


BMJ Open Virtual reality-based relaxation for enhancement of perioperative well-being and quality of life: protocol for a randomised pilot trial

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ABSTRACT

Introduction Patients with cancer undergoing surgery often suffer from reduced quality of life and various forms of distress. Untreated distress can negatively affect coping resources as well as surgical and oncological outcomes. A virtual reality-based stress reduction intervention may increase quality of life and well-being and reduce distress in the perioperative phase for patients with cancer. This pilot trial aims to explore the feasibility of the proposed intervention, assess patient acceptability and obtain estimates of effect to provide data for sample size calculations.

Methods and analysis Patients with colorectal cancer and liver metastasis undergoing elective surgery will be recruited for this single-centre, randomised pilot trial with a three-arm design. A total of 54 participants will be randomised at 1:1:1 ratio to one of two intervention groups or a control receiving standard treatment. Those randomised to an intervention group will either receive perioperative virtual reality-based stress reduction exercises twice daily or listen to classical music twice daily. Primary feasibility outcomes are number and proportions of participants recruited, screened, consented and randomised. Furthermore, adherence to the intervention, compliance with the completion of the quality of life questionnaires and feasibility of implementing the trial procedures will be assessed. Secondary clinical outcomes are measurements of the effectiveness of the interventions to inform sample size calculations.

Ethics and dissemination The study protocol, the patient information and the informed consent form have been approved by the ethics committee of the Ludwigs-Maximilians-University, Munich, Germany (Reference Number: 19–915). Study findings will be submitted for publication in peer-reviewed journals.

Trial registration number DRKS00020909.

INTRODUCTION

Perioperative psychosocial issues and quality of life

The diagnosis of cancer is a heavy burden for patients and can cause a significant level of psychological distress.^{1–3} Distress in patients

Strengths and limitations of this study

- This pilot trial will assess the feasibility of the trial design and protocol as well as patient compliance and patient acceptance of a virtual reality-based stress reduction intervention.
- Using the QLQ-C30 questionnaire with additional items will increase measurement precision for core quality of life domains.
- The virtual reality-based stress reduction intervention is non-invasive and aims at increasing well-being and quality of life in patients with cancer.
- The use of a randomised three-arm design will reduce potential bias.
- Implementation of the stress reduction intervention in a general surgery population might be more complicated compared with other cancer patient populations and might influence feasibility and clinical outcomes.

with cancer is defined as a ‘multifactorial unpleasant experience of a psychological, social, spiritual and/or physical nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment’.² Patients with cancer undergoing surgery often suffer from distress in the perioperative phase.^{4 5} The observed prevalence of distress is 25%–50% in patients with cancer, and it has been reported that in a general surgery population, about one-third of patients suffer from anxiety and half suffer from depression.^{2 5–7} Distress can manifest itself in a wide range of symptoms from normal feelings of sadness and fear to depressive episodes, sleep disorders, reduced quality of life, anxiety disorders and existential crisis in severe cases.^{1 2 4} The presence of coexisting psychiatric issues such as distress, anxiety and depression can negatively influence a patient’s coping resources, surgical



and oncological outcomes.⁸⁻¹² Untreated preoperative distress was associated with reduced well-being and quality of life 2 years after surgery.^{4,13} In the perioperative setting, the unfamiliar hospital environment, the large number of documents to be signed, the work processes that are difficult to understand for the patient and the short contact with constantly changing hospital staff can further unsettle patients who are already burdened by their diagnosis and upcoming examinations and operations.^{14,15}

The European Organisation for Research and Treatment of Cancer (EORTC) evaluated quality of life data for over 23 000 patients with cancer using the *Quality of Life Questionnaire Core 30 (QLQ-C30)*.^{16,17} Four items (worry, tension, irritability and depression) of the QLQ-C30 are combined into the 'emotional functioning' (EF) scale (scored on a 0–100 points scale, higher values correspond to a lower burden). A score below 70 is regarded as a clinically relevant burden and for patients with colorectal cancer (CRC), the EF scale averaged 68 points.^{17,18} Based on EORTC data, 47% of patients with colorectal cancer have an EF scale score below 70.¹⁷

