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Use of virtual reality in port implantation to reduce perioperative anxiety and pain: protocol for a randomised controlled pilot trial at a single German university hospital (VIP-trial; DRKS00028508)

Sandra Graf,[1,2] Hannah Feldmann,[1] Lisa S Hunold,[1,2] Kira C Steinkraus,[1,3] Nadir Nasir,[1,3] Christoph W Michalski,[1,2] Colette Dörr-Harim,[1,2] Felix J Hüttner [1,3]

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For numbered affiliations see end of article.

Correspondence to
Dr Felix J Hüttner;
felix.huettner@uniklinik-ulm.de

ABSTRACT

Introduction Intravenous access port implantation is commonly performed under local anaesthesia, which offers advantages such as increased patient satisfaction and resource savings compared with general anaesthesia. However, patients may experience increased perioperative stress and anxiety in the operating room setting without general anaesthesia. Virtual reality (VR) distraction or hypnosis during surgery under local anaesthesia may help patients to auditorily and visually separate from their real environment and engage with a virtual environment through hypnorelaxing guidance. Previous studies suggested that VR hypnosedation may reduce the use of sedatives or general anaesthesia, and may offer additional benefits such as reducing postoperative pain and nausea, and promoting faster patient discharge.

Methods and analysis The VIP trial is a randomised controlled pilot trial comparing the usage of VR during port implantation with the current standard of care (local anaesthesia and analgosedation if needed). A total of 120 adult patients are included after screening for eligibility and obtaining informed consent. Patients are randomised preoperatively in a 1:1 ratio to the trial groups. The main outcomes are change of perioperative anxiety and pain. Further outcomes include patient satisfaction and tolerability, perioperative analgesia and sedation, occurrence of postoperative nausea, vomiting and VR sickness symptoms, surgeon's satisfaction, procedure duration, postoperative complications until postoperative day 30 and patient willingness to hypothetically undergo port implantation again under the same conditions.

Ethics and dissemination The VIP trial has been approved by the Ethics Committee of the Medical Faculty of Ulm University (reference number 03/22). If the intervention demonstrates that VR can effectively reduce perioperative anxiety and pain, it may become a novel standard of care to minimise the need for analgosedation or general anaesthesia in port implantation procedures and improve patient outcomes. The results will be submitted to a peer-reviewed journal in the field and will be presented at applicable conferences to ensure rigorous evaluation and access for the academic community.

Trial registration number German Clinical Trials Register: DRKS00028508; registration date 15 March 2022; Universal Trial Number: U1111-1275-4995.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ VIP is a randomised controlled pilot trial with meticulous methodology and clearly defined endpoints.
⇒ The trial is focused on patient-relevance with a selection of clearly defined endpoints and validated patient-reported outcome measures.
⇒ A limitation of the trial is its pilot status with a rather small sample size, forming the basis for a subsequent larger confirmatory multicentre trial.

INTRODUCTION

Within the last decade, the number of outpatient surgical procedures has grown substantially.[1] Totally implantable intravenous access port implantation is one of these procedures, which is usually performed in an outpatient setting and under local anaesthesia.[2 3] Compared with general anaesthesia, port implantation under local anaesthesia has been shown to save material resources and manpower, leading to potential economic benefits due to faster turnaround times.[4] Furthermore, local anaesthesia offers several advantages over general anaesthesia such as reduced postoperative pain and nausea, as well as a reduced risk of adverse reactions associated with systemic drug administration and faster patient discharge.[5] However, surgical interventions without general anaesthesia can result in increased perioperative stress and anxiety, as patients often feel a loss

of control, have fear of pain and experience discomfort in the operation room setting. Studies on perioperative anxiety suggest that its magnitude may have an impact on postoperative pain intensity, the requirement for analgesics, and, depending on the procedure, even morbidity and mortality.[6] The anxiety triggered by surgery leads to a stress response that both increases the need for analgesics, affects postoperative recovery and increases the risk of infection by reducing the immune response.[7] Furthermore, greater preoperative anxiety may be associated with a higher likelihood of chronic pain.[8]

