ZUYDERLAND MEDISCH CENTRUM

VRAP-G

The effect of **V**irtual **R**eality on **A**nxiety and **P**ain in patients undergoing **G**ynecological surgery; a randomised controlled trial

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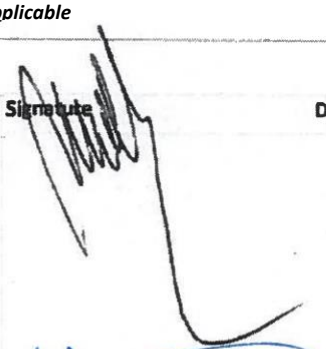
PROTOCOL SIGNATURE SHEET

Name	**Signature**	**Date**
Dhr Max Wellens (RVE 1 Manager, Zuyderland Medisch Centrum)		13-02-2020
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AR	**Adverse Reaction**
ASA	**American Society of Anesthesiologists**
BMI	**Body Mass Index**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CE	**Conformité Européenne**
CTCM	**Clinical Trial Centre Maastricht**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IASP	**International Association for the Study of Pain**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
LMWH	**Low Molecular Weight Heparin**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
NRS	**Numeric Rating Scale**
PCS	**Pain Catastrophizing Scale**

RCT	**Randomized Controlled Trial**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst**
STAI	**State-Trait Anxiety Inventory**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
VR	**Virtual Reality**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

1. SUMMARY

Rationale: Lack of postoperative acute pain management is associated with increased morbidity, longer recovery time, more opioid use and subsequently increased health care costs. There is increasing evidence virtual reality (VR) is effective in the reduction of acute pain. Alternative methods to reduce postoperative pain and multimodal analgesia are necessary for acute postoperative pain management and to reduce opioid use and their adverse effects.

Objective: The aim of this study is to explore the effect of VR on pain in the immediate postoperative period after elective gynecological surgery.
Secondary objectives are evaluating pre-and postoperative anxiety, pain catastrophizing, analgesic use, length of hospital stay between both groups and to explore tolerability, feasibility and satisfaction of VR use.

Study design: The study concerns a non-blinded, single centre, randomised controlled trial.

Study population: Eligible women fulfill the inclusion criteria and receive elective gynecological surgery under spinal anesthesia in the Zuyderland Medical Centre location Heerlen.

Intervention: The study population will be randomly divided into the intervention group (VR-group) or the standard care- group. The intervention group can choose for an immersive guided relaxation VR experience or an interactive VR experience during the pre- and postoperative period additional to the usual standard care. The participants randomised to the standard care- group will receive only the usual standard care pre-and postoperative.

Main study parameters: The primary outcome is postoperative pain measured on a numeric rating scale (NRS). A total of 30 patients have to be included in each group. This means that a total of 60 women will have to be included in the study.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
The study population experiences a small medical risk when participating to this study. They can experience side-effects of VR for example dizziness or nausea and in rare cases epileptic insults.
Participants of the study have to fill in a questionnaire before randomization and pre-and postoperative score of pain and anxiety on a zero to ten score scale.

2. INTRODUCTION AND RATIONALE

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage", this is the definition of pain according to the International Association for the Study of Pain (IASP) [1]. Severe post-operative pain is experienced by approximately 50-80% of the patients [2, 3].
Lack of postoperative acute pain management is associated with increased morbidity, longer recovery time, more opioid use and subsequently increased health care costs [2, 4, 5]. Postoperative pain can cause a higher morbidity, because of cardiovascular, pulmonic and gastro-intestinal problems [4, 5].
Besides, surgery and acute pain are both independent risk factors for the development of chronic pain [4, 6]. The reduction of acute pain and therefore managing postoperative pain may contribute to the prevention of chronic pain [6].
In general, nowadays, medication is the treatment of choice for acute pain and mainly opioid analgesics are used for pain relief [7]. Worldwide this contributes to excessive drug dependence and opioid abuse. Opioid use comes with several negative side effects, for example a potential delay in recovery and an increased risk of permanent disability [8].

Nowadays, new methods related to pain management are developed. For example, Virtual reality (VR) is an upcoming technology used within healthcare. It is thought that the perception of pain is related to the amount of attention that is given to pain stimuli [9]. The theory behind the working mechanism of VR to reduce pain is that VR acts as a distraction to limit the user's processing of nociceptive stimuli, by stimulating the visual cortex in the brain [10]. In 2000, Hoffman published the first preliminary evidence for the beneficial effect of VR in reducing pain in a burn care unit [11]. They also showed a trend to experience less anxiety during VR use. In the next upcoming years, a growing body of research was done to explore the effects of VR.
A recent systematic review and meta-analysis showed VR to be an effective treatment for reducing acute pain [8]. Next to being effective in reducing pain, it is also a proven useful tool in reducing preoperative anxiety [12, 13]. VR can be used as a safe, non-invasive, analgesic method, without risks of drug addiction and minimum side effects [14, 15].

