The effects of relaxation using Virtual Reality in forensic psychiatric patients. A randomized cross-over clinical trial.

Short title: **VRelax Study**

ONZ-2023-0315

Clinical Investigation Plan (CIP)

November 10, 2023

List of Abbreviations

ADE	=	Adverse Device Effect
AE	=	Adverse Event
CA	=	Competent Authority
CIP	=	Clinical Investigation Plan
CTU	=	Clinical Trial Unit
EC	=	Ethics Committee
eCRF	=	electronic Case Report Form
GCP	=	Good Clinical Practice
GDPR	=	General Data Protection Regulation
HIRUZ	=	Health, Innovation and Research Institute UZ Ghent
ICF	=	Informed Consent Form
IEC	=	Independent Ethics Committee
ISO	=	International Organization for Standardization
LSLV	=	Last subject, last visit
PI	=	Principal Investigator
SADE	=	Serious Adverse Device Effect
SAE	=	Serious Adverse Event
SOP	=	Standard Operating Procedure
USADE	=	Unanticipated Serious Adverse Device Effect
PSS	=	Perceived Stress Scale
VAS	=	Visual Analog Scale
VR	=	Virtual Reality

Synopsis of the clinical investigation

TITLE	The effects of relaxation using Virtual Reality, by forensic psychiatric patients. A randomized crossover clinical trial
ACRONYM	VRelax study
SPONSOR	UGent-UZGent
COORDINATING INVESTIGATOR	Prof. Dr. Kurt Audenaert
NAME OF DEVICE	- *PICO VR bril, de software is VRelax* - *Embrace plus*
MANUFACTURER	- *PICOXR.com* - *Vrelax.com* - *Empatica.com*
STUDY DESIGN	*Cross-over randomized controlled trial*
CENTER(S) / COUNTRY(IES)	*UZGent en PC Sint-Jan Baptist, in Zelzate, Belgium*
OBJECTIVES	**Primary Objective** To determine whether VR relaxation has a significant effect on a person's stress level. This will be assessed, among other measures, through a change in the VAS relaxation score, where an average improvement of 0.5 out of 10 is considered clinically relevant. With this study, we aim to gain insight into the effects of VR relaxation on both subjective and objective stress, heart rate, and other physiological parameters. **Secondary Objectives** We will also examine changes in the VAS score for happiness, where an average improvement of 0.5 out of 10 is considered clinically relevant. We aim to assess whether VR relaxation has a greater relaxing effect compared to standard relaxation. Additionally, we want to gain insight into the feasibility of implementation and evaluate the user-friendliness of the application. Furthermore, we intend to identify the most suitable types of VR environments for relaxation and investigate whether the effect may be greater in patients with intellectual disabilities or other psychiatric disorders.

ENDPOINTS	**Primary Endpoint** A change in the VAS score for relaxation, where an average improvement of 0.5 out of 10 is considered clinically relevant. **Secondary Endpoints** A change in the VAS score for happiness, where an average improvement of 0.5 out of 10 is considered clinically relevant.
STUDY DURATION	*3 years*
NUMBER OF PATIENTS	*54*
INCLUSION CRITERIA	Be admitted for at least 4 months as a forensic psychiatric patient within medium or high security, at Sint-Jan Baptist in Zelzate.
EXCLUSION CRITERIA	Acute psychosis, acute mania, epilepsy, pacemaker, balance disorders, individuals in the acute withdrawal phase of substance or alcohol abuse, severe cardiac abnormalities, serious eye disorders, pregnancy.
PROCEDURES	Relaxation therapy with or without VR, heart rate measurements using the Embrace Plus device, and questionnaires.
COMPARATIVE DEVICE	none

3. Title of the Clinical Investigation

The effects of relaxation using Virtual Reality in forensic psychiatric patients. A randomized crossover clinical trial.
Acronym: VRelax study

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4. Single Identification Number of the Clinical Investigation

Eudamed number: ONZ-2023-0315

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5. General Information

5.1 Sponsor – Coordinating Investigator
Sponsor of the clinical investigation:
University Hospital Ghent
Department of Psychiatry and Medical Psychology
C. Heymanslaan 10
9000 Ghent