Virtual reality (VR) as a method of relaxation and distraction, has been shown to effectively reduce pain, anxiety, depression, fatigue and increases the patient's satisfaction in a wide range of disciplines. A significant reduction in pain was demonstrated for both, during and after various interventions with VR.[9–12] As positive side effects, patients also reported a better sense of well-being, less emotional discomfort and less time spent worrying about pain during the procedure compared with control groups. VR experience may create a sense of calm and relaxation promoted by the immersive visuals and soothing sounds. This relaxation component may have an incremental value regarding pain relief and may contribute to a change in perceptions. Also, by immersing a virtual environment, VR may block peripheral stimuli by reducing the brain's processing pain signals.[13] The tolerability of a VR headset was associated with fewer side effects in comparison to pharmacological analgesics and was perceived by patients as pleasant and fun. Most patients indicated a willingness to use VR again for future procedures.[14] Thus, VR with its minimal side effects (eg, dizziness, nausea, vomiting, headache and motion sickness) could be established to enhance the patient's overall experience in the operating room and to minimise the use of analgesics and sedation, thereby reducing the risk of adverse drug effects.[15]

A study by Alaterre *et al* investigated the use of VR distraction during local anaesthesia for minor hand surgeries. The researchers found that patients who used VR reported significantly lower pain scores and higher satisfaction levels compared with a control group without VR distraction.[16] This suggests that VR distraction can be a valuable adjunct to local anaesthesia for pain management in certain procedures. Another study by Martinez-Bernal *et al* published in 2021 examined the use of VR during local anaesthesia for dental extractions.[17] The researchers observed that patients who experienced VR distraction during the procedure reported reduced anxiety levels and less pain during the dental extraction.

These recent studies and others highlight the potential benefits of using VR during interventions under local anaesthesia to improve patient comfort, decrease anxiety and manage pain effectively. As VR technology continues to evolve, more research is likely to emerge, exploring its applications in different medical settings and procedures. Although more studies are needed to further validate its efficacy and optimal use, the current evidence suggests that VR can be a valuable tool in the context of local anaesthesia to enhance patient care and satisfaction.

But not all types of VR are the same; for instance, a distinction is made between VR hypnosis and VR alone. Previous studies have shown that conscious sedation or 'hypnosedation' under local anaesthesia may result in reduced postoperative pain, reduced anxiety and stress levels and a reduced need for anxiolytic and analgesic medications. In reviews, initial evidence has been found that the combination of VR with an immersive hypnotic factor may involve a better outcome for the patient than use of VR as a distraction from surgery alone.[18] Research on interventions associated with cancer, which includes the field of port implantation, also calls for further studies on immersive VR for anxiety and pain reduction.[19] For intraoperative management of these factors under local anaesthesia, audiovisual versus relaxation-based interventions have been previously compared. Both resulted in an efficient reduction of pain and anxiety. However, it was demonstrated that especially regarding intraoperative anxiety, a relaxation-based measure might be more effective. But, there is a need for further studies in this area.[20]

In view of the promising results from previous studies and meta-analysis, the hypothesis of the VIP-trial is that VR hypnosedation during port implantation under local anaesthesia might have positive effects on perioperative anxiety and pain, patient's satisfaction and tolerability of the procedure.

METHODS AND ANALYSIS

Trial design

The VIP-trial is a monocentric, randomised controlled trial at the development stage (according to the IDEAL recommendations)[21 22] with two parallel intervention groups and a 1:1 allocation ratio.

Patients scheduled for elective port implantation, regardless of the underlying disease, will be informed about the trial in detail. After assessing eligibility criteria, written informed consent will be obtained. It is planned to include a total of 120 eligible patients in the trial. The first patient was included on 29 April 2022 into the trial and recruitment will last approximately until the end of 2023. Patients will be randomised preoperatively to one of the treatment groups in a 1:1 ratio. Assuming a post-randomisation dropout rate of <10%, data of at least 55 patients in each group will be finally analysed in an intention-to-treat principle (figure 1). This sample size was estimated to be sufficient for generation of first efficacy data allowing for a reliable sample size calculation for a subsequent confirmatory trial based on the rules of thumb for sample size estimation in pilot trials by Whitehead *et al*.[23] Even with a rather small standardised difference ($\delta \leq 0.1$), a number of 50 patients or more per group would be sufficient to calculate a reliable sample size for a subsequent confirmatory trial with 80% power.