In this study, we want to explore the effect of VR on postoperative pain in patients undergoing elective gynecological surgery as a serious alternative for pain medication. We hypothesize VR will reduce post-operative pain and consequently postoperative opioid use and anxiety reduction.

3. OBJECTIVES

The aim of this study is to determine whether VR used in the immediate postoperative period after gynecological surgery will decrease pain scores.

Primary Outcome measure: reduction in postoperative pain score (NRS, numeric rating scale)

Secondary Outcome measures:
- Pre-operative anxiety (State-Trait Anxiety Inventory (STAI)-6 questionnaire)
- Pain catastrophizing (Pain Catastrophizing Scale questionnaire)
- Difference in anxiety scores pre-and post VR intervention (NRS)
- Analgesic use (daily use of paracetamol, NSAIDs, opioids)
- Length of hospital stay
- Tolerability, feasibility and satisfaction of VR use (questionnaire)
- Preoperative pain score (NRS)

4. STUDY DESIGN

The design of this study is a single centre, randomised controlled trial (RCT). Eligible patients will be randomised to either the VR- group and receive additional VR during the pre- and postoperative period or undergo standard pre- and postoperative management (standard care- group).

5. STUDY POPULATION

5.1 Population (base)

Patients who fulfill the inclusion criteria and receive elective gynecological surgery under spinal anesthesia in the Zuyderland Medical Centre.

5.2 Inclusion criteria

- Written and orally given informed consent
- 18 years and older
- Native Dutch speaker
- Indication for elective gynecological surgery under spinal anesthesia
- No contra-indication to spinal anesthesia:
  - Use of coumarines
  - Use of low molecular weight heparin (LMWH) in a therapeutic dosage
  - Use of LMWH in a prophylactic dosage used < 10 hours before surgery
  - Thrombocytes < 80x 10^9/L
  - Use of thrombocytes aggregation inhibitors or increased risk of bleeding
  - Coagulation disorder
  - Allergy or hypersensitivity to anesthetics
  - Spinal problem

5.3 Exclusion criteria

- Chronic pain patients; defined as ‘persistent or recurrent pain lasting longer than 3 months’ [16]. The pain is not due to the gynecological problem.
- Chronical use of pain medication (opioids)
- History of prior opioid use defined as use within 8 to 90 days prior to the surgical procedure
- Alcohol or drug abuse
- Known car sickness
- Epileptic insults in previous history
- Psychotically seizures in previous history
- Claustrophobic
- Blindness
- History of mental illness

5.4 Sample size calculation

We are planning a study of independent cases and controls with 1 control(s) per case.
To be able to make an adequate sample size calculation the VR was set as the reference test, standard care will be compared to this procedures. Our hypothesis is that VR (intervention) will significantly improve the mean NRS for pain after surgery with 15 mm with a standard deviation of 20mm.
On the assumption of an effect of 15 mm we would need 26 patients per group; 30 taking into account loss of follow-up. Thus 60 patients need to be included. With this sample size we are able to achieve a power of 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.
We changed the sample size collection in consultation with the Orthopedic Department of the Zuyderland Medical Centre. They are planning to start with a comparable study. We strive for comparable studies, to if possible, eventually are able to perform collective analyses.

6. TREATMENT OF SUBJECTS

6.1 Investigational product/treatment

The study population will be randomly divided into the intervention group (VR-group) or the standard care-group.

Intervention group (VR-group):
The participants randomised into this group can choose for an immersive guided relaxation VR experience or an interactive VR experience. We will register which option the patients choose. The options are explained in paragraph 9.3. Pre-operatively when arriving at the pre-operative anesthetic room, the level of anxiety and pain is scored using the numeric rating scale (NRS) (T1a). After this, the VR- group will receive their VR experience of own choice on the pre-operative anesthetic room during 10-15 minutes. Directly after this VR intervention, the level of anxiety and pain is scored from 0-10 (T1b).
Direct postoperatively after arriving on the recovery ward, NRS score and level of anxiety from 0-10 will be scored by the participant (T2). Subsequently, the VR-group will receive the VR experience of own choice during 10 minutes. Before leaving the recovery ward, NRS score and level of anxiety from 0-10 will be measured (T3). Depending on the duration of stay on the recovery ward, an extra VR intervention will be given. If the patient stays for less than 3 hours, there will only be one VR intervention. If this is longer than 3 hours, there will be two interventions. The VR intervention is additional to the standard postoperative care management, the standard pain protocol is explained below.

