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Virtual Reality and Sound Intervention under Chemotherapy (ViSu): study protocol for a three-arm randomized-controlled trial

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Abstract

Introduction: Patients undergoing chemotherapy often experience side effects during treatment, including psychological distress and symptoms of anxiety and depression. Interventions during chemotherapy that divert attention from potentially aversive environmental factors have been demonstrated to have a beneficial impact on these symptoms. Virtual reality (VR) offers the potential to visually and audibly disengage from the surrounding environment and can create an alternative sense of presence. This could facilitate the implementation of active guided interventions that may prove more effective than receptive interventions, such as listening to music. The present ViSu study examines the feasibility, acceptance and effectiveness of a VR intervention and a music intervention during chemotherapy.

Methods: The single center three-arm, randomized-controlled trial investigates the efficacy of a VR mindfulness intervention and a music intervention in cancer patients undergoing chemotherapy at the University Hospital Düsseldorf, Germany. Patients were randomly assigned to receive either (1) the VR mindfulness intervention, (2) the receptive music intervention, or (3) the standard care (control group) in two consecutive chemotherapy sessions. A comprehensive psychological assessment and self-ratings using visual analog scales will be conducted with situational anxiety as the primary outcome measure. Additionally, secondary measures will be employed to assess cancer-related anxiety, self-efficacy, and chemotherapy-related side effects. Furthermore, salivary cortisol, heart rate, and blood pressure will be recorded. At the end of the study, an evaluation questionnaire will be completed. It is planned to enroll 82 patients.

Ethics and dissemination: The study has been approved by the ethics committee of the medical faculty of the Heinrich-Heine-University Düsseldorf (2022-1880). Written informed consent is obtained from the patients prior to participation. The results will be published in international scientific, peer-reviewed journals. Conference presentations are also planned.

Keywords: Virtual reality, mindfulness, music, psycho-oncology, anxiety, chemotherapy

Trail Registration: German Clinical Trials Register (DRKS) – ID: DRKS00029738, registered August 16th, 2022

Protocol version #1, September 22, 2024

Strengths and limitations of this study

- Feasibility of an active VR mindfulness intervention during the application of chemotherapy.
- Randomized controlled trial that compares the effectiveness of two interventions (VR and music) to a control group.
- Both interventions are easy to applicate and therefore suitable for outpatient treatment.
- In addition to psychological assessments and self-ratings, saliva samples used to measure cortisol levels, heart rate and blood pressure are evaluated and provide a more objective method.

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Competing interests statement

None declared.

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Introduction

Although chemotherapy is an essential part of treatment and a potential condition for healing, many patients in oncology experience chemotherapy distressing and time consuming, taking place in an unpleasant surrounding. Chemotherapy cycles are frequently accompanied by adverse side effects such as nausea, fatigue or symptoms of anxiety and depression [1]. Negative psychological side effects can have an additional negative impact on health-related quality of life [2, 3] or even reduced treatment adherence [4, 5], which is associated with a poorer overall prognosis [6, 7].

Psychological interventions that are already offered during chemotherapy sessions have the potential to alleviate distress and mitigate side effects, thereby helping patients cope with the unpleasant environment. These interventions can be broadly categorized into receptive and active types. Receptive interventions, such as listening to music, have been shown to reduce anxiety, depressive symptoms and distress during chemotherapy [8, 9]. Active interventions like progressive muscle relaxation [10] guided imagery [11] or mindfulness-based interventions [12] showed reducing effects on several psychological outcomes like anxiety, depression and distress. Additionally, active interventions may enhance patients' self-efficacy during their whole cancer treatment [13]. However, these interventions often require some instructions and guidance from a third person, an active participating role from the patient, and some level of training. The unpleasant context during chemotherapy offers various sources of distraction that may hinder patients in carrying out the intervention successfully.

Virtual reality (VR) offers a novel approach to supportive psycho-oncological interventions and could be beneficial as the feelings of presence and immersion could help patients to focus on the task. VR has been perceived as helpful during mindfulness training [14], and research suggests that VR-based mindfulness training may be superior to traditional mindfulness practices in reducing anxiety, stress, depressive symptoms, mood disturbances, and sleep problems [15] For oncology patients undergoing chemotherapy, VR has been used primarily as a passive distraction intervention, proving more effective than other commonly used interventions, such as music [16]. Furthermore, an observational study has reported that VR-based active interventions incorporating mindfulness practice can have positive effects on psychological side effects [17].

A recent systematic review and meta-analysis of VR use in cancer patients receiving chemotherapy reported 12 RCTs [18], all of them are using VR as a passive distraction intervention. However, there is limited evidence regarding the potential superiority of immersive, active VR interventions over passive ones during chemotherapy. Additionally, little is known about the factors that influence the feasibility of implementing such active or passive VR-based interventions in a clinical setting, which is particularly important given the technical challenges associated with VR setup compared to more routine interventions like music therapy.

Therefore, the ViSu study aimed to investigate the effect of an active VR-based mindfulness intervention compared to a receptive music intervention and a control group on both subjective and objective psychological outcomes during two consecutive chemotherapy sessions. Given that active VR-based interventions may offer advantages over receptive music interventions due to the enhanced immersion and presence they provide, which may increase patient engagement, we hypothesize that the effects will be more pronounced in the VR group compared to the music group. Nonetheless, both interventions are expected to be superior to the control group, that receives only standard care. Additionally, this study is among the first to explore factors related to the feasibility of implementing VR-based and music interventions in an outpatient chemotherapy setting.

Methods

Study Design

The ViSu study is a single center, three-arm, non-blinded, randomized, controlled trial designed to investigate the efficacy of a VR mindfulness intervention and a music intervention in cancer patients undergoing chemotherapy at the Interdisciplinary Outpatient Chemotherapy Center (IAC), University Hospital Düsseldorf, Germany. Participants will be randomly assigned to one of three study arms: (1) an intervention group receiving a VR-based mindfulness task, (2) an intervention group listening to music, and (3) a control group with no intervention. The study protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting guidelines [19]. The checklist can be found in Appendix A.

The primary objective is to compare the effectiveness of the two interventions against a control group in reducing patients' anxiety during two consecutive chemotherapy sessions. To evaluate whether the active VR intervention leads to any training or habituation effects, each participant will take part in two intervention sessions. Data collection will be conducted at both time points. Due to individual differences in chemotherapy schedules, the exact duration of chemotherapy treatment may differ between participants.

Sample

Patients are either referred to the study by their attending physician during their consultation hours, recruited by the study team at the IAC, or contacted by the study team independently. For patients recruited by the study team or who self-refer, the study team will obtain the consent of the attending physician. All patients are pre-screened for eligibility by their attending physician. The eligibility criteria for the study include a) the general physical condition of the patient, b) the presence of a gynecological (C51-55), senological (C50), hematological (C81-85, C91-95) or gastrointestinal cancer (C15ff, C16ff, C18ff, C20ff, C22, C23, C25ff) diagnosis according to ICD-10, c) a chemotherapy duration of at least 60 minutes, d) the presence of at least five remaining consecutive chemotherapy sessions, e) sufficient knowledge of the German language, and f) at least moderate anxiety as measured by the Generalized Anxiety Disorder-7 questionnaire [20, 21].

Patients are not eligible for the study if they have a) severe visual and/or hearing impairment, b) brain metastases, c) pre-existing neurological and/or psychiatric conditions affecting the vestibular system, impair balance, or alter visual perception, d) epilepsy, e) claustrophobia, f) severe side effects after the first chemotherapy session, or g) wearing cooling gloves or a cooling cap during the chemotherapy sessions.

Patients can withdraw from the study at any time. Participation will be terminated if chemotherapy sessions have to be interrupted due to the patient's physical weakness or if chemotherapy is interrupted due to technical malfunctions. Participation will also be terminated if acute side effects or allergic reactions occur during chemotherapy, or if the oncological disease progresses negatively during ongoing therapy.

Interventions

Virtual reality mindfulness intervention

The VR mindfulness intervention is delivered via a VR headset (Quest 2) [22] and circumaural headphones (Bose Corporation) [23] and was developed as a self-management intervention in the course of another project of our study group [24]. Patients find themselves in a virtual natural environment, sitting on a park bench surrounded by flowers and trees overlooking a mountain lake (see Figure 1). At the outset, patients are afforded a maximum of five minutes to acclimate themselves to the environment and then start the exercise independently. Under the guidance of a male narrator, patients are guided through an environment meditation consisting of a general opening sequence that suggests a brief recap of the day and includes elements of breathing meditation. In the main body of the meditation, the narrator directs the patient's attention to different areas of the environment and asks the patient to describe them as accurately and as nonjudgmentally as possible. Special emphasis is placed on the description of colors and shapes.

The final sequence contains short reflection questions on the content of the exercise. The exercise takes 15 minutes to complete.

The Quest 2 is a standalone VR system consisting of a mobile head-mounted display (HMD) with built-in stereo speakers and inside-out optical head motion tracking to provide 6 DoF positional tracking. The HMD is used with the flexible headstrap and weighs 503g. Interaction with the VR environment can be performed using two separate hand controllers or the integrated hand tracking. Patients were instructed to use the hand controllers. The Oculus Quest has two binocular OLED displays with a resolution of 1832 x 1920pixels per eye, a refresh rate of 72 Hz and a field of view of ~100°. The VR intervention was created using Unity3D. Circumaural headphones are connected to the VR headset to avoid noise disturbance to other patients in the room.

The Quest 2 system setup involved the study team starting up the VR headset. This required configuring the Guardian to the patient's room and then selecting the study application from the main menu. The VR headset was then handed to the patient and adjusted to the shape of the patient's head.

Music intervention

The receptive music intervention is delivered via an mp3-player (Apple iPod) [25] and circumaural headphones (Bose Corporation) [23]. Prior to the first intervention, the participants can choose between four genres (classic, jazz, meditation, lounge) and will listen to this genre at both intervention time points. The playlists consist of music titles chosen according to the recommendations of Nilsson [26] and used in a previous project of our group [27]. They can be accessed in Appendix B. All tracks are instrumental, vary between 60 and 80 beats per minute. The music intervention lasts 15-20 minutes. Table 1 presents a comparative overview of the VR and the music intervention.

Table 1

Comparative overview of the VR and the music intervention

Intervention design feature	VR intervention	Music intervention
Intervention type	Active	Receptive
Delivery format	Immersive VR environment via head mounted display with headphones	Music via mp3-player and headphones
Technology	Quest 2 (Meta), Bose headphones	Apple iPod, Bose headphones
Intervention content	Mindfulness exercise, environment meditation in a natural environment with nature sounds	Listening to instrumental music (60 – 80 bpm)
Degree of user choice	Predefined meditation without choice options	Choice of four different music genres: classic, jazz, meditation or lounge
Type of guidance	Verbal guidance by a male narrator (directing attention to various aspects of the environment)	No guidance

Duration	15 minutes (+ up to 5 minutes for acclimatization)	15- 20 minutes

Note: VR – Virtual Reality, bpm – beats per minute

Measures

Patients complete four different types of questionnaires during their study participation at the following measurement time points: after recruitment (T0; baseline), before the intervention (pre-intervention), after the intervention (post-intervention), and at the end of the study (evaluation). Additionally, physiological parameters (heart rate and blood pressure) are measured during the intervention phase. The pre-intervention, during-intervention, and post-intervention measurements are administered twice over two consecutive chemotherapy sessions (T1 and T2). Table 2 outlines the measures employed and the corresponding time points at which they are collected. Furthermore, saliva samples are collected both before and 25 minutes after the intervention, while heart rate and blood pressure are recorded at 5-minute intervals during the intervention. Below is a detailed presentation of all measures used in the study.

Table 2

Overview of measures used for the study and the measurement time points.

Measure	Baseline	Pre-intervention	During intervention	Post-intervention	Evaluation
Demographic data	X				
Cancer-related data	X				
VAS-Social support	X				
Previous experiences with mindfulness and music for relaxation	X				
ASKU	X				
PHQ-4	X	X			
STAI-Trait	X				
Salivary cortisol		X		X	
STAI-State		X		X	
PA-F-KF		X		X	
MIDOS-2		X		X	
VAS-Anxiety		X		X	
VAS-Relaxation		X		X	
Heart rate			X		
Blood pressure			X		
VAS-Tolerability of chemotherapy				X	
VAS-Perceived duration of chemotherapy				X	
PSSUQ					X

VR-specific evaluation (self-developed)	X
Music-specific evaluation (self-developed)	X

Note: VAS – visual analogue scale; ASKU – Short Scale for Measuring General Self-efficacy Beliefs; PHQ-4 – Patient-Health-Questionnaire-4; STAI – State-Trait-Anxiety-Inventory; PA-F-KF – Fear of Progression Questionnaire Short Form; MIDOS – Minimal Documentation System; PSSUQ – Post-study System Usability Questionnaire; VR – Virtual Reality

Baseline measures

Screening

In order to determine the reasons for a lack of interest in participating in the study, even though the patients addressed in the IAC fulfill the inclusion criteria, a screening form will be distributed. This screening form has been developed by the first authors on the basis of verbal feedback received during recruitment conversations on site. On this form, patients can tick items such as: "Concern about too much additional effort during therapy", "No need, as chemotherapy is not perceived as unpleasant or stressful", or "No interest in the research question or in the VR technology". A refusal to provide further feedback is also possible, as well as a statement of unstated reasons. Completion of the screening questionnaire is voluntary and anonymous. The screening form can be viewed in Appendix C.

Generalized Anxiety Disorder-7 Questionnaire (GAD-7)

Patients are screened for generalized anxiety using the German version of the Generalized Anxiety Disorder-7 Questionnaire [21], translated by Löwe et al. [28]. It measures how much subjects have been bothered by the following problems over the past two weeks indicated on a 4-point Likert scale (0 = *not at all*, 1 = *for several days*, 2 = *more than half the days*, 3 = *nearly every day*): feeling nervous, anxious, or on edge; not being able to stop or control worrying; worrying too much about different things; trouble relaxing; being so restless that it is hard to sit still; becoming easily annoyed or irritable; feeling afraid, as if something awful might happen. Participants can score a value between 0 and 21 with higher values indicating a higher degree of generalized anxiety symptoms. A recent study confirmed the reliability and validity of the GAD-7 in a German population sample with overall good internal consistency of $\alpha = .85$ [20]. Patients are screened for a score of at least 5 indicating a mild generalized anxiety [21].

Demographic and cancer-related data

Patients are asked to indicate their gender (female, male, divers), age, highest educational level (based on the German educational system), and family status (unwed, in a partnership, married/ civil partnership, divorced/ civil partnership annulled, widowed/ registered partner deceased).

Further, cancer-related data is assessed based on the Basic Documentation for Psycho-Oncology [29, 30]. Patients are asked to report their main cancer diagnosis, whether it is the first diagnosis and whether there has been a previous cycle of chemotherapy, what treatments they have received in the last 2 months, whether they have previously received psychiatric treatment or psychotherapy, and whether they are currently taking any psychopharmacological medication.

Short Scale for Measuring General Self-efficacy Beliefs (ASKU)

The Short Scale for Measuring General Self-efficacy Beliefs [31] is a self-report based questionnaire assessing the participant's perceived self-efficacy using three items on a 5-point Likert scale (1 = *never or very rarely true*; 5 = *very often or always true*). The ASKU reveals a reliability of between $\omega = .81$ and $\omega = .86$. The factorial validity can be described as sufficient with factor loadings of .77 and higher and the model fit is validated. The construct validity of the questionnaire was also validated by comparing the items to questionnaires assessing similar constructs [31].

The State-Trait-Anxiety-Inventory (STAI-Trait)

The short trait-version of the STAI [32] assesses trait-anxiety as a relatively stable personality characteristic and consists of 10 items that are rated on a 8-point Likert-Scale (1 = *not at all*; 8 = *completely*). Three of the 10 items have to be inverted prior to calculation. Total scores can range between 10 and 80 with higher scores indicating higher trait-anxiety. The trait-version reveals also excellent internal consistency ranging between α = .88 and α = .94 and the criterion validity was confirmed by correlating the items to other measures assessing similar constructs [33].

Primary outcome measure

The State-Trait-Anxiety-Inventory (STAI-State)

The State-Trait-Anxiety-Inventory (STAI) [32] is a self-report questionnaire that can assess both situational state-anxiety and stable trait-anxiety. The short version with 10 items was used to assess the situational state-anxiety as the primary outcome [32]. The response for each of the 10 items is based on an 8-point Likert scale (1 = *not at all*; 8 = *completely*). Four items need to be inversed before calculating the total score. The STAI-state score ranges between 10 and 80. Higher values indicate higher state-anxiety. The STAI reveals an excellent internal consistency of α = .90 [32].

Secondary outcome measures

Visual Analogue Scales (VAS)

Visual analogue scales (VAS) are used to assess anxiety ('How anxious do you feel in this moment?' from 'not anxious at all' to 'maximally anxious'), relaxation ('How do you feel at this moment?' from 'maximally tense' to 'maximally relaxed'), social support ('How much do you feel supported by your social network in the moment?' from 'not at all supported' to 'maximally supported'), tolerance of the chemotherapy session ('How bearable did you perceive today's chemotherapy treatment?' from 'minimally tolerable' to 'maximally tolerable'), and the perceived duration of the chemotherapy session ('How quickly do you feel today's chemotherapy session has gone so far?' from 'not quick at all' to 'maximally quick'). Patients are asked to rate their answer by marking a point on a 10 cm long line from 0 to 100, with 0 indicating total disagreement and 100 indicating total agreement. Visual analogue scales are a quick and economical method for the assessment of different subjective states and symptoms [34, 35].

Patient-Health-Questionnaire-4 (PHQ-4)

The German version of the Patient-Health-Questionnaire-4 [28] assesses anxiety and depression using four items on a 4-point Likert scale (0 = *not at all*; 3 = *almost every day*). The values are added for the total score, higher values indicating a greater extend of anxiety and depression. The scale showed good internal consistency with α > .80. A factor analysis revealed good fit with 84% of total variance explained. In a recent study, the internal consistency of the instrument for the German population could be again confirmed as good (ω = .85) [36].

Fear of Progression Questionnaire Short Form (PA-F-KF)

The Fear of Progression Questionnaire Short Form [37] consists of 12 items that are answered on a 5-point Likert scale (1 = *never*; 5 = *very often*). The questionnaire assesses patient's fear of progression on five dimensions (affective reaction, partnership/family, occupation, loss of autonomy) and shows overall good internal consistency (α = .87) [37]. The construct validity of the items was confirmed by correlating the items to other measures assessing similar constructs (HADS, PCL-C, SF-8, LAP-R). A factor analysis revealed a one-dimensional structure, explaining 42% of the total variance [37]. The psychometric properties were also confirmed in more recent studies. For example, a study by Hahn [38] found an internal consistency of α = .88 for the PA-F-KF.

Minimal Documentation System (MIDOS-2)

The Minimal Documentation System (MIDOS-2) [39] is a self-report questionnaire assessing participant's symptom-related afflictions due to chemotherapy-associated side effects on a 4-point Likert scale (0 = *none*; 3 = *major afflictions*). In total, there are 13 items. Ten items are measuring the side effects pain, nausea, regurgitation, shortness of breath, constipation, weakness, lack of appetite, fatigue, depression and anxiety. Two more items leave open spaces for naming other afflictions and one more item assesses how the participant is feeling that day, ranging from 0 (*very bad*) to 4 (*very good*). The sum score of each item describes the extend of complaints for each participant. The questionnaire reveals good psychometric properties, with internal consistencies varying between α = .67 and .73 and the test-retest variability varying between r = .69 and r = .57 [39]. The psychometric properties were also confirmed for patient groups in non-palliative care [40].

Heart rate and blood pressure

Heart rate and blood pressure is measured from the beginning to the end of the intervention in 5-minute intervals in beats per minute (bpm) using a pulse oximeter.

Saliva cortisol

Salivary samples are assessed to measure levels of cortisol in nmol/l. For this purpose, each participant insalivates a cotton swab for at least 30 seconds before the beginning of the intervention and 25 minutes after the end of the intervention. All saliva samples are stored in dark at -20 degrees Celsius. Analyses will be carried out by Dresden LabService GmbH, Technical University of Dresden, Germany, using chemiluminescence immunoassay.

Evaluation

The evaluation was conducted for all three study arms, with tailored formats for each intervention group as well as the control group. For the VR group, seven items from the Post-Study System Usability Questionnaire (PSSUQ) [41] (items 1, 6, 11, 16–19) were used. The full questionnaire consists of 21 items and was translated into German during a previous study conducted by our group [42]. The selected items have been slightly adapted to better fit the specific VR application used in the study. Responses are given on a 7-point Likert scale (1 = *strongly disagree*, 7 = *strongly agree*), with the overall score reflecting the perceived usability of the VR system by the patients.

Additionally, patients were asked to rate several self-developed items that were tailored to the specific intervention (VR or music). These items assess whether the intervention was pleasing, relaxing, boring, or annoying, whether it helped to alleviate any unpleasant feelings, induce calmness, and create a pleasant atmosphere during the chemotherapy session. Patients also rated whether they liked the intervention, whether they would choose to use it again in a future chemotherapy session, whether they could focus more on the intervention than on their own thoughts, and whether they were already familiar with the intervention. All these items are also rated on a 7-point Likert scale (1 = *strongly disagree*, 7 = *strongly agree*).