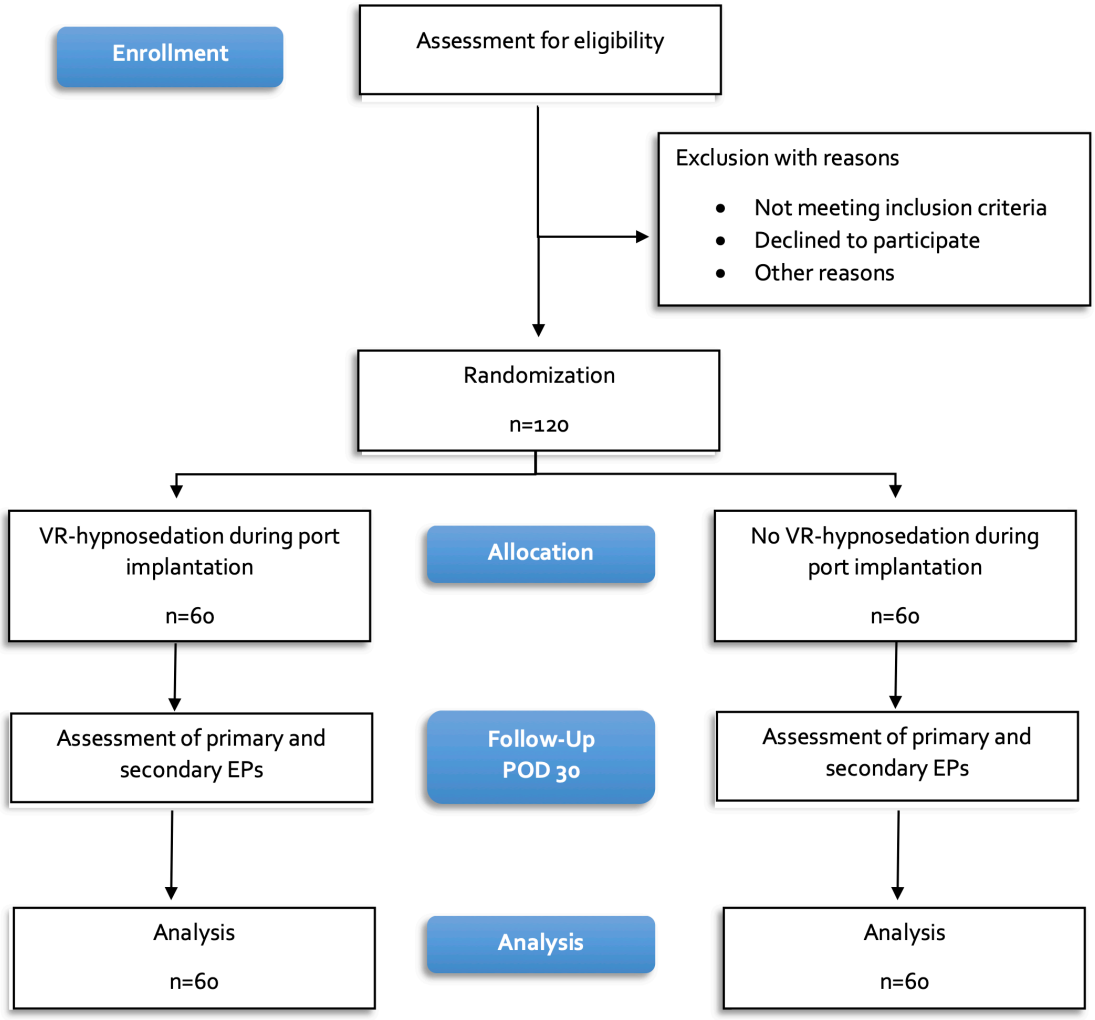

Figure 1 Trial flow chart. EP, endpoint; POD, postoperative day; VR, virtual reality.

Trial population and eligibility criteria

Adult patients undergoing port implantation without general anaesthesia, regardless of their underlying disease, will be included. Only patients with the ability to understand the nature and extent of the trial and providing informed consent will be included. The following preoperative exclusion criteria were chosen, in order to exclude patients at risk of interference with the usage of the VR headset (box 1).