The VR-intervention will be given using the Oculus Go Virtual Reality glasses with touchpad.

Standard pre-and postoperative management (standard care- group):
The participants randomized into the standard care- group will receive the usual standard pre-and postoperative management. Pre-operatively when arriving at the pre-operative anesthetic room, the level of anxiety and pain is scored from 0-10 (T1a). After 10-15 minutes the level of pain and anxiety is again scored from a scale from 0-10 (T1b). Direct postoperatively after arriving on the recovery ward, measurements like NRS score and level of anxiety from 0-10 will be scored by the participant (T2). Before leaving the recovery ward, NRS score and level of anxiety from 0-10 will be measured (T3).

Standard pain protocol:

1. Preoperative (arrival day-care unit) start with 1000mg paracetamol orally administered.
2. Postoperative Meloxicam 15mg orally administered, or when oral medication is not possible (due to nausea e.g.) than diclofenac supp 100mg or diclofenac i.v. 75mg.
3. On recovery ward, when necessary depending on pain score (NRS>4): dipidolor 2.5-5mg i.v. and 10-15mg i.m. after consulting the anesthesiologist.
4. Postoperative at home 4dd1000mg paracetamol will be continued, in combination with meloxicam 1dd15mg during 3 days. Also tramadol 50mg with a maximum of 4dd will be prescribed.

6.2 Use of co-intervention (if applicable)

Not applicable.

6.3 Escape medication (if applicable)

In case a patient will get a seizure because of using the VR glasses, the glasses will immediately be taken off. When the seizure will not stop after 5 minutes, 10 mg midazolam nasal can be administered. This can be repeated once. If midazolam is not effective, the neurologist will be asked for consultation.

7. INVESTIGATIONAL PRODUCT

7.1 Name and description of investigational product(s)

Oculus Go Virtual Reality glasses and touchpad. The Oculus Go is easy to use and wireless. It provides lifelike experiences using clear images, to offer visual clarity.

The CE-numbers of the products are known. Virtual reality glasses: R-CMM-0C8-MH-A and controller: R-CRM-0C8-MI-A. Following the technical service of the Zuyderland Medical Centre, the Virtual Reality glasses will be used as a distraction, no additional quality marks are necessary to use the glasses in this study.

7.2 Summary of findings from non-clinical studies

VR can be safely used in different settings, for example in the educative sector, in the sector of architects, or in healthcare.

7.3 Summary of findings from clinical studies

Different hospitals in the Netherlands are already using the VR glasses. Until now, only dizziness and nausea have been reported, and no other side-effects have been reported. This will be explained in paragraph 7.4.

7.4 Summary of known and potential risks and benefits

The user of the VR glasses can possibly experience complaints of nausea and dizziness. This is called motion sickness, and the side-effects of VR are comparable to the symptoms of carsickness or seasickness. Motion sickness refers to symptoms that can occur during the experience of a virtual environment. The main cause is the conflict of the visual feeling and the physical feeling that you can experience of the virtual environment. When those complaints occur, the intervention can be stopped immediately. Next to dizziness and nausea, also the risk of getting an epileptic insult can occur by using VR, this occurs in 1:4000 healthy persons. When a patient is known with epileptic insults, this will be an exclusion criteria and it is not possible to join the study. The chance of injury in the face by turning of the head of the person using VR is very small. With the least risk of a possible harmful effect of the glasses, the VR intervention will be stopped.

7.5 Description and justification of route of administration and dosage

Patients will use the VR glasses as glasses, this is the only ‘route of administration’.

7.6 Dosages, dosage modifications and method of administration

The VR glasses will be used as glasses. It is not used in dosages, but used in you can state that one ‘dosage’ of Virtual Reality matches with use of VR for 15 minutes.

7.7 Preparation and labelling of Investigational Medicinal Product

The Oculus Go Virtual Reality glasses will be used as a distraction and not as a medical device. Multiple Medical Technique departments of different hospitals (Maasstad Medical Centre, Catherina Hospital, Zuyderland Medical Centre, Martini Hospital and Onze Lieve Vrouwe Gasthuis) have decided that the use of VR-glasses as a distraction not counts as a medical device. This is decided after e-mail contact with Jacqueline Jennekes from the METC-Z.