Lastly, all groups were asked to indicate which type of intervention (VR, music, or none) they would prefer to use during a future chemotherapy session, rated on a 7-point Likert scale (1 = *not at all,* 7 = *very much*). The evaluation questionnaire also includes two additional free-text fields titled "Suggestions for Enhancing the Utilization of VR/Music" and "Other Comments." The complete evaluation questionnaire is available for review in Appendix D

Recruitment and participant timeline

The study team initiates contact with patients during their outpatient visit to the IAC and inquires about their interest in participating in the study. Subsequently, the treating physicians are consulted to confirm the patients' eligibility for the study, and their approval is sought once eligibility is confirmed. Patients are then contacted again by the study team during their next chemotherapy session. All patients provide written informed consent prior to their participation in the study. The patient information and consent form can be found in Appendix E.

The study team screens for general anxiety symptoms using the Generalized Anxiety Disorder-7 Questionnaire (GAD-7) [20, 21]. To ensure that participants are experiencing a level of anxiety significant enough to benefit from the interventions and demonstrate measurable changes in the primary outcome variable, only patients with at least moderate anxiety (defined as a score ≥5) are included in the study. Patients are randomly assigned to one of three intervention arms using computer-generated random numbers; however, they remain blinded to their group allocation until the first intervention time point (T1).

After recruitment, participants complete the first questionnaire for baseline assessment (T0). The intervention begins during the subsequent chemotherapy session at the IAC (T1). At this point, patients are informed of their study allocation and receive the pre-intervention questionnaire. Following the completion of the questionnaires, and after the flushing and premedication processes as part of the chemotherapy session, patients provide the first saliva sample by insalivating a cotton swab. The study team then assists patients in initiating the intervention.

Patients in intervention group 1 wear a VR headset and headphones and begin the mindfulness exercise. Patients in intervention group 2 put on headphones and listen to music. Patients in the control group (3) receive no additional treatment. A member of the study team remains with the patient, collecting data on heart rate and blood pressure at 5-minute intervals. After approximately 15-20 minutes, the intervention concludes. Patients then complete the post-intervention questionnaire, and a second saliva sample is collected after 25 minutes. This procedure is repeated during the subsequent chemotherapy session (T2). Finally, patients in all groups receive a questionnaire specifically evaluating the intervention immediately after the second measurement time point. Participants in groups 2 and 3 are given the opportunity to try the VR intervention independently of data collection.

Sample Size

Based on previous literature, we estimate an effect size of 0.25. The G*Power 3.1.9.7 software [43] was employed to determine the requisite sample size. Assuming that the probability of error does not exceed α=.05 and that the power (1-β) is at least 0.95, an analysis of variance with three groups and two time points with $N = 66$ subjects can demonstrate an effect size of 0.25. Based on previous research projects, we calculate a drop-out rate of 20%, which increases the total sample size to $N = 82$.

Risk to Patients

Possible risks that can arise, particularly during the VR intervention, are cybersickness [44] and increased stress levels or anxiety due to the complex technical set-up and instructions. In addition, the sensory isolation from the environment can lead to a feeling of loss of control. To counteract this, it was ensured that at least one person from the study team was always present with the patients during the intervention. Patients were able to contact the study team directly if they had any questions, problems or felt unwell. In addition, care was taken to ensure that patients were shielded from disturbances as much as possible. During the data collection phase, study personnel will be present to monitor and record any spontaneously occurring adverse events; if such events occur, they will be discussed with the treating physician and reviewed during the weekly team meetings.

Data Monitoring and Management

A randomization file will be used to allocate a participant code to the intervention arms. A recruitment file is used to allocate the participant code to all included patients and, further, contains patients' diagnoses, medical clearance and information about the recruitment process (treating physicians' approval for study participation, checklist for how many attempts were needed to meet the patient in the IAC, date of informed consent). A data file contains pseudonymized survey data of patients to each measurement time point. Another file will be used to anonymously assess drop-outs, screening failures and reasons for non-participation or lack of interest. The data will be entered by the study team accountable for implementation of the study

and will be double checked by another team member. Supervision by the study team during chemotherapy sessions ensures the questionnaires are fully completed by participants. Data records will be kept separately from the consent forms. Data records of patients who did not meet the inclusion criteria (screening failures) will be disposed of in accordance with data protection regulations. After collection, salivary cortisol samples will be temporarily stored in a freezer (-20 degree Celsius) and sent to a laboratory (Dresden LabService GmbH, Technical University of Dresden, Germany). Questionnaires and cortisol levels derived from saliva samples will be stored as combined research data for at least 10 years (in accordance with the principles of Good Clinical Practice). Access to the anonymized final trial dataset will be granted upon request to the study team; the intended use of the data must be disclosed, after which the appropriate dataset will be provided.

Patients will receive standard medical care during the whole participation. No adverse side effects are expected due to the interventions and participating patients do not face higher risks compared to patients who are not participating in the current study. As a member of the study team will supervise each session, participants can terminate the intervention at any time. Participants can report any side effects to the study team and use the evaluation questionnaires for thorough feedback. Therefore, study monitoring is not needed.

Randomization, Blinding, and Treatment Allocation

Randomization is conducted using random numbers. Using a computer program (Microsoft Excel, Microsoft Corporation), a team member who does not participate in recruiting patients generates an excel sheet with numbers representing intervention groups. In this sheet, the numbers are masked until a new patient is enrolled, which assures that members of the study team accountable for participant recruitment are blinded until patients' consent. Patients are blinded about their study arm allocation until the first intervention time-point (T1). There is no further blinding of the study team.

Statistical Analysis

All characteristics collected in the study are described in detail using descriptive methods. Qualitative characteristics are indicated by absolute and relative frequencies. Quantitative characteristics are described using mean values, standard deviation, median, minimum and maximum. Parametric and non-parametric analysis methods are used to evaluate the primary and secondary target variables.

The primary target variable of situational anxiety is analyzed using separate 3x2 mixed factorial ANOVAs for each of the two chemotherapy sessions, with the between-subject factor "intervention" (virtual reality vs. music vs. control) and the within-subject factors "time" (before vs. after intervention). A probability of error of α=.05 is set. The secondary outcome criteria are analyzed exploratively. There is no adjustment of the probability of error. The statistical analysis is carried out with the help of standard statistical software (e.g., R, SAS, SPSS).

The feasibility of the intervention will also be evaluated. This will be done through a descriptive analysis of the screening data and the evaluation questionnaire. In this context, the participants' comments in the free text fields of the evaluation questionnaire will be analyzed qualitatively.

Protocol Amendments

Protocol amendments were requested initially on November 4th, 2022 to extend the sample due to a lack of subjects matching the inclusion criteria. Before the amendment, participants consisted solely of patients with a gynecological or senological diagnosis. After the amendment, participants with gastrointestinal and hematological diagnoses were also included. To improve the homogeneity of the sample, the GAD-7 with its cut-off criterion of a value ≥ 5 was introduced as a screening tool. These protocol amendments were granted November 19, 2022.

A second request to amend protocol was issued on August 3rd, 2023 to introduce a self-constructed screening questionnaire for further inquiry of reasons why patients may be

disinterested in participation in the study. This protocol amendment was granted on August 9th, 2023.

Ethics and dissemination

The ethics committee of the medical faculty of Heinrich-Heine-University Düsseldorf has been obtained (2022-1880). Divergences or modifications of the study protocol will be documented and relevant cases will be reported to the ethics committee. For all processed data adherence to data protection regulations is warranted. Written informed consent is obtained from patients by the study team and patients are informed that they can withdraw their consent without explanation at any time without facing any consequences. Further, patients are informed that all stored personal data can be deleted upon demand at any point. All personal identifiers will be pseudonymized. The final data set can be assessed only by the study team. After the end of the study, the ethics committee will be informed within 90 days.

Findings of the trial will be reported by publishing in international scientific, peer-reviewed journals. Given several outcome parameters, several publications are planned. Further, presentations at conferences are planned. Until publication, the study team commits to full disclosure of the trial results.

Patient and Public Involvement

Patients and the public were not involved in the design, conduct, or reporting of this study. The research questions, study design, outcome measures, recruitment strategies, and dissemination plans were developed by the research team without direct input from patients, carers, or members of the public. This decision was made based on the specific nature and feasibility constraints of the study.

References

1. Wagland R, Richardson A, Armes J, Hankins M, Lennan E, Griffiths P. Treatment-related problems experienced by cancer patients undergoing chemotherapy: a scoping review. Eur J Cancer Care (Engl). 2014;24(5):605-17. doi:10.1111/ecc.12246.
2. Redeker NS, Lev EL, Ruggiero J. Insomnia, fatigue, anxiety, depression, and quality of life of cancer patients undergoing chemotherapy. Sch Inq Nurs Pract. 2000;14(4):275-290.
3. So WK, Marsh G, Ling WM, Leung FY, Lo JC, Yeung M, et al. The symptom cluster of fatigue, pain, anxiety, and depression and the effect on the quality of life of women receiving treatment for breast cancer: a multicenter study. Oncol Nurs Forum. 2009;36(4). doi:10.1188/09.ONF.E205-E14.
4. Puts MT, Tu HA, Tourangeau A, Fitch M, Springall E, Alibhai SMH. Factors influencing adherence to cancer treatment in older adults with cancer: a systematic review. Ann Oncol. 2014;25(3):564-77. doi:10.1093/annonc/mdt433.
5. Theofilou P, Panagiotaki H. A literature review to investigate the link between psychosocial characteristics and treatment adherence in cancer patients. Oncol Rev. 2012;6(1). doi:10.4081/oncol.2012.e5.
6. Arrieta O, Angulo LP, Núñez-Valencia C, Dorantes-Gallareta Y, Macedo EO, Martínez-López D, et al. Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. Ann Surg Oncol. 2012;20(6):1941-48. doi:10.1245/s10434-012-2793-5.
7. Fukushima T, Suzuki K, Tanaka T, Isobe K, Kubo A, Nakagawa Y, et al. Global quality of life and mortality risk in patients with cancer: a systematic review and meta-analysis. Qual Life Res. 2024;33(5):1391-407. doi:10.1007/s11136-024-03691-3.
8. Nguyen KT, Xiao J, Chan DN, Zhang M, Chan CW. Effects of music intervention on anxiety, depression, and quality of life of cancer patients receiving chemotherapy: a systematic review and meta-analysis. Support Care Cancer. 2022;30(7):5615-26. doi:10.1007/s00520-022-06881-2.
9. Trigueros-Murillo A, Martinez-Calderon J, Casuso-Holgado MJ, González-García P, Heredia-Rizo AM. Effects of music-based interventions on cancer-related pain, fatigue, and distress: an overview of systematic reviews. Support Care Cancer. 2023;31(8):5835-44. doi:10.1007/s00520-023-07938-6.
10. Pelekasis P, Matsouka I, Koumarianou A. Progressive muscle relaxation as a supportive intervention for cancer patients undergoing chemotherapy: a systematic review. Palliat Support Care. 2016;15(4):465-73. doi:10.1017/S1478951516000870.
11. Roffe L, Schmidt K, Ernst E. A systematic review of guided imagery as an adjuvant cancer therapy. Psychooncology. 2005;14(8):607-17. doi:10.1002/pon.889.
12. Cillessen L, Johannsen M, Speckens AE, Zachariae R. Mindfulness-based interventions for psychological and physical health outcomes in cancer patients and survivors: a systematic review and meta-analysis of randomized controlled trials. Psychooncology. 2019;28(12):2257-69. doi:10.1002/pon.5214.
13. Merluzzi TV, Pustejovsky JE, Philip EJ, Sohl SJ, Berendsen M, Salsman JM. Interventions to enhance self-efficacy in cancer patients: a meta-analysis of randomized controlled trials. Psychooncology. 2019;28(9):1781-90. doi:10.1002/pon.5148.
14. Seabrook E, Kelly R, Foley F, Theiler S, Thomas N, Wadley G, et al. Understanding how virtual reality can support mindfulness practice: mixed methods study. J Med Internet Res. 2020;22(3). doi:10.2196/16106.
15. Ma J, Zhao D, Xu N, Yang J. The effectiveness of immersive virtual reality (VR) based mindfulness training on improvement mental-health in adults: a narrative systematic review. Explore (NY). 2023;19(3):310-18. doi:10.1016/j.explore.2022.08.001.
16. Chirico A, Maiorano P, Indovina P, Milanese C, Giordano GG, Alivernini F, et al. Virtual reality and music therapy as distraction interventions to alleviate anxiety and improve mood states in breast cancer patients during chemotherapy. J Cell Physiol. 2020;235(6):5353-62. doi:10.1002/jcp.29422.

17. Wilson K, Scorsone G. The use of virtual reality technologies to reduce anxiety and improve experience in chemotherapy patients during treatment. Front Virtual Real. 2021;2:695449. doi:10.3389/frvir.2021.695449.
18. Gautama MSN, Huang TW, Haryani H. A systematic review and meta-analysis of randomized controlled trials on the effectiveness of immersive virtual reality in cancer patients receiving chemotherapy. Eur J Oncol Nurs. 2023;67:102424. doi:10.1016/j.ejon.2023.102424.
19. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586. doi: 10.1136/bmj.e7586.
20. Hinz A, Klein AM, Brähler E, Glaesmer H, Luck T, Riedel-Heller SG, et al. Psychometric evaluation of the generalized anxiety disorder screener GAD-7, based on a large German general population sample. J Affect Disord. 2017;210:338-44. doi:10.1016/j.jad.2016.12.012.
21. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder. Arch Intern Med. 2006;166(10):1092-7. doi:10.1001/archinte.166.10.1092.
22. META. META Quest 2 [VR headset]. Menlo Park, CA: META; 2020. Available from: https://www.meta.com/quest-2/
23. Bose. Bose QuietComfort [Bluetooth headphones]. Frisco, TX: Bose Corporation; 2023. Available from: https://www.bose.com/en_us/products/headphones/quietcomfort.html
24. Hemsen B, Wittenborn A, Holsteg S, Karger A, Freitag S, Mildner P, et al. DeepVR: Konzeptuelle Grundlagen und Umsetzung eines Virtual Reality basierten Unterstützungssystems in der psychotherapeutischen Depressions-Behandlung. Mensch Comput. 2021. doi:10.1145/3473856.3474016.
25. Apple Inc. Apple iPod [Internet]. Frisco, TX: Apple Inc.; 2023. Available from: https://www.apple.com/ipod/
26. Nilsson U. The anxiety- and pain-reducing effects of music interventions: a systematic review. AORN J. 2008;87(4):780-807. doi:10.1016/j.aorn.2007.09.013.
27. Schaal NK, Brückner J, Wolf OT, Ruckhäberle E, Fehm T, Hepp P. The effects of a music intervention during port catheter placement on anxiety and stress. Sci Rep. 2021;11(1):85139. doi:10.1038/s41598-021-85139-z.
28. Löwe B, Decker O, Müller S, et al. Validation and Standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the General Population. Med Care. 2008;46(3):266-274. doi:10.1097/mlr.0b013e318160d093.
29. Herschbach P, Book K, Brandl T, Keller M, Marten-Mittag B. The Basic Documentation for Psycho-Oncology (PO-Bado) – an Expert Rating Scale for the Psychosocial Experience of Cancer Patients. Oncol Res Treat. 2008;31(11):591-596. doi:10.1159/000162287.
30. Knight L, Mussell M, Brandl T, et al. Development and psychometric evaluation of the Basic Documentation for Psycho-Oncology, a tool for standardized assessment of cancer patients. J Psychosom Res. 2008;64(4):373-381. doi:10.1016/j.jpsychores.2008.01.003.
31. Beierlein C, Kemper CJ, Kovaleva A, Rammstedt B. Kurzskala zur Erfassung allgemeiner Selbstwirksamkeitserwartungen (ASKU). Methoden Daten Anal. 2013;7(2):28. doi:10.12758/mda.2013.014.
32. Grimm J. State-Trait-Anxiety Inventory nach Spielberger: Deutsche Lang- und Kurzversion. Methodenforum der Universität Wien. MF-Working Paper. 2009;2.
33. Laux L, Glanzmann P, Schaffner P, Spielberger CD. Das State-Trait-Angstinventar. Weinheim: Beltz; 1981.
34. Heller GZ, Manuguerra M, Chow R. How to analyze the Visual Analogue Scale: Myths, truths and clinical relevance. Scand J Pain. 2016;13(1):67-75. doi:10.1016/j.sjpain.2016.06.012.

35. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. Res Nurs Health. 1990;13(4):227-236. doi:10.1002/nur.4770130405.
36. Wicke FS, Krakau L, Löwe B, Beutel ME, Brähler E. Update of the standardization of the Patient Health Questionnaire-4 (PHQ-4) in the general population. J Affect Disord. 2022;312:310-314. doi:10.1016/j.jad.2022.06.054.
37. Mehnert A, Herschbach P, Berg P, Henrich G, Koch U. Progredienzangst bei Brustkrebspatientinnen - Validierung der Kurzform des Progredienzangstfragebogens PA-F-KF/ Fear of progression in breast cancer patients – validation of the short form of the Fear of Progression Questionnaire (FoP-Q-SF). Z Psychosom Med Psychother. 2006;52(3):274-288. doi:10.13109/zptm.2006.52.3.274.
38. Hahn AJS. Prädiktoren von Progredienzangst bei Prostatakrebspatienten nach radikaler Prostatektomie: Spielen subjektive Krankheitsrepräsentationen und die Familienanamnese eine Rolle? [dissertation]. München: Technische Universität München; 2015.
39. Stiel S, Matthes ME, Bertram L, et al. Validierung der neuen Fassung des Minimalen Dokumentationssystems (MIDOS2) für Patienten in der Palliativmedizin. Schmerz. 2010;24(6):596-604. doi:10.1007/s00482-010-0972-5.
40. Plöger MM. MIDOS-Validierung des Minimalen Dokumentationssystems für Palliativpatienten-Vergleichsgruppen mit chronisch kranken und gesunden Probanden [dissertation]. Bonn: Universitäts- und Landesbibliothek Bonn; 2016.
41. Lewis JR. Psychometric Evaluation of the Post-Study System Usability Questionnaire: The PSSUQ. Proc Hum Factors Soc Annu Meet. 1992;36(16):1259-1260. doi:10.1177/154193129203601617.
42. Holsteg S, Askeridis JM, Krajewski J, et al. Virtual reality roleplays for patients with depression: A user experience evaluation. Internet Interv. 2024;35:100713. Doi: 10.1016/j.invent.2024.100713.
43. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39(2):175-191. doi:10.3758/bf03193146.
44. Behr KM, Nosper A, Klimmt C, Hartmann T. Some Practical Considerations of Ethical Issues in VR Research. Presence (Camb Mass). 2005;14(6):668-676. doi:10.1162/105474605775196535.

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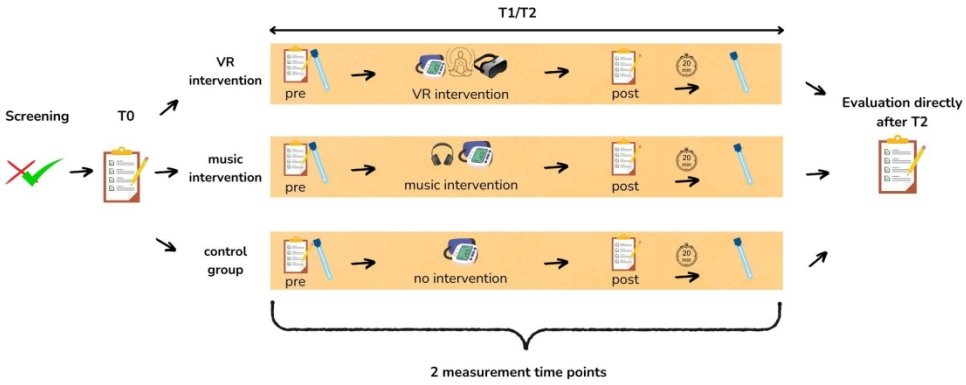
All authors provided final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Screenshot of the Virtual Reality mindfulness intervention.