Box 1 Exclusion criteria of the trial

Exclusion criteria

⇒ American Society of Anesthesiologists grade >3.
⇒ Chronic pain (ongoing and longer lasting than 6 months).
⇒ Missing cognitive capacity of following the virtual reality (VR) procedure (eg, patients with dementia, psychotic episodes or psychiatric pathologies prohibiting VR use).
⇒ Uncontrolled epilepsy or visually triggered epileptic seizures in patient's history.
⇒ Auditory and/or visual disorders implying a contraindication for the use of VR.
⇒ Implanted hearing aids or cardiac pacemakers/defibrillators.
⇒ Participation in another interventional trial with interference of intervention and/or outcome of this study.

Subject withdrawal

Patients are free to withdraw from the trial at any time and without giving reasons for their decision. Subjects may be withdrawn from the trial for the following reasons:

1. Patients may decide to withdraw from the trial at any time with or without providing any specific reason for their decision.
2. If, in the investigator's opinion, continuation of the trial would be detrimental to the subject's well-being. In this case, the reason for withdrawal must be recorded in the case report form and in the patient's medical records.

Trial-specific procedures

Standard preoperative, perioperative and postoperative management in both groups (control intervention)

Patients scheduled for elective port implantation will be screened for eligibility during outpatient visceral oncology consultation. Each patient's case is discussed in our multidisciplinary tumour board. If neoadjuvant or adjuvant

systemic treatment is recommended, port implantation will be usually indicated. When the written consent for the surgical procedure will be obtained, patients will be informed about the trial and invited to participate. The current standard of care as described in the following was chosen as control intervention, because an improvement of the standard of care is the objective. Furthermore, a sham or placebo VR intervention could not be reasonably achieved. The primary approach for port implantation will be venae sectio of the cephalic vein. If primary venae sectio is not successful, a modified Seldinger's technique will be applied and only if unsuccessful, the subclavian vein will be punctured under sonographic guidance as described in the PORTAS-3 trial.[24] The port is usually implanted on the non-dominant side (eg, on the left side in right-handed patients), if no other reasons for a specific side are present. A commercially available CE-certified port system will be used. The standard size of the port catheter is 8 French, but a 6.6 French port catheter may also be used in patients with a narrow vein.

In the operating room, the region of the deltopectoral groove is infiltrated with local anaesthesia (eg, ropivacaine) and, only if necessary, additional analgesics (eg, metamizole or piritramide) or sedatives (eg, remifentanil or propofol) may be applied during the procedure.

After the procedure patients will be monitored for 1–2 hours in the outpatient surgery centre and are usually discharged thereafter. In case of puncture, a postoperative chest X-ray was carried out to rule out a pneumothorax. Postoperative complications were monitored including surgical site infections, dislocation or dysfunction of the port system.

Experimental intervention

On arrival of the patient in the outpatient surgery centre, the VR headset (PICO G2 4K All-In-One headset; Pico Technology, Beijing, China) will be presented to the patient and a VR environment according to the patient's preferences will be chosen from the HypnoVR application (HypnoVR SAS, Lampertheim, France).

Throughout the operation, patients will be monitored by an anaesthesiologist and will be able to talk to the medical staff around them. At any time, patients can ask to stop the VR application in case of discomfort. In this case, further treatment will be performed according to the standard of care. Figure 2 shows a photograph of the intraoperative setting.

The use of VR will be discontinued immediately if any of the following symptoms occur: convulsions, loss of consciousness, eyestrain/eye pain, eye or muscle twitching, involuntary movements, altered/clouded vision, double vision or other visual abnormalities, dizziness, disorientation, impaired sense of balance, profuse sweating, increased salivation, nausea, lightheadedness, headache, fatigue/exhaustion, other symptoms resembling motion/seasickness.

After completing the procedure, the VR headset is removed and will be cleaned following the hygiene protocol.

Used device for experimental intervention group

The PICO G2 4K All-In-One headset (Pico Technology, Beijing, China) is a commercially available VR headset.