7.8 Drug accountability

Not applicable

8. NON-INVESTIGATIONAL PRODUCT

8.1 Name and description of non-investigational product(s)
Not applicable

8.2 Summary of findings from non-clinical studies
Not applicable

8.3 Summary of findings from clinical studies
Not applicable

8.4 Summary of known and potential risks and benefits
Not applicable

8.5 Description and justification of route of administration and dosage
Not applicable

8.6 Dosages, dosage modifications and method of administration
Not applicable

8.7 Preparation and labelling of Non-Investigational Medicinal Product
Not applicable

8.8 Drug accountability
Not applicable

9. METHODS

9.1 Study parameters

9.1.1 Main study parameter
The primary outcome is postoperative pain measured on a numeric rating scale (NRS).

9.1.2 Secondary study parameters
Secondary outcomes will be:

- Pre-operative anxiety (State-Trait Anxiety Inventory (STAI)-6 questionnaire)
- Pain catastrophizing (Pain Catastrophizing Scale questionnaire)
- Difference in anxiety scores pre- and post VR intervention (NRS)
- Analgesic use (daily use of paracetamol, NSAIDs, opioids)
- Length of hospital stay
- Tolerability, feasibility and satisfaction of VR use (questionnaire)
- Preoperative pain score (NRS)

9.1.3 Other study parameters
The following baseline characteristics will be collected pre-operatively; age, BMI, ethnicity, education level, marital status, vaginal parity, ASA-classification, medication use, intoxications, chronic pain, surgical history, indication of surgery, type of planned surgery. When patients do not want to answer certain questions, for example marital status or education level, they are free to answer ‘unknown’. It is possible that these characteristics may be of influence of pain experience or the experiences in VR. These can be confounders in the study.

9.2 Randomisation, blinding and treatment allocation

After receiving written informed consent, randomisation will by the Datamanagement randomisation programme of 'Bureau Wetenschappelijk Onderzoek' Zuyderland Medical Centre. Randomisation will be 1:1 for intervention and the standard care- group. The study will be an open label, non-blinded study.

9.3 Study procedures

Patients who were planned for elective gynecological surgery under spinal anesthesia will be informed about the study during their visit at the outpatient clinic. Eligible patients who fulfill the inclusion criteria will be identified and counselled by the research coordinator or staff of the Zuyderland Medical Centre.

Before entry into the study, the research coordinator and/or the staff will explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study. They will be informed that their participation is voluntary and that they may withdraw consent to participate at any time during the study. They will be informed that choosing not to participate will not affect their care. After giving sufficient information, written informed consent must be obtained.

After receiving written informed consent and before randomisation, pre-operatively a baseline questionnaire pre-operative anxiety (STAI-6 questionnaire) and pain catastrophizing scale (PCS) questionnaire (T0) will be filled in pre-operatively on the ward. Subsequently the randomisation procedure will be proceeded.

Intervention (VR-group)

The participant can choose a VR- intervention of own preference. They can choose between an immersive guided relaxation or an interactive VR experience. A total of four scenarios can be chosen;

1. Interactive mini-games, such as a game in which the patient immerses into a 360 environment (e.g. Erasmus Bridge Rotterdam), and is asked to guess the name of this environment
2. Mindfulness exercises, in which the patient immerses into relaxing environments and is guided by a mindfulness coach (i.e. guided audio);
3. 360-videos of either relaxing or stimulating environments
4. Speedreading exercises, in which the participant is challenged to read certain articles at his/her highest possible reading speed (in words per minute).

The VR-glasses will be used following the VR-hygiene protocol (see attachment 1).
The participants in the intervention group will also receive the usual standard pre- and postoperative management including the standard pain protocol.

Standard care- group:

The participants randomised into the standard care- group will receive the usual standard pre-and postoperative management.

Standard pain protocol:

1. Preoperative (arrival day-care unit) start with 1000mg paracetamol orally administered.
2. Postoperative Meloxicam 15mg orally administered, or when oral medication is not possible (due to nausea e.g.) than diclofenac supp 100mg or diclofenac i.v. 75mg.
3. On recovery ward, when necessary depending on pain score (NRS>4): dipidolor 2.5-5mg i.v. and 10-15mg i.m. after consulting the anesthesiologist.
4. Postoperative at home 4dd1000mg paracetamol will be continued, in combination with meloxicam 1dd15mg during 3 days. Also tramadol 50mg with a maximum of 4dd will be prescribed.