Coordinating Investigator:
Prof. Dr. Kurt Audenaert

Contact person:
Dr. Saskia Roggeman

5.2 Device Name and Manufacturer

- Pico VR headset – Picoxr.com
- VRelax software – Vrelax.com
- Embrace Plus – Empatica, Empatica.com

5.3 Investigational Sites and Principal Investigators

- Prof. Dr. Kurt Audenaert, Department of Psychiatry and Medical Psychology, Faculty of Medicine and Health Sciences, Ghent University (UGent) and University Hospital Ghent (UZGent), C. Heymanslaan 10, 9000 Ghent
- Dr. Frank Van Steenkiste, Chief Physician, PC Sint-Jan Baptist, Suikerkaai 81, 9060 Zelzate
- Dr. Saskia Roggeman, Postdoctoral Researcher at Psychiatric Center Sint-Jan Baptist, Suikerkaai 81, 9060 Zelzate; affiliated with the Department of Psychiatry and Medical Psychology, Faculty of Medicine and Health Sciences, UGent-UZGent

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5.4 Departments/Laboratories Involved in the Clinical Investigation

- Department of Psychiatry and Medical Psychology, Faculty of Medicine and Health Sciences, UGent, and the Psychiatry Department of UZGent, Ghent
- Research and Policy Department, Science Team, PC Sint-Jan Baptist, Zelzate

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5.5 Financing of the Clinical Investigation
This study is funded by PC Sint-Jan Baptist and partially supported by a research grant from the Brothers of Charity.

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6. Introduction

6.1 Background Information

Stress is a well-established factor in the onset and persistence of burnout, anxiety, mood, and psychotic disorders. Sleep disorders further predispose individuals to, and exacerbate, these psychiatric symptoms. Individuals with mental health problems tend to have higher (social) stress reactivity and impaired stress recovery, which is compounded by sleep disturbances and sleep deprivation.

Relaxation can reduce stress, thereby potentially improving mental health symptoms. Moreover, stress-reducing interventions may enhance quality of life, social functioning, and occupational performance. While current stress-reducing interventions appear effective, they often require mental effort—such as focus and concentration—which may be compromised in patients.

To bridge this gap, a new e-Health application called **VRelax** has been developed. VRelax is a virtual reality self-management tool designed to reduce stress. It requires significantly less effort than traditional relaxation exercises due to its immersive qualities and has an immediate effect on perceived stress and emotional mental states.

Following a comprehensive literature review on the potential applications of Virtual Reality (VR) in forensic psychiatric populations—published in November 2021 in the *Tijdschrift voor Psychiatrie*—this study will be the first to assess the effects of VR-based relaxation in such a setting. The study aims to determine whether VR relaxation provides added value for both patients and staff, and how best to implement this technology within the hospital's operations.

Given that VR environments can simulate highly realistic situations that forensic psychiatric patients would otherwise be unable to experience due to their restricted freedoms, VR offers a powerful tool that addresses the limitations of confinement. The highly immersive nature of the application also benefits patients who are unable to engage in traditional relaxation exercises due to limited imagination or empathy skills.

This study will investigate the short- and medium-term effects of VRelax on both acute and chronic stress and compare these effects to a standard relaxation exercise of the participant's choice (Treatment As Usual, TAU). The study is based on previous work by Veling et al. (2021), in which the same VRelax application was tested in an outpatient setting.

6.2 Rationale of the Clinical Investigation

There is a clear need for stress-reducing interventions in forensic psychiatry. The ability of VR environments to create highly realistic scenarios—unavailable to patients due to their limited freedom—makes VR an especially valuable tool in this context. Moreover, the immersive experience supports patients who are otherwise unable to perform standard relaxation techniques due to cognitive or emotional limitations.

This study will be the first to test VRelax in a residential forensic psychiatric setting. During the COVID-19 pandemic, several small-scale studies were conducted using VRelax to reduce stress among healthcare workers in general hospitals (Nijland et al., 2021).