HypnoVR (HypnoVR SAS, Lampertheim, France) is a CE-certified software application (www.hypnovr.io),

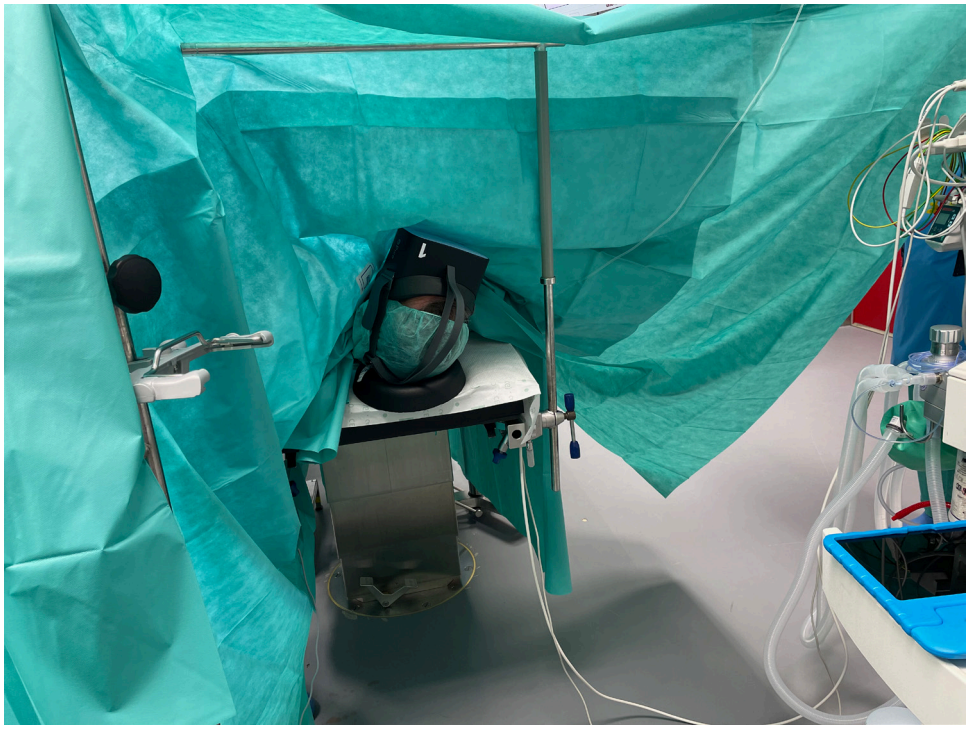

Figure 2 Photograph of the intraoperative setting with the patient wearing the virtual reality headset in the operating room.

which is intended to improve pain, stress and anxiety during medical procedures.

The patient can choose a VR environment (Winter Magic, Forest, Tropical Beach, Deep Sea Diving, Space Voyage, Four Seasons), a musical atmosphere (relaxation, serenity, lounge, symphony, soft guitar, Asian ambience) and a voice of guidance (male or female) providing breathing instructions and engaging in the scenario. Within the VR environment, the surroundings move only slowly to prevent motion sickness.

Due to the constant need for communication during the surgery, headphones are not used and the music and voice guidance are rendered through the speakers of the VR headset.

Data capture and trial endpoints

The following baseline and demographic parameters will be captured in all patients: year of birth (year), gender (female/male/diverse), height (cm), weight (kg), body mass index, spectacle/contact lens wearer (yes/no), American Society of Anesthesiologists class (I/II/III), underlying disease leading to port implantation, reason for port implantation, previous port implantations (yes/no; if yes: number), relevant comorbidities/medical history and calculation of the updated Charlson Comorbidity Index (cardiac, pulmonary, renal, hepatic, rheumatism, dementia, diabetes, hemiplegia/paraplegia, malignant disease, AIDS/HIV) and checking the inclusion and exclusion criteria.

On the day of surgery, the following data will be gathered: preoperative questionnaire, perioperative pain (Numerical Rating Scale (NRS)), duration of surgery (min), implantation technique (left/right cephalic/subclavian/jugular vein), sonography guided puncture (yes/no), intraoperative complications, type and amount of perioperative analgesia, sedation and local anaesthesia, satisfaction of the surgeon (Likert scale: 1=very satisfied – 5=extremely dissatisfied), immediately postoperative questionnaire, time of discharge, duration between end of operation and discharge (min), questionnaire before discharge and postoperative complications until discharge.

Postoperative complications are recorded and documented according to the Clavien-Dindo classification.[25] The following postoperative complications will be assessed: surgical site infections, postoperative bleeding/haematoma, thrombosis, pneumothorax or haemathorax, dislocation or dysfunction of the port system, catheter sepsis and nerve palsy.

If the patient is randomised to the intervention group, previous experience with VR is also recorded. In addition, the selected VR scenario, hypnotic voice, musical atmosphere and whether the VR procedure was discontinued before the end of surgery is recorded.

