The effect of Virtual Reality on postoperative pain and anxiety in cardiac surgery. (VRECOVERY trial)

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

3D	**Three Dimensional**
AE	**Adverse Event**
CABG	**Coronary Artery Bypass Grafting**
CV	**Curriculum Vitae**
IC	**Informed Consent**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
RCT	**Randomized Control Trial**
(S)AE	**(Serious) Adverse Event**
VR	**Virtual Reality**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Post-operative pain and anxiety are common problems in cardiac surgery. These two components can lead to many adverse outcomes in patients, resulting in a longer recovery time and a lower overall well-being. Common treatment of these problems is by use of analgesics such as opioids, NSAIDS and paracetamol. However, analgesics come with side effects which affect the quality of life. Therefore there is a need for alternative pain and anxiety management.

Virtual Reality (VR) modalities are currently emerging as non-pharmacological tools for post-operative pain and anxiety management. Earlier studies in other surgical fields showed the potential positive effects of VR modalities on postoperative pain and anxiety. However, such a study is never performed in the field of cardiac surgery. Therefore we decided to perform a randomized control trial (RCT) in which we assess the feasibility of VR in postoperative pain and anxiety management in the field of cardiac surgery.

Objective: The objective of this study is to investigate the effect of VR on post-operative pain and anxiety management in cardiac surgery patients undergoing a coronary artery bypass grafting (CABG) procedure.

Study design: This study is a single-center randomized control trial.

Study population: Patients who have undergone a CABG procedure (n=100).

Intervention: The intervention group (n=50) will use the VR distraction therapy device at day 1, 2 and 3 after surgery on the general ward. The control group (n=50) will be treated with conventional post-operative pain and anxiety management.

Main study parameters/endpoints: The main study parameters at day 1, 2 and 3 after surgery. These are the Numeric Rating Scale (NRS) to assess the effect of pain on mobility, the Quality of Recovery-15 questionnaire, the State-Trait Anxiety Inventory-6 questionnaire and assessment of analgesic use. At follow-up, participants will be called to gather one-time QoR-15 and STAI-6 questionnaire data 6 weeks after the surgery.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: This is a study with use of a digital VR distraction therapy device. This device is known to have potential adverse effects of nausea and dizziness. However, the

used software is optimized to minimize these adverse effects. And the potential benefits of reducing pain and anxiety in the post-surgical phase outweigh these potential adverse effects.

1. INTRODUCTION AND RATIONALE

Post-operative pain and anxiety are common problems in all surgical fields.**[1]** These pain and anxiety are due to the surgical tissue damage and the unpleasant psychological experience of undergoing a surgical procedure.**[2]** Those two components can lead to many adverse outcomes in patients, resulting in a longer recovery time and a lower overall well-being.**[3]** Pain and anxiety levels after cardiac surgery are often more severe than average due to the relative more invasive surgical procedures. The incidence of chronic pain and/or anxiety after cardiac surgery is 21-55%.**[4]** The occurring pain syndromes know a wide variety (visceral, musculoskeletal or neurogenic) and are commonly treated by use of analgesics such as opioids, NSAIDS and paracetamol. However, due to the many side effects of these analgesics which affect the quality of life **[5]** there is a need for alternative pain and anxiety management.

Virtually Reality (VR) modalities are currently emerging as non-pharmacological tools for post-operative pain and anxiety management. The effective potential of these modalities are due to their possibilities for distraction from reality, resulting in distraction therapy. Virtual reality environments are taught to divert the patients attention away from the nociceptive input, resulting in less attention for pain perception and therefore more comfort in the clinical recovery path.

A recently published systematic review and meta-analysis **[6]** showed that the effects in general are still not clear as several studies yielded both positive and non-significant results for VR distraction therapy devices. The preliminary conclusion on this is that the application of VR distraction therapy can relief post-operative pain and anxiety, however this could not be stated firmly yet because of the heterogeneity in most studies due to different types of surgery and various timing of VR usage.

Also, there are no studies performed yet in the field of cardiac surgery concerning post-operative pain and anxiety management using VR distraction therapy. Therefore we decided to perform a randomized control trial (RCT) in which we assess the feasibility of VR in postoperative pain and anxiety management in the field of cardiac surgery. Also we will assess if there are predictive factors to select specific patients who can mostly benefit from this innovative intervention. The used VR distraction therapy device in this study will be the Healthy Mind VR device. This is a CE-mark Class I device.**[7]**

2. OBJECTIVES

Primary Objective: To investigate the effect of VR distraction therapy with breathing exercises in post-operative pain and anxiety management in cardiac surgery patients undergoing coronary artery bypass grafting (CABG) procedure.