677x381mm (72 x 72 DPI)



Participant timeline and study procedure. / Note: VR – Virtual Reality

508x285mm (96 x 96 DPI)

Appendix A

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups	n/a

		overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a

Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12

Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found,	n/a

		if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	2
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	10
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

Appendix B

Music Title Overview

			Duration
Jazz	1.	Bill Evans, Danny Boy	3:41
	2.	The Niall O'Sullivan Quartet, Moon Love	4:16
	3.	Keith Jarrett, Don't ever leave me	3:22
	4.	Billy Higgins, Silence	8:45
	5.	Keith Jarrett, Over the Rainbow	6:02
	6.	Keith Jarrett, Paint my Heart Red	6:15
	7.	Bill Evans, Some Other Time	5:19
	8.	Miles Davies, My funny Valentine	6:02
	9.	Bill Evans, When I fall in Love	4:54
	10.	Coltrane Quartet, It's easy to remember	2:47
	11.	Billy Higgins, Round Midnight	11:36
Klassik	1.	Johann Sebastian Bach – Orchestersuite Nr. 3 D-Dur („Air")	5:28
	2.	Yiruma – River Flows In You	3:06
	3.	Claude Debussy – Prelude No. 8 „La Fille aux cheveux de lin"	2:47
	4.	Wolfgang Amadeus Mozart – Serenade in G, K. 525 „Eine Kleine Nachtmusik"	3:35
	5.	Camille Saint-Saëns – Le carnaval des animaux – le cygne	2:50
	6.	Frédéric Chopin - Nocturne in Es-Dur, Op. 9, No. 2	4:05
	7.	Georg Friedrich Händel – Wassermusik, Suite Nr. 1 in F-Dur, „Air"	7:36
	8.	Gabriel Fauré – Pavane, Op. 50	5:37
	9.	Claude Debussy – Suite bergamasque „Clair de lune"	4:39
	10.	Wolfgang Amadeus Mozart – Violinkonzert No.3, 2. Satz: Adagio	8:49
	11.	Wolfgang Amadeus Mozart – 21. Klavierkonzert, 2. Satz: Andante	7:07
	12.	Edvard Grieg – Peer-Gynt-Suite Nr. 1, „Morgenstimmung"	3:53
	13.	Wolfgang Amadeus Mozart – Klarinettenkonzert, 2. Satz: Adagio	7:00
	14.	Ludovico Einaudi – Le Onde	5:24
	15.	Georg Friedrich Händel – Oboenkonzert Nr. 1, 1. Satz: Adagio	3:26
	16.	Philip Glass – Metamorphosis Two	7:17
Lounge	1.	Chillout	6:10
	2.	Wonderful Chill Out Music	4:55
	3.	Portrait of Me	5:08
	4.	Sex Music	5:01
	5.	Brand New (Inspirational Music)	6:10
	6.	Life	4:45
	7.	Real and True	4:39
	8.	Weekend Lounge	5:54
	9.	Pilates Music	5:08
	10.	Meditation Music for Relaxation	4:48
	11.	Soft Chillout Music	3:54
	12.	Stop (Breathing and Positive Thou)	4:42
	13.	Chilled Moods	5:28
	14.	Pure Chill Out	6:22
Meditation	*CD: MusiCure 1. The Journey*		
	1.	Titel 1	15:37
	2.	Titel 2	15:23
	3.	Titel 3	9:30
	4.	Titel 4	11:49
	5.	Titel 5	9:20
	6.	Titel 6	3:11
	7.	Titel 7	5:53

ViSu
Virtual Reality & Sound Intervention under Chemotherapy

Screening Form

Patient-ID: (only after inclusion)

Date of Screening: ☐☐.☐☐.2 0 2 ☐

Inclusion Criteria

Age of patient:	☐ ≥18 years ☐ <18 years
Does the patient have sufficient language skills to participate?	☐ yes ☐ no
Is there a confirmed diagnosis of cancer?	☐ yes ☐ no
Is the patient receiving intravenous chemotherapy (duration of application including flushing at least 60 minutes)?	☐ yes ☐ no
Will the first survey take place at least at the second chemotherapy session?	☐ yes ☐ no
At least five chemotherapy sessions outstanding?	☐ yes ☐ no
GAD-7 ≥ 5?	☐ yes ☐ no

Exclusion Criteria

Are there any serious visual and/or hearing impairments?	☐ yes ☐ no
Are there any relevant pre-existing conditions?[1]	☐ yes ☐ no
Were there any serious side effects from the first chemotherapy?	☐ yes ☐ no
Is the chemotherapy being carried out as part of another study?	☐ yes ☐ no
Are there any brain metastases?	☐ yes ☐ no

Inclusion

Education has taken place	☐ yes ☐ no
Inclusion and exclusion criteria enable participation	☐ yes ☐ no

Does the patient consent to participate in the study?	☐ yes ☐ no

In case of "Yes", the declaration of consent will be signed. In case of "No", the second page will be filled in.

[1] Neurological/psychiatric pre-existing conditions that affect the vestibular system, impair the sense of balance or alter visual perception, epilepsy or claustrophobia.

ViSu
Virtual Reality & Sound Intervention under Chemotherapy

Screening Form

Please check all that apply:

Multiple responses possible

☐ Own current state of health (physical, mental) speaks against participation.

☐ Focus should be on chemotherapy, participation is perceived as disruptive.

☐ Concern about too much additional effort during therapy.

☐ Concern about possible side effects.

☐ Concern about data protection.

☐ Concern about the collection of saliva samples.

☐ No need, as chemotherapy is not perceived as unpleasant or stressful.

☐ No need, as own strategies for distraction and bridging time are used (reading, smartphone/tablet, accompanying person, fellow patients, sleeping,…)

☐ No interest in participating in clinical trials in general.

☐ No interest in the question or in the VR technology.

☐ No interest in or skepticism about the effectiveness of the interventions.

☐ No interest in psycho-oncological support services.

If none of the points above apply or if further comments should be made, the free text field below may be used:

☐ No further indications of reasons.

Many thanks!

☐ Patient did not want to provide feedback. *(Only to be filled in by the research team)*

ViSu
Virtual Reality & Sound Intervention under Chemotherapy

Date: _____

Patient-ID: _____

Evaluation Form VR Group

Below you are asked to rate the user-friendliness of the virtual reality application you have just tested. Please read each statement and mark the answer option that best applies to you.

	does not apply at all						applies completely
	1	2	3	4	5	6	7
Overall, I am pleased with how easy it was to use the VR application.	☐	☐	☐	☐	☐	☐	☐
I felt comfortable while using the VR application.	☐	☐	☐	☐	☐	☐	☐
The information presented through the VR application was clearly understandable.	☐	☐	☐	☐	☐	☐	☐
The presentation and design of the VR mindfulness exercise was pleasant.	☐	☐	☐	☐	☐	☐	☐
I enjoyed the VR application.	☐	☐	☐	☐	☐	☐	☐
The application of virtual reality offers all the possibilities I expected from it.	☐	☐	☐	☐	☐	☐	☐
Overall, I am satisfied with the use of the VR application.	☐	☐	☐	☐	☐	☐	☐
Wearing the VR glasses was comfortable.	☐	☐	☐	☐	☐	☐	☐
The VR glasses were disruptive.	☐	☐	☐	☐	☐	☐	☐
The VR mindfulness exercise was pleasant.	☐	☐	☐	☐	☐	☐	☐
The VR mindfulness exercise was relaxing.	☐	☐	☐	☐	☐	☐	☐
I would like to do this or another VR mindfulness exercise again at a future appointment.	☐	☐	☐	☐	☐	☐	☐
The VR mindfulness exercise helped me to tolerate unpleasant feelings.	☐	☐	☐	☐	☐	☐	☐
The VR mindfulness exercise made the atmosphere pleasant during chemotherapy.	☐	☐	☐	☐	☐	☐	☐
The VR mindfulness exercise calmed me down.	☐	☐	☐	☐	☐	☐	☐
I enjoyed the VR mindfulness exercise.	☐	☐	☐	☐	☐	☐	☐
I already knew the mindfulness exercise.	☐	☐	☐	☐	☐	☐	☐

Three interventions were compared in this project: the use of a VR mindfulness exercise, the use of music (selection from four genres: meditation, classical, lounge, jazz) and a control condition without intervention.

Please rate the statements by ticking the box that most closely matches your feelings:

	Not at all						Very much
At my next chemotherapy appointment, I would like to use the VR application again.	☐	☐	☐	☐	☐	☐	☐
At my next chemotherapy session, I would like to listen to music (selection from the genres mentioned above).	☐	☐	☐	☐	☐	☐	☐
At my next chemotherapy session, I would like to use neither the VR mindfulness exercise nor the music (selection from the genres mentioned above).	☐	☐	☐	☐	☐	☐	☐

Do you have any suggestions for improving the use of VR glasses?

Other notes:

Thank you for your participation!

ViSu
Virtual Reality & Sound Intervention under Chemotherapy

Date: _____

Patient-ID: _____

Evaluation Form Music Group

Please check the box that best reflects your feelings.

	does not apply at all						applies completely
	1	2	3	4	5	6	7
The music intervention was pleasant.	☐	☐	☐	☐	☐	☐	☐
The music intervention was relaxing.	☐	☐	☐	☐	☐	☐	☐
I would like to hear this or similar music again at my next appointment.	☐	☐	☐	☐	☐	☐	☐
The music was disruptive.	☐	☐	☐	☐	☐	☐	☐
The music helped me to endure unpleasant feelings.	☐	☐	☐	☐	☐	☐	☐
The music made the atmosphere pleasant during chemotherapy.	☐	☐	☐	☐	☐	☐	☐
The music calmed me down.	☐	☐	☐	☐	☐	☐	☐
I enjoyed the music.	☐	☐	☐	☐	☐	☐	☐
I already knew some of the songs.	☐	☐	☐	☐	☐	☐	☐

Three interventions were compared in this project, the use of a VR mindfulness exercise, the use of music (selection from four genres: meditation, classical, lounge, jazz) and a control condition without intervention.

Please rate the statements by ticking the box that most closely matches your feelings:

	Not at all						Very much
At my next chemotherapy appointment, I would like to listen to music again (selection from the genres mentioned above).	☐	☐	☐	☐	☐	☐	☐
At my next chemotherapy appointment, I would like to use the VR application.	☐	☐	☐	☐	☐	☐	☐
At my next chemotherapy appointment, I would like to use neither the VR mindfulness exercise nor the music (selection from the genres mentioned above).	☐	☐	☐	☐	☐	☐	☐

Do you have any suggestions for improving the use of music?

Other notes:

Thank you four your participation!

ViSu
Virtual Reality & Sound Intervention under Chemotherapy

Date: _____

Patient-ID: _____

Evaluation Form Control Group

In this project, three interventions were compared: the use of a VR mindfulness exercise, the use of music (selection from 4 genres: meditation, classical, lounge, jazz) and a control condition without intervention. **Please rate the statements by checking the box that most closely matches your feelings:**

	Not at all						Very much
At my next chemotherapy appointment, I would like to use the VR application.	☐	☐	☐	☐	☐	☐	☐
At my next chemotherapy appointment, I would like to listen to music (selection from the genres mentioned above).	☐	☐	☐	☐	☐	☐	☐
At my next chemotherapy appointment, I would like to use neither the VR mindfulness exercise nor the music (selection from the genres mentioned above).	☐	☐	☐	☐	☐	☐	☐

Do you have any suggestions for improving the use of music?

Other notes:

Thank you for your participation!

BMJ Open

Virtual Reality and Sound Intervention under Chemotherapy (ViSu): study protocol for a three-arm randomized-controlled trial

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Secondary Subject Heading:	Oncology, Public health

Keywords:	Virtual Reality, Mindfulness, CHEMOTHERAPY, eHealth, Stress, Psychological, Stress, Physiological

Virtual Reality and Sound Intervention under Chemotherapy (ViSu): study protocol for a three-arm randomized-controlled trial

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Abstract

Introduction: Patients undergoing chemotherapy often experience side effects during treatment, including psychological distress and symptoms of anxiety and depression. Interventions during chemotherapy that divert attention from potentially aversive environmental factors have been demonstrated to have a beneficial impact on these symptoms. Virtual reality (VR) offers the potential to visually and audibly disengage from the surrounding environment and can create an alternative sense of presence. This could facilitate the implementation of active guided interventions that may prove more effective than receptive interventions, such as listening to music. The present ViSu study examines the feasibility, acceptance and effectiveness of a VR intervention and a music intervention during chemotherapy.

Methods: The single center three-arm, randomized-controlled trial investigates the efficacy of a VR mindfulness intervention and a music intervention in cancer patients undergoing chemotherapy at the University Hospital Düsseldorf, Germany. Patients were randomly assigned to receive either (1) the VR mindfulness intervention, (2) the receptive music intervention, or (3) the standard care (control group) in two consecutive chemotherapy sessions. A comprehensive psychological assessment and self-ratings using visual analog scales will be conducted with situational anxiety as the primary outcome measure. Additionally, secondary measures will be employed to assess cancer-related anxiety, self-efficacy, and chemotherapy-related side effects. Furthermore, salivary cortisol, heart rate, and blood pressure will be recorded. At the end of the study, an evaluation questionnaire will be completed. It is planned to enroll 82 patients.

Ethics and dissemination: The study has been approved by the ethics committee of the medical faculty of the Heinrich-Heine-University Düsseldorf (2022-1880). Written informed consent is obtained from the patients prior to participation. The results will be published in international scientific, peer-reviewed journals. Conference presentations are also planned.

Keywords: Virtual reality, mindfulness, music, psycho-oncology, anxiety, chemotherapy

Trail Registration: German Clinical Trials Register (DRKS) – ID: DRKS00029738, registered August 16th, 2022

Protocol version #3, 17. February 2025

Strengths and limitations of this study

- Feasibility of an active VR mindfulness intervention during the application of chemotherapy.
- Randomized controlled trial that compares the effectiveness of two interventions (VR and music) to a control group.
- Both interventions are easy to applicate and therefore suitable for outpatient treatment.
- In addition to psychological assessments and self-ratings, saliva samples used to measure cortisol levels, heart rate and blood pressure are evaluated and provide a more objective method.
- Limited standardization of the assessment environment, making it challenging to control for potential confounding variables during data collection.

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Competing interests statement

None declared.

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Introduction

Although chemotherapy is an essential part of treatment and a potential condition for healing, many patients in oncology experience chemotherapy distressing and time consuming, taking place in an unpleasant surrounding. Chemotherapy cycles are frequently accompanied by adverse side effects such as nausea, fatigue or symptoms of anxiety and depression [1]. Negative psychological side effects can have an additional negative impact on health-related quality of life [2, 3] or even reduced treatment adherence [4, 5], which is associated with a poorer overall prognosis [6, 7].

Psychological interventions that are already offered during chemotherapy sessions have the potential to alleviate distress and mitigate side effects, thereby helping patients cope with the unpleasant environment. These interventions can be broadly categorized into receptive and active types. Receptive interventions, such as listening to music, have been shown to reduce anxiety, depressive symptoms and distress during chemotherapy [8, 9]. Active interventions like progressive muscle relaxation [10] guided imagery [11] or mindfulness-based interventions [12] showed reducing effects on several psychological outcomes like anxiety, depression and distress. Additionally, active interventions may enhance patients' self-efficacy during their whole cancer treatment [13]. However, these interventions often require some instructions and guidance from a third person, an active participating role from the patient, and some level of training. The unpleasant context during chemotherapy, characterized by shared treatment rooms, noise, and variability in treatment duration, offers various sources of distraction that can prevent patients from successfully performing or concentrating on the intervention.

Virtual reality (VR) offers a novel approach to supportive psycho-oncological interventions and could be beneficial as the feelings of presence and immersion could help patients to focus on the task by shielding them from distracting environmental factors. VR has been perceived as helpful during mindfulness training [14], and research suggests that VR-based mindfulness training may be superior to traditional mindfulness practices in reducing anxiety, stress, depressive symptoms, mood disturbances, and sleep problems [15]. For oncology patients undergoing chemotherapy, VR has been used primarily as a passive distraction intervention, proving more effective than other commonly used interventions, such as music [16]. Furthermore, an observational study has reported that VR-based active interventions incorporating mindfulness practice can have positive effects on psychological side effects [17].

Despite promising findings, the use of VR in chemotherapy remains underexplored, particularly as an active intervention. A recent systematic review and meta-analysis of VR use in cancer patients receiving chemotherapy reported 12 RCTs [18], all of them are using VR as a passive distraction intervention. This highlights a significant gap in understanding the potential benefits of immersive, active VR interventions compared to passive approaches. Additionally, little is known about the factors that influence the feasibility of implementing such active or passive VR-based interventions in a clinical setting, which is particularly important given the technical challenges associated with VR setup compared to more routine interventions like music therapy.

Therefore, the ViSu study aimed to investigate the effects of an active VR-based mindfulness intervention compared to a receptive music intervention and a control group on both subjective and objective psychological outcomes during two consecutive chemotherapy sessions. Given that active VR-based interventions may offer advantages over receptive music interventions due to the enhanced immersion and presence they provide, which may increase patient engagement, we hypothesize that the effects will be more pronounced in the VR group compared to the music group. Nonetheless, both interventions are expected to be superior to the control group, that receives only standard care. Furthermore, this study aims to identify key factors influencing the feasibility of implementing VR and music-based interventions in an outpatient chemotherapy setting, contributing to the growing body of evidence on supportive care in oncology.

Methods

Study Design

The ViSu study is a single center, three-arm, non-blinded, randomized, controlled trial designed to investigate the efficacy of a VR mindfulness intervention and a music intervention in cancer patients undergoing chemotherapy at the Interdisciplinary Outpatient Chemotherapy Center (IAC), University Hospital Düsseldorf, Germany. Participants will be randomly assigned to one of three study arms: (1) an intervention group receiving a VR-based mindfulness task, (2) an intervention group listening to music, and (3) a control group with no intervention. The study protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting guidelines [19]. The checklist can be found in Appendix A.

The primary objective is to compare the effectiveness of the two interventions against a control group in reducing patients' anxiety during two consecutive chemotherapy sessions. To evaluate whether the active VR intervention leads to any training or habituation effects, each participant will take part in two intervention sessions. Data collection will be conducted at both time points. Due to individual differences in chemotherapy schedules, the exact duration of chemotherapy treatment may differ between participants.

Sample

Patients are either referred to the study by their attending physician during their consultation hours, recruited by the study team at the IAC, or contacted by the study team independently. For patients recruited by the study team or who self-refer, the study team will obtain the consent of the attending physician. All patients are pre-screened for eligibility by their attending physician. The eligibility criteria for the study include a) the general physical condition of the patient, b) an age of 18 years or older, c) the presence of a gynecological (C51-55), senological (C50), hematological (C81-85, C91-95) or gastrointestinal cancer (C15ff, C16ff, C18ff, C20ff, C22, C23, C25ff) diagnosis according to ICD-10, d) a chemotherapy duration of at least 60 minutes, e) the presence of at least five remaining consecutive chemotherapy sessions, f) sufficient knowledge of the German language, and g) at least moderate anxiety as measured by the Generalized Anxiety Disorder-7 questionnaire [20, 21].

Patients are not eligible for the study if they have a) severe visual and/or hearing impairment (self-reported), b) brain metastases, c) pre-existing neurological and/or psychiatric conditions affecting the vestibular system, impair balance, or alter visual perception, d) epilepsy, e) claustrophobia, f) severe side effects after the first chemotherapy session, or g) wearing cooling gloves or a cooling cap during the chemotherapy sessions.

Patients can withdraw from the study at any time. Participation will be terminated if chemotherapy sessions have to be interrupted due to the patient's physical weakness or if chemotherapy is interrupted due to technical malfunctions. Participation will also be terminated if acute side effects or allergic reactions occur during chemotherapy, or if the oncological disease progresses negatively during ongoing therapy.

Interventions

Virtual reality mindfulness intervention

Mindfulness, as defined by Kabat-Zinn [22], refers to the intentional self-regulation of attention to the present moment without judgment. To cultivate mindfulness skills, these practices are typically embedded in meditation exercises [22]. Over time, this concept has been integrated into psychological interventions and has evolved into a variety of meditation practices, many of which have been tested in randomized controlled trials [23]. Such exercises involve directing attention to thoughts, emotions, and bodily sensations, simply observing them as they arise and pass away [24]. Potential mechanisms underlying the effects of mindfulness include attention and emotion

regulation, increased body awareness, and a shift in perspective on the self [24]. VR may offer several advantages for mindfulness meditation. By shielding users from distracting environmental factors that might otherwise interfere with meditation, VR can create a more focused and immersive experience [14, 15]. The sense of presence that arises during VR exercises is described as engaging and is considered to enhance mindfulness [14]. The combination of audiovisual stimuli in VR may further reduce mind-wandering by anchoring attention [14, 25].

In the present study, the VR mindfulness intervention is delivered via a VR headset (Quest 2) [26] and circumaural headphones (Bose Corporation) [27] and was developed as a self-management intervention in the course of another project of our study group [28]. Patients find themselves in a virtual natural environment, sitting on a park bench surrounded by flowers and trees overlooking a mountain lake (see Figure 1). At the outset, patients are afforded a maximum of five minutes to acclimate themselves to the environment and then start the exercise independently. Under the guidance of a male narrator, patients are guided through an environment meditation consisting of a general opening sequence that suggests a brief recap of the day and includes elements of breathing meditation. In the main body of the meditation, the narrator directs the patient's attention to different areas of the environment and asks the patient to describe them as accurately and as nonjudgmentally as possible. Special emphasis is placed on the description of colors and shapes. The final sequence contains short reflection questions on the content of the exercise. The exercise takes 15 minutes to complete.

The Quest 2 is a standalone VR system consisting of a mobile head-mounted display (HMD) with built-in stereo speakers and inside-out optical head motion tracking to provide 6 DoF positional tracking. The HMD is used with the flexible headstrap and weighs 503g. Interaction with the VR environment can be performed using two separate hand controllers or the integrated hand tracking. Patients were instructed to use the hand controllers. The Oculus Quest has two binocular OLED displays with a resolution of 1832 x 1920pixels per eye, a refresh rate of 72 Hz and a field of view of ~100°. The VR intervention was created using Unity3D. Circumaural headphones are connected to the VR headset to avoid noise disturbance to other patients in the room.