On postoperative day 30, patients are contacted by phone to assess postoperative complications, which occurred after discharge. Furthermore, they are asked whether there is still pain in the area of port implantation (yes/no) and whether they would hypothetically be willing to undergo port implantation under the same circumstances again (yes/no).

Questionnaires

On the day of surgery, a questionnaire is administered three times: preoperatively, immediately postoperative and before discharge. The questionnaire includes the patient's current pain level assessed on an NRS (0=no pain – 10=worst imaginable pain). Furthermore, the six-item State-Trait Anxiety Inventory (STAI-6) is included to assess perioperative anxiety and stress.[26]

In addition to the NRS and STAI-6, the questionnaire before discharge includes questions about symptoms such as nausea, vomiting, dizziness, headache, fatigue, as well as tolerance of the procedure (Likert scale: 1=very tolerable – 5=not tolerable at all) and patient satisfaction with the operation (Likert scale: 1=very satisfied – 5=extremely dissatisfied).

In addition, surgeon's satisfaction with the procedure will be assessed (Likert scale: 1=very satisfied—5=extremely dissatisfied).

A template of the perioperative questionnaire is provided in the supplementary material (online supplemental file 1).

Patient timelines and description of trial visits

Table 1 provides an overview about trial visits. Patients scheduled for elective port implantation will be screened during the preoperative outpatient consultation and, if eligible, will be included in the study. Subsequently, the baseline data will be collected (visit 1).

Randomisation will be performed preoperatively, usually on the day before surgery. On the day of surgery, the above-mentioned perioperative parameters, questionnaires and further endpoints will be assessed (visit 2).

On postoperative day 30, a structured telephone interview will be performed as final follow-up visit within the trial (visit 3).

Safety objectives and assessment of safety

Safety will be assessed by monitoring intraoperative and postoperative complications according to the Clavien-Dindo classification. Within this classification, grade 1–2 complications represent adverse events, whereas grades 3–5 represent serious adverse events.[25] Furthermore, potential VR-related symptoms will be assessed as described above.

Data handling and monitoring

The electronic data capture software (REDCap) hosted on a server at the coordinating investigator's institution will be used for data capture and management.[27] An investigator or a designated representative will enter all data that are collected within the trial as soon as possible after its collection into the electronic case report forms (eCRF).

The completed eCRF will be reviewed and signed by the investigator or by a designated subinvestigator.

Table 1 Trial visits and assessment of parameters

	V1	V2				V3
		Day of surgery				
Visit	Screening	Pre-OP	Intra-OP	Post-OP	Immediately before discharge	POD 30
Eligibility criteria	X					
Informed consent	X					
Demographics and baseline clinical data	X					
Randomisation		X*				
Surgical intervention			X			
Assessment of anxiety questionnaire (STAI-6)		X		X	X	
Assessment of NRS		X		X	X	
Assessment of postoperative complications				X	X	X
Assessment of other outcome parameters				X	X	X

*Randomisation may be performed within 1 week before surgery.
intra-OP, intraoperative; NRS, Numerical Rating Scale; POD, postoperative day; post-OP, postoperative; pre-OP, preoperative; STAI-6, six-item State-Trait Anxiety Inventory.

All data will be pseudonymised. Completeness, validity and plausibility of data will be checked in time of data entry (edit-checks). Data will finally be downloaded from REDCap and used for statistical analysis. All data management procedures will be performed in compliance with Good Clinical Practice (GCP).

Statistical analysis

All analyses will be exploratory with the main aim being the estimation of standardised effect sizes and CIs as a basis for sample size calculation of a potential subsequent confirmatory (non-inferiority) trial. Since the current trial is a pilot trial without formal sample size calculation, there is no primary outcome, which is per definition the outcome parameter on which the sample size calculation is based. Thus, we refrained from using the term 'primary outcome' and used the term 'main outcome' and 'further outcome' parameters instead.

All patients treated with one of the trial interventions will be considered in the final analysis. The primary analysis strategy will be intention-to-treat analysing all patients in the group that they were randomised to. A per-protocol analysis will be performed as secondary analysis.