3. STUDY DESIGN

This study is a single-center randomized control trial.

The study will consist of 100 participants who have undergone an uncomplicated surgical CABG procedure. The intervention group includes 50 patients using a VR distraction therapy device with 3D interactive nature environments in the post-operative stage for pain and anxiety management and breathing exercises. The VR distraction therapy device consists of a head-mounted display and a configuration tablet. The control group includes 50 patients who will be treated with conventional post-operative pain and anxiety management.

The intervention group will test-use the VR distraction therapy device on the day of clinical admission prior to surgery and use it therapeutic at day 1, 2 and 3 after surgery on the general ward. Daily usage of this tool consists of two sessions each day (morning and afternoon) with a duration of 20 minutes per session. The specific virtual environment for each session will be selected freely by the participants.

Outcomes will be measured daily, at the end of each session. Outcomes will be measured by using the Numeric Rating Scale (NRS) to assess the effect of pain on mobility (in retrospect), Quality of Recovery-15 (QoR-15) questionnaire, State-Trait Anxiety Inventory-6 (STAI-6) questionnaire and assessment of analgesic use.

At follow-up, participants will be called to gather one-time QoR-15 and STAI-6 questionnaire data 6 weeks after the surgery.

P	100 participants who have undergone an uncomplicated surgical CABG procedure
I	VR distraction therapy device with 3D interactive nature environments in the post-operative stage for pain and anxiety management. 50 participants will use the VR distraction therapy device at day 1, 2 and 3 after surgery on the general ward. Daily usage of this tool consists of two sessions each day (morning and afternoon) with a duration of 20 minutes per session. 6 week after surgery data on pain and anxiety at follow-up will be gathered by phone call using two questionnaires.
C	Conventional post-operative pain and anxiety management in 50 participants
O	• Numeric Rating Scale (NRS) to assess the effect of pain on mobility • Quality of Recovery-15 (QoR-15) questionnaire • State-Trait Anxiety Inventory-6 (STAI-6) questionnaire • Assessment of analgesic use

4. STUDY POPULATION

4.1 Population (base)

The study population consists of patients who are ≥18 years of age and have undergone a surgical CABG procedure.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age ≥18 years or older with written informed consent
- Patients undergoing surgical CABG

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Major comorbidities besides coronary artery disease
- Complicated surgical procedure
- Hearing and/or visual impairments
- Psychiatric impairments
- Complaints of vomiting and nausea
- History of epilepsy
- Claustrophobia
- Facial wounds and skin defects at site of application
- Patients placed in clinical isolation
- Readmission to the intensive care unit

4.4 Sample size calculation

In total, 100 subjects will be included in this study. 50 subjects in the patient group that will receive VR therapy and 50 subjects in the patient group that will not receive VR therapy. Since literature is limited about our primary outcomes in the field of cardiac surgery, a retrospective pilot was done in our clinical pool of CABG patients for the assessment of one of our primary outcomes (NRS-score) upon which we based our sample size calculation. See below for details.

A retrospective assessment for NRS-score is performed in 35 patients who have undergone an uncomplicated CABG procedure in our department the past year (2020). Since the data was non-normally distributed, a two-sided Wilcoxon (Mann-Whitney) Rank-Sum test was performed in nQuery Advisor version 8.5.1 **[8]** on Windows with P(X<Y) =0.5 and a test significance level of 0.05. Since this statistical test allows only a maximum

of 8 categories and none of the pilot patients scored 0, 9 or 10 for the NRS-score, only NRS-scores 1 - 8 were used as categories in this test. This resulted in a power of 92,7% for a sample size of 100 subjects (50 per group) (**Table 1**).

MTT2-1 / Wilcoxon (Mann-Whitney) Rank-Sum Test that P(X<Y) = 0.5

	1	2
Test Significance Level, α	0,050	0,050
1 or 2 Sided Test?	2	2
Number of Categories, k	8	8
Side Table Name	MTT2S-1	MTT2S-2
p1 = P(X<Y)	0,311	
Power (%)	**92,7**	**92,7**
Sample Size per Group, n	50	50

Category	Proportion in Group 1 (X)	Proportion in Group 2 (Y)
1	0,059	0,050
2	0,059	0,302
3	0,088	0,180
4	0,328	0,250
5	0,119	0,050
6	0,147	0,090
7	0,060	0,060
8	0,140	0,018
$\sum \pi_i$	1,000	1,000
$p_1 = P(X<Y)$	0,311	