References:

- Veling, W., Lestestuiver, B., Jongma, M., Hoenders, H.J.R., & van Driel, C. (2021). *Virtual Reality Relaxation for Patients With a Psychiatric Disorder: Crossover Randomized Controlled Trial*. Journal of Medical Internet Research, 23(1), e17233.
- Nijland, J.W.H.M., Veling, W., Lestestuiver, B.P., & van Driel, C.M.G. (2021). *Virtual Reality Relaxation for Reducing Perceived Stress of Intensive Care Nurses During the COVID-19 Pandemic*. Frontiers in Psychology, 12, Article 706527.

Hypothesis of the Clinical Investigation

1. VRelax will reduce acute stress: the PRE-VAS score will be higher than the POST-VAS score.
2. VR relaxation will have a greater relaxing effect than standard relaxation: VAS scores and biomarkers will reflect a stronger relaxation effect.
3. VRelax will also reduce chronic stress through a cumulative effect, meaning the post-intervention PSS score will be lower than the pre-intervention PSS score.
4. There will be a difference in the acute effect over time; in other words, as the number of sessions increases, habituation or boredom may occur for both standard and VR relaxation. This will be measured by a decreasing difference between pre- and post-VAS scores per individual over time.

Sub-hypotheses:

1. The difference in effect between standard and VR relaxation will be greater in patients with intellectual disabilities, as they have a less developed capacity for imagination.

2. There are differences in video preferences among patients with different psychiatric disorders. For example, individuals with autism may prefer static videos, while those with borderline personality disorder may prefer interactive videos.
3. The relaxing effect will manifest more quickly when using VR than with standard relaxation.

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7. Objective of the Clinical Investigation

7.1 Primary Objectives

The main objective is to examine the relaxing effect of VRelax. We aim to measure the magnitude and duration of the effect and assess the difference compared to standard relaxation exercises. What is the immediate effect, and what is the long-term impact? Is there any habituation? Which physiological parameters are most influenced?

7.2 Secondary Objectives

This study also serves to provide a scientifically grounded basis for deciding whether to implement VR in clinical practice. Therefore, we will evaluate applicability, usability, and implementation potential of the technology. Is investment in this relatively expensive technology justified?

Additionally, this study will help identify possible barriers and challenges associated with VR usage. It also serves as a starting point for the implementation of other e-health technologies in the future, with the experience and expertise gained through this study becoming a valuable asset.

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8. Endpoints

8.1 Primary Endpoint

The primary endpoint is the VAS score for relaxation. We will examine whether there is a change in the relaxation VAS score between the time points before and after a relaxation session, with an average improvement of 0.5 out of 10 considered clinically relevant.
The main goal is to determine whether VR relaxation is an effective method for our population.

8.2 Secondary Endpoints

The secondary endpoint is the VAS score for happiness. We will assess whether there is a change in the VAS happiness score before and after a relaxation session, with a clinically relevant threshold of 0.5 out of 10.
Additionally, physiological parameters measured using the Embrace Plus device are also considered important secondary endpoints.

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9. Design of the Clinical Investigation

The study design is a crossover randomized controlled trial. In this way, each participant serves as their own control, which helps eliminate individual/genetic effects on the measurements. Since this study involves a heterogeneous patient population with varying diagnoses and comorbidities, this design helps limit variability to obtain statistically significant results with a feasible sample size. It also minimizes the influence of external factors on the study outcomes.

The study protocol was extensively tested among volunteer staff members at Sint-Jan Baptist to identify and resolve potential errors or problems before the official start of the trial, ensuring a relevant and high-quality protocol.

This is also the first clinical study to test the VRelax app in a forensic psychiatric inpatient population, while also incorporating physiological parameters.

10. Population

10.1 Number of Subjects

The primary endpoint selected is a change in the VAS relaxation score, where an average improvement of 0.5 out of 10 is considered clinically relevant between pre- and post-session time points.

The standard deviations used (0.83 for standard relaxation and 0.74 for VRelax) were estimated based on the results of a comparable study in an outpatient population, as described in the article by Veling et al. (2021).

