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Effect of functional relaxation on the quality of life in patients with periprosthetic joint infection: Protocol for a randomised controlled trial

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ABSTRACT

Introduction Periprosthetic joint infection (PJI) is a devastating complication in orthopaedic and trauma surgery, which puts a high burden on the patients involving recurrent hospitalisation, prolonged courses of antibiotic medication, severe pain and long periods of immobility as well as high levels of psychological distress. Thus, this multicentre study aims at implementing body-oriented psychotherapy in clinical practice and evaluating its therapeutic effect on the quality of life.

Methods and analysis A prospective, parallel two-armed randomised controlled trial with approximately n=270 patients with verified PJI treated surgically with a one-staged exchange, or a two-staged exchange will be conducted. Functional relaxation (FR) therapy will be implemented as a group therapy. FR originally belongs to the psychodynamically based body-oriented psychotherapy. Intervention techniques consist of minute movements of small joints, which are performed during relaxed expiration accompanied by an exploration of differences of body feelings. A group will include 3–8 patients, led by a specialist physiotherapist certified in FR once a week. The participants are consecutively admitted to the class and participate in 12 sessions. The control group will consist of patients receiving an unspecific 'placebo relaxation' intervention for the same duration. The primary efficacy endpoint is the mental component summary and physical component summary of quality of life assessed by the 36-Item Short Form Health Survey (SF-36) after 6 months. Secondary outcomes include SF-36 scores after 12 months, consumption of pain medication, mobility measured by the Parker mobility score and the physical activity measured by daily steps with an accelerometer (actibelt).

Ethics and dissemination Approval from the Ethical Committee of the University Hospital Regensburg was received (file number: 21-2226-101). Written, informed consent to participate will be obtained from all participants. Results will be made available in the form of peer-reviewed publications and presentation in congresses.

Trial registration number DRKS00028881; German Clinical Trials Register.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will provide the first multisite, randomised-controlled trial to investigate the effect of an adjunct psychological intervention on the quality of life of patients with prosthetic joint infection.
⇒ A major strength of the present trial is the implementation of participatory research. Thus, by involving patient representatives in the planning and design phase of the clinical trial, the perspective of those affected could already be incorporated into the identification of priority research questions, the selection of the intervention and primary endpoints, and subsequently, the development of the research design.
⇒ The primary limitation is the lack of previous studies, and hence, the calculation of the required sample size was based on pilot data.
⇒ Another limitation might be a loss to follow-up and the challenge to handle missing data with the Markov chain Monte Carlo method

INTRODUCTION

Background

Joint replacement is a life-enhancing procedure for millions of people all over the world. It provides pain relief, restores function, and preserves independence, especially in elderly patients. In Germany, primary total knee arthroplasty (TKA) is among the most common surgeries with 168 772 TKA procedures performed in 2016, whereby future numbers are expected to increase until 2040 by 45%.[1] However, periprosthetic joint infection (PJI) is a devastating complication in orthopaedic and trauma surgery, which puts a high burden on the patients involving recurrent hospitalisation, prolonged courses of antibiotic medication, severe pain and long periods of immobility. In addition, the crude mortality is 3.7 times greater in patients with PJI than without following TKA during the first 2 years after the procedure.[2] Thus, PJI represents a relevant psychosocial stressor for the patients. Various surgical procedures are available; however, treatment success is mainly defined as the eradication of the infection symptoms and especially the patients' mental well-being is rarely considered, even though PJI has a profound impact leading to

high levels of psychological distress.[3] It has been shown that patients with PJI patients suffer from significantly lower quality of life compared with normative data as well as depression, even years after surgically successful treatment.[4] Hence, the psychological impact of PJI treatment is clearly underestimated in the literature,[5] and the need for more psychological support has explicitly been reported by patients.[6]

It is well established that mental health does impact outcomes after surgery. For instance, it has been shown that a concomitant diagnosis of depression leads to an increased risk of infection after joint replacement, higher odds of adverse events, and worse clinical outcomes.[7 8] Also, the prevalence for developing psychological disorders after surgery has been highlighted.[9] A few studies indicate the beneficial effect of psychological support and the efficacy of relaxation therapy in patients undergoing total knee replacement.[10–12] However, concerning PJI, a gap in the literature was identified by a recent review screening 4,213 articles for the treatment of PJI finding none, which evaluated psychological interventions.[13]

Functional relaxation (FR) originally belongs to the psychodynamically based body-oriented psychotherapy, frequently applied in the field of psychosomatic medicine. Intervention techniques consist of small movements of joints, which are performed during expiration accompanied by an exploration of differences of body feelings. Results of previous clinical studies support the efficacy of FR for diverse disorders and show a significant reduction of pain, anxiety and stress.[14–19]

Thus, it is hypothesised that providing the patients with an easy method useful for self-regulation, stress management, the reduction of anxiety and coping with fears, results in a clinically relevant increase of quality of life scores after adjunct FR therapy, associated with shorter length of stay, reduced pain and less limitations in the execution of daily tasks.