Additionally, fatigue and sleep disturbances are symptoms frequently reported by patients with cancer.^{17,19-21} Three items (feeling tired, weakness and need to rest) are combined into the 'fatigue' (FA) scale (0–100 points, lower values correspond to a lower burden) of the QLQ-C30. A score above 39 indicates a clinically relevant burden in the FA scale.¹⁸ About 37% of patients with CRC have an FA subscale score above that threshold. Additionally, 27% of patients with CRC suffer from severe or moderate sleep disturbances.¹⁷

Stress reduction and clinical use of virtual reality (VR)

Various forms of stress reduction for patients in the perioperative period have been studied. Renzi *et al*²² showed that proctologic patients who experienced relaxing music and lyrics before, during and after the procedure had significantly better sleep quality and showed a trend towards less postoperative pain. Studies suggest that perioperative stress reduction has a positive effect on quality of life and possibly positive immunological effects.²³ These immunological effects manifest themselves, for example, in improved wound healing.^{23,24} Preoperative reduction of psychological stress is also part of a larger concept known as prehabilitation with the goal of increasing physiological reserves in anticipation of surgery, improving adherence and outcomes.²⁵ Prehabilitation programmes consisting of physical training, nutritional adjustment and stress reduction interventions have shown to improve postoperative exercise capacity in certain patients with CRC.²⁶ Technological progress has widened the spectrum of potential tools for stress reduction. VR is an immersive and interactive technology that visually, acoustically and haptically simulates a virtual environment and evokes a sense of presence in that environment.²⁷⁻²⁹ The sense of presence that is often defined as the sensation of being in the virtual scene is created by realism of the

graphics and by the potential of a VR experience to elicit emotional responses.^{30,31} VR is being explored in various clinical settings and has attracted much attention as a cost-effective intervention, especially in psychiatry.³² A recent meta-analysis has shown that VR-based treatments lead to significant improvements in anxiety disorders and depression.³³ VR interventions have been successfully used in children and adults for the treatment of acute and peri-interventional pain and has shown usefulness in addressing psychological well-being in children and adolescents with cancer.^{28,34-36} Virtual environments, especially those with a high degree of immersion, create a strong distraction from the real environment or painful procedures because the patient cannot see his immediate surroundings through the VR headset, and a sense of presence in VR environment is evoked.^{29,37} In addition, there may be active patient interaction with the VR environment, which adds to the distraction.³⁶ VR systems have shown the ability to produce positive emotional experiences, and evidence is emerging that VR technology can increase emotional, psychological and social well-being.^{30,38} Based on these findings, VR-based interventions could be used for perioperative stress reduction and relaxation that might improve various aspects of quality of life, perioperative sleep, well-being and patient satisfaction in cancer patients undergoing major abdominal surgery.

Rationale for a pilot trial

Currently, little is known about the feasibility and acceptance of VR-based stress reduction interventions in patients with cancer. There is no existing data that can be used to estimate the size of the effect and thus to enable a high-quality sample size calculation. Therefore, this pilot trial aims to explore the feasibility of the proposed intervention and to assess whether the design and protocol used are feasible in terms of patient recruitment, patient compliance and patient acceptance of the intervention. The second goal is to obtain estimates of the effect on quality of life, sleep, patient satisfaction and surgical outcome to provide data for sample size calculations.

METHODS

Trial design and study population

This pilot trial features a single-centre, randomised, three-arm design with a 1:1:1 allocation. The design is displayed in the trial flow chart (figure 1). Patients undergoing elective abdominal surgery for colorectal cancer or liver metastases of colorectal cancer will be recruited. Participants will be randomised to one of two intervention groups or a control group that receives the standard treatment. Those randomised to an intervention group will either receive a preoperative and postoperative VR-based stress reduction interventions or a music-based stress reduction intervention.

Informed consent

All participants are required to provide informed written consent. Consent for study participation and data