The chosen statistical power is 80%, and the type I error rate was set at 0.05.
An expected dropout rate of 30% was included.
Calculations were performed using the GPower software.
The calculated required sample size for detecting a difference in VAS relaxation scores is **54**.

All participants are forensic psychiatric patients admitted to PC Sint-Jan Baptist in Zelzate and expected to remain there for at least 4 more months, ensuring their availability throughout the entire study period.

10.2 Vulnerable Population (pregnant, children, elderly, immune-compromised or breastfeeding individuals)

No vulnerable populations will participate in this study.

If a patient is under legal guardianship, consent must be obtained from the legal guardian for participation.
Participation is only possible after a positive recommendation from the medical support team of the patient's unit. The patient's therapy schedule will be temporarily adjusted to allow participation without negative consequences.

10.3 Inclusion Criteria

Patients will be included if they are forensic psychiatric patients (aged 18 or older) admitted to PC Sint-Jan Baptist in Zelzate, with an expected stay of at least four more months to ensure full participation. Final inclusion is only possible after approval by the patient's unit medical support team and with the patient's own consent.

10.4 Exclusion Criteria

Exclusion criteria include:
Acute psychosis, acute mania, epilepsy, pacemaker, balance disorders, individuals in acute withdrawal from substance or alcohol use, severe cardiac conditions, serious eye disorders, pregnancy, or fear of using VR.

10.5 Withdrawal and Replacement of Subjects

Criteria for Withdrawal

Subjects may discontinue the clinical investigation at any time. A premature discontinuation is defined as a subject not undergoing the end-of-study evaluation.

Subjects can be withdrawn under the following circumstances:

- At their own request
- If the investigator believes continued participation is not in the subject's best interest
- If the subject violates the informed consent terms or disregards investigator instructions
- In the case of significant non-compliance with the study intervention
- If the subject develops VR sickness or an eye condition that makes VR headset use no longer possible
- If treatment is discontinued and the patient is discharged from the hospital

In all cases, the reason for withdrawal must be thoroughly documented in the (e)CRF and the subject's medical record.

A subject will be considered lost to follow-up if they do not return for scheduled visits and cannot be contacted by study staff.

Follow-up actions include:

- Attempt to contact and reschedule the visit
- At least 3 phone call attempts and, if needed, a certified letter to the subject's last known address
- If still unreachable, the subject is considered a dropout due to loss to follow-up

Replacement Policy

Dropouts will be registered during the study, including the reason for discontinuation. If the number of dropouts is too high and threatens the quality of the research, additional participants will be recruited.

10.6 Restrictions and Prohibitions for the Subjects

Patients are not required to follow any additional restrictions for this study. The only request is to avoid intense physical activity immediately before the sessions in order to prevent disruption of physiological measurements.

10.7 Possible Advantages and Risks for the Subjects

Patients at PC Sint-Jan Baptist are under no obligation to participate in this study. Participation or refusal to participate will have no impact on their ongoing treatment.

Participation may result in a reduction in stress levels, but it is also possible that no benefits or results will be observed. However, the findings of this study may lead to the development of new and more effective methods for treating stress using emerging technologies such as Virtual Reality.

As Virtual Reality is a widely used and commercially available technology, and the VRelax software has already obtained a European conformity certificate, potential health risks are considered minimal. The likelihood of harm from participation is extremely low. If VR sickness occurs during sessions, symptoms such as nausea or dizziness are typically mild and short-lived.

It is possible that unknown risks or discomforts may arise during the study. Therefore, it is crucial to report any new health complaints to the researcher as soon as possible, regardless of whether the participant believes it is related to the study.

Participants have the right to ask questions at any time regarding the known or potential risks of the study. If new information becomes available during the study that may affect a participant's willingness to continue, they will be informed promptly. Should any harm arise from participation, appropriate treatment will be provided.

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11. Identification and Description of the Investigational Device

11.1 Medical Device Description

This study uses PICO VR headsets and Embrace Plus monitoring devices. Both devices are market-compliant and are being used for their intended purpose in this study.
The VRelax software is a VR relaxation program that utilizes 360° videos, also used in accordance with its design. This software has received EU conformity certification.