The empirical distribution of all endpoints will be calculated, including mean, SD and quartiles in case of continuous variables and scores and with absolute and relative frequencies in case of categorical data. 95% CIs will be calculated. Descriptive p values of the corresponding statistical tests, χ^2 test for categorical variables and Mann-Whitney U test for continuous variables, comparing the treatment groups and associated 95% CIs will be given. Whenever appropriate, statistical graphics will be used to visualise the findings.

The homogeneity of the treatment groups will be described by comparison of the demographic data and the baseline values.

Missing data will be minimised by consequent documentation and all other reasonable measures. No interpolation of missing data will be performed.

Methods for minimising bias

Minimising selection bias

Patients scheduled for port implantation will be consecutively screened for eligibility. The patient flow will be documented and reported with reasons for exclusion at each stage (screening, inclusion, randomisation, analysis) and dropouts will be explained in a Consolidated Standards of Reporting Trials (CONSORT) flow chart.[28] If no exclusion criteria are present, patients will be randomised by central web-based randomisation via REDCap. A balanced permuted block randomisation procedure will be used. Persons with the right to randomise patients within the trial do not have the right to read or edit the randomisation design and will be unaware of the block length.

Minimising performance and detection bias

Given the obvious difference in the interventions, there is no reasonable possibility for blinding patients or treating physicians within the current trial. Furthermore, all outcomes that could have been assessed by blinded data collectors or outcome assessors were pain and the STAI-6 questionnaire, representing patient-reported outcomes. Therefore, blinding of data collectors or outcome assessors was also not reasonable. Thus, none of the five relevant trial contributors will be blinded.[29]

Minimising attrition bias

Missing data will be minimised by consequent documentation and all other reasonable methods. No interpolation of missing data will be performed. The trial results

will be reported according to the recommendations set out in the CONSORT statement.[28]

Minimising reporting bias

To assure transparent trial conduct and subsequent reporting and to avoid selective reporting, the trial protocol (including full information about its prespecified outcomes and statistical analysis) is hereby published according to the Standard Protocol Items: Recommendations for Interventional Trials statement.[30] Furthermore, the trial was registered with the publicly accessible German Clinical Trials Register before inclusion of the first subject. All planned endpoints will be reported in the final results publication.

ETHICS

The present trial is conducted in accordance with the Declaration of Helsinki in its actual version,[31] the internationally recognised Good Clinical Practice guidelines by the International Council for Harmonisation (ICH-GCP), German state and national laws and regulations for data protection, the European General Data Protection Regulation and the German Medical Association's Code of Conduct. The protocol was reviewed and approved by the Ethics Committee of the Medical Faculty of the University of Ulm (reference number 03/22).

Patient and public involvement

Patients or the public were not directly involved in the design of the present trial. However, given the potential positive effects of patient's distraction in the operating room, it may be assumed that avoiding the visual experience of the operating room by VR, will be of high patient relevance. If novel insights will be available during the conduct of this trial, patients and the public will be promptly informed.

Dissemination

The final trial results will be published in a peer-reviewed journal. Furthermore, results will be communicated to the scientific community at appropriate national and international conferences. Furthermore, social media will be used to disseminate the results of the trial to the scientific community, patients and the public.

Trial status

The trial is currently in the recruitment phase. The first patient was included on 29 April 2022.

Author affiliations
[1]Department of General and Visceral Surgery, Ulm University Hospital, Ulm, Germany
[2]Department of General, Visceral and Transplantation Surgery, Heidelberg University, Heidelberg, Germany
[3]Clinical Trial Centre ulmCARES, Department of Surgery, Ulm University Hospital, Ulm, Germany

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Contributors SG, HF, CD-H, CM and FJH developed the trial concept and wrote the protocol and the first draft of the manuscript of the protocol publication. LSH, KCS and NN helped to develop the trial concept and revised the manuscript critically for important intellectual content. All authors actively participate in the conduct of the trial, including patient recruitment, treatment and follow-up. All authors approved the final version for publication, agreed to be accountable for all aspects of the work and ensure that any questions related to the accuracy or integrity of any part of the work will be appropriately investigated and resolved.

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Disclaimer This is an investigator-initiated trial. A commercially available and CE-certified VR headset and software is used within the trial. The manufacturer and distributor of the device and/or software had no role in trial design and does not have a role in data collection, data analysis, interpretation of trial results or writing of the report.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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ORCID iD
Felix J Hüttner http://orcid.org/0000-0002-2299-964X

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