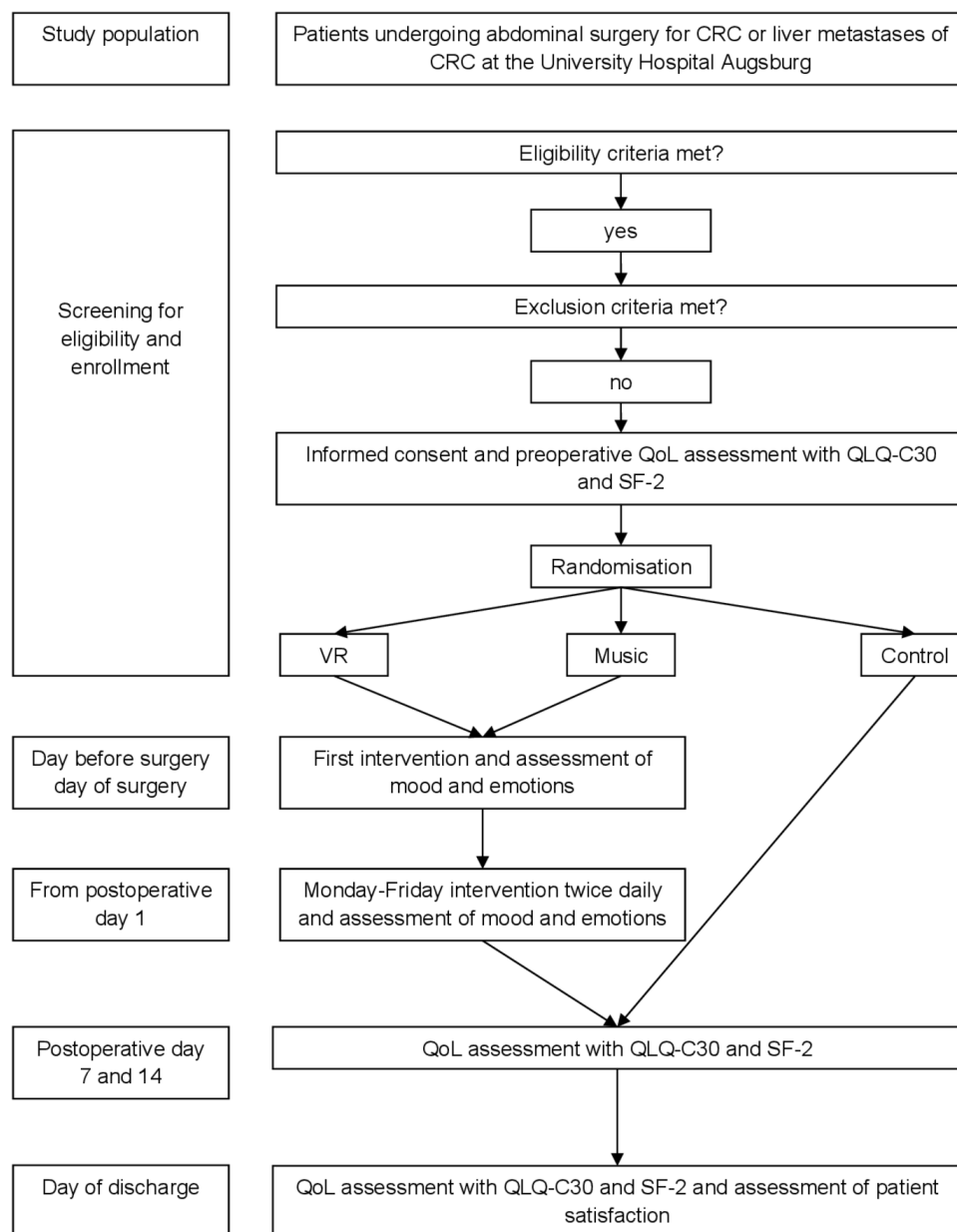


Figure 1 Trial flow chart. QoL quality of life, QLQ-C30 Quality of Life Questionnaire Core 30, SF-2 Short Form 002

collection will be obtained at least 1 day before surgery by physicians of the University Hospital Augsburg.

Eligibility criteria

- ▶ Aged 18–75 years.
- ▶ Elective abdominal surgery for colorectal cancer or liver metastases of colorectal cancer.

Exclusion criteria

The decision to exclude patients with certain pre-existing medical conditions is based on general safety recommendations for VR headsets.

- ▶ Non-consentable patients (such as patients who are unable to provide informed consent or patients under legal guardianship).
- ▶ Underage patients.
- ▶ Pregnant patients.

- ▶ Patients admitted as an emergency.
- ▶ Participation in another clinical study that may have a potential impact on the endpoints of this study.
- ▶ Patients with a medical history of dementia, schizophrenia, hallucinations, panic attacks and epileptic seizures.
- ▶ Patients who carry a pacemaker or defibrillator device.
- ▶ Patients taking neuroleptic or antiepileptic drugs.
- ▶ Patients with active alcohol and/or substance abuse.
- ▶ Lack of German or English language skills.