11.2 Manufacturer

- PICOXR.com
- VRelax.com
- Empatica.com

11.3 Intended Use

VR headsets are widely used both commercially and professionally for a variety of purposes, including gaming, leisure, therapy, and training/education.

11.4 Instructions for Use

Refer to the user manual.

11.5 Delivery and Return of the Medical Device

The VR headsets and Embrace Plus devices have already been purchased and tested, as has the VRelax software. The license for VRelax and the accompanying GRIP app will be renewed annually. Two Apple iPad Pros were also purchased for use with the GRIP viewer app for VRelax.

11.6 Storage of the Medical Device

All equipment is stored in the hospital's VR room, where the study sessions will also take place. This room is accessible only to authorized personnel.

11.7 Traceability and Accountability of the Medical Device

The devices are registered in our list of medical equipment, maintained through the hospital pharmacy.

11.8 Known Reactions/Side Effects of the Medical Device

Known side effects of VR include VR sickness, which may present as nausea, dizziness, or dry eyes.

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12. Identification and Description of the Comparative Device

(Not applicable or not specified)

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13. Methodology

13.1 Study-Specific Procedures

The study consists of two blocks of 10 sessions: one block with VR and one without. Each participant thus serves as their own control.
The control sessions take place in the VR room, seated, with a total duration of 30 minutes (including 20 minutes of relaxation of their choice, e.g., reading, listening to music, watching a short film, body scan, etc.). The selected relaxation method is recorded for each session.

The VR sessions also take place in the VR room, seated, with a duration of 30 minutes (including 20 minutes of VRelax with one or more 360° videos of the participant's choice). Guided meditation sessions are excluded, as they require the eyes to be closed. The selected videos are recorded per session.

Before and after each session, stress is assessed using VAS scores for stress/tension and happiness. At the beginning and end of each 10-session block, general stress levels are measured using the Perceived Stress Scale (PSS). After the final session of each block, a structured qualitative interview is conducted regarding the user experience. All groups receive the same pre- and post-intervention assessments.

During each relaxation session, physiological parameters are also measured using the Embrace Plus device (www.Empatica.com), including heart rate, heart rate variability (HRV), respiratory rate, skin conductance, and skin temperature.

13.2 Flowchart

1. Information sessions per ward and registration of candidate participants
2. Approval for participation by the patient's medical team
3. Final inclusion of the participant
4. Start of the experiment
5. End of the experiment
6. Data processing

13.3 Start of the Clinical Investigation

During a group session on each ward, the study will be explained, and patients will be asked whether they are interested in participating. After this session, individual caregivers will have one week to ask the patient whether or not they wish to participate. Patients who express interest will be discussed during the ward's multidisciplinary team meeting two weeks after the information session. Their participation will then be formally approved or declined.

Once approved, the ward psychologist will provide the investigator with the list of participants. The therapy schedules of the patients will then be adjusted to enable participation in the planned relaxation sessions.

13.4 End of the Clinical Investigation

The expected duration of participation for each patient is a maximum of 4 months. The entire study will have a maximum duration of 3 years.

13.5 Randomisation

As soon as all participants are confirmed, randomisation will be carried out using SAS software to assign them to one of the two groups.

13.6 Prior and Concomitant Medication/Treatments

There are no restrictions.

14. Safety reporting

14.1. Definitions

Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in context of a clinical investigation, whether or not related to the investigational medical device. (MDR Art 2(57))

Note:

a. This definition includes events that are anticipated as well as unanticipated events

b. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

Serious Adverse Event (SAE)

Any adverse event that led to any of the following:

a) death,

b) serious deterioration in the health of the subject, that resulted in any of the following:

i. life-threatening illness or injury,

ii. permanent impairment of a body structure or a body function,

iii. hospitalisation or prolongation of patient hospitalisation,

iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body

function,

v. chronic disease,

c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect

(MDR Article 2(58))

Device deficiency

Any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device.

NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. Procedures associated with the use of a device should be addressed in the risk assessment, which makes it possible to determine whether the procedure related SAEs are Unanticipated Serious Adverse Device Effect or not. SAEs related to procedures imposed by the clinical investigation plan but not with the use of the device should not be considered Serious Adverse Device Effects.

NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk assessment.

14.2. Causality assessment

The relationship between the use of the medical device (including the medical – surgical procedure) and the occurrence of each adverse event shall be assessed and categorized. During causality assessment activity, clinical judgment shall be used and the relevant documents, such as the Investigator’s Brochure and the Clinical Protocol shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

For the purpose of harmonizing reports, each SAE will be classified according to four different levels of causality. The investigators and the sponsor will use the following definitions to assess the relationship of the serious adverse event to the investigational medical device, the comparator or the investigation procedures.

1) Not related: relationship to the device or procedures can be excluded when:

- the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
- the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
- the event involves a body-site or an organ that cannot be affected by the device or procedure;
- the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis9, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

2) Possible the relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

3) Probable the relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot reasonably explained by another cause.

4) Causal relationship: the serious event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

The sponsor and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications caused by concomitant treatments not imposed by the clinical investigation plan are considered not related. Similarly, several routine diagnostic or patient management procedures are applied to patients regardless of the clinical investigation plan. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related..

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where an investigator assessment is not available and/or the sponsor remains uncertain about classifying the serious event, the sponsor should not exclude the relatedness and classify the event as “possible” and the reporting should not be delayed.

Particular attention shall be given to the causality evaluation of unanticipated serious adverse (device) events. The occurrence of unanticipated events related could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

14.3. Reporting of adverse events

14.3.1. Reporting of (S)AEs and device deficiencies by the investigator to the sponsor

Adverse events will be reported between the first use of the medical device and the last study related activity. Medical events that occur between signing of the Informed Consent and the first use of the medical device will be documented as medical history data.

All (S)AEs will be recorded in the patient’s file and in the eCRF.

All SAEs and device deficiencies will be reported immediately but no later than 3 calendar days after investigational site study personnel’s awareness of the event to:

- Sponsor: Prof. Kurt Audenaert. E-mail: kurt.audenaert@Ugent.be
- Health Innovation and Research Institute:
  E-mail: hiruz.ctu@uzgent.be

  Tel: 09/332.09.05.00

  Fax +32 9 332 05 20

  Address: Corneel Heymanslaan 10, 1K5, 9000 Gent

This reporting is done by using the appropriate SAE form and device deficiency form. Follow-up information should be provided as necessary

14.4. Annual Safety and progress Reporting

Sponsor will inform all principal investigators at least annually in writing of all the serious adverse events at all investigation sites that have been reported to the sponsor, and ensure that they are reported to their local EC, if defined by their institution's procedure.

15 Notification of end of clinical investigation, early termination and temporary halt

Early termination or temporary halt of the clinical investigation or an investigational site may be necessary in case of major non-compliance, critical safety issues or premature study discontinuation. This can occur at any time by the sponsor, principal investigator of the local site, IEC. ISO 14155:2011 shall be followed.

Alle deelnemers zullen hiervan persoonlijk of via hun individueel begeleider (IB) op de hoogte worden gesteld.

In case of an early termination, all study materials will be retained and the terminating party shall justify its decision in writing.

Study Analysis

16.1 Sample Size Calculation

The primary endpoint selected was a change in the VAS score for relaxation, where an average improvement of 0.5 out of 10 is considered clinically relevant.
The standard deviations used (0.83 for standard relaxation and 0.74 for VRelax) were estimated based on the results of a comparable study in an outpatient setting, as described in the article by Veling et al. (2021).
The chosen statistical power was 80%, and the type I error rate (alpha) was set at 0.05.
Calculations were performed using the software program **GPower**.
To determine the required sample size using the VAS relaxation score as the primary outcome measure:

- With an expected dropout rate of 30%, the final **sample size = 54**.