Objectives

The objective of this trial is to examine the effect of FR therapy on the quality of life in patients with PJI.

METHODS AND ANALYSIS

Trial design

This is a prospective, parallel two-armed randomised controlled trial (figure 1). All patients presenting in the participating centres with verified PJI (according to the European Bone and Joint Infection Society consensus for diagnosis[20]) will be assessed for eligibility. In the recruitment period of 30 months, a total of n=490 patients will be screened. Here, it is expected that n=270 patients meet the inclusion criteria and are willing to participate in the trial. Then, a clinical baseline assessment will be conducted, and demographics, treatment characteristics (as specified under 1.5), the SF-36 quality of life scores and daily steps will be recorded. A web-based randomisation will be used to determine the treatment arm with an allocation ratio of 1:1, stratified by centre (n=135 patients in each group). The participants will not be informed of the treatment allocation. The FR group as well as the control group will be held continually three times a week and patients will be consecutively allocated after individual randomisation. Each session will take place as a group therapy, whereby each group will consist of 3–8 patients. One session will have a duration of 45 min. A manual to guide the sessions was already created in previous clinical trials and the sessions will be held by a physiotherapist certified in FR, and previously trained on the manual. Patients will participate in the session during their stationary time in the hospital, sessions will also take place as an outpatient procedure. After completion of 12 sessions in 12 weeks, procedures will be the same for both study groups. Follow-up examinations will be performed at the treating centre after 3 months, 6 months, and 12 months. During the examination, the SF-36, the Parker mobility score, the number of daily steps as measured with an accelerometer (actibelt), pain medication and concomitant medications will be assessed. Also, any signs of a reinfection will be documented. Treatment success will be determined by the primary endpoints, the mental component summary (MCS) and physical component summary (PCS) of the SF-36 after 6 months. Key secondary endpoints will be the SF-36 scores MCS and PCS after 12 months, consumption of pain medication, mobility measured by the Parker mobility score and the physical activity measured by the daily steps.

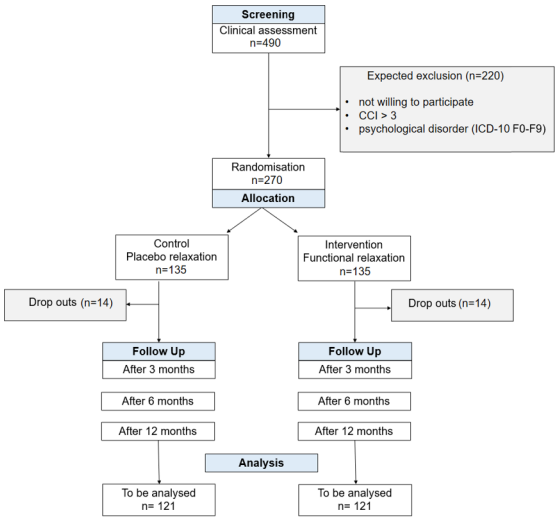

Figure 1 Schematic overview of the trial flow. CCI: Charlson-Comorbidity Index.

Study setting

The study will be carried out in level 1 trauma centres (n=4) located in the South of Germany (University Hospital Regensburg, Caritas-Hospital St. Josef Regensburg, Hospital Barmherzige Brüder Regensburg, Innklinikum Altötting).

Administrative information is shown in online supplemental file 1.

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Eligibility criteria

Key inclusion criteria

Patients with verified PJI aged 18 or older will be recruited. Written informed consent and surgical treatment including a one-staged exchange, or a two-staged exchange is a prerequisite for participation.

Key exclusion criteria

Patients diagnosed with a concomitant psychological disorder (ICD-10 F0-F9) or a Charlson-Comorbidity Index (CCI)>3 will be excluded. Further, patients surgically treated with a debridement, antibiotics and implant retention approach or with an arthrodesis, as well as patients with a Girdlestone situation will be excluded.

Informed consent

Participants will be approached on the hospital ward and given verbal explanation of the study by a study researcher. A written participant information and consent form will be provided (online supplemental file 2). Participants will be informed that their decision whether or not to participate in the study will not impact their access to routine care and that they can discontinue the participation in the study at any time. Participants will be given the opportunity to read, discuss and ask questions. Those willing to participate will sign the consent form.