Secondary exclusion criteria and adverse events

A new diagnosis of any of the conditions listed under exclusion criteria will result in exclusion from the VR or music group. The new beginning or continued use of any of the medications mentioned under exclusion criteria

will result in exclusion from the VR or music group. In case patients are readmitted to the intensive care unit or experience postoperative delirium, reduced vigilance or physical inability to sit in bed for 10 min, the VR and music interventions are not performed.

The exclusion criteria and secondary exclusion criteria reflect the fact that VR headsets could potentially cause seizures, blurred vision, dizziness, light-headedness, nausea and other symptoms. All interventions are performed under direct supervision with participants sitting on a chair or in bed to ensure safety for trial participants. In case trial participants experience a symptom or event that could be related to the intervention, the session will be stopped immediately, and no further sessions will be carried out. Any adverse event or unintended effect of the trial interventions will be documented and assessed.

Randomisation

Participants will be randomised by block randomisation with the aim to reduce a selection bias and to ensure equal group sizes. The size of the blocks will be made public after the end of the study in order to prevent prediction of group allocation. The randomisation is done by staff who is not involved in the data collection, data analysis or supervision of the study patients and is carried out by picking a sealed opaque envelope.

Blinding

Blinding of patients and staff supervising the study interventions does not take place due to the nature of the interventions. However, the physicians involved in the surgical treatment of the patients are blinded to the intervention.

Sample size estimation

A formal sample size calculation was not performed as there are no data that could serve as a foundation for a formal sample size calculation. For pilot studies with an expected medium standardised effect size, a case number of 15 per group has been recommended for a later study with a power of 90%.³⁹ Therefore, we have chosen to recruit 15 patients plus an additional three patients (20%) per group to compensate for incomplete questionnaires and patients who cancel their participation in the study early.

Interventions

VR group

For the intervention in the VR group, a commercially available standalone VR headset (Oculus Go for Business) with external headphones and commercially available meditation software TRIPP developed by TRIPP Inc (TRIPP Inc, Los Angeles, California, USA) is used. The headset features a 5.5" fast-switching LCD at a 2560×1440 resolution (1280×1440 per eye). Two different VR experiences are presented to each patient in the VR group every day from Monday to Friday. Two sessions per day (morning and evening) will be held. The exercises start on the day of admission for patients admitted before their surgery. Patients admitted on the day of surgery will only

have a preoperative session if the patient is operated in the afternoon of the admission day. The last preoperative session will be on the evening before the operation for all patients undergoing surgery in the morning and in the morning on the day of the operation for all patients who undergo surgery in the afternoon. The first postoperative session will take place on the first postoperative day or as soon as the patient is transferred from the intensive care unit (ICU) to a regular ward. The sessions are held until the patient is discharged from hospital. During the intervention, patients will sit in a chair or in a hospital bed depending on patient condition and preference. The immersive VR experiences are meditative and designed to produce a calming effect. The VR environment is updated daily to encourage ongoing engagement. Despite the daily changing environment, the morning and evening sessions consist of recurring components that are part of every session. The morning VR experience, which lasts 7–8 min, has four levels incorporating binaural audio, procedurally generated music, guided reflections, breathing exercises with breath visualisation and a mini-game, all designed to focus attention. The audio is delivered through headphones worn by the patient. The patient is guided through the experience by a narrator. The instructions are in English. Patients with insufficient knowledge of English will be instructed in German by an employee of the University Hospital Augsburg who is simultaneously listening to the VR experience. The evening VR session is designed to produce a more calming effect and consists of three levels. The guided meditation content is more expansive than in the morning session. Two out of the three levels incorporate interactive breathing exercises with breath visualisation. The evening sessions last 10 min but can be adjusted to last longer, if the patient desires. Before and after the intervention, heart rate and blood pressure are measured.

Music group

In the music group, each participant listens to soothing classical music through headphones for 7–10 min twice a day from Monday to Friday. Patients will be wearing a VR headset, which is switched off. The exercises start on the day of admission for patients admitted before their surgery. Patients admitted on the day of surgery will only have a preoperative session if the patient is operated in the afternoon of the admission day. The last preoperative session will be on the evening before the operation for all patients undergoing surgery in the morning and in the morning on the day of the operation for all patients who undergo surgery in the afternoon. The first postoperative session will take place on the first postoperative day or as soon as the patient is transferred from the ICU to a regular ward. The sessions are held until the patient is discharged from hospital. Before and after the intervention, heart rate and blood pressure are measured.