16.2 Statistical Analysis

Randomisation of participants into the two groups will be performed using SAS software.
The relaxing effect will be calculated by comparing the changes in VAS scores before and after each session. This is calculated as:
1 – (VAS score before / VAS score after)

Descriptive statistics (mean, standard deviation, minimum, and maximum) will be computed for demographic, clinical, and outcome variables.
VAS scores for relaxation and happiness, as well as physiological parameters (heart rate, HRV, skin conductance, respiration), will be compared using **paired t-tests** between pre- and post-session time points.
Perceived Stress Scale (PSS) scores will also be compared between pre- and post-therapy blocks (each block consisting of 10 sessions) using a paired t-test.

To estimate the difference in effect between the VR treatment and standard relaxation, a **mixed model multilevel regression analysis** will be used. The model will include:

- Time (before vs after)
- Treatment (VR vs standard)
- Group (1 vs 2)
- Interaction term: Time × Treatment
  (with random intercept for "participant")

The **interaction between time and treatment** is the primary parameter of interest.

Finally, **carry-over effects** will be examined by comparing VAS scores and physiological parameters between session 1, session 5, and session 10 using paired t-tests (S1 vs S5 and S5 vs S10).

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17. Final Clinical Investigation Report

Within one year after the final completion of the clinical investigation, the sponsor will prepare a comprehensive final report.
In case of early termination, the report will be submitted within 3 months after LPLV (Last Patient Last Visit).
The report will include a critical evaluation of all collected data and will also address any negative findings.

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18. Publication Policy

This study will be registered in a public clinical trial registry prior to the inclusion of the first subject. The study results will also be submitted to this public registry.

19. Indemnity insurance

During their participation in the study the patients will be insured as defined by legal requirements. An insurance with no fault responsibility has been foreseen for the Belgian participants by the sponsor in accordance with the Belgian law of 22 december 2020 concerning medical devices.

20. Authorization of the clinical investigation

This study must obtain approval from the IEC prior to the start of the study. Any additional requirements imposed by the IEC shall be followed. Substantial protocol amendments will be notified to the IEC during the course of the study according to the requirements and within the timelines as defined by the national law.

21. Protocol compliance

Prospective, planned deviations or waivers to the CIP are not allowed. Under emergency circumstances, deviations from the CIP to protect the rights, safety or well-being of human subjects may proceed without prior approval of the sponsor and the IEC. Such deviations shall be documented and reported to the sponsor by email (kurt.audenaert@ugent.be and hiruz.ctu@uzgent.be) and the IEC as soon as possible. Accidental protocol deviations must be adequately documented and reported in the eCRF on the protocol deviation log. In case accidental protocol deviations are considered as critical issues that significantly affect patient safety, data integrity and/or study conduct these should be reported to the sponsor immediately by email (kurt.audenaert@ugent.be and hiruz.ctu@uzgent.be). The sponsor will subsequently communicate and discuss this with the IEC.

The following items will be documented on the protocol deviation log: date of deviation, description of deviation, actions taken and classification of deviation. Deviations will be classified as minor or major. A minor protocol deviation is a deviation that does not affect the safety, rights or well-being of subjects or the quality of their data. A major protocol deviation is a deviation that affects safety, rights or well-being of subjects or quality of their data.

Any deviation that potentially interferes with and/or affects the efficiency and/or quality conduct of the study will be discussed by the monitor with the PI and will be documented on the monitoring report including a proposed plan of action for resolution if applicable.

22. Good Clinical Practice (ISO 14155)

This study will be conducted in accordance with the protocol, ISO 14155 which addresses good clinical practices and applicable national and European legislations including but not limited to the General Data Protection Regulation EU2016/679 (“GDPR”), the EU Medical Device Regulation MDR 2017/745, the Belgian royal decree of 18 May 2021 concerning clinical investigations of medical devices and the Belgian law of 22 Dec 2020 concerning medical devices.

ISO 14155 is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical investigations that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the study data are credible.