Table 1. *Sample size calculation using a two-sided Wilcoxon (Mann-Whitney) Rank-Sum test in nQuery Advisor version 8.5.1 on Windows with P(X<Y) =0.5.*

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The investigational product that will be used in this study is the Healthy Mind Virtual Reality device.**[7]** VR distraction therapy device aimed to reduce pain and anxiety in hospitalized patients. This is a CE mark class I medical device. The device contains software which puts patients in immersive virtual experiences to distract them from reality using advanced psychological principles like medical hypnosis. The software also contains breathing exercises which are essential in the postoperative setting in cardiac surgery.

By using the brain's cognitive and affective capacities, pain pathways are modulated through combined visual and auditory stimulations, attention diversion and relaxation. With the use of virtual reality the patient is transported into a designed 3D environment to journey through natural experiences of choice. This device is designed to eventually be a drug-free therapeutic tool that facilitates the work of caregivers, transform conventional clinical pathways of patients and improve their recovery.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product

Our investigational product is the Healthy Mind Virtual Reality device. **[7]** This product is intended to be a VR distraction therapy device to reduce pain and anxiety by usage of software which gives patients an immersive experience in a calming VR environment with integrated breathing exercises.

6.2 Summary of findings from non-clinical studies

This device is developed with evidence based efficiency of VR treatment modalities in reducing pain and anxiety throughout different medical fields. See the literature review of the Healthy Mind VR device for an extensive description of these previous studies.**[9]**

At the current moment there are no completed studies in which the Healthy Mind VR device is used as investigational product. However, there are several ongoing clinical trials in France and Switzerland.

6.3 Summary of known and potential risks and benefits

Potential risks:

Some patients may present a non-adherence to the VR relaxation technique, resulting in discomfort and/or nausea and dizziness. The limitations of VR can be related to lacking physical adaptation which can potentially result in cyber-sickness.

The brain uses three sources of data to inform the body about its position and movements: the inner ear, muscles, and eyes. Once the head mounted display is on your head, the eyes indicate that you are in a different environment, but the inner ear and muscles say that this is not the case: this inconsistency of sensory information usually translates into temporary symptoms such eye fatigue, disorientation (dizziness, imbalance) and nausea. However, the Healthy Mind software was created specifically for patients with reduced mobility (lying or sitting) and optimized to minimize adverse effects such as nausea. For example, the user is not in constant movement in the virtual environment. Users remain static and are being teleported to new areas of the environment. This way, the gap between the inner ear and the virtual world is minimalized. Furthermore, participants in this study will be excluded from further participation as soon as the above mentioned symptoms are noticed.

Potential benefits:

The VR technique of Healthy Mind uses the brain's cognitive and affective capacities to modulate pain pathways through combined visual and auditory stimulations, attention diversion and relaxation. The software on this device puts patients in immersive experiences in VR to distract them from reality. The software also integrates breathing exercises which are essential in the postoperative setting in cardiac surgery for lung recovery.

Altogether, the potential benefits of these elements would be pain reduction, anxiety reduction, improved lung recovery and faster general post-operative recovery.

6.4 Description and justification of route of administration and dosage

Since this a non-pharmaceutical investigational product, there is no evidence based description of dosage. However, usage for 2-3 sessions each day is maintained as the standard use in various clinics with similar VR therapeutic devices. Administration in this case is usage of a head-mounted device with earphones bringing the participants in a virtual reality environment for a session of 20 minutes.

7. METHODS

7.1 Study parameters

7.1.1 Main study parameters

The main study parameters are:

- Numeric Rating Scale (NRS) to assess the effect of pain on mobility
- Quality of Recovery-15 (QoR-15) questionnaire
- State-Trait Anxiety Inventory-6 (STAI-6) questionnaire
- Assessment of analgesic use

7.1.2 Secondary study parameters

The secondary study parameters are:

- Functional Ambulation Categories Score

7.2 Randomisation, blinding and treatment allocation

For randomisation, we use a simple random allocation approach. This randomization sequence will be prepared in SPSS 26.0 (SPSS Inc, Chicago, IL) for Windows. This randomization will be performed postoperatively by the research team, in case of an uncomplicated procedure, directly after the patient returns to the clinical ward after surgery. Blinding however, is not possible in this study as usage of the medical device is clear.

7.3 Study procedures

The study will consist of 100 participants who have undergone an uncomplicated surgical CABG procedure.