The Quest 2 system setup involved the study team starting up the VR headset. This required configuring the Guardian to the patient's room and then selecting the study application from the main menu. The VR headset was then handed to the patient and adjusted to the shape of the patient's head.

Music intervention

The receptive music intervention is delivered via an mp3-player (Apple iPod) [29] and circumaural headphones (Bose Corporation) [27]. Prior to the first intervention, the participants can choose between four genres (classic, jazz, meditation, lounge) and will listen to this genre at both intervention time points. The playlists consist of music titles selected by a music psychologist according to the recommendations of Nilsson [30] and used in a previous project of our group [31]. They can be accessed in Appendix B. All tracks are instrumental, vary between 60 and 80 beats per minute. The music intervention lasts 15-20 minutes. Table 1 presents a comparative overview of the VR and the music intervention.

Table 1

Comparative overview of the VR and the music intervention

Intervention design feature	VR intervention	Music intervention
Intervention type	Active	Receptive
Delivery format	Immersive VR environment via head mounted display with headphones	Music via mp3-player and headphones

Technology	Quest 2 (Meta), Bose headphones	Apple iPod, Bose headphones
Intervention content	Mindfulness exercise, environment meditation in a natural environment with nature sounds	Listening to instrumental music (60 – 80 bpm)
Degree of user choice	Predefined meditation without choice options	Choice of four different music genres: classic, jazz, meditation or lounge
Type of guidance	Verbal guidance by a male narrator (directing attention to various aspects of the environment)	No guidance
Duration	15 minutes (+ up to 5 minutes for acclimatization)	15- 20 minutes

Note: VR – Virtual Reality, bpm – beats per minute

Implementation and quality assurance of the intervention

To optimize intervention effectiveness, several strategies are being implemented. Recruitment data, reasons for non-participation (via a screening questionnaire), and dropout rates are systematically documented to assess feasibility. Following recruitment, participants receive standardized instructions for correct VR and music intervention application. Additionally, study staff are trained to provide consistent guidance and address technical difficulties.

To further ensure procedural consistency, a structured documentation form includes a checklist for standardization and records start/end times and disruptions. Noise-canceling headphones are used to minimize external distractions, ensuring participants can fully engage in the intervention.

Furthermore, weekly team meetings facilitate continuous process evaluation, allowing for structured feedback on data collection, recruitment challenges, and potential implementation barriers. At the end of the study, feasibility and user experience data, including responses from an evaluation questionnaire, will be analyzed to identify challenges and potential areas for improvement.

Measures

Patients complete four different types of questionnaires during their study participation at the following measurement time points: after recruitment (T0; baseline), before the intervention (pre-intervention), after the intervention (post-intervention), and at the end of the study (evaluation). All questionnaires were used in the German version. Additionally, physiological parameters (heart rate and blood pressure) are measured during the intervention phase. The pre-intervention, during-intervention, and post-intervention measurements are administered twice over two consecutive chemotherapy sessions (T1 and T2). Table 2 outlines the measures employed and the corresponding time points at which they are collected. Furthermore, saliva samples are collected both before and 25 minutes after the intervention, while heart rate and blood pressure are recorded at 5-minute intervals during the intervention. Below is a detailed presentation of all measures used in the study.

Table 2

Overview of measures used for the study and the measurement time points.

Measure	Baseline	Pre-intervention	During intervention	Post-intervention	Evaluation
Demographic data	X				
Cancer-related data	X				
VAS-Social support	X				
Previous experiences with mindfulness and music for relaxation	X				
ASKU	X				
PHQ-4	X	X			
STAI-Trait	X				
Salivary cortisol		X		X	
STAI-State		X		X	
PA-F-KF		X		X	
MIDOS-2		X		X	
VAS-Anxiety		X		X	
VAS-Relaxation		X		X	
Heart rate			X		
Blood pressure			X		
VAS-Tolerability of chemotherapy				X	
VAS-Perceived duration of chemotherapy				X	
PSSUQ					X
VR-specific evaluation (self-developed)					X
Music-specific evaluation (self-developed)					X

Note: VAS – visual analogue scale; ASKU – Short Scale for Measuring General Self-efficacy Beliefs; PHQ-4 – Patient-Health-Questionnaire-4; STAI – State-Trait-Anxiety-Inventory; PA-F-KF – Fear of Progression Questionnaire Short Form; MIDOS – Minimal Documentation System; PSSUQ – Post-study System Usability Questionnaire; VR – Virtual Reality

Baseline measures

Screening

In order to determine the reasons for a lack of interest in participating in the study, even though the patients addressed in the IAC fulfill the inclusion criteria, a screening form will be distributed. This screening form has been developed by the first authors on the basis of verbal feedback received during recruitment conversations on site. On this form, patients can tick items such as: "Concern about too much additional effort during therapy", "No need, as chemotherapy is not perceived as unpleasant or stressful", or "No interest in the research question or in the VR

technology". A refusal to provide further feedback is also possible, as well as a statement of unstated reasons. Completion of the screening questionnaire is voluntary and anonymous. The screening form can be viewed in Appendix C.

Generalized Anxiety Disorder-7 Questionnaire (GAD-7)

Patients are screened for generalized anxiety using the German version of the Generalized Anxiety Disorder-7 Questionnaire [21], translated by Löwe et al. [32]. It measures how much subjects have been bothered by the following problems over the past two weeks indicated on a 4-point Likert scale (0 = *not at all*, 1 = *for several days*, 2 = *more than half the days*, 3 = *nearly every day*): feeling nervous, anxious, or on edge; not being able to stop or control worrying; worrying too much about different things; trouble relaxing; being so restless that it is hard to sit still; becoming easily annoyed or irritable; feeling afraid, as if something awful might happen. Participants can score a value between 0 and 21 with higher values indicating a higher degree of generalized anxiety symptoms. A recent study confirmed the reliability and validity of the GAD-7 in a German population sample with overall good internal consistency of α = .85 [20]. Patients are screened for a score of at least 5 indicating a mild generalized anxiety [21].

Demographic and cancer-related data

Patients are asked to indicate their gender (female, male, diverse), age, highest educational level (based on the German educational system), and family status (unwed, in a partnership, married/ civil partnership, divorced/ civil partnership annulled, widowed/ registered partner deceased).

Further, cancer-related data is assessed based on the Basic Documentation for Psycho-Oncology [33, 34]. Patients are asked to report their main cancer diagnosis, whether it is the first diagnosis and whether there has been a previous cycle of chemotherapy, what treatments they have received in the last 2 months, whether they have previously received psychiatric treatment or psychotherapy, and whether they are currently taking any psychopharmacological medication.

Short Scale for Measuring General Self-efficacy Beliefs (ASKU)

The Short Scale for Measuring General Self-efficacy Beliefs [35] is a self-report based questionnaire assessing the participant's perceived self-efficacy using three items on a 5-point Likert scale (1 = *never or very rarely true*; 5 = *very often or always true*). The ASKU reveals a reliability of between ω = .81 and ω = .86. The factorial validity can be described as sufficient with factor loadings of .77 and higher and the model fit is validated. The construct validity of the questionnaire was also validated by comparing the items to questionnaires assessing similar constructs [35].

The State-Trait-Anxiety-Inventory (STAI-Trait)

The short trait-version of the STAI [36] assesses trait-anxiety as a relatively stable personality characteristic and consists of 10 items that are rated on a 8-point Likert-Scale (1 = *not at all*; 8 = *completely*). Three of the 10 items have to be inverted prior to calculation. Total scores can range between 10 and 80 with higher scores indicating higher trait-anxiety. The trait-version reveals also excellent internal consistency ranging between α = .88 and α = .94 and the criterion validity was confirmed by correlating the items to other measures assessing similar constructs [37].

Primary outcome measure

The State-Trait-Anxiety-Inventory (STAI-State)

The State-Trait-Anxiety-Inventory (STAI) [36] is a self-report questionnaire that can assess both situational state-anxiety and stable trait-anxiety. The short version with 10 items was used to assess the situational state-anxiety as the primary outcome [36]. The response for each of the 10 items is based on an 8-point Likert scale (1 = *not at all*; 8 = *completely*). Four items need to be inversed before calculating the total score. The STAI-state score ranges between 10 and 80. Higher

values indicate higher state-anxiety. The STAI reveals an excellent internal consistency of α = .90 [36].

Secondary outcome measures

Visual Analogue Scales (VAS)

Visual analogue scales (VAS) are used to assess anxiety ('How anxious do you feel in this moment?' from 'not anxious at all' to 'maximally anxious'), relaxation ('How do you feel at this moment?' from 'maximally tense' to 'maximally relaxed'), social support ('How much do you feel supported by your social network in the moment?' from 'not at all supported' to 'maximally supported'), tolerance of the chemotherapy session ('How bearable did you perceive today's chemotherapy treatment?' from 'minimally tolerable' to 'maximally tolerable'), and the perceived duration of the chemotherapy session ('How quickly do you feel today's chemotherapy session has gone so far?' from 'not quick at all' to 'maximally quick'). Patients are asked to rate their answer by marking a point on a 10 cm long line from 0 to 100, with 0 indicating total disagreement and 100 indicating total agreement. Visual analogue scales are a quick and economical method for the assessment of different subjective states and symptoms [38, 39].

Patient-Health-Questionnaire-4 (PHQ-4)

The German version of the Patient-Health-Questionnaire-4 [40] assesses anxiety and depression using four items on a 4-point Likert scale (0 = *not at all*; 3 = *almost every day*). The values are added for the total score, higher values indicating a greater extend of anxiety and depression. The scale showed good internal consistency with α > .80. A factor analysis revealed good fit with 84% of total variance explained. In a recent study, the internal consistency of the instrument for the German population could be again confirmed as good (ω = .85) [41].

Fear of Progression Questionnaire Short Form (PA-F-KF)

The Fear of Progression Questionnaire Short Form [42] consists of 12 items that are answered on a 5-point Likert scale (1 = *never*; 5 = *very often*). The questionnaire assesses patient's fear of progression on five dimensions (affective reaction, partnership/family, occupation, loss of autonomy) and shows overall good internal consistency (α = .87) [42]. The construct validity of the items was confirmed by correlating the items to other measures assessing similar constructs (HADS, PCL-C, SF-8, LAP-R). A factor analysis revealed a one-dimensional structure, explaining 42% of the total variance [42]. The psychometric properties were also confirmed in more recent studies. For example, a study by Hahn [43] found an internal consistency of α = .88 for the PA-F-KF.

Minimal Documentation System (MIDOS-2)

The Minimal Documentation System (MIDOS-2) [44] is a self-report questionnaire assessing participant's symptom-related afflictions due to chemotherapy-associated side effects on a 4-point Likert scale (0 = *none*; 3 = *major afflictions*). In total, there are 13 items. Ten items are measuring the side effects pain, nausea, regurgitation, shortness of breath, constipation, weakness, lack of appetite, fatigue, depression and anxiety. Two more items leave open spaces for naming other afflictions and one more item assesses how the participant is feeling that day, ranging from 0 (*very bad*) to 4 (*very good*). The sum score of each item describes the extend of complaints for each participant. The questionnaire reveals good psychometric properties, with internal consistencies varying between α = .67 and .73 and the test-retest variability varying between r = .69 and r = .57 [44]. The psychometric properties were also confirmed for patient groups in non-palliative care [45].

Heart rate and blood pressure

Heart rate and blood pressure are measured continuously from the beginning to the end of the intervention in 5-minute intervals in beats per minute (bpm) using a pulse oximeter and blood

pressure monitor. A member of the study team records these values while accompanying the intervention.

Saliva cortisol

Salivary samples are assessed to measure levels of cortisol in nmol/l. For this purpose, each participant insalivates a cotton swab for at least 30 seconds before the beginning of the intervention and 25 minutes after the end of the intervention. All saliva samples are stored in dark at -20 degrees Celsius. Analyses will be carried out by Dresden LabService GmbH, Technical University of Dresden, Germany, using chemiluminescence immunoassay.

Evaluation

The evaluation was conducted for all three study arms, with tailored formats for each intervention group as well as the control group. For the VR group, seven items from the Post-Study System Usability Questionnaire (PSSUQ) [46] (items 1, 6, 11, 16–19) were used. The full questionnaire consists of 21 items and was translated into German during a previous study conducted by our group [47]. The selected items have been slightly adapted to better fit the specific VR application used in the study. Responses are given on a 7-point Likert scale (1 = *strongly disagree*, 7 = *strongly agree*), with the overall score reflecting the perceived usability of the VR system by the patients.

Additionally, patients were asked to rate several self-developed items that were tailored to the specific intervention (VR or music). These items assess whether the intervention was pleasing, relaxing, boring, or annoying, whether it helped to alleviate any unpleasant feelings, induce calmness, and create a pleasant atmosphere during the chemotherapy session. Patients also rated whether they liked the intervention, whether they would choose to use it again in a future chemotherapy session, whether they could focus more on the intervention than on their own thoughts, and whether they were already familiar with the intervention. All these items are also rated on a 7-point Likert scale (1 = *strongly disagree*, 7 = *strongly agree*).

Lastly, all groups were asked to indicate which type of intervention (VR, music, or none) they would prefer to use during a future chemotherapy session, rated on a 7-point Likert scale (1 = *not at all,* 7 = *very much*). The evaluation questionnaire also includes two additional free-text fields titled "Suggestions for Enhancing the Utilization of VR/Music" and "Other Comments." The complete evaluation questionnaire is available for review in Appendix D

Recruitment and participant timeline

The study team initiates contact with patients during their outpatient visit to the IAC and inquires about their interest in participating in the study. Subsequently, the treating physicians are consulted to confirm the patients' eligibility for the study, and their approval is sought once eligibility is confirmed. Patients are then contacted again by the study team during their next chemotherapy session. All patients provide written informed consent prior to their participation in the study. Figure 2 shows the participant timeline. The patient information and consent form can be found in Appendix E.

The study team screens for general anxiety symptoms using the Generalized Anxiety Disorder-7 Questionnaire (GAD-7) [20, 21]. To ensure that participants are experiencing a level of anxiety significant enough to benefit from the interventions and demonstrate measurable changes in the primary outcome variable, only patients with at least moderate anxiety (defined as a score ≥5) are included in the study. Patients are randomly assigned to one of three intervention arms using computer-generated random numbers; however, they remain blinded to their group allocation until the first intervention time point (T1).

After recruitment, participants complete the first questionnaire for baseline assessment (T0). The intervention begins during the subsequent chemotherapy session at the IAC (T1). At this point, patients are informed of their study allocation and receive the pre-intervention questionnaire. Following the completion of the questionnaires, and after the flushing and premedication

processes as part of the chemotherapy session, patients provide the first saliva sample by insalivating a cotton swab. The study team then assists patients in initiating the intervention.

Patients in intervention group 1 wear a VR headset and headphones and begin the mindfulness exercise. Patients in intervention group 2 put on headphones and listen to music. Patients in the control group (3) receive no additional treatment. A member of the study team remains with the patient, collecting data on heart rate and blood pressure at 5-minute intervals. After approximately 15-20 minutes, the intervention concludes. Patients then complete the post-intervention questionnaire, and a second saliva sample is collected after 25 minutes. This procedure is repeated during the subsequent chemotherapy session (T2). Finally, patients in all groups receive a questionnaire specifically evaluating the intervention immediately after the second measurement time point. Participants in groups 2 and 3 are given the opportunity to try the VR intervention independently of data collection.

Sample Size

Based on previous literature, we estimate an effect size of 0.25. The G*Power 3.1.9.7 software [48] was employed to determine the requisite sample size. Assuming that the probability of error does not exceed α=.05 and that the power (1-β) is at least 0.95, an analysis of variance with three groups and two time points with N = 66 subjects can demonstrate an effect size of 0.25. Based on previous research projects, we calculate a drop-out rate of 20%, which increases the total sample size to N = 82.

Risk to Patients

Possible risks that can arise, particularly during the VR intervention, are cybersickness [49] and increased stress levels or anxiety due to the complex technical set-up and instructions. In addition, the sensory isolation from the environment can lead to a feeling of loss of control. To counteract this, it was ensured that at least one person from the study team was always present with the patients during the intervention. Patients were able to contact the study team directly if they had any questions, problems or felt unwell. In addition, care was taken to ensure that patients were shielded from disturbances as much as possible. During the data collection phase, study personnel will be present to monitor and record any spontaneously occurring adverse events; if such events occur, they will be discussed with the treating physician and reviewed during the weekly team meetings. Patients will continue to receive ongoing medical care after the end of the trial, where potential side effects can still be discussed. In addition, short-term access to psycho-oncological support will be provided through the department of psychosomatic medicine and psychotherapy for patients who express a need for psychological support after study completion.

Data Monitoring and Management

A randomization file will be used to allocate a participant code to the intervention arms. A recruitment file is used to allocate the participant code to all included patients and, further, contains patients' diagnoses, medical clearance and information about the recruitment process (treating physicians' approval for study participation, checklist for how many attempts were needed to meet the patient in the IAC, date of informed consent). A data file contains pseudonymized survey data of patients to each measurement time point. Another file will be used to anonymously assess drop-outs, screening failures and reasons for non-participation or lack of interest. The data will be entered by the study team accountable for implementation of the study and will be double checked by another team member. Supervision by the study team during chemotherapy sessions ensures the questionnaires are fully completed by participants. Data records will be kept separately from the consent forms. Data records of patients who did not meet the inclusion criteria (screening failures) will be disposed of in accordance with data protection regulations. After collection, salivary cortisol samples will be temporarily stored in a freezer (-20 degree Celsius) and sent to a laboratory (Dresden LabService GmbH, Technical University of Dresden, Germany). Questionnaires and cortisol levels derived from saliva samples will be stored as combined research data for at least 10 years (in accordance with the principles of Good Clinical

Practice). Access to the anonymized final trial dataset will be granted upon request to the study team; the intended use of the data must be disclosed, after which the appropriate dataset will be provided.

Patients will receive standard medical care during the whole participation. No adverse side effects are expected due to the interventions and participating patients do not face higher risks compared to patients who are not participating in the current study. As a member of the study team will supervise each session, participants can terminate the intervention at any time. Participants can report any side effects to the study team and use the evaluation questionnaires for thorough feedback. Therefore, study monitoring is not needed.

Randomization, Blinding, and Treatment Allocation

Randomization is conducted using random numbers. Using a computer program (Microsoft Excel, Microsoft Corporation), a team member who does not participate in recruiting patients generates an excel sheet with numbers representing the three intervention groups (using the command "=RANDBETWEEN(1,3)"). The random allocation sequence assigns patients in equal proportions to one of the three intervention groups. In this sheet, the numbers are masked until a new patient is enrolled, which assures that members of the study team accountable for participant recruitment are blinded until patients' consent. Patients are blinded about their study arm allocation until the first intervention time-point (T1). There is no further blinding of the study team.

Statistical Analysis

All characteristics collected in the study are described in detail using descriptive methods. Qualitative characteristics are indicated by absolute and relative frequencies. Quantitative characteristics are described using mean values, standard deviation, median, minimum and maximum. Parametric analysis methods are used to evaluate the primary and secondary target variables. If assumptions for parametric tests are violated, appropriate non-parametric alternatives will be considered.

Situational anxiety as the primary outcome (measured using the STAI state) is analyzed using separate 3x2 mixed factorial ANOVAs for each of the two chemotherapy sessions, with the between-subject factor "intervention" (virtual reality vs. music vs. control) and the within-subject factors "time" (before vs. after intervention). A probability of error of α=.05 is set. The unit of analysis is individual patients. Effect sizes will be reported using partial eta squared (η^2) for ANOVA analyses. Cohen's d is calculated for post-hoc comparisons when appropriate. The secondary outcome criteria are analyzed exploratively, also using ANOVAs and post hoc tests as appropriate. There is no adjustment of the probability of error. The statistical analysis is carried out with the help of standard statistical software (e.g., R, SAS, SPSS). Both an intention-to-treat analysis and a per-protocol analysis will be performed. The results will be compared and discussed.

The feasibility of the intervention will be evaluated based on multiple data sources. A descriptive analysis of the screening and recruitment data will provide insights into patient participation and reasons for non-participation. Additionally, feasibility will be assessed based on study staff documentation during data collection sessions, as well as recorded reasons for dropout, and potential side effects. Furthermore, the evaluation questionnaire, which includes both usability assessment and self-developed items, will be analyzed. The participants' comments in the free text fields of the evaluation questionnaire will be categorized based on their content into issues and suggestions for improvement.

Protocol Amendments

Protocol amendments were requested initially on November 4th, 2022 to extend the sample due to a lack of subjects matching the inclusion criteria. Before the amendment, participants consisted solely of patients with a gynecological or senological diagnosis. After the amendment, participants with gastrointestinal and hematological diagnoses were also included. To improve the

homogeneity of the sample, the GAD-7 with its cut-off criterion of a value ≥ 5 was introduced as a screening tool. These protocol amendments were granted November 19, 2022.

A second request to amend protocol was issued on August 3rd, 2023 to introduce a self-constructed screening questionnaire for further inquiry of reasons why patients may be disinterested in participation in the study. This protocol amendment was granted on August 9th, 2023.