Study schedule

T0 = Pre-operative ward on day of surgery (when arriving on ward) before randomisation

1. VR-group = Baseline questionnaire, pre-operative anxiety (STAI-6 questionnaire) and pain catastrophizing scale (PCS)
2. Standard care-group = Baseline questionnaire, pre-operative anxiety (STAI-6 questionnaire) and pain catastrophizing scale (PCS)

T1 = Pre-operative anesthetic room

1. VR-group = before VR intervention: pain score (NRS) and anxiety score (NRS) (T1a)
   VR-group = after VR intervention: pain score (NRS) and anxiety score (NRS) (T1b)
2. Standard care-group = pain score (NRS) and anxiety scores (NRS) (T1a)
   Standard care-group = pain score (NRS) and anxiety scores (NRS) (T1b)

T2= Directly postoperative on recovery ward

1. VR-group = pain score (NRS) and anxiety score (NRS), after this the VR-intervention
2. Standard care-group = pain score (NRS) and anxiety score (NRS)

T3 = Before leaving the recovery ward

1. VR-group = pain score (NRS) and anxiety score (NRS)
2. Standard care-group = pain score (NRS) and anxiety score (NRS)

Questionnaires:

Baseline questionnaire (see attachment 2)

The baseline questionnaire will collect the following variables; age, BMI, ethnicity, education level, vaginal parity, ASA-classification, medication use, intoxications, chronic pain, surgical history, indication of surgery, type of planned surgery.

Pre-operative anxiety (State-Trait Anxiety Inventory (STAI)-6 questionnaire) (see attachment 3)

The State-Trait Anxiety Inventory-6 questionnaire is a short questionnaire about the feelings of a person in that specific moment [17]. It consists of questions about anxiety, satisfaction and worries. Women were asked to rank on a 4-point scale (0= not at all, 4 = completely) reflecting on the feelings in that specific moment. To calculate the total STAI score, you have to reverse scoring of positive items (calm, relax, content etc) so 1=4 points, 2=3 points, 3=2 points, 4=1points. You can sum all the scores, multiply the total score by 20 and divide this by 6 [17]. The score ranges from 20 to 90 and the higher the score the more anxiety the person experiences. The STAI questionnaire shows the experience of anxiety at baseline.

Pain catastrophizing (Pain Catastrophizing Scale questionnaire) (see attachment 4)

The pain catastrophizing scale (PCS) has been designed to assess three various dimensions of catastrophizing concerning rumination, magnification and helplessness. It consists of 13 statements describing different feelings and thoughts that can be experienced when in pain. Women were asked to rank on a five-point scale (0 = not at all; 4 = all the time) reflecting on a painful experience in the past [18]. The subscales of the PCS can be calculated separately or overall with a maximum total score of 52 [18, 19]. The higher the score, the more catastrophizing thoughts are present. (see attachments for full questionnaire). The PCS shows how people are able to cope with pain and various thoughts.

NRS:

How did you experience the pain after the surgery?

No pain Worst imaginable pain

Anxiety:

How frightened where you after surgery?

No fear Worst imaginable fear

VR- questionnaire (see attachment 5)

After the surgery, at the medical ward, a questionnaire will be given to evaluate the experience of VR.

Study schedule

	Informed consent	**Baseline questionnaire**	**PCS and STAI**	**Pain score (NRS)**	**Anxiety score (NRS)**
Outpatient clinic					
Preoperative (T0) 1. VR-group 2. Standard care group					
Preoperative (T1) 1. VR: before VR intervention (T1A) 2. VR: after VR intervention (T1B) 3. Standard care-group (T1A) 4. Standard care-group after 10-15min (T1B)					
Postoperative (T2), after arriving on recovery 1. VR-group 2. Standard care-group					
Postoperative (T3) before leaving recovery 1. VR- group 2. Standard care- group					

9.4 Withdrawal of individual subjects

Subjects can immediately withdraw from participating to the study at any time for any reason without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

9.4.1 Specific criteria for withdrawal

We do not expect specific complaints or side effects of the VR treatment which are reasons to withdraw from the study. Whenever dangerous situations would occur, for example an epileptic insult, the patient will be withdrawn from the study.

9.5 Replacement of individual subjects after withdrawal

After withdrawal of a participant, it is not possible to replace this patient with a new participant.

9.6 Follow-up of subjects withdrawn from treatment

After withdrawal from a participant in case of the VR-group or standard care-group, then the patient is asked to agree with obtaining the measurements (NRS score, anxiety score etc) and using this data. When she wants to withdraw completely, then she can be replaced by a new patient.