The intervention group includes 50 patients using a VR distraction therapy device with 3D interactive nature environments in the post-operative stage for pain and anxiety management. The control group includes 50 patients who will be treated with conventional post-operative pain and anxiety management.

The intervention group will test-use the VR distraction therapy device on the day of clinical admission prior to surgery and use it therapeutic at day 1, 2 and 3 after surgery on the general ward.

Daily usage of the VR distraction therapy device consists of two sessions each day (morning and afternoon) with a duration of 20 minutes per session. The specific virtual environment for each session will be selected freely by the participants.

Outcomes will be measured daily, at the end of each session, which is done 1) after the doctor's ward visit in the morning and 2) after the shift change of the nurse team. Outcomes will be measured at the same aforementioned moments in the control group. Outcomes will be measured by using the Numeric Rating Scale (NRS) to assess the effect of pain on mobility, Quality of Recovery-15 questionnaire, State-Trait Anxiety Inventory-6 questionnaire and assessment of analgesic use.

At follow-up, participants will be called to gather one-time QoR-15 and STAI-6 questionnaire data 6 weeks after the surgery.

Numeric Rating Scale (NRS) score

The NRS score is a numeric scale in which individuals rate pain from 0 (no pain) tot 10 (worst pain). This is a subjective score which is assessed verbally and used frequently in standard clinical care in multiple medical specialties.

Quality of Recovery-15 (QoR-15) questionnaire

The QoR-15 questionnaire is a clinical validated instrument to measure post-operative quality of recovery.

State-Trait Anxiety Inventory-6 questionnaire

The STAI-6 questionnaire is a validated psychological inventory designed to measure worry, tension and anxiety in an individual.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.5 Replacement of individual subjects after withdrawal

Upon withdrawal of a subject, the data collected will not be used for the study and will be deleted.

7.6 Follow-up of subjects withdrawn from treatment

Not applicable.

7.7 Premature termination of the study

Study participants can withdraw their consent at any time during the study. Patients that experience eye fatigue, nausea or disorientation will not be included in this study. In addition, since all the elements of this study are harmless and carry no significant risks, it is unlikely that premature termination will occur during the study.

7.8 Potential risk analysis due to COVID-19 regulations

The main risk for our study due to unexpected upscaling of COVID-19 regulations would be the delay of elective CABG surgery. This would be due to a (temporary) reduced intensive care unit capacity. However, this would not impact the study feasibility, as a consequence the study will take longer to include the target number of inclusions.

8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the investigating group will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The investigating group 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.

8.2 AEs and SAEs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study considered caused by the study. All adverse events caused by the study will be reported and recorded by the investigator or his staff.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect caused by the study 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;
- is a congenital anomaly or birth defect; or
- 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.

The direct investigator will report all SAEs which are caused by the study to the principal investigator without undue delay after obtaining knowledge of the events.

The investigator will report these SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for

SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the investigator has first knowledge of the serious adverse events.

8.3 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

9. STATISTICAL ANALYSIS

9.1 Primary study parameters

The included data (NRS score, STAI-6 score, QoR-15 score) will be presented as mean ± standard deviation. Ratios will be given for statistical assessment of non-continuous variables (assessment of analgesic use). Because the data is expected to be non-normally distributed, Wilcoxon (Mann-Whitney) Rank-Sum testing will be performed to analyze differences between groups. Differences between groups will be assessed for each measurement at each point in the study (day 1, 2 and 3) and cumulative as mean values. SPSS 26.0 (SPSS Inc, Chicago, IL) for Windows is used to assess statistical analyses.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (version 2013, Fortaleza, Brazil) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

10.2 Recruitment and consent

Eligible patients will be recruited from a surgery waiting-list of the Heartcenter. Since only healthcare providers with a treatment-relationship with the patient have access the patient record file, the treating physician will be asked to contact the patient for his/her willingness to participate in this study. After the patient gives permission to be contacted by the investigator (S. el Mathari), the investigator will contact the patient by phone with additional information about the study to inquire if the patient is interested in study participation. And if so, patient information will be sent to their home address. Patients will be then given 7 days to read the patient information and to consider the study participation. After this 7-day period, the patients will be contacted again by the aforementioned investigator. If they are willing to participate, an informed consent form will be handed out at clinical admission for signing.

10.3 Benefits and risks assessment, group relatedness

The used VR device has a risk for inducing, eye fatigue, nausea or disorientation. However, the potential benefits of reducing post-operative pain and anxiety and shortening post-surgical recovery time, outweigh these risks.