Control group

There is no intervention in the control group.

Quality of life assessment

The assessment of quality of life in this study will be performed with the QLQ-C30,¹⁶ a valid and widely used questionnaire in patients with cancer. To improve measurement precision, we included additional items selected from the EORTC computerised adaptive testing (CAT) core item banks (a collection of question databases) to form so-called short forms.⁴⁰ Ten additional items were included for the measurement of 'sleeplessness' (three items), 'fatigue' (three items) and 'emotional functioning' (four items), following recommendations of the EORTC. The 10 additional items are summarised in the questionnaire EORTC short form 002 (SF2). Items were added based on our demographic data and based on the study's objectives. The quality of life will be assessed preoperatively before the first intervention, on the 7th and 14th postoperative day and at discharge using the QLQ-C30 and EORTC-SF2 (figure 1). At discharge, all patients will receive additional questions regarding patient satisfaction.

Assessment of mood and emotions

In order to assess immediate effects of the VR and music interventions, each patient will receive a questionnaire consisting of two questions concerning the current emotional state and mood immediately before and after each intervention (online supplemental file 1).

Outcomes

Primary feasibility outcomes

- ▶ Participation, recruitment and retention rates. Participation rate is the proportion of participants providing consent of those who meet the inclusion criteria. Recruitment rate is the number of participants recruited per month. Retention rate is the number of participants who complete the full number of planned interventions.
- ▶ Intervention adherence. Adherence is the proportion of planned interventions that have been completed by each participant.
- ▶ Patient compliance with completion of questionnaires. Compliance with completion of questionnaires is the proportion of completed questionnaires at the prespecified dates.
- ▶ Adverse events. The frequency (number of participants and number of cases) and nature (eg, dizziness, vertigo and motion sickness) and severity will be recorded. Participants experiencing adverse events will be managed by the research team.
- ▶ Deviations from study protocol. Number of deviations from study protocol (such as skipped interventions) and reason for deviation from study protocol (patient related, staff related and organisational).

Clinical outcomes

- ▶ Change of mood and well-being before and after intervention.

- ▶ Change of vital signs such as heart rate, breathing rate, blood pressure before and after the intervention. Heart rate, breathing rate and blood pressure are measured manually before and after each intervention.
- ▶ Difference in change of vital signs between the music and VR group. Changes in vital signs before and after the intervention will be compared between the music and the VR group.
- ▶ Change in quality of life during the hospital stay. Quality of life is measured at predefined dates for each patient. Score and SD in the quality of life questionnaire, as well as the score and SD in all subscales, in particular emotional functioning, sleep and fatigue, are compared.
- ▶ Difference in quality of life between the three study groups. Score and SD in the quality of life questionnaire are compared between all three study groups.
- ▶ Difference in number and severity of surgical complications between the three study groups.
- ▶ Difference in length of hospital stay between the three study groups.

Data collection and management

Paper-based case report forms are used for documentation of patient-related data and clinical variables including vital signs before and after the intervention, age, ECOG status, body mass index, postoperative complications, comorbidities, tumour stage and length of hospital stay. Quality of life data are collected using paper-based version of the QLQ-C30, which has been customised in accordance with the EORTC to fit the specific needs of this study. All patient-related data are collected and analysed in pseudonymised form. For this purpose, each participant will be assigned a randomly generated numeric four-digit code on receipt of the written consent to participate in the study.

All data collected in accordance with the study protocol are manually transferred from the case report forms to an electronic SPSS database sheet (SPSS® for Windows®, Version 24, IBM, Armonk, New York, USA). Electronic data are stored in a folder with restricted access on a protected server of the University Hospital Augsburg. Paper-based data are stored in a locked office at the study site.

Access to the original data and the pseudonymisation lists is restricted to employees of the Department of General and Transplant Surgery of the University Hospital Augsburg. The data will be deleted as soon as they are no longer used for research projects at the University Hospital Augsburg.

Pseudonymised quality of life data will be shared with researchers from University of Copenhagen and the EORTC with the purpose of statistical analysis of the customised EORTC quality of life questionnaire. A transfer of patient-related data to other institutions or companies does not take place.