Ethics and dissemination

The ethics committee of the medical faculty of Heinrich-Heine-University Düsseldorf has been obtained (2022-1880). Divergences or modifications of the study protocol will be documented and relevant cases will be reported to the ethics committee. For all processed data adherence to data protection regulations is warranted. Written informed consent is obtained from patients by the study team and patients are informed that they can withdraw their consent without explanation at any time without facing any consequences. Further, patients are informed that all stored personal data can be deleted upon demand at any point. All personal identifiers will be pseudonymized. The final data set can be assessed only by the study team. After the end of the study, the ethics committee will be informed within 90 days.

Findings of the trial will be reported by publishing in international scientific, peer-reviewed journals. Given several outcome parameters, several publications are planned. Further, presentations at conferences are planned. Until publication, the study team commits to full disclosure of the trial results.

Patient and Public Involvement

Patients and the public were not involved in the design, conduct, or reporting of this study. The research questions, study design, outcome measures, recruitment strategies, and dissemination plans were developed by the research team without direct input from patients, carers, or members of the public. This decision was made based on the specific nature and feasibility constraints of the study.

References

1. Wagland R, Richardson A, Armes J, Hankins M, Lennan E, Griffiths P. Treatment-related problems experienced by cancer patients undergoing chemotherapy: a scoping review. Eur J Cancer Care (Engl). 2014;24(5):605-17. doi:10.1111/ecc.12246.
2. Redeker NS, Lev EL, Ruggiero J. Insomnia, fatigue, anxiety, depression, and quality of life of cancer patients undergoing chemotherapy. Sch Inq Nurs Pract. 2000;14(4):275-290.
3. So WK, Marsh G, Ling WM, Leung FY, Lo JC, Yeung M, et al. The symptom cluster of fatigue, pain, anxiety, and depression and the effect on the quality of life of women receiving treatment for breast cancer: a multicenter study. Oncol Nurs Forum. 2009;36(4):E205-E214. doi:10.1188/09.ONF.E205-E14.
4. Puts MT, Tu HA, Tourangeau A, Fitch M, Springall E, Alibhai SMH. Factors influencing adherence to cancer treatment in older adults with cancer: a systematic review. Ann Oncol. 2014;25(3):564-77. doi:10.1093/annonc/mdt433.
5. Theofilou P, Panagiotaki H. A literature review to investigate the link between psychosocial characteristics and treatment adherence in cancer patients. Oncol Rev. 2012;6(1). doi:10.4081/oncol.2012.e5.
6. Arrieta O, Angulo LP, Núñez-Valencia C, Dorantes-Gallareta Y, Macedo EO, Martínez-López D, et al. Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. Ann Surg Oncol. 2012;20(6):1941-48. doi:10.1245/s10434-012-2793-5.
7. Fukushima T, Suzuki K, Tanaka T, Isobe K, Kubo A, Nakagawa Y, et al. Global quality of life and mortality risk in patients with cancer: a systematic review and meta-analysis. Qual Life Res. 2024;33(5):1391-407. doi:10.1007/s11136-024-03691-3.
8. Nguyen KT, Xiao J, Chan DN, Zhang M, Chan CW. Effects of music intervention on anxiety, depression, and quality of life of cancer patients receiving chemotherapy: a systematic review and meta-analysis. Support Care Cancer. 2022;30(7):5615-26. doi:10.1007/s00520-022-06881-2.
9. Trigueros-Murillo A, Martinez-Calderon J, Casuso-Holgado MJ, González-García P, Heredia-Rizo AM. Effects of music-based interventions on cancer-related pain, fatigue, and distress: an overview of systematic reviews. Support Care Cancer. 2023;31(8):5835-44. doi:10.1007/s00520-023-07938-6.
10. Pelekasis P, Matsouka I, Koumarianou A. Progressive muscle relaxation as a supportive intervention for cancer patients undergoing chemotherapy: a systematic review. Palliat Support Care. 2016;15(4):465-73. doi:10.1017/S1478951516000870.
11. Roffe L, Schmidt K, Ernst E. A systematic review of guided imagery as an adjuvant cancer therapy. Psychooncology. 2005;14(8):607-17. doi:10.1002/pon.889.
12. Cillessen L, Johannsen M, Speckens AE, Zachariae R. Mindfulness-based interventions for psychological and physical health outcomes in cancer patients and survivors: a systematic review and meta-analysis of randomized controlled trials. Psychooncology. 2019;28(12):2257-69. doi:10.1002/pon.5214.
13. Merluzzi TV, Pustejovsky JE, Philip EJ, Sohl SJ, Berendsen M, Salsman JM. Interventions to enhance self-efficacy in cancer patients: a meta-analysis of randomized controlled trials. Psychooncology. 2019;28(9):1781-90. doi:10.1002/pon.5148.
14. Seabrook E, Kelly R, Foley F, Theiler S, Thomas N, Wadley G, et al. Understanding how virtual reality can support mindfulness practice: mixed methods study. J Med Internet Res. 2020;22(3). doi:10.2196/16106.
15. Ma J, Zhao D, Xu N, Yang J. The effectiveness of immersive virtual reality (VR) based mindfulness training on improvement mental-health in adults: a narrative systematic review. Explore (NY). 2023;19(3):310-18. doi:10.1016/j.explore.2022.08.001.
16. Chirico A, Maiorano P, Indovina P, Milanese C, Giordano GG, Alivernini F, et al. Virtual reality and music therapy as distraction interventions to alleviate anxiety and improve mood states in breast cancer patients during chemotherapy. J Cell Physiol. 2020;235(6):5353-62. doi:10.1002/jcp.29422.

17. Wilson K, Scorsone G. The use of virtual reality technologies to reduce anxiety and improve experience in chemotherapy patients during treatment. Front Virtual Real. 2021;2:695449. doi:10.3389/frvir.2021.695449.
18. Gautama MSN, Huang TW, Haryani H. A systematic review and meta-analysis of randomized controlled trials on the effectiveness of immersive virtual reality in cancer patients receiving chemotherapy. Eur J Oncol Nurs. 2023;67:102424. doi:10.1016/j.ejon.2023.102424.
19. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, et al. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586. doi:10.1136/bmj.e7586.
20. Hinz A, Klein AM, Brähler E, Glaesmer H, Luck T, Riedel-Heller SG, et al. Psychometric evaluation of the generalized anxiety disorder screener GAD-7, based on a large German general population sample. J Affect Disord. 2017;210:338-44. doi:10.1016/j.jad.2016.12.012.
21. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder. Arch Intern Med. 2006;166(10):1092-7. doi:10.1001/archinte.166.10.1092.
22. Kabat-Zinn J. Mindfulness-based interventions in context: past, present, and future. *Clin Psychol Sci Pract.* 2003;10(2):144-56. doi:10.1093/clipsy/bpg016.
23. Goldberg SB, Riordan KM, Sun S, Davidson RJ. The empirical status of mindfulness-based interventions: A systematic review of 44 meta-analyses of randomized controlled trials. *Perspect Psychol Sci.* 2022;17(1):108-30. doi:10.1177/1745691620968771.
24. Hölzel BK, Lazar SW, Gard T, Schuman-Olivier Z, Vago DR, Ott U. How does mindfulness meditation work? Proposing mechanisms of action from a conceptual and neural perspective. *Perspect Psychol Sci.* 2011;6(6):537-59. doi:10.1177/1745691611419671.
25. Navarro-Haro MV, López-del-Hoyo Y, Campos D, Linehan MM, Hoffman HG, García-Palacios A, et al. Meditation experts try virtual reality mindfulness: A pilot study evaluation of the feasibility and acceptability of virtual reality to facilitate mindfulness practice in people attending a mindfulness conference. *PLoS One.* 2017;12(11):e0187777. doi:10.1371/journal.pone.0187777.
26. META. META Quest 2 [VR headset]. Menlo Park, CA: META; 2020. Available from: https://www.meta.com/quest-2/
27. Bose. Bose QuietComfort [Bluetooth headphones]. Frisco, TX: Bose Corporation; 2023. Available from: https://www.bose.com/en_us/products/headphones/quietcomfort.html
28. Hemsen B, Wittenborn A, Holsteg S, Karger A, Freitag S, Mildner P, et al. DeepVR: Konzeptuelle Grundlagen und Umsetzung eines Virtual Reality basierten Unterstützungssystems in der psychotherapeutischen Depressions-Behandlung. Mensch Comput. 2021. doi:10.1145/3473856.3474016.
29. Apple Inc. Apple iPod [Internet]. Frisco, TX: Apple Inc.; 2023. Available from: https://www.apple.com/ipod/
30. Nilsson U. The anxiety- and pain-reducing effects of music interventions: a systematic review. AORN J. 2008;87(4):780-807. doi:10.1016/j.aorn.2007.09.013.
31. Schaal NK, Brückner J, Wolf OT, Ruckhäberle E, Fehm T, Hepp P. The effects of a music intervention during port catheter placement on anxiety and stress. Sci Rep. 2021;11(1):85139. doi:10.1038/s41598-021-85139-z.
32. Löwe B, Decker O, Müller S, et al. Validation and Standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the General Population. Med Care. 2008;46(3):266-274. doi:10.1097/mlr.0b013e318160d093.
33. Herschbach P, Book K, Brandl T, Keller M, Marten-Mittag B. The Basic Documentation for Psycho-Oncology (PO-Bado) – an Expert Rating Scale for the Psychosocial Experience of Cancer Patients. Oncol Res Treat. 2008;31(11):591-596. doi:10.1159/000162287.

34. Knight L, Mussell M, Brandl T, et al. Development and psychometric evaluation of the Basic Documentation for Psycho-Oncology, a tool for standardized assessment of cancer patients. J Psychosom Res. 2008;64(4):373-381. doi:10.1016/j.jpsychores.2008.01.003.
35. Beierlein C, Kemper CJ, Kovaleva A, Rammstedt B. Kurzskala zur Erfassung allgemeiner Selbstwirksamkeitserwartungen (ASKU). Methoden Daten Anal. 2013;7(2):28. doi:10.12758/mda.2013.014.
36. Grimm J. State-Trait-Anxiety Inventory nach Spielberger: Deutsche Lang- und Kurzversion. Methodenforum der Universität Wien. MF-Working Paper. 2009;2.
37. Laux L, Glanzmann P, Schaffner P, Spielberger CD. Das State-Trait-Angstinventar. Weinheim: Beltz; 1981.
38. Heller GZ, Manuguerra M, Chow R. How to analyze the Visual Analogue Scale: Myths, truths and clinical relevance. Scand J Pain. 2016;13(1):67-75. doi:10.1016/j.sjpain.2016.06.012.
39. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. Res Nurs Health. 1990;13(4):227-236. doi:10.1002/nur.4770130405.
40. Löwe B, Wahl I, Rose M, Spitzer C, Glaesmer H, Wingenfeld K, et al. A 4-item measure of depression and anxiety: Validation and standardization of the Patient Health Questionnaire-4 (PHQ-4) in the general population. *J Affect Disord.* 2010;122(1-2):86-95. doi:10.1016/j.jad.2009.06.019.
41. Wicke FS, Krakau L, Löwe B, Beutel ME, Brähler E. Update of the standardization of the Patient Health Questionnaire-4 (PHQ-4) in the general population. J Affect Disord. 2022;312:310-314. doi:10.1016/j.jad.2022.06.054.
42. Mehnert A, Herschbach P, Berg P, Henrich G, Koch U. Progredienzangst bei Brustkrebspatientinnen - Validierung der Kurzform des Progredienzangstfragebogens PA-F-KF/ Fear of progression in breast cancer patients – validation of the short form of the Fear of Progression Questionnaire (FoP-Q-SF). Z Psychosom Med Psychother. 2006;52(3):274-288. doi:10.13109/zptm.2006.52.3.274.
43. Hahn AJS. Prädiktoren von Progredienzangst bei Prostatakrebspatienten nach radikaler Prostatektomie: Spielen subjektive Krankheitsrepräsentationen und die Familienanamnese eine Rolle? [dissertation]. München: Technische Universität München; 2015.
44. Stiel S, Matthes ME, Bertram L, et al. Validierung der neuen Fassung des Minimalen Dokumentationssystems (MIDOS2) für Patienten in der Palliativmedizin. Schmerz. 2010;24(6):596-604. doi:10.1007/s00482-010-0972-5.
45. Plöger MM. MIDOS-Validierung des Minimalen Dokumentationssystems für Palliativpatienten-Vergleichsgruppen mit chronisch kranken und gesunden Probanden [dissertation]. Bonn: Universitäts- und Landesbibliothek Bonn; 2016.
46. Lewis JR. Psychometric Evaluation of the Post-Study System Usability Questionnaire: The PSSUQ. Proc Hum Factors Soc Annu Meet. 1992;36(16):1259-1260. doi:10.1177/154193129203601617.
47. Holsteg S, Askeridis JM, Krajewski J, et al. Virtual reality roleplays for patients with depression: A user experience evaluation. Internet Interv. 2024;35:100713. doi:10.1016/j.invent.2024.100713.
48. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39(2):175-191. doi:10.3758/bf03193146.
49. Behr KM, Nosper A, Klimmt C, Hartmann T. Some Practical Considerations of Ethical Issues in VR Research. Presence (Camb Mass). 2005;14(6):668-676. doi:10.1162/105474605775196535.

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Steffen Holsteg and Luisa Ersten contributed equally to this paper. All authors provided final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The DeepVR project consortium (IXP GmbH, Düsseldorf; Nuromedia GmbH, Cologne; Clinical Institute for Psychosomatic Medicine and Psychotherapy, Heinrich-Heine-University Düsseldorf) provided the VR mindfulness intervention for use in the study.

Steffen Holsteg is responsible for the overall content as guarantor.

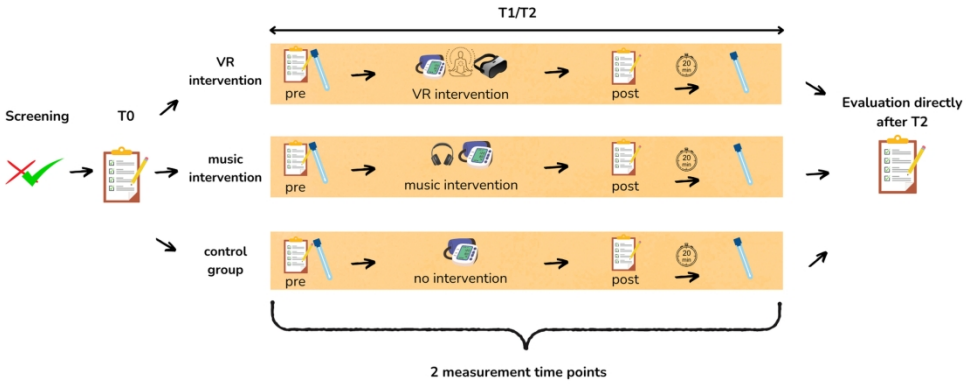
Figure Legend

Figure 1. Screenshot of the VR environment

Figure 2. Participant timeline

Screenshot of the Virtual Reality mindfulness intervention.

89x89mm (300 x 300 DPI)



Participant timeline and study procedure. / Note: VR – Virtual Reality

209x118mm (300 x 300 DPI)

Appendix A

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups	n/a

		overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7

Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12

Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found,	n/a

		if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	2
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	10
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

Appendix B

Music Title Overview

			Duration
Jazz	1.	Bill Evans, Danny Boy	3:41
	2.	The Niall O'Sullivan Quartet, Moon Love	4:16
	3.	Keith Jarrett, Don't ever leave me	3:22
	4.	Billy Higgins, Silence	8:45
	5.	Keith Jarrett, Over the Rainbow	6:02
	6.	Keith Jarrett, Paint my Heart Red	6:15
	7.	Bill Evans, Some Other Time	5:19
	8.	Miles Davies, My funny Valentine	6:02
	9.	Bill Evans, When I fall in Love	4:54
	10.	Coltrane Quartet, It's easy to remember	2:47
	11.	Billy Higgins, Round Midnight	11:36
Klassik	1.	Johann Sebastian Bach – Orchestersuite Nr. 3 D-Dur („Air")	5:28
	2.	Yiruma – River Flows In You	3:06
	3.	Claude Debussy – Prelude No. 8 „La Fille aux cheveux de lin"	2:47
	4.	Wolfgang Amadeus Mozart – Serenade in G, K. 525 „Eine Kleine Nachtmusik"	3:35
	5.	Camille Saint-Saëns – Le carnaval des animaux – le cygne	2:50
	6.	Frédéric Chopin - Nocturne in Es-Dur, Op. 9, No. 2	4:05
	7.	Georg Friedrich Händel – Wassermusik, Suite Nr. 1 in F-Dur, „Air"	7:36
	8.	Gabriel Fauré – Pavane, Op. 50	5:37
	9.	Claude Debussy – Suite bergamasque „Clair de lune"	4:39
	10.	Wolfgang Amadeus Mozart – Violinkonzert No.3, 2. Satz: Adagio	8:49
	11.	Wolfgang Amadeus Mozart – 21. Klavierkonzert, 2. Satz: Andante	7:07
	12.	Edvard Grieg – Peer-Gynt-Suite Nr. 1, „Morgenstimmung"	3:53
	13.	Wolfgang Amadeus Mozart – Klarinettenkonzert, 2. Satz: Adagio	7:00
	14.	Ludovico Einaudi – Le Onde	5:24
	15.	Georg Friedrich Händel – Oboenkonzert Nr. 1, 1. Satz: Adagio	3:26
	16.	Philip Glass – Metamorphosis Two	7:17
Lounge	1.	Chillout	6:10
	2.	Wonderful Chill Out Music	4:55
	3.	Portrait of Me	5:08
	4.	Sex Music	5:01
	5.	Brand New (Inspirational Music)	6:10
	6.	Life	4:45
	7.	Real and True	4:39
	8.	Weekend Lounge	5:54
	9.	Pilates Music	5:08
	10.	Meditation Music for Relaxation	4:48
	11.	Soft Chillout Music	3:54
	12.	Stop (Breathing and Positive Thou)	4:42
	13.	Chilled Moods	5:28
	14.	Pure Chill Out	6:22
Meditation	*CD: MusiCure 1. The Journey*		
	1.	Titel 1	15:37
	2.	Titel 2	15:23
	3.	Titel 3	9:30
	4.	Titel 4	11:49
	5.	Titel 5	9:20
	6.	Titel 6	3:11
	7.	Titel 7	5:53

ViSu
Virtual Reality & Sound Intervention under Chemotherapy

Screening Form

Patient-ID: (only after inclusion)

Date of Screening: ☐☐.☐☐.2 0 2 ☐

Inclusion Criteria

Age of patient:	☐ ≥18 years ☐ <18 years
Does the patient have sufficient language skills to participate?	☐ yes ☐ no
Is there a confirmed diagnosis of cancer?	☐ yes ☐ no
Is the patient receiving intravenous chemotherapy (duration of application including flushing at least 60 minutes)?	☐ yes ☐ no
Will the first survey take place at least at the second chemotherapy session?	☐ yes ☐ no
At least five chemotherapy sessions outstanding?	☐ yes ☐ no
GAD-7 ≥ 5?	☐ yes ☐ no

Exclusion Criteria

Are there any serious visual and/or hearing impairments?	☐ yes ☐ no
Are there any relevant pre-existing conditions?[1]	☐ yes ☐ no
Were there any serious side effects from the first chemotherapy?	☐ yes ☐ no
Is the chemotherapy being carried out as part of another study?	☐ yes ☐ no
Are there any brain metastases?	☐ yes ☐ no

Inclusion

Education has taken place	☐ yes ☐ no
Inclusion and exclusion criteria enable participation	☐ yes ☐ no

Does the patient consent to participate in the study?	☐ yes ☐ no

In case of "Yes", the declaration of consent will be signed. In case of "No", the second page will be filled in.

[1] Neurological/psychiatric pre-existing conditions that affect the vestibular system, impair the sense of balance or alter visual perception, epilepsy or claustrophobia.

ViSu
Virtual Reality & Sound Intervention under Chemotherapy

Screening Form

Please check all that apply:

Multiple responses possible

☐ Own current state of health (physical, mental) speaks against participation.

☐ Focus should be on chemotherapy, participation is perceived as disruptive.

☐ Concern about too much additional effort during therapy.

☐ Concern about possible side effects.

☐ Concern about data protection.

☐ Concern about the collection of saliva samples.

☐ No need, as chemotherapy is not perceived as unpleasant or stressful.

☐ No need, as own strategies for distraction and bridging time are used (reading, smartphone/tablet, accompanying person, fellow patients, sleeping,…)

☐ No interest in participating in clinical trials in general.

☐ No interest in the question or in the VR technology.

☐ No interest in or skepticism about the effectiveness of the interventions.

☐ No interest in psycho-oncological support services.

If none of the points above apply or if further comments should be made, the free text field below may be used:

☐ No further indications of reasons.

Many thanks!