When a patient only wants to withdraw from treatment, thus VR intervention, and agrees with the measurements, then the data will be included in the analyses.

9.7 Premature termination of the study

We do not expect the study has to be terminated premature before enrolling the required participants. No interim analysis will be performed because of the small number of subjects that have to be included.

10. SAFETY REPORTING

10.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

10.2 AEs, SAEs and SUSARs

10.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. Given the negligible risk on side effects we decided not standard register adverse events (AE).

10.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.
May a serious adverse event occur, this will be reported by the head-investigator within one week after the event at the website http://www.toetsingonline.nl.

10.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

10.3 Annual safety report

Not applicable.

10.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

10.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

No DSMB will be necessary.

11. STATISTICAL ANALYSIS

The data will be analyzed using the program SPSS (version 22). A Chi-square test will be used to assess categorical variables, and the independent sample T-test will be used for continuous variables in case of normal distribution based on the skewness, kurtosis, and graphical representation (histogram) of the continuous variables. The mean NRS-score with standard deviation will be calculated for pain as well as anxiety in both groups, when the data is normally divided. When the data is not normally divided, then a median with interquartile range will be calculated. For categorical variables, frequency and percentage will be calculated. Depending on the amount of missing values, the missing values will be excluded or imputed. This depends on the amount of missing values.

11.1 Primary study parameter(s)

The differences in postoperative NRS-scores of pain in between both groups (VR-intervention and standard-care group) will be analyzed using the linear mixed models analysis. The NRS-score of pain of the VR group and standard-care group will be compared to see whether VR influences the pain experience. Different variables, like age, BMI, ethnicity, education level, marital status, vaginal parity, ASA-classification, medication use, intoxications, chronic pain, surgical history, indication of surgery, type of planned surgery, will be considered in the statistical analysis. These are taken into account because these variables can be possible confounders in the results of the study.

11.2 Secondary study parameter(s)

The differences in NRS-scores pre- and postoperative of anxiety in both groups (VR-intervention and standard-care group) will be analyzed using the linear mixed models analysis. The results of the STAI-questionnaire, PCS questionnaire, analgesic use and length of hospital stay will be calculated into means with standard deviation and confidence interval. We want to compare the baseline characteristics and questionnaires (STAI and PCS) to see whether the groups are equally divided. The STAI and PCS questionnaire are continuous variables, we will use the independent sample t-test. The tolerability, feasibility and satisfaction of VR use will be calculated into means and frequencies.

11.3 Other study parameters

Not applicable

11.4 Interim analysis

Not applicable

12. ETHICAL CONSIDERATIONS

12.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 64, WMA General Assembly, Fortaleza, Brazil, October 2013)*)* and in accordance with the Medical Research Involving Human Subjects Act (WMO).

12.2 Recruitment and consent

Women who were planned for elective gynecological surgery under spinal anesthesia will be informed about the study during their visit at the outpatient clinic. Eligible patients who fulfill the inclusion criteria will be identified and counselled by the research coordinator or staff of the Zuyderland Medical Centre. Before entry into the study, the research coordinator and/or the staff will explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study. They will be informed that their participation is voluntary and that they may withdraw consent to participate at any time during the study. They will be informed that choosing not to participate will not affect their care. After giving sufficient information, written informed consent must be obtained

12.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

12.4 Benefits and risks assessment, group relatedness

The risks of this research will be small, according to the CTCM. Possible rare side-effects of the use of VR can be: nausea, dizziness and vomiting. Whenever a patient experiences side-effects or hindrance of the study, she can decide to withdraw. Benefits of the study: probably less pain after gynecological surgery with spinal anesthesia and less anxiety in the pre- and postoperative setting.
Previous studies reported transient adverse events such as nausea and dizziness, but no major adverse events [20-24]. The risks of VR therapy for the participants are negligible.
Previous studies described significant reductions of acute pain scores after a single VR session.

12.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.
The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

12.6 Incentives

Not applicable.

13. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

13.1 Handling and storage of data and documents

An encrypted Excel keyfile will be made. In this file, the patient numbers will be linked to the concerning study number. Only the (head)investigators will have access to this file. The obtained data will be saved as eCRF in the program 'Research Manager'. Also, here only the (head) investigators have access. The data will be saved for 15 years, according to the regular agreements. As well as for the Excel keyfile as for the Research Manager a password is necessary. All paper documents (informed consent and questionnaires) will be stored in one folder. This folder will be saved in a locked closet in the room of the head investigator. On the informed consent form no study number will be mentioned, so that a study number cannot be traced back on paper to a patient. The data will be collected in a digital data management system (research manager).
When data of a patient must be derived from the electronic patient files, then this will be done by investigator I. Bekkers. In principle, all the information can be given by the patient, and the patient file does not have to be seen.