23. Subject information and informed consent

23.1. Recruitment and informed consent procedure

Prior to entry in the study, the investigator will explain to potential subjects or their legal representatives the study and the implication of participation. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. Participating subjects will be told that their records may be accessed by competent authorities and by authorized persons without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) and/or regulations. By signing the Informed Consent Form (ICF), the subjects or legally acceptable representatives are authorizing such access.

After this explanation and before entry to the study, written, dated and signed informed consent should be obtained from the subject or legally acceptable representative. The ICF should be provided in a

language sufficiently understood by the subject. Subjects must be given the opportunity to ask questions.

The subject or legally acceptable representative will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry to the study, consent should be appropriately recorded by means of either the subject's or his/her legal representative's dated signature or the signature of an independent witness who certifies the subject's consent in writing. After having obtained the consent, a copy of the ICF must be given to the subject.
Subjects who are unable to comprehend the information provided can only be enrolled after consent of a legally acceptable representative.

The participant or the participant's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participation in the study.

23.2. Compensation for study participants

Er wordt geen vergoeding gegeven aan de deelnemers. Het voordeel voor de deelnemers is dat zij gratis 20 relaxatiesessies aangeboden krijgen door deel te nemen aan de studie.

24. Data Handling

24.1. Data collection and processing

Data collection and processing will be done in full compliance with the European Regulation 2016/679 of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (GDPR).

24.2. Case Report Form (CRF)

The source documents are to be completed at the time of the subject's visit. The eCRFs are to be completed within reasonable time after the subject's visit. Only the data required by the protocol are captured in the eCRF. For this study both an electronic data capture system (eCRF) and a paper CRF will be used. REDCap is provided and maintained by Vanderbilt University; a license for use was granted to the Health, Innovation and Research Institute (HIRUZ). REDCap is a web-based system.

The study site staff is responsible for data entry in REDCap. For each subject enrolled the eCRF will be signed by the principal investigator or co-investigator. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the eCRF. CRF entries and corrections will only be performed by study site staff, authorized by the investigator and in accordance with ISO 14155.

The entries will be checked by trained personnel and any errors or inconsistencies will be changed immediately.

The Principal investigator must verify that all data entries in the eCRFs are accurate and correct. If certain information is Not Done, Not Available or Not Applicable, "N.D." or "N.AV." or "N.AP", should be entered in the appropriate space.

Saskia Roggeman (affiliated with the Psychiatric Center Sint-Jan Baptist and Ghent University) will conduct the study at Sint-Jan Baptist. All questionnaires and VAS scores will be collected on paper. Measurements obtained via the Embrace Plus device will be stored on a secure server of the manufacturer (Empatica), with access to the raw data restricted to the investigator only.

The data will be entered into **REDCap**, and subsequently also stored on a designated location on the PC Sint-Jan Baptist server, accessible only to the study investigators. Data monitoring and verification will be carried out by the investigator, Saskia Roggeman. **Pseudonymisation codes** will be accessible only to the researchers of the Sint-Jan Baptist Hospital.

24.3. Data directly collected in the CRF (no source available)

The questionnaires will be administered on paper. The physiological data from the Embrace Plus device will be stored in a cloud environment that is accessible only to the investigator, Saskia Roggeman.

24.4. Access to source data / documents

The investigator will permit audits, IEC review, and regulatory inspection(s), providing direct access to source data/documents.

24.5. Archiving

The investigator and sponsor specific essential documents will be retained for at least 10 years. At that moment, it will be judged whether it is necessary to retain them for a longer period, according to applicable regulatory or other requirement(s).

25. Quality assurance and periodic monitoring

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be classified into two different categories: investigator's file, and subject clinical source documents.

The investigator's file will contain the documents as per EUROPENAN Standard of EN ISO 14155 (incl. GCP) and local regulations.

Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, will verify that the clinical investigation is conducted and data are generated, documented and reported in compliance with the protocol, ISO 14155 and the applicable regulatory requirements. The frequency, extent and nature of the monitoring will depend on the risk assessment of the study. The monitor will be working according to SOPs and will provide a monitoring report after each visit for the sponsor and a follow-up letter to the investigator. Depending on the quality of the data, additional monitoring visits will be necessary according to the sponsor’s discretion.