☐ Patient did not want to provide feedback. *(Only to be filled in by the research team)*

ViSu
Virtual Reality & Sound Intervention under Chemotherapy

Date: _____

Patient-ID: _____

Evaluation Form VR Group

Below you are asked to rate the user-friendliness of the virtual reality application you have just tested. Please read each statement and mark the answer option that best applies to you.

	does not apply at all						applies completely
	1	2	3	4	5	6	7
Overall, I am pleased with how easy it was to use the VR application.	☐	☐	☐	☐	☐	☐	☐
I felt comfortable while using the VR application.	☐	☐	☐	☐	☐	☐	☐
The information presented through the VR application was clearly understandable.	☐	☐	☐	☐	☐	☐	☐
The presentation and design of the VR mindfulness exercise was pleasant.	☐	☐	☐	☐	☐	☐	☐
I enjoyed the VR application.	☐	☐	☐	☐	☐	☐	☐
The application of virtual reality offers all the possibilities I expected from it.	☐	☐	☐	☐	☐	☐	☐
Overall, I am satisfied with the use of the VR application.	☐	☐	☐	☐	☐	☐	☐
Wearing the VR glasses was comfortable.	☐	☐	☐	☐	☐	☐	☐
The VR glasses were disruptive.	☐	☐	☐	☐	☐	☐	☐
The VR mindfulness exercise was pleasant.	☐	☐	☐	☐	☐	☐	☐
The VR mindfulness exercise was relaxing.	☐	☐	☐	☐	☐	☐	☐
I would like to do this or another VR mindfulness exercise again at a future appointment.	☐	☐	☐	☐	☐	☐	☐
The VR mindfulness exercise helped me to tolerate unpleasant feelings.	☐	☐	☐	☐	☐	☐	☐
The VR mindfulness exercise made the atmosphere pleasant during chemotherapy.	☐	☐	☐	☐	☐	☐	☐
The VR mindfulness exercise calmed me down.	☐	☐	☐	☐	☐	☐	☐
I enjoyed the VR mindfulness exercise.	☐	☐	☐	☐	☐	☐	☐
I already knew the mindfulness exercise.	☐	☐	☐	☐	☐	☐	☐

Three interventions were compared in this project: the use of a VR mindfulness exercise, the use of music (selection from four genres: meditation, classical, lounge, jazz) and a control condition without intervention.

Please rate the statements by ticking the box that most closely matches your feelings:

	Not at all						Very much
At my next chemotherapy appointment, I would like to use the VR application again.	☐	☐	☐	☐	☐	☐	☐
At my next chemotherapy session, I would like to listen to music (selection from the genres mentioned above).	☐	☐	☐	☐	☐	☐	☐
At my next chemotherapy session, I would like to use neither the VR mindfulness exercise nor the music (selection from the genres mentioned above).	☐	☐	☐	☐	☐	☐	☐

Do you have any suggestions for improving the use of VR glasses?

Other notes:

Thank you for your participation!

ViSu
Virtual Reality & Sound Intervention under Chemotherapy

Date: _____

Patient-ID: _____

Evaluation Form Music Group

Please check the box that best reflects your feelings.

	does not apply at all						applies completely
	1	2	3	4	5	6	7
The music intervention was pleasant.	☐	☐	☐	☐	☐	☐	☐
The music intervention was relaxing.	☐	☐	☐	☐	☐	☐	☐
I would like to hear this or similar music again at my next appointment.	☐	☐	☐	☐	☐	☐	☐
The music was disruptive.	☐	☐	☐	☐	☐	☐	☐
The music helped me to endure unpleasant feelings.	☐	☐	☐	☐	☐	☐	☐
The music made the atmosphere pleasant during chemotherapy.	☐	☐	☐	☐	☐	☐	☐
The music calmed me down.	☐	☐	☐	☐	☐	☐	☐
I enjoyed the music.	☐	☐	☐	☐	☐	☐	☐
I already knew some of the songs.	☐	☐	☐	☐	☐	☐	☐

Three interventions were compared in this project, the use of a VR mindfulness exercise, the use of music (selection from four genres: meditation, classical, lounge, jazz) and a control condition without intervention.

Please rate the statements by ticking the box that most closely matches your feelings:

	Not at all						Very much
At my next chemotherapy appointment, I would like to listen to music again (selection from the genres mentioned above).	☐	☐	☐	☐	☐	☐	☐
At my next chemotherapy appointment, I would like to use the VR application.	☐	☐	☐	☐	☐	☐	☐
At my next chemotherapy appointment, I would like to use neither the VR mindfulness exercise nor the music (selection from the genres mentioned above).	☐	☐	☐	☐	☐	☐	☐

Do you have any suggestions for improving the use of music?

Other notes:

Thank you four your participation!

ViSu
Virtual Reality & Sound Intervention under Chemotherapy

Date: _____

Patient-ID: _____

Evaluation Form Control Group

In this project, three interventions were compared: the use of a VR mindfulness exercise, the use of music (selection from 4 genres: meditation, classical, lounge, jazz) and a control condition without intervention. **Please rate the statements by checking the box that most closely matches your feelings:**

	Not at all						Very much
At my next chemotherapy appointment, I would like to use the VR application.	☐	☐	☐	☐	☐	☐	☐
At my next chemotherapy appointment, I would like to listen to music (selection from the genres mentioned above).	☐	☐	☐	☐	☐	☐	☐
At my next chemotherapy appointment, I would like to use neither the VR mindfulness exercise nor the music (selection from the genres mentioned above).	☐	☐	☐	☐	☐	☐	☐

Do you have any suggestions for improving the use of music?

Other notes:

Thank you for your participation!

BMJ Open

Virtual Reality and Sound Intervention under Chemotherapy (ViSu): study protocol for a three-arm randomized-controlled trial

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Date Submitted by the Author:	18-Mar-2025
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Oncology, Public health

Keywords:	Virtual Reality, Mindfulness, CHEMOTHERAPY, eHealth, Stress, Psychological, Stress, Physiological

Virtual Reality and Sound Intervention under Chemotherapy (ViSu): study protocol for a three-arm randomized-controlled trial

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Word count: 5521

Abstract

Introduction: Patients undergoing chemotherapy often experience side effects during treatment, including psychological distress and symptoms of anxiety and depression. Interventions during chemotherapy that divert attention from potentially aversive environmental factors have been demonstrated to have a beneficial impact on these symptoms. Virtual reality (VR) offers the potential to visually and audibly disengage from the surrounding environment and can create an alternative sense of presence. This could facilitate the implementation of active guided interventions that may prove more effective than receptive interventions, such as listening to music. The present ViSu study examines the feasibility, acceptance and effectiveness of a VR intervention and a music intervention during chemotherapy.

Methods: The single center three-arm, randomized-controlled trial investigates the efficacy of a VR mindfulness intervention and a music intervention in cancer patients undergoing chemotherapy at the University Hospital Düsseldorf, Germany. Patients were randomly assigned to receive either (1) the VR mindfulness intervention, (2) the receptive music intervention, or (3) the standard care (control group) in two consecutive chemotherapy sessions. A comprehensive psychological assessment and self-ratings using visual analog scales will be conducted with situational anxiety as the primary outcome measure. Additionally, secondary measures will be employed to assess cancer-related anxiety, self-efficacy, and chemotherapy-related side effects. Furthermore, salivary cortisol, heart rate, and blood pressure will be recorded. At the end of the study, an evaluation questionnaire will be completed. It is planned to enroll 82 patients.

Ethics and dissemination: The study has been approved by the ethics committee of the medical faculty of the Heinrich-Heine-University Düsseldorf (2022-1880). Written informed consent is obtained from the patients prior to participation. The results will be published in international scientific, peer-reviewed journals. Conference presentations are also planned.

Keywords: Virtual reality, mindfulness, music, psycho-oncology, anxiety, chemotherapy

Trail Registration: German Clinical Trials Register (DRKS) – ID: DRKS00029738, registered August 16th, 2022

Protocol version #4, 17. March 2025

Strengths and limitations of this study

- Randomized controlled trial that compares the effectiveness of two interventions (VR mindfulness and music) to a control group.
- Assessment of a clinical population undergoing active oncological treatment.
- In addition to psychological assessments and self-ratings, saliva samples used to measure cortisol levels, heart rate and blood pressure are evaluated and provide a more objective method.
- Limited standardization of the assessment environment, making it challenging to control for potential confounding variables during data collection.

Funding statement

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Competing interests statement

None declared.

Acknowledgments

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We would also like to thank the DeepVR project consortium (IXP GmbH, Düsseldorf; Nuromedia GmbH, Cologne; Clinical Institute for Psychosomatic Medicine and Psychotherapy, Heinrich-Heine-University Düsseldorf) for permission to use the joint VR Mindfulness application.

Introduction

Although chemotherapy is an essential part of treatment and a potential condition for healing, many patients in oncology experience chemotherapy distressing and time consuming, taking place in an unpleasant surrounding. Chemotherapy cycles are frequently accompanied by adverse side effects such as nausea, fatigue or symptoms of anxiety and depression [1]. Negative psychological side effects can have an additional negative impact on health-related quality of life [2, 3] or even reduced treatment adherence [4, 5], which is associated with a poorer overall prognosis [6, 7].

Psychological interventions that are already offered during chemotherapy sessions have the potential to alleviate distress and mitigate side effects, thereby helping patients cope with the unpleasant environment. These interventions can be broadly categorized into receptive and active types. Receptive interventions, such as listening to music, have been shown to reduce anxiety, depressive symptoms and distress during chemotherapy [8, 9]. Active interventions like progressive muscle relaxation [10] guided imagery [11] or mindfulness-based interventions [12] showed reducing effects on several psychological outcomes like anxiety, depression and distress. Additionally, active interventions may enhance patients' self-efficacy during their whole cancer treatment [13]. However, these interventions often require some instructions and guidance from a third person, an active participating role from the patient, and some level of training. The unpleasant context during chemotherapy, characterized by shared treatment rooms, noise, and variability in treatment duration, offers various sources of distraction that can prevent patients from successfully performing or concentrating on the intervention.

Virtual reality (VR) offers a novel approach to supportive psycho-oncological interventions and could be beneficial as the feelings of presence and immersion could help patients to focus on the task by shielding them from distracting environmental factors. VR has been perceived as helpful during mindfulness training [14], and research suggests that VR-based mindfulness training may be superior to traditional mindfulness practices in reducing anxiety, stress, depressive symptoms, mood disturbances, and sleep problems [15]. For oncology patients undergoing chemotherapy, VR has been used primarily as a passive distraction intervention, proving more effective than other commonly used interventions, such as music [16]. Furthermore, an observational study has reported that VR-based active interventions incorporating mindfulness practice can have positive effects on psychological side effects [17].

Despite promising findings, the use of VR in chemotherapy remains underexplored, particularly as an active intervention. A recent systematic review and meta-analysis of VR use in cancer patients receiving chemotherapy reported 12 RCTs [18], all of them are using VR as a passive distraction intervention. This highlights a significant gap in understanding the potential benefits of immersive, active VR interventions compared to passive approaches. Additionally, little is known about the factors that influence the feasibility of implementing such active or passive VR-based interventions in a clinical setting, which is particularly important given the technical challenges associated with VR setup compared to more routine interventions like music therapy.

Therefore, the ViSu study aimed to investigate the effects of an active VR-based mindfulness intervention compared to a receptive music intervention and a control group on both subjective and objective psychological outcomes during two consecutive chemotherapy sessions. Given that active VR-based interventions may offer advantages over receptive music interventions due to the enhanced immersion and presence they provide, which may increase patient engagement, we hypothesize that the effects will be more pronounced in the VR group compared to the music group. Nonetheless, both interventions are expected to be superior to the control group, that receives only standard care. Furthermore, this study aims to identify key factors influencing the feasibility of implementing VR and music-based interventions in an outpatient chemotherapy setting, contributing to the growing body of evidence on supportive care in oncology.

Methods

Study Design

The ViSu study is a single center, three-arm, non-blinded, randomized, controlled trial designed to investigate the efficacy of a VR mindfulness intervention and a music intervention in cancer patients undergoing chemotherapy at the Interdisciplinary Outpatient Chemotherapy Center (IAC), University Hospital Düsseldorf, Germany. Participants will be randomly assigned to one of three study arms: (1) an intervention group receiving a VR-based mindfulness task, (2) an intervention group listening to music, and (3) a control group with no intervention. The study protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting guidelines [19]. The checklist can be found in Appendix A.

The primary objective is to compare the effectiveness of the two interventions against a control group in reducing patients' anxiety during two consecutive chemotherapy sessions. To evaluate whether the active VR intervention leads to any training or habituation effects, each participant will take part in two intervention sessions. Data collection will be conducted at both time points. Due to individual differences in chemotherapy schedules, the exact duration of chemotherapy treatment may differ between participants.

Sample

Patients are either referred to the study by their attending physician during their consultation hours, recruited by the study team at the IAC, or contacted by the study team independently. For patients recruited by the study team or who self-refer, the study team will obtain the consent of the attending physician. All patients are pre-screened for eligibility by their attending physician. The eligibility criteria for the study include a) the general physical condition of the patient, b) an age of 18 years or older, c) the presence of a gynecological (C51-55), senological (C50), hematological (C81-85, C91-95) or gastrointestinal cancer (C15ff, C16ff, C18ff, C20ff, C22, C23, C25ff) diagnosis according to ICD-10, d) a chemotherapy duration of at least 60 minutes, e) the presence of at least five remaining consecutive chemotherapy sessions, f) sufficient knowledge of the German language, and g) at least moderate anxiety as measured by the Generalized Anxiety Disorder-7 questionnaire [20, 21].

Patients are not eligible for the study if they have a) severe visual and/or hearing impairment (self-reported), b) brain metastases, c) pre-existing neurological and/or psychiatric conditions affecting the vestibular system, impair balance, or alter visual perception, d) epilepsy, e) claustrophobia, f) severe side effects after the first chemotherapy session, or g) wearing cooling gloves or a cooling cap during the chemotherapy sessions.

Patients can withdraw from the study at any time. Participation will be terminated if chemotherapy sessions have to be interrupted due to the patient's physical weakness or if chemotherapy is interrupted due to technical malfunctions. Participation will also be terminated if acute side effects or allergic reactions occur during chemotherapy, or if the oncological disease progresses negatively during ongoing therapy.

Interventions

Virtual reality mindfulness intervention

Mindfulness, as defined by Kabat-Zinn [22], refers to the intentional self-regulation of attention to the present moment without judgment. To cultivate mindfulness skills, these practices are typically embedded in meditation exercises [22]. Over time, this concept has been integrated into psychological interventions and has evolved into a variety of meditation practices, many of which have been tested in randomized controlled trials [23]. Such exercises involve directing attention to thoughts, emotions, and bodily sensations, simply observing them as they arise and pass away [24]. Potential mechanisms underlying the effects of mindfulness include attention and emotion

regulation, increased body awareness, and a shift in perspective on the self [24]. VR may offer several advantages for mindfulness meditation. By shielding users from distracting environmental factors that might otherwise interfere with meditation, VR can create a more focused and immersive experience [14, 15]. The sense of presence that arises during VR exercises is described as engaging and is considered to enhance mindfulness [14]. The combination of audiovisual stimuli in VR may further reduce mind-wandering by anchoring attention [14, 25].

In the present study, the VR mindfulness intervention is delivered via a VR headset (Quest 2) [26] and circumaural headphones (Bose Corporation) [27] and was developed as a self-management intervention in the course of another project of our study group [28]. Patients find themselves in a virtual natural environment, sitting on a park bench surrounded by flowers and trees overlooking a mountain lake (see Figure 1). At the outset, patients are afforded a maximum of five minutes to acclimate themselves to the environment and then start the exercise independently. Under the guidance of a male narrator, patients are guided through an environment meditation consisting of a general opening sequence that suggests a brief recap of the day and includes elements of breathing meditation. In the main body of the meditation, the narrator directs the patient's attention to different areas of the environment and asks the patient to describe them as accurately and as nonjudgmentally as possible. Special emphasis is placed on the description of colors and shapes. The final sequence contains short reflection questions on the content of the exercise. The exercise takes 15 minutes to complete.

The Quest 2 is a standalone VR system consisting of a mobile head-mounted display (HMD) with built-in stereo speakers and inside-out optical head motion tracking to provide 6 DoF positional tracking. The HMD is used with the flexible headstrap and weighs 503g. Interaction with the VR environment can be performed using two separate hand controllers or the integrated hand tracking. Patients were instructed to use the hand controllers. The Oculus Quest has two binocular OLED displays with a resolution of 1832 x 1920pixels per eye, a refresh rate of 72 Hz and a field of view of ~100°. The VR intervention was created using Unity3D. Circumaural headphones are connected to the VR headset to avoid noise disturbance to other patients in the room.

The Quest 2 system setup involved the study team starting up the VR headset. This required configuring the Guardian to the patient's room and then selecting the study application from the main menu. The VR headset was then handed to the patient and adjusted to the shape of the patient's head.

Music intervention

The receptive music intervention is delivered via an mp3-player (Apple iPod) [29] and circumaural headphones (Bose Corporation) [27]. Prior to the first intervention, the participants can choose between four genres (classic, jazz, meditation, lounge) and will listen to this genre at both intervention time points. The playlists consist of music titles selected by a music psychologist according to the recommendations of Nilsson [30] and used in a previous project of our group [31]. They can be accessed in Appendix B. All tracks are instrumental, vary between 60 and 80 beats per minute. The music intervention lasts 15-20 minutes. Table 1 presents a comparative overview of the VR and the music intervention.

Table 1

Comparative overview of the VR and the music intervention

Intervention design feature	VR intervention	Music intervention
Intervention type	Active	Receptive
Delivery format	Immersive VR environment via head mounted display with headphones	Music via mp3-player and headphones

Technology	Quest 2 (Meta), Bose headphones	Apple iPod, Bose headphones
Intervention content	Mindfulness exercise, environment meditation in a natural environment with nature sounds	Listening to instrumental music (60 – 80 bpm)
Degree of user choice	Predefined meditation without choice options	Choice of four different music genres: classic, jazz, meditation or lounge
Type of guidance	Verbal guidance by a male narrator (directing attention to various aspects of the environment)	No guidance
Duration	15 minutes (+ up to 5 minutes for acclimatization)	15- 20 minutes

Note: VR – Virtual Reality, bpm – beats per minute

Implementation and quality assurance of the intervention

To optimize intervention effectiveness, several strategies are being implemented. Recruitment data, reasons for non-participation (via a screening questionnaire), and dropout rates are systematically documented to assess feasibility. Following recruitment, participants receive standardized instructions for correct VR and music intervention application. Additionally, study staff are trained to provide consistent guidance and address technical difficulties.

To further ensure procedural consistency, a structured documentation form includes a checklist for standardization and records start/end times and disruptions. Noise-canceling headphones are used to minimize external distractions, ensuring participants can fully engage in the intervention.

Furthermore, weekly team meetings facilitate continuous process evaluation, allowing for structured feedback on data collection, recruitment challenges, and potential implementation barriers. At the end of the study, feasibility and user experience data, including responses from an evaluation questionnaire, will be analyzed to identify challenges and potential areas for improvement.

Measures

Patients complete four different types of questionnaires during their study participation at the following measurement time points: after recruitment (T0; baseline), before the intervention (pre-intervention), after the intervention (post-intervention), and at the end of the study (evaluation). All questionnaires were used in the German version. Additionally, physiological parameters (heart rate and blood pressure) are measured during the intervention phase. The pre-intervention, during-intervention, and post-intervention measurements are administered twice over two consecutive chemotherapy sessions (T1 and T2). Table 2 outlines the measures employed and the corresponding time points at which they are collected. Furthermore, saliva samples are collected both before and 25 minutes after the intervention, while heart rate and blood pressure are recorded at 5-minute intervals during the intervention. Below is a detailed presentation of all measures used in the study.

Table 2

Overview of measures used for the study and the measurement time points.

Measure	Baseline	Pre-intervention	During intervention	Post-intervention	Evaluation
Demographic data	X				
Cancer-related data	X				
VAS-Social support	X				
Previous experiences with mindfulness and music for relaxation	X				
ASKU	X				
PHQ-4	X	X			
STAI-Trait	X				
Salivary cortisol		X		X	
STAI-State		X		X	
PA-F-KF		X		X	
MIDOS-2		X		X	
VAS-Anxiety		X		X	
VAS-Relaxation		X		X	
Heart rate			X		
Blood pressure			X		
VAS-Tolerability of chemotherapy				X	
VAS-Perceived duration of chemotherapy				X	
PSSUQ					X
VR-specific evaluation (self-developed)					X
Music-specific evaluation (self-developed)					X

Note: VAS – visual analogue scale; ASKU – Short Scale for Measuring General Self-efficacy Beliefs; PHQ-4 – Patient-Health-Questionnaire-4; STAI – State-Trait-Anxiety-Inventory; PA-F-KF – Fear of Progression Questionnaire Short Form; MIDOS – Minimal Documentation System; PSSUQ – Post-study System Usability Questionnaire; VR – Virtual Reality

Baseline measures

Screening

In order to determine the reasons for a lack of interest in participating in the study, even though the patients addressed in the IAC fulfill the inclusion criteria, a screening form will be distributed. This screening form has been developed by the first authors on the basis of verbal feedback received during recruitment conversations on site. On this form, patients can tick items such as: "Concern about too much additional effort during therapy", "No need, as chemotherapy is not perceived as unpleasant or stressful", or "No interest in the research question or in the VR

technology". A refusal to provide further feedback is also possible, as well as a statement of unstated reasons. Completion of the screening questionnaire is voluntary and anonymous. The screening form can be viewed in Appendix C.