The VR software collects anonymous usage data (eg, frequency of use, duration of use and type of selected relaxation exercise) and two anonymous questions of well-being and forwards them to third-party companies. Since the VR headsets are also being used outside the study, external companies are not aware whether the headset is being used by study participants, hospital staff, other patients or other persons. There is no input or transmission of further data, in particular no disclosure of data that could give an indication of the identity of the current user.

Planned analysis

Continuous data will be presented as mean±SD or median with IQR, depending on distribution. Categorical data will be presented as numbers with percentages. Approximately normally distributed continuous variables will be compared using the independent t-test. Non-normally distributed continuous variables will be compared using the Mann-Whitney U test. Categorical data will be compared using the χ^2 test. Fisher's exact test will be used for categorical data when the requirements for χ^2 test were not met. A two-sided $p < 0.05$ will be considered significant. The QLQ-C30 questionnaire will be scored according the EORTC QLQ-C30 scoring manual, and the short forms will be scored using the EORTC short form scoring software.⁴⁰ Repeated measurements analysis of variance is used to evaluate changes in quality of life measures and changes in vital signs during the study period.

Patient and public involvement statement

No patient involved.

Ethics approval and dissemination

The study protocol, the patient information and the informed consent form have been approved by the ethics committee of the Ludwigs-Maximilians-University, Munich, Germany (Reference Number: 19-915) and by the legal department of the University Hospital Augsburg, Germany.

We plan to publish the findings in peer-reviewed journals and share our findings at academic conferences.

Trial registration and trial status

A WHO Universal Trial Number (U1111-1242-6074) has been obtained. The trial has been prospectively registered at the German Clinical Trials Register (DRKS00020909). The trial is currently open for recruitment.

DISCUSSION

Improving quality of life and well-being for patients with cancer is one of the main goals for every caregiver involved in cancer treatment. The high prevalence of psychological distress, anxiety and depression in patients with cancer undergoing surgical or medical treatment is a call for action.^{2 6 7} Unfortunately, in many health-care systems, a shortage of staff and financial resources often prevent a more holistic treatment that goes beyond

pharmacological or surgical treatment. VR-based interventions are emerging in many different fields in medicine because they are non-invasive, easy to apply and often cost-effective especially when compared with interventions that require more medical personnel and equipment. VR-based interventions using head-mounted devices can be performed at any location and without the need for scheduled appointments thereby potentially offering a greater degree of flexibility for patients than traditional stress reduction interventions. Anxiety disorders and depression have been successfully treated using VR applications, and VR has shown to effectively distract patients during painful procedures resulting in less perceived pain and a more pleasant experience.^{32 33 37}

A recent review suggests that VR-based emotion regulation training have a favourable influence on well-being.³⁰ Currently, there are no data regarding the perioperative use of VR-based interventions for perioperative stress reduction and relaxation. Therefore, we initiated a pilot study in order to investigate the usefulness and feasibility of a VR-based meditation intervention for perioperative stress reduction. Since EORTC data have shown that a significant number of patients with colorectal carcinoma suffer from depressive symptoms, sleep disorders, fatigue and a reduced quality of life, we have chosen to focus on this patient population.¹⁷

The three-arm randomised design of this study has been chosen for two reasons. First, a standard two-arm design comparing a control group versus a VR group neglects the possibility that the additional attention and more frequent visits from medical personnel related to the intervention might be a strong bias. More contact with caregivers during the hospital stay might elicit the feeling of improved medical care and thereby already improve quality of life and patient satisfaction. We also took into consideration that other relaxing activities such listening to calming music might be equally effective thereby rendering a more expensive intervention unnecessary. We recognise this in our pilot trial by choosing a three-arm design.

The proposed pilot trial will be a first step in assessing the feasibility of VR-based interventions in the perioperative phase and with the ultimate goal to improve patient care for patients with cancer.

Contributors MCS, JP, JG and MA designed the study protocol. MCS, HV, MP and SW developed the evaluation plan. MCS drafted the initial manuscript. MM, SW, FS and MA critically revised the manuscript for important intellectual content. Final approval of the version to be published was given by all authors. MCS and MA take responsibility for the work and controlled the decision to publish. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethics Committee of the Ludwigs-Maximilians-University, Munich, Germany (Reference Number: 19-915).

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