When the patient participates in the study, this will be noted in the patients document of the hospital.
The study number will be determined at the day of surgery. The inclusion will be done by one of the doctors of the Gynecology department of the Zuyderland Medical Centre. They will be instructed how to include the patients and which patients are suitable to be included in the study. Data of the study will not be shared with persons and/or organizations other than the Zuyderland Medical Centre.

13.2 Monitoring and Quality Assurance

According to the local guidelines of 'Bureau Wetenschappelijk Onderzoek (BWO)' the study will be monitored by Clinical Trial Centre Maastricht (CTCM). The CTCM classified the study as 'negligible/low risk'. They are producing the monitoring plan. When the monitoring plan is finished, it will be uploaded on Research Manager.
In our opinion, this study adds a rare small chance of reversible mild damage and consequently adds a negligible risk according to the risk classification of the "Nederlandse Federatie van Universitaire Medische Centra" (NFU). Monitoring will be conducted in accordance with negligible risk monitoring guidelines of the NFU, which will be reported in a monitoring plan.

13.3 Amendments

Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion.

13.4 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

13.5 Temporary halt and (prematurely) end of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.
Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

13.6 Public disclosure and publication policy

Not applicable

14. STRUCTURED RISK ANALYSIS

Not applicable

14.1 Potential issues of concern

The potential risk of the study is negligible. Virtual Reality in the medical world has been used for a couple of years nowadays. The chance of interaction with medication or other products is zero. Participants of the study will get an explanation of VR before using the product.

14.2 Synthesis

Not applicable.

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Attachments:

Attachment 1. VR Hygiëneprotocol

Goal and area of use: to prevent infections and contamination from patient to patient. To apply when using the VR glasses.

Legal capacity: nurses, doctors and other competent health care providers.

Indication: clinical patients who fulfill the criteria. Health care providers must know the hygiene protocol.

Accessories:

- Fake leather VR glass cover
- Hairnet
- Incidin oxyfoam or comparable alcoholic disinfection
- 10x10 gauze pads

Preparation: In the VR glasses there is a fake leather VR glasses cover. When the VR glasses has a foam rubber cover, this needs to be replaced with the fake leather cover.

Performance: the patients gets a clean hairnet and the VR-glasses with fake leather cover on the head. By using the net, the headbands of the glasses will stay clean. After use of the VR-glasses, it needs to be cleaned using the Incidin Oxyfoam (or comparable alcoholic disinfection). After use the hairnet can be trown away. The VR glasses are ready to be used by the next patient.

Attachment 2. Baseline characteristics

Age, BMI, ethnicity, education level, marital status, vaginal parity, ASA-classification, medication use, intoxications, chronic pain, surgical history, indication of surgery

1. Age

….. years

2. Length

…… cm

3. Weight

…….kg

4. Etnicity (when you rather not fulfill this question, you can fil in ‘unknown’)

- o Kaukasion
- o Latin-American
- o Azian
- o African
- o Turkish
- o Other etnicity
- o Unknown

5. Education (when you rather not fulfill this question, you can fil in ‘unknown’)

- o Primary school
- o High school
- o Community college
- o University
- o Unknown

6. Marital status (when you rather not fulfill this question, you can fil in ‘unknown’)

- o Single
- o Living together
- o Married
- o Unknown

7. Smoking

- o Yes,….. sigars/sigarrettes per day/week/month
- o No

8. Alcohol

- o Yes,…. glasses per day/week/month
- o No

9. Drugs

- o Yes,……. per day/week/month
- o No

10.Vaginal delivery's

- o 0
- o 1
- o 2
- o 3
- o 4
- o >5

11. Medication use

……..

12. When using medication, do you use morfine? (e.g. oxycodon, oxycontin, morfine, fentanyl or others?)

……

13. Do you have chronical pain (existing for more then 6 months) not related to the reason of the surgery?

- o Yes
- o No

14. Have you ever had surgery before?

- o Yes
- o No

15. When you answered 'yes' on question 14, what kind of surgery did you have?

……..