Generalized Anxiety Disorder-7 Questionnaire (GAD-7)

Patients are screened for generalized anxiety using the German version of the Generalized Anxiety Disorder-7 Questionnaire [21], translated by Löwe et al. [32]. It measures how much subjects have been bothered by the following problems over the past two weeks indicated on a 4-point Likert scale (0 = *not at all*, 1 = *for several days*, 2 = *more than half the days*, 3 = *nearly every day*): feeling nervous, anxious, or on edge; not being able to stop or control worrying; worrying too much about different things; trouble relaxing; being so restless that it is hard to sit still; becoming easily annoyed or irritable; feeling afraid, as if something awful might happen. Participants can score a value between 0 and 21 with higher values indicating a higher degree of generalized anxiety symptoms. A recent study confirmed the reliability and validity of the GAD-7 in a German population sample with overall good internal consistency of α = .85 [20]. Patients are screened for a score of at least 5 indicating a mild generalized anxiety [21].

Demographic and cancer-related data

Patients are asked to indicate their gender (female, male, diverse), age, highest educational level (based on the German educational system), and family status (unwed, in a partnership, married/ civil partnership, divorced/ civil partnership annulled, widowed/ registered partner deceased).

Further, cancer-related data is assessed based on the Basic Documentation for Psycho-Oncology [33, 34]. Patients are asked to report their main cancer diagnosis, whether it is the first diagnosis and whether there has been a previous cycle of chemotherapy, what treatments they have received in the last 2 months, whether they have previously received psychiatric treatment or psychotherapy, and whether they are currently taking any psychopharmacological medication.

Short Scale for Measuring General Self-efficacy Beliefs (ASKU)

The Short Scale for Measuring General Self-efficacy Beliefs [35] is a self-report based questionnaire assessing the participant's perceived self-efficacy using three items on a 5-point Likert scale (1 = *never or very rarely true*; 5 = *very often or always true*). The ASKU reveals a reliability of between ω = .81 and ω = .86. The factorial validity can be described as sufficient with factor loadings of .77 and higher and the model fit is validated. The construct validity of the questionnaire was also validated by comparing the items to questionnaires assessing similar constructs [35].

The State-Trait-Anxiety-Inventory (STAI-Trait)

The short trait-version of the STAI [36] assesses trait-anxiety as a relatively stable personality characteristic and consists of 10 items that are rated on a 8-point Likert-Scale (1 = *not at all*; 8 = *completely*). Three of the 10 items have to be inverted prior to calculation. Total scores can range between 10 and 80 with higher scores indicating higher trait-anxiety. The trait-version reveals also excellent internal consistency ranging between α = .88 and α = .94 and the criterion validity was confirmed by correlating the items to other measures assessing similar constructs [37].

Primary outcome measure

The State-Trait-Anxiety-Inventory (STAI-State)

The State-Trait-Anxiety-Inventory (STAI) [36] is a self-report questionnaire that can assess both situational state-anxiety and stable trait-anxiety. The short version with 10 items was used to assess the situational state-anxiety as the primary outcome [36]. The response for each of the 10 items is based on an 8-point Likert scale (1 = *not at all*; 8 = *completely*). Four items need to be inversed before calculating the total score. The STAI-state score ranges between 10 and 80. Higher

values indicate higher state-anxiety. The STAI reveals an excellent internal consistency of α = .90 [36].

Secondary outcome measures

Visual Analogue Scales (VAS)

Visual analogue scales (VAS) are used to assess anxiety ('How anxious do you feel in this moment?' from 'not anxious at all' to 'maximally anxious'), relaxation ('How do you feel at this moment?' from 'maximally tense' to 'maximally relaxed'), social support ('How much do you feel supported by your social network in the moment?' from 'not at all supported' to 'maximally supported'), tolerance of the chemotherapy session ('How bearable did you perceive today's chemotherapy treatment?' from 'minimally tolerable' to 'maximally tolerable'), and the perceived duration of the chemotherapy session ('How quickly do you feel today's chemotherapy session has gone so far?' from 'not quick at all' to 'maximally quick'). Patients are asked to rate their answer by marking a point on a 10 cm long line from 0 to 100, with 0 indicating total disagreement and 100 indicating total agreement. Visual analogue scales are a quick and economical method for the assessment of different subjective states and symptoms [38, 39].

Patient-Health-Questionnaire-4 (PHQ-4)

The German version of the Patient-Health-Questionnaire-4 [40] assesses anxiety and depression using four items on a 4-point Likert scale (0 = *not at all*; 3 = *almost every day*). The values are added for the total score, higher values indicating a greater extend of anxiety and depression. The scale showed good internal consistency with α > .80. A factor analysis revealed good fit with 84% of total variance explained. In a recent study, the internal consistency of the instrument for the German population could be again confirmed as good (ω = .85) [41].

Fear of Progression Questionnaire Short Form (PA-F-KF)

The Fear of Progression Questionnaire Short Form [42] consists of 12 items that are answered on a 5-point Likert scale (1 = *never*; 5 = *very often*). The questionnaire assesses patient's fear of progression on five dimensions (affective reaction, partnership/family, occupation, loss of autonomy) and shows overall good internal consistency (α = .87) [42]. The construct validity of the items was confirmed by correlating the items to other measures assessing similar constructs (HADS, PCL-C, SF-8, LAP-R). A factor analysis revealed a one-dimensional structure, explaining 42% of the total variance [42]. The psychometric properties were also confirmed in more recent studies. For example, a study by Hahn [43] found an internal consistency of α = .88 for the PA-F-KF.

Minimal Documentation System (MIDOS-2)

The Minimal Documentation System (MIDOS-2) [44] is a self-report questionnaire assessing participant's symptom-related afflictions due to chemotherapy-associated side effects on a 4-point Likert scale (0 = *none*; 3 = *major afflictions*). In total, there are 13 items. Ten items are measuring the side effects pain, nausea, regurgitation, shortness of breath, constipation, weakness, lack of appetite, fatigue, depression and anxiety. Two more items leave open spaces for naming other afflictions and one more item assesses how the participant is feeling that day, ranging from 0 (*very bad*) to 4 (*very good*). The sum score of each item describes the extend of complaints for each participant. The questionnaire reveals good psychometric properties, with internal consistencies varying between α = .67 and .73 and the test-retest variability varying between r = .69 and r = .57 [44]. The psychometric properties were also confirmed for patient groups in non-palliative care [45].

Heart rate and blood pressure

Heart rate and blood pressure are measured continuously from the beginning to the end of the intervention in 5-minute intervals in beats per minute (bpm) using a pulse oximeter and blood

pressure monitor. A member of the study team records these values while accompanying the intervention.

Saliva cortisol

Salivary samples are assessed to measure levels of cortisol in nmol/l. For this purpose, each participant insalivates a cotton swab for at least 30 seconds before the beginning of the intervention and 25 minutes after the end of the intervention. All saliva samples are stored in dark at -20 degrees Celsius. Analyses will be carried out by Dresden LabService GmbH, Technical University of Dresden, Germany, using chemiluminescence immunoassay.

Evaluation

The evaluation was conducted for all three study arms, with tailored formats for each intervention group as well as the control group. For the VR group, seven items from the Post-Study System Usability Questionnaire (PSSUQ) [46] (items 1, 6, 11, 16–19) were used. The full questionnaire consists of 21 items and was translated into German during a previous study conducted by our group [47]. The selected items have been slightly adapted to better fit the specific VR application used in the study. Responses are given on a 7-point Likert scale (1 = *strongly disagree*, 7 = *strongly agree*), with the overall score reflecting the perceived usability of the VR system by the patients.

Additionally, patients were asked to rate several self-developed items that were tailored to the specific intervention (VR or music). These items assess whether the intervention was pleasing, relaxing, boring, or annoying, whether it helped to alleviate any unpleasant feelings, induce calmness, and create a pleasant atmosphere during the chemotherapy session. Patients also rated whether they liked the intervention, whether they would choose to use it again in a future chemotherapy session, whether they could focus more on the intervention than on their own thoughts, and whether they were already familiar with the intervention. All these items are also rated on a 7-point Likert scale (1 = *strongly disagree*, 7 = *strongly agree*).

Lastly, all groups were asked to indicate which type of intervention (VR, music, or none) they would prefer to use during a future chemotherapy session, rated on a 7-point Likert scale (1 = *not at all,* 7 = *very much*). The evaluation questionnaire also includes two additional free-text fields titled "Suggestions for Enhancing the Utilization of VR/Music" and "Other Comments." The complete evaluation questionnaire is available for review in Appendix D

Recruitment and participant timeline

The study team initiates contact with patients during their outpatient visit to the IAC and inquires about their interest in participating in the study. Subsequently, the treating physicians are consulted to confirm the patients' eligibility for the study, and their approval is sought once eligibility is confirmed. Patients are then contacted again by the study team during their next chemotherapy session. All patients provide written informed consent prior to their participation in the study. Figure 2 shows the participant timeline. The patient information and consent form can be found in Appendix E.

The study team screens for general anxiety symptoms using the Generalized Anxiety Disorder-7 Questionnaire (GAD-7) [20, 21]. To ensure that participants are experiencing a level of anxiety significant enough to benefit from the interventions and demonstrate measurable changes in the primary outcome variable, only patients with at least moderate anxiety (defined as a score ≥5) are included in the study. Patients are randomly assigned to one of three intervention arms using computer-generated random numbers; however, they remain blinded to their group allocation until the first intervention time point (T1).

After recruitment, participants complete the first questionnaire for baseline assessment (T0). The intervention begins during the subsequent chemotherapy session at the IAC (T1). At this point, patients are informed of their study allocation and receive the pre-intervention questionnaire. Following the completion of the questionnaires, and after the flushing and premedication

processes as part of the chemotherapy session, patients provide the first saliva sample by insalivating a cotton swab. The study team then assists patients in initiating the intervention.

Patients in intervention group 1 wear a VR headset and headphones and begin the mindfulness exercise. Patients in intervention group 2 put on headphones and listen to music. Patients in the control group (3) receive no additional treatment. A member of the study team remains with the patient, collecting data on heart rate and blood pressure at 5-minute intervals. After approximately 15-20 minutes, the intervention concludes. Patients then complete the post-intervention questionnaire, and a second saliva sample is collected after 25 minutes. This procedure is repeated during the subsequent chemotherapy session (T2). Finally, patients in all groups receive a questionnaire specifically evaluating the intervention immediately after the second measurement time point. Participants in groups 2 and 3 are given the opportunity to try the VR intervention independently of data collection.

Sample Size

Based on previous literature, we estimate an effect size of 0.25. The G*Power 3.1.9.7 software [48] was employed to determine the requisite sample size. Assuming that the probability of error does not exceed α=.05 and that the power (1-β) is at least 0.95, an analysis of variance with three groups and two time points with N = 66 subjects can demonstrate an effect size of 0.25. Based on previous research projects, we calculate a drop-out rate of 20%, which increases the total sample size to N = 82.

Risk to Patients

Possible risks that can arise, particularly during the VR intervention, are cybersickness [49] and increased stress levels or anxiety due to the complex technical set-up and instructions. In addition, the sensory isolation from the environment can lead to a feeling of loss of control. To counteract this, it was ensured that at least one person from the study team was always present with the patients during the intervention. Patients were able to contact the study team directly if they had any questions, problems or felt unwell. In addition, care was taken to ensure that patients were shielded from disturbances as much as possible. During the data collection phase, study personnel will be present to monitor and record any spontaneously occurring adverse events; if such events occur, they will be discussed with the treating physician and reviewed during the weekly team meetings. Patients will continue to receive ongoing medical care after the end of the trial, where potential side effects can still be discussed. In addition, short-term access to psycho-oncological support will be provided through the department of psychosomatic medicine and psychotherapy for patients who express a need for psychological support after study completion.

Data Monitoring and Management

A randomization file will be used to allocate a participant code to the intervention arms. A recruitment file is used to allocate the participant code to all included patients and, further, contains patients' diagnoses, medical clearance and information about the recruitment process (treating physicians' approval for study participation, checklist for how many attempts were needed to meet the patient in the IAC, date of informed consent). A data file contains pseudonymized survey data of patients to each measurement time point. Another file will be used to anonymously assess drop-outs, screening failures and reasons for non-participation or lack of interest. The data will be entered by the study team accountable for implementation of the study and will be double checked by another team member. Supervision by the study team during chemotherapy sessions ensures the questionnaires are fully completed by participants. Data records will be kept separately from the consent forms. Data records of patients who did not meet the inclusion criteria (screening failures) will be disposed of in accordance with data protection regulations. After collection, salivary cortisol samples will be temporarily stored in a freezer (-20 degree Celsius) and sent to a laboratory (Dresden LabService GmbH, Technical University of Dresden, Germany). Questionnaires and cortisol levels derived from saliva samples will be stored as combined research data for at least 10 years (in accordance with the principles of Good Clinical

Practice). Access to the anonymized final trial dataset will be granted upon request to the study team; the intended use of the data must be disclosed, after which the appropriate dataset will be provided.

Patients will receive standard medical care during the whole participation. No adverse side effects are expected due to the interventions and participating patients do not face higher risks compared to patients who are not participating in the current study. As a member of the study team will supervise each session, participants can terminate the intervention at any time. Participants can report any side effects to the study team and use the evaluation questionnaires for thorough feedback. Therefore, study monitoring is not needed.

Randomization, Blinding, and Treatment Allocation

Randomization is conducted using random numbers. Using a computer program (Microsoft Excel, Microsoft Corporation), a team member who does not participate in recruiting patients generates an excel sheet with numbers representing the three intervention groups (using the command "=RANDBETWEEN(1,3)"). The random allocation sequence assigns patients in equal proportions to one of the three intervention groups. In this sheet, the numbers are masked until a new patient is enrolled, which assures that members of the study team accountable for participant recruitment are blinded until patients' consent. Patients are blinded about their study arm allocation until the first intervention time-point (T1). There is no further blinding of the study team.

Statistical Analysis

All characteristics collected in the study are described in detail using descriptive methods. Qualitative characteristics are indicated by absolute and relative frequencies. Quantitative characteristics are described using mean values, standard deviation, median, minimum and maximum. Parametric analysis methods are used to evaluate the primary and secondary target variables. If assumptions for parametric tests are violated, appropriate non-parametric alternatives will be considered.

Situational anxiety as the primary outcome (measured using the STAI state) is analyzed using separate 3x2 mixed factorial ANOVAs for each of the two chemotherapy sessions, with the between-subject factor "intervention" (virtual reality vs. music vs. control) and the within-subject factors "time" (before vs. after intervention). A probability of error of α=.05 is set. The unit of analysis is individual patients. Effect sizes will be reported using partial eta squared (η^2) for ANOVA analyses. Cohen's d is calculated for post-hoc comparisons when appropriate. The secondary outcome criteria are analyzed exploratively, also using ANOVAs and post hoc tests as appropriate. There is no adjustment of the probability of error. The statistical analysis is carried out with the help of standard statistical software (SPSS 29). Participants will be included in the statistical analysis if they have completed both assessment time points and received the intervention for a minimum of 10 minutes per session. Furthermore, the intervention must be administered in consecutive sessions as scheduled. Participants who do not meet these criteria will be classified as dropouts. Both an intention-to-treat analysis and a per-protocol analysis will be performed. The results will be compared and discussed.

The feasibility of the intervention will be evaluated based on multiple data sources. A descriptive analysis of the screening and recruitment data will provide insights into patient participation and reasons for non-participation. Additionally, feasibility will be assessed based on study staff documentation during data collection sessions, as well as recorded reasons for dropout, and potential side effects. Furthermore, the evaluation questionnaire, which includes both usability assessment and self-developed items, will be analyzed. The participants' comments in the free text fields of the evaluation questionnaire will be categorized based on their content into issues and suggestions for improvement.

Protocol Amendments

Protocol amendments were requested initially on November 4th, 2022 to extend the sample due to a lack of subjects matching the inclusion criteria. Before the amendment, participants consisted solely of patients with a gynecological or senological diagnosis. After the amendment, participants with gastrointestinal and hematological diagnoses were also included. To improve the homogeneity of the sample, the GAD-7 with its cut-off criterion of a value ≥ 5 was introduced as a screening tool. These protocol amendments were granted November 19, 2022.

A second request to amend protocol was issued on August 3rd, 2023 to introduce a self-constructed screening questionnaire for further inquiry of reasons why patients may be disinterested in participation in the study. This protocol amendment was granted on August 9th, 2023.

Ethics and dissemination

The ethics committee of the medical faculty of Heinrich-Heine-University Düsseldorf has been obtained (2022-1880). Divergences or modifications of the study protocol will be documented and relevant cases will be reported to the ethics committee. For all processed data adherence to data protection regulations is warranted. Written informed consent is obtained from patients by the study team and patients are informed that they can withdraw their consent without explanation at any time without facing any consequences. Further, patients are informed that all stored personal data can be deleted upon demand at any point. All personal identifiers will be pseudonymized. The final data set can be assessed only by the study team. After the end of the study, the ethics committee will be informed within 90 days.

Findings of the trial will be reported by publishing in international scientific, peer-reviewed journals. Given several outcome parameters, several publications are planned. Further, presentations at conferences are planned. Until publication, the study team commits to full disclosure of the trial results.

Patient and Public Involvement

Patients and the public were not involved in the design, conduct, or reporting of this study. The research questions, study design, outcome measures, recruitment strategies, and dissemination plans were developed by the research team without direct input from patients, carers, or members of the public. This decision was made based on the specific nature and feasibility constraints of the study.

References

1. Wagland R, Richardson A, Armes J, Hankins M, Lennan E, Griffiths P. Treatment-related problems experienced by cancer patients undergoing chemotherapy: a scoping review. Eur J Cancer Care (Engl). 2014;24(5):605-17. doi:10.1111/ecc.12246.
2. Redeker NS, Lev EL, Ruggiero J. Insomnia, fatigue, anxiety, depression, and quality of life of cancer patients undergoing chemotherapy. Sch Inq Nurs Pract. 2000;14(4):275-290.
3. So WK, Marsh G, Ling WM, Leung FY, Lo JC, Yeung M, et al. The symptom cluster of fatigue, pain, anxiety, and depression and the effect on the quality of life of women receiving treatment for breast cancer: a multicenter study. Oncol Nurs Forum. 2009;36(4):E205-E214. doi:10.1188/09.ONF.E205-E14.
4. Puts MT, Tu HA, Tourangeau A, Fitch M, Springall E, Alibhai SMH. Factors influencing adherence to cancer treatment in older adults with cancer: a systematic review. Ann Oncol. 2014;25(3):564-77. doi:10.1093/annonc/mdt433.
5. Theofilou P, Panagiotaki H. A literature review to investigate the link between psychosocial characteristics and treatment adherence in cancer patients. Oncol Rev. 2012;6(1). doi:10.4081/oncol.2012.e5.
6. Arrieta O, Angulo LP, Núñez-Valencia C, Dorantes-Gallareta Y, Macedo EO, Martínez-López D, et al. Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. Ann Surg Oncol. 2012;20(6):1941-48. doi:10.1245/s10434-012-2793-5.
7. Fukushima T, Suzuki K, Tanaka T, Isobe K, Kubo A, Nakagawa Y, et al. Global quality of life and mortality risk in patients with cancer: a systematic review and meta-analysis. Qual Life Res. 2024;33(5):1391-407. doi:10.1007/s11136-024-03691-3.
8. Nguyen KT, Xiao J, Chan DN, Zhang M, Chan CW. Effects of music intervention on anxiety, depression, and quality of life of cancer patients receiving chemotherapy: a systematic review and meta-analysis. Support Care Cancer. 2022;30(7):5615-26. doi:10.1007/s00520-022-06881-2.
9. Trigueros-Murillo A, Martinez-Calderon J, Casuso-Holgado MJ, González-García P, Heredia-Rizo AM. Effects of music-based interventions on cancer-related pain, fatigue, and distress: an overview of systematic reviews. Support Care Cancer. 2023;31(8):5835-44. doi:10.1007/s00520-023-07938-6.
10. Pelekasis P, Matsouka I, Koumarianou A. Progressive muscle relaxation as a supportive intervention for cancer patients undergoing chemotherapy: a systematic review. Palliat Support Care. 2016;15(4):465-73. doi:10.1017/S1478951516000870.
11. Roffe L, Schmidt K, Ernst E. A systematic review of guided imagery as an adjuvant cancer therapy. Psychooncology. 2005;14(8):607-17. doi:10.1002/pon.889.
12. Cillessen L, Johannsen M, Speckens AE, Zachariae R. Mindfulness-based interventions for psychological and physical health outcomes in cancer patients and survivors: a systematic review and meta-analysis of randomized controlled trials. Psychooncology. 2019;28(12):2257-69. doi:10.1002/pon.5214.
13. Merluzzi TV, Pustejovsky JE, Philip EJ, Sohl SJ, Berendsen M, Salsman JM. Interventions to enhance self-efficacy in cancer patients: a meta-analysis of randomized controlled trials. Psychooncology. 2019;28(9):1781-90. doi:10.1002/pon.5148.
14. Seabrook E, Kelly R, Foley F, Theiler S, Thomas N, Wadley G, et al. Understanding how virtual reality can support mindfulness practice: mixed methods study. J Med Internet Res. 2020;22(3). doi:10.2196/16106.
15. Ma J, Zhao D, Xu N, Yang J. The effectiveness of immersive virtual reality (VR) based mindfulness training on improvement mental-health in adults: a narrative systematic review. Explore (NY). 2023;19(3):310-18. doi:10.1016/j.explore.2022.08.001.
16. Chirico A, Maiorano P, Indovina P, Milanese C, Giordano GG, Alivernini F, et al. Virtual reality and music therapy as distraction interventions to alleviate anxiety and improve mood states in breast cancer patients during chemotherapy. J Cell Physiol. 2020;235(6):5353-62. doi:10.1002/jcp.29422.

