain in outpatient hysteroscopy: a randomised controlled trial. BJOG. 2021 Jan;128(1):87-95. doi: 10.1111/1471-0528.16377. Epub 2020 Jul 22. PMID: 32575151.

12. APPENDICES

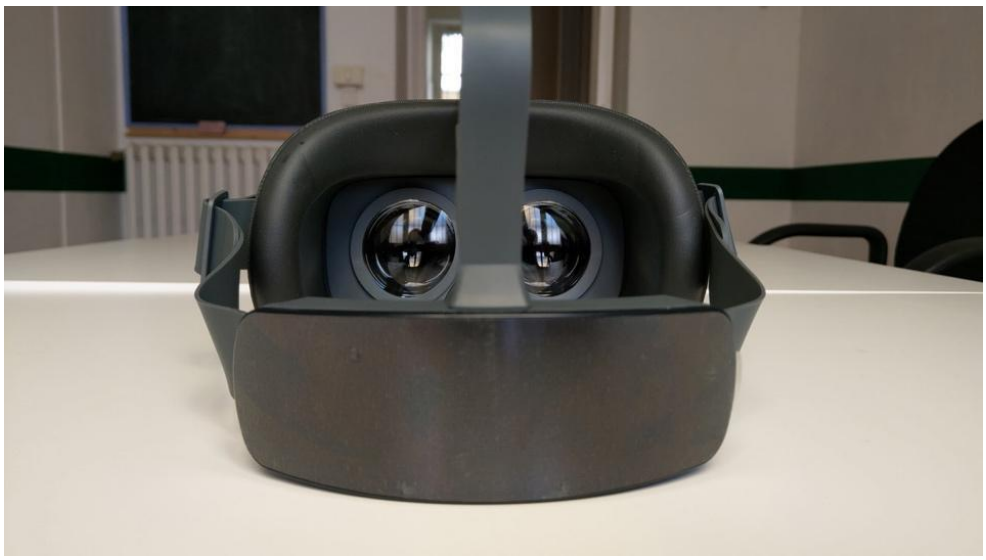
12.1 Appendix 1 VR headset and controller as supplied by Sync VR Healthcare.

17.1 Figure VR





left: VR headset top view, right: controller



VR headset view from behind