16. ASA classification (will be filled in by your doctor)

- o ASA 1
- o ASA 2
- o ASA 3
- o ASA 4

17. Indication of surgery (will be filled in by your doctor)

……

Attachment 3. State Trait Anxiety Inventory (STAI)

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the most appropriate number to indicate how you feel right now, at this moment. There are no right or wrong answers. Do not spend too much time on any statement but give the answer which seems to describe your present feelings best.

1. I feel calm
   - o Not at all
   - o Somewhat
   - o Moderately
   - o Very much

2. I am tense
   - o Not at all
   - o Somewhat
   - o Moderately
   - o Very much

3. I feel upset
   - o Not at all
   - o Somewhat
   - o Moderately
   - o Very much

4. I am relaxed
   - o Not at all
   - o Somewhat
   - o Moderately
   - o Very much

5. I feel confident
   - o Not at all
   - o Somewhat
   - o Moderately
   - o Very much

6. I am worried
   - o Not at all
   - o Somewhat
   - o Moderately
   - o Very much

Attachment 4. Pain catastrophizing scale (PCS)

Pain can give you certain thoughts and feelings. With this questionnaire, we want to measure what you experience when having pain. Down below are 13 allegations about different thoughts and feelings that may have a connection with pain. Try to fill in, in which way these thoughts and feelings are applicable for you. Use the following ranking:

0 = Not at all

1 = Slightly

2 = to a certain extent

3 = largely

4 = always

Circle the number that is most applicable

When I am in pain……

1. I constantly wonder whether the pain will stop.	0	1	2	3	4
2. I feel I cannot continue like this	0	1	2	3	4
3. It is horrible, and I think it will never get any better.	0	1	2	3	4
4. it is awful and I feel the pain is overwhelming me.	0	1	2	3	4
5. I feel I cannot longer hold on.	0	1	2	3	4
6. I am afraid the pain will get worse.	0	1	2	3	4
7. I keep thinking about other painful events.	0	1	2	3	4
8. I desire that the pain will stop.	0	1	2	3	4
9. I cannot get the pain out of my mind	0	1	2	3	4
10. I keep thinking how much it hurts.	0	1	2	3	4
11. I keep thinking how much I would like the pain to stop.	0	1	2	3	4
12. there is nothing I can do to reduce the intensity of the pain.	0	1	2	3	4
13. I wonder whether something bad can happen.	0	1	2	3	4

Attachment 5. VR-questionnaire

We would like to ask you some questions about your experience with Virtual Reality (VR).

1. How did you experience the use of VR before surgery?
   - o Very pleasant
   - o Pleasant
   - o Neutral
   - o Unpleasant
   - o Very unpleasant

2. How did you experience the use of VR after your surgery?
   - o Very pleasant
   - o Pleasant
   - o Neutral
   - o Unpleasant
   - o Very unpleasant

3. Did the VR-experience contribute in reducing your pain experience before your surgery?
   - o Very likely
   - o Likely
   - o Pretty likely
   - o Not likely
   - o Not likely at all

4. Did the VR-experience contribute in reducing your pain experience after your surgery?
   - o Very likely
   - o Likely
   - o Pretty likely
   - o Not likely
   - o Not likely at all

5. Did the VR-experience reduce your anxiety level before surgery?
   - o Very likely
   - o Likely
   - o Pretty likely
   - o Not likely
   - o Not likely at all

6. Did the VR-experience reduce your anxiety level after the surgery?
   - o Very likely
   - o Likely
   - o Pretty likely
   - o Not likely
   - o Not likely at all

7. Would you choose the use of VR during a surgery under spinal anesthesia the next time you will have to get surgery?
   - o Very likely
   - o Likely
   - o Pretty likely
   - o Not likely
   - o Not likely at all

8. The use of the VR-app is easy:
   - o Completely agree

- o Agree
- o Neutral
- o Disagree
- o Completely disagree

9. Would you recommend the use of VR during a surgery under spinal anesthesia to your friends, family or others?

- o Very likely
- o Likely
- o Pretty likely
- o Not likely
- o Not likely at all

10. How easy was the use of VR before or after surgery?

- o Very easy
- o Easy
- o Pretty easy
- o Not that easy
- o Not easy at all

11. How visually attractive was the VR-experience before and after surgery

- o Very attractive
- o Attractive
- o Pretty attractive
- o Not that attractive
- o Not attractive at all

12. Did you prefer anything else in the VR-app?

- ○ No
- ○ Yes, if yes circle what you prefer,

A more active game component
A less active game component
Only relaxing images

13. Did you experience any side-effects during the use of the VR-app?

- ○ No
- ○ Yes, if yes circle the side-effects;

Nausea
Dizziness
Other: …….