17. Wilson K, Scorsone G. The use of virtual reality technologies to reduce anxiety and improve experience in chemotherapy patients during treatment. Front Virtual Real. 2021;2:695449. doi:10.3389/frvir.2021.695449.
18. Gautama MSN, Huang TW, Haryani H. A systematic review and meta-analysis of randomized controlled trials on the effectiveness of immersive virtual reality in cancer patients receiving chemotherapy. Eur J Oncol Nurs. 2023;67:102424. doi:10.1016/j.ejon.2023.102424.
19. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, et al. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586. doi:10.1136/bmj.e7586.
20. Hinz A, Klein AM, Brähler E, Glaesmer H, Luck T, Riedel-Heller SG, et al. Psychometric evaluation of the generalized anxiety disorder screener GAD-7, based on a large German general population sample. J Affect Disord. 2017;210:338-44. doi:10.1016/j.jad.2016.12.012.
21. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder. Arch Intern Med. 2006;166(10):1092-7. doi:10.1001/archinte.166.10.1092.
22. Kabat-Zinn J. Mindfulness-based interventions in context: past, present, and future. *Clin Psychol Sci Pract.* 2003;10(2):144-56. doi:10.1093/clipsy/bpg016.
23. Goldberg SB, Riordan KM, Sun S, Davidson RJ. The empirical status of mindfulness-based interventions: A systematic review of 44 meta-analyses of randomized controlled trials. *Perspect Psychol Sci.* 2022;17(1):108-30. doi:10.1177/1745691620968771.
24. Hölzel BK, Lazar SW, Gard T, Schuman-Olivier Z, Vago DR, Ott U. How does mindfulness meditation work? Proposing mechanisms of action from a conceptual and neural perspective. *Perspect Psychol Sci.* 2011;6(6):537-59. doi:10.1177/1745691611419671.
25. Navarro-Haro MV, López-del-Hoyo Y, Campos D, Linehan MM, Hoffman HG, García-Palacios A, et al. Meditation experts try virtual reality mindfulness: A pilot study evaluation of the feasibility and acceptability of virtual reality to facilitate mindfulness practice in people attending a mindfulness conference. *PLoS One.* 2017;12(11):e0187777. doi:10.1371/journal.pone.0187777.
26. META. META Quest 2 [VR headset]. Menlo Park, CA: META; 2020. Available from: https://www.meta.com/quest-2/
27. Bose. Bose QuietComfort [Bluetooth headphones]. Frisco, TX: Bose Corporation; 2023. Available from: https://www.bose.com/en_us/products/headphones/quietcomfort.html
28. Hemsen B, Wittenborn A, Holsteg S, Karger A, Freitag S, Mildner P, et al. DeepVR: Konzeptuelle Grundlagen und Umsetzung eines Virtual Reality basierten Unterstützungssystems in der psychotherapeutischen Depressions-Behandlung. Mensch Comput. 2021. doi:10.1145/3473856.3474016.
29. Apple Inc. Apple iPod [Internet]. Frisco, TX: Apple Inc.; 2023. Available from: https://www.apple.com/ipod/
30. Nilsson U. The anxiety- and pain-reducing effects of music interventions: a systematic review. AORN J. 2008;87(4):780-807. doi:10.1016/j.aorn.2007.09.013.
31. Schaal NK, Brückner J, Wolf OT, Ruckhäberle E, Fehm T, Hepp P. The effects of a music intervention during port catheter placement on anxiety and stress. Sci Rep. 2021;11(1):85139. doi:10.1038/s41598-021-85139-z.
32. Löwe B, Decker O, Müller S, et al. Validation and Standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the General Population. Med Care. 2008;46(3):266-274. doi:10.1097/mlr.0b013e318160d093.
33. Herschbach P, Book K, Brandl T, Keller M, Marten-Mittag B. The Basic Documentation for Psycho-Oncology (PO-Bado) – an Expert Rating Scale for the Psychosocial Experience of Cancer Patients. Oncol Res Treat. 2008;31(11):591-596. doi:10.1159/000162287.

34. Knight L, Mussell M, Brandl T, et al. Development and psychometric evaluation of the Basic Documentation for Psycho-Oncology, a tool for standardized assessment of cancer patients. J Psychosom Res. 2008;64(4):373-381. doi:10.1016/j.jpsychores.2008.01.003.
35. Beierlein C, Kemper CJ, Kovaleva A, Rammstedt B. Kurzskala zur Erfassung allgemeiner Selbstwirksamkeitserwartungen (ASKU). Methoden Daten Anal. 2013;7(2):28. doi:10.12758/mda.2013.014.
36. Grimm J. State-Trait-Anxiety Inventory nach Spielberger: Deutsche Lang- und Kurzversion. Methodenforum der Universität Wien. MF-Working Paper. 2009;2.
37. Laux L, Glanzmann P, Schaffner P, Spielberger CD. Das State-Trait-Angstinventar. Weinheim: Beltz; 1981.
38. Heller GZ, Manuguerra M, Chow R. How to analyze the Visual Analogue Scale: Myths, truths and clinical relevance. Scand J Pain. 2016;13(1):67-75. doi:10.1016/j.sjpain.2016.06.012.
39. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. Res Nurs Health. 1990;13(4):227-236. doi:10.1002/nur.4770130405.
40. Löwe B, Wahl I, Rose M, Spitzer C, Glaesmer H, Wingenfeld K, et al. A 4-item measure of depression and anxiety: Validation and standardization of the Patient Health Questionnaire-4 (PHQ-4) in the general population. *J Affect Disord.* 2010;122(1-2):86-95. doi:10.1016/j.jad.2009.06.019.
41. Wicke FS, Krakau L, Löwe B, Beutel ME, Brähler E. Update of the standardization of the Patient Health Questionnaire-4 (PHQ-4) in the general population. J Affect Disord. 2022;312:310-314. doi:10.1016/j.jad.2022.06.054.
42. Mehnert A, Herschbach P, Berg P, Henrich G, Koch U. Progredienzangst bei Brustkrebspatientinnen - Validierung der Kurzform des Progredienzangstfragebogens PA-F-KF/ Fear of progression in breast cancer patients – validation of the short form of the Fear of Progression Questionnaire (FoP-Q-SF). Z Psychosom Med Psychother. 2006;52(3):274-288. doi:10.13109/zptm.2006.52.3.274.
43. Hahn AJS. Prädiktoren von Progredienzangst bei Prostatakrebspatienten nach radikaler Prostatektomie: Spielen subjektive Krankheitsrepräsentationen und die Familienanamnese eine Rolle? [dissertation]. München: Technische Universität München; 2015.
44. Stiel S, Matthes ME, Bertram L, et al. Validierung der neuen Fassung des Minimalen Dokumentationssystems (MIDOS2) für Patienten in der Palliativmedizin. Schmerz. 2010;24(6):596-604. doi:10.1007/s00482-010-0972-5.
45. Plöger MM. MIDOS-Validierung des Minimalen Dokumentationssystems für Palliativpatienten-Vergleichsgruppen mit chronisch kranken und gesunden Probanden [dissertation]. Bonn: Universitäts- und Landesbibliothek Bonn; 2016.
46. Lewis JR. Psychometric Evaluation of the Post-Study System Usability Questionnaire: The PSSUQ. Proc Hum Factors Soc Annu Meet. 1992;36(16):1259-1260. doi:10.1177/154193129203601617.
47. Holsteg S, Askeridis JM, Krajewski J, et al. Virtual reality roleplays for patients with depression: A user experience evaluation. Internet Interv. 2024;35:100713. doi:10.1016/j.invent.2024.100713.
48. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39(2):175-191. doi:10.3758/bf03193146.
49. Behr KM, Nosper A, Klimmt C, Hartmann T. Some Practical Considerations of Ethical Issues in VR Research. Presence (Camb Mass). 2005;14(6):668-676. doi:10.1162/105474605775196535.

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Steffen Holsteg is responsible for the overall content as guarantor.

Figure Legend

Figure 1. Screenshot of the VR environment

Figure 2. Participant timeline

Screenshot of the Virtual Reality mindfulness intervention.

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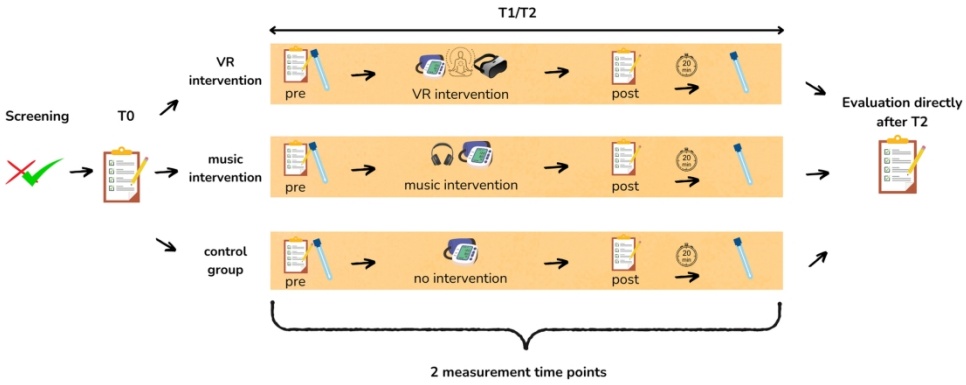

Participant timeline and study procedure. / Note: VR – Virtual Reality

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Appendix A

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups	n/a

		overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7

Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12

Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found,	n/a

		if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	2
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	10
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

Appendix B

Music Title Overview

			Duration
Jazz	1.	Bill Evans, Danny Boy	3:41
	2.	The Niall O'Sullivan Quartet, Moon Love	4:16
	3.	Keith Jarrett, Don't ever leave me	3:22
	4.	Billy Higgins, Silence	8:45
	5.	Keith Jarrett, Over the Rainbow	6:02
	6.	Keith Jarrett, Paint my Heart Red	6:15
	7.	Bill Evans, Some Other Time	5:19
	8.	Miles Davies, My funny Valentine	6:02
	9.	Bill Evans, When I fall in Love	4:54
	10.	Coltrane Quartet, It's easy to remember	2:47
	11.	Billy Higgins, Round Midnight	11:36
Klassik	1.	Johann Sebastian Bach – Orchestersuite Nr. 3 D-Dur („Air")	5:28
	2.	Yiruma – River Flows In You	3:06
	3.	Claude Debussy – Prelude No. 8 „La Fille aux cheveux de lin"	2:47
	4.	Wolfgang Amadeus Mozart – Serenade in G, K. 525 „Eine Kleine Nachtmusik"	3:35
	5.	Camille Saint-Saëns – Le carnaval des animaux – le cygne	2:50
	6.	Frédéric Chopin - Nocturne in Es-Dur, Op. 9, No. 2	4:05
	7.	Georg Friedrich Händel – Wassermusik, Suite Nr. 1 in F-Dur, „Air"	7:36
	8.	Gabriel Fauré – Pavane, Op. 50	5:37
	9.	Claude Debussy – Suite bergamasque „Clair de lune"	4:39
	10.	Wolfgang Amadeus Mozart – Violinkonzert No.3, 2. Satz: Adagio	8:49
	11.	Wolfgang Amadeus Mozart – 21. Klavierkonzert, 2. Satz: Andante	7:07
	12.	Edvard Grieg – Peer-Gynt-Suite Nr. 1, „Morgenstimmung"	3:53
	13.	Wolfgang Amadeus Mozart – Klarinettenkonzert, 2. Satz: Adagio	7:00
	14.	Ludovico Einaudi – Le Onde	5:24
	15.	Georg Friedrich Händel – Oboenkonzert Nr. 1, 1. Satz: Adagio	3:26
	16.	Philip Glass – Metamorphosis Two	7:17
Lounge	1.	Chillout	6:10
	2.	Wonderful Chill Out Music	4:55
	3.	Portrait of Me	5:08
	4.	Sex Music	5:01
	5.	Brand New (Inspirational Music)	6:10
	6.	Life	4:45
	7.	Real and True	4:39
	8.	Weekend Lounge	5:54
	9.	Pilates Music	5:08
	10.	Meditation Music for Relaxation	4:48
	11.	Soft Chillout Music	3:54
	12.	Stop (Breathing and Positive Thou)	4:42
	13.	Chilled Moods	5:28
	14.	Pure Chill Out	6:22
Meditation	*CD: MusiCure 1. The Journey*		
	1.	Titel 1	15:37
	2.	Titel 2	15:23
	3.	Titel 3	9:30
	4.	Titel 4	11:49
	5.	Titel 5	9:20
	6.	Titel 6	3:11
	7.	Titel 7	5:53

ViSu
Virtual Reality & Sound Intervention under Chemotherapy

Screening Form

Patient-ID: (only after inclusion)

Date of Screening: ☐☐.☐☐.2 0 2 ☐

Inclusion Criteria

Age of patient:	☐ ≥18 years ☐ <18 years
Does the patient have sufficient language skills to participate?	☐ yes ☐ no
Is there a confirmed diagnosis of cancer?	☐ yes ☐ no
Is the patient receiving intravenous chemotherapy (duration of application including flushing at least 60 minutes)?	☐ yes ☐ no
Will the first survey take place at least at the second chemotherapy session?	☐ yes ☐ no
At least five chemotherapy sessions outstanding?	☐ yes ☐ no
GAD-7 ≥ 5?	☐ yes ☐ no

Exclusion Criteria

Are there any serious visual and/or hearing impairments?	☐ yes ☐ no
Are there any relevant pre-existing conditions?[1]	☐ yes ☐ no
Were there any serious side effects from the first chemotherapy?	☐ yes ☐ no
Is the chemotherapy being carried out as part of another study?	☐ yes ☐ no
Are there any brain metastases?	☐ yes ☐ no

Inclusion

Education has taken place	☐ yes ☐ no
Inclusion and exclusion criteria enable participation	☐ yes ☐ no

Does the patient consent to participate in the study?	☐ yes ☐ no

In case of "Yes", the declaration of consent will be signed. In case of "No", the second page will be filled in.

[1] Neurological/psychiatric pre-existing conditions that affect the vestibular system, impair the sense of balance or alter visual perception, epilepsy or claustrophobia.

ViSu
Virtual Reality & Sound Intervention under Chemotherapy

Screening Form

Please check all that apply:

Multiple responses possible

☐ Own current state of health (physical, mental) speaks against participation.

☐ Focus should be on chemotherapy, participation is perceived as disruptive.

☐ Concern about too much additional effort during therapy.

☐ Concern about possible side effects.

☐ Concern about data protection.

☐ Concern about the collection of saliva samples.

☐ No need, as chemotherapy is not perceived as unpleasant or stressful.

☐ No need, as own strategies for distraction and bridging time are used (reading, smartphone/tablet, accompanying person, fellow patients, sleeping,…)

☐ No interest in participating in clinical trials in general.

☐ No interest in the question or in the VR technology.

☐ No interest in or skepticism about the effectiveness of the interventions.

☐ No interest in psycho-oncological support services.

If none of the points above apply or if further comments should be made, the free text field below may be used:

☐ No further indications of reasons.

Many thanks!

☐ Patient did not want to provide feedback. *(Only to be filled in by the research team)*

ViSu
Virtual Reality & Sound Intervention under Chemotherapy

Date: _____

Patient-ID: _____

Evaluation Form VR Group

Below you are asked to rate the user-friendliness of the virtual reality application you have just tested. Please read each statement and mark the answer option that best applies to you.

	does not apply at all						applies completely
	1	2	3	4	5	6	7
Overall, I am pleased with how easy it was to use the VR application.	☐	☐	☐	☐	☐	☐	☐
I felt comfortable while using the VR application.	☐	☐	☐	☐	☐	☐	☐
The information presented through the VR application was clearly understandable.	☐	☐	☐	☐	☐	☐	☐
The presentation and design of the VR mindfulness exercise was pleasant.	☐	☐	☐	☐	☐	☐	☐
I enjoyed the VR application.	☐	☐	☐	☐	☐	☐	☐
The application of virtual reality offers all the possibilities I expected from it.	☐	☐	☐	☐	☐	☐	☐
Overall, I am satisfied with the use of the VR application.	☐	☐	☐	☐	☐	☐	☐
Wearing the VR glasses was comfortable.	☐	☐	☐	☐	☐	☐	☐
The VR glasses were disruptive.	☐	☐	☐	☐	☐	☐	☐
The VR mindfulness exercise was pleasant.	☐	☐	☐	☐	☐	☐	☐
The VR mindfulness exercise was relaxing.	☐	☐	☐	☐	☐	☐	☐
I would like to do this or another VR mindfulness exercise again at a future appointment.	☐	☐	☐	☐	☐	☐	☐
The VR mindfulness exercise helped me to tolerate unpleasant feelings.	☐	☐	☐	☐	☐	☐	☐
The VR mindfulness exercise made the atmosphere pleasant during chemotherapy.	☐	☐	☐	☐	☐	☐	☐
The VR mindfulness exercise calmed me down.	☐	☐	☐	☐	☐	☐	☐
I enjoyed the VR mindfulness exercise.	☐	☐	☐	☐	☐	☐	☐
I already knew the mindfulness exercise.	☐	☐	☐	☐	☐	☐	☐

Three interventions were compared in this project: the use of a VR mindfulness exercise, the use of music (selection from four genres: meditation, classical, lounge, jazz) and a control condition without intervention.

Please rate the statements by ticking the box that most closely matches your feelings:

	Not at all						Very much
At my next chemotherapy appointment, I would like to use the VR application again.	☐	☐	☐	☐	☐	☐	☐
At my next chemotherapy session, I would like to listen to music (selection from the genres mentioned above).	☐	☐	☐	☐	☐	☐	☐
At my next chemotherapy session, I would like to use neither the VR mindfulness exercise nor the music (selection from the genres mentioned above).	☐	☐	☐	☐	☐	☐	☐

Do you have any suggestions for improving the use of VR glasses?

Other notes:

Thank you for your participation!

ViSu
Virtual Reality & Sound Intervention under Chemotherapy

Date: _____

Patient-ID: _____

Evaluation Form Music Group

Please check the box that best reflects your feelings.

	does not apply at all						applies completely
	1	2	3	4	5	6	7
The music intervention was pleasant.	☐	☐	☐	☐	☐	☐	☐
The music intervention was relaxing.	☐	☐	☐	☐	☐	☐	☐
I would like to hear this or similar music again at my next appointment.	☐	☐	☐	☐	☐	☐	☐
The music was disruptive.	☐	☐	☐	☐	☐	☐	☐
The music helped me to endure unpleasant feelings.	☐	☐	☐	☐	☐	☐	☐
The music made the atmosphere pleasant during chemotherapy.	☐	☐	☐	☐	☐	☐	☐
The music calmed me down.	☐	☐	☐	☐	☐	☐	☐
I enjoyed the music.	☐	☐	☐	☐	☐	☐	☐
I already knew some of the songs.	☐	☐	☐	☐	☐	☐	☐

Three interventions were compared in this project, the use of a VR mindfulness exercise, the use of music (selection from four genres: meditation, classical, lounge, jazz) and a control condition without intervention.

Please rate the statements by ticking the box that most closely matches your feelings:

	Not at all						Very much
At my next chemotherapy appointment, I would like to listen to music again (selection from the genres mentioned above).	☐	☐	☐	☐	☐	☐	☐
At my next chemotherapy appointment, I would like to use the VR application.	☐	☐	☐	☐	☐	☐	☐
At my next chemotherapy appointment, I would like to use neither the VR mindfulness exercise nor the music (selection from the genres mentioned above).	☐	☐	☐	☐	☐	☐	☐

Do you have any suggestions for improving the use of music?

Other notes:

Thank you four your participation!

ViSu
Virtual Reality & Sound Intervention under Chemotherapy

Date: _____

Patient-ID: _____

Evaluation Form Control Group

In this project, three interventions were compared: the use of a VR mindfulness exercise, the use of music (selection from 4 genres: meditation, classical, lounge, jazz) and a control condition without intervention. **Please rate the statements by checking the box that most closely matches your feelings:**

	Not at all						Very much
At my next chemotherapy appointment, I would like to use the VR application.	☐	☐	☐	☐	☐	☐	☐
At my next chemotherapy appointment, I would like to listen to music (selection from the genres mentioned above).	☐	☐	☐	☐	☐	☐	☐
At my next chemotherapy appointment, I would like to use neither the VR mindfulness exercise nor the music (selection from the genres mentioned above).	☐	☐	☐	☐	☐	☐	☐

Do you have any suggestions for improving the use of music?

Other notes:

Thank you for your participation!