10.4 Compensation for injury

The investigator (AmsterdamUMC) has a liability insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). The Medical Ethical Commission granted exemption for a damage/injury insurance in accordance with the WMO.

10.5 Incentives

The subjects will receive no financial compensation or other incentives.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

The participant's identity will remain confidential. His or her name will not be published and will not be disclosed to anyone outside the research group. All personal details and other identifiable data provided or collected during this study will be kept in the strictest confidence. Participants will be assigned a code number following their first contact with the researcher. This number will be used throughout the project and will be the only identifier on all data. No identifiable (e.g. name etc.) of participants will be revealed at scientific meetings, conferences, presentations, publications or any other vehicles of public communication. In any such publication arising from this research the individual results will not be identifiable. Only the research team will have access to the collected data.

- Each researcher will store documents bearing identifiable and personal information in a locked cabinet with access strictly restricted to members of the research group.
- All computerised data/information will be stored on pass-word protected computers, to which only a member of the research team has access.
- Code numbers will be used for all computerised data/information collected. These data are therefore stored in a coded fashion.
- All gathered data/information will be stored for the duration of the study. It will then be kept in a locked cabinet for up to 15 years

11.2 Amendments

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

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the investigators.

11.3 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.

11.4 Temporary halt and (prematurely) end of study report

The investigator will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The investigator will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the investigator will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

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 and the Competent Authority.

11.5 Public disclosure and publication policy

This project is sponsored by Healthy Mind VR providing the needed VR devices for this study. Healthy Mind VR will be mentioned in the acknowledgements at publication and the Healthy Mind device will be mentioned in the study materials. Further, no special arrangements are made regarding the disclosure of publication material and will be disclosed unreservedly.

11.6 Monitoring and Quality Assurance

Monitoring of the conduct of the study will be done by the Clinical Monitoring Center (CMC) of the AmsterdamUMC. The CMC performs quality control measurements to ensure protection of the rights, safety and well-being of the research subjects and

scientific quality of the research data. After approval of the protocol by the METC the investigators will have an intake appointment with the CMC to prepare a monitoring plan. The monitoring visits will be planned and the frequency of these visits will be conform the NFU-standards depending on the risk-stratification and duration of the study.

12. STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

a. Level of knowledge about mechanism of action

The software on the Healthy Mind VR device puts patients in immersive experiences in VR to distract them from reality using advanced psychological principles like medical hypnosis. By using the brain's cognitive and affective capacities, pain pathways are modulated through combined visual and auditory stimulations, attention diversion and relaxation.

b. Previous exposure of human beings with the test product

Similar studies in which subjects were exposed to a similar product were mainly performed in pediatric patient populations. In all these studies, the used VR devices seemed to be an effective tool in pain and anxiety reduction in these patients.**[10]**

Regarding the specific Healthy Mind VR device, there are no published studies yet. However, there are several ongoing clinical trials in France and Switzerland with the Healthy Mind VR device and similar VR distraction therapy devices. **[11-13]**

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

Not applicable.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Not applicable.

e. Analysis of potential effect

Potential adverse effects of the Healthy Mind VR device are nausea and dizziness due to non-adherence to the virtual relaxation technique. This could be related to lacking physical adaptation which can potentially result in cyber-sickness. However, the Healthy Mind software is optimized to minimize these adverse effects by avoiding constant movement and using static teleportation when moving to other digital environments. Furthermore, participants in this study will be excluded from further participation as soon as the above mentioned symptoms are noticed. Additionally we would like to address that these potential symptom are very unlikely to result in significant (lasting) damaging effect.

f. Pharmacokinetic considerations

Not applicable.

g. Study population

The study population consists of patients which are 18 years or older of age and have undergone an uncomplicated surgical CABG procedure. All included subjects are on the general clinical ward and are in stable condition.

h. Interaction with other products

Not applicable.

i. Predictability of effect

Not applicable.

j. Can effects be managed?

As mentioned above, the potential adverse effects in this study are nausea and dizziness. These effects can be effectively managed when observed. The device will be tuned off immediately and common management for these adverse effects will be applied. This will be either expectant policy or supplementation of commonly used anti-emetics.

12.2 Synthesis

Altogether, there are no significant risks to this study. The software of the device is optimized to reduce the potential adverse effects being nausea and dizziness. Also adequate management strategies are available for these potential effects. Since these potential effects are highly unlikely to result in significant (remaining) damage, the potential benefits of reducing pain and anxiety in the post-surgical phase outweigh these.

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