Patient and public involvement

Patient representatives ('Forschungspartner') from the Rheuma-Liga (https://www.rheuma-liga.de/) were involved in the sense of participatory research in the conceptualisation of the study. These will participate during the whole research process. Further, focus group discussion will be held twice at University Hospital Regensburg, first to present the research strategy and preliminary results as well as to evaluate whether additional endpoints are of interest from the patient's perspective. Second, it will be evaluated how patient-oriented, complementary treatment concepts can be established in daily clinical practice and medical aftercare. Regular meetings with the project partners will take place every 3 months.

Additionally, invitations to FR courses and preliminary results will be distributed to patients via the German Association for medical relaxation methods (https://www.dgaehat.de/).

Additional consent provisions for collection and use of participant data and biological specimens

Not applicable as biologic specimens are not collected for this study.

Interventions

Choice of comparators

FR will be compared with a placebo relaxation technique as carried out by previous studies. The groups will be guided by an already established manual.[15 17 18] Previous randomised-controlled trials showed an effectiveness of FR in other medical conditions with treatment durations of 3 weeks,[18] 4 weeks,[14] 5 weeks[16] and 10 weeks.[19] Thus, to ensure the expediency, it was chosen to carry out the intervention once a week with a duration of 45 min for 12 weeks.

Intervention

FR originally belongs to the psychodynamically based body-oriented psychotherapy. Intervention techniques consist of small movements of joints, which are performed during expiration accompanied by an exploration of differences of body feelings. Results of clinical studies support the efficacy of FR for diverse disorders and show a significant reduction of pain, anxiety and stress.[14–19] Here, 12 weekly sessions with a duration of 45 min each will be held by a physiotherapist certified in FR. The group interventions include 5–10 patients and will be guided by a manual, which was generated during previous studies.[15 17 18] The placebo group will receive isotonic exercises, which requires an equivalent amount of motion. Thus, patients will be instructed to hold specific postures for several minutes in a relaxed manner, but without focusing on enhancing bodily awareness as in the treatment group, The experimental treatment and the control treatment will be performed by the same physiotherapist.

Criteria for discontinuation

a. For the individual patients: As guaranteed in the patient information sheet previously to study inclusion, the individual patient will be excluded from study participation, if the patient withdraws his informed consent due to any reasons.
b. For participating centres: Recruitment and data assessment of the follow-up examinations will be monitored by the Data Safety and Monitoring Board throughout the entire trial period. For recruitment of study patients, we have defined milestones at different time points. If recruitment at the 50% landmark is below 20% of the total targeted number of patients, the enrolling centre will have to be excluded from participating in the trial.
c. For the whole trial: If recruitment is not achievable in more than one centre, interim analysis of the achieved effect size and subsequent re-analyses of the required sample size will reveal whether continuation of the trial is still realistic.

Strategies to improve adherence

For the total duration of the trial, a telephone line will be opened up, and patients are encouraged to call any time in case that questions regarding the trial procedure occur. Further, to enhance confidentiality, relatives of all participating patients will have the possibility to take part in a certified training course in FR. Additionally, the trial management will monitor all patient follow-up and will contact patients who missed a follow-up appointment. Also, the dates for follow-up visits are set at the end of the previous appointment and patients are reminded of the appointment 1 week before the scheduled appointment

by phone or email. A 14-day window, defined as 7 days before and 7 days after the due date, will be available to complete the follow-up visits.

Relevant concomitant care prohibited during the trial

This trial does not prohibit other treatments.

Provisions for post-trial care

After the completion of the 12 sessions (either FR or a placebo intervention), follow-up visits will take place after 3 months, 6 months and 12 months.

Outcomes

Primary efficacy endpoint

MCS and PCS of quality of life assessed by the SF-36 health survey after 6 months.

Key secondary endpoint(s)

SF-36 scores after 12 months, consumption of pain medication, mobility measured by the Parker mobility score and the physical activity measured by daily steps with an accelometer (actibelt).

Quality of life, pain medication consumption and physical activity were selected as outcomes to appropriately capture the health status of patients affected with PJI. The SF-36 shows good reliability and validity and is the most widely used quality of life questionnaire worldwide. No other appropriate questionnaire assessing quality of life specifically for this indication exists and the SF-36 was chosen to ensure the comparability with the literature. Due to its structure with separate summary scores for the mental and physical domain, the instrument is sensitive to reflect changes in quality of life due to a relaxation intervention.

Participant timeline

The participant timeline is given in table 1.

Sample size

Assumptions

Based on prospective sampled data of patients (n=56) with prosthetic joint replacement without any additional interventions a slight improvement in quality of life, measured by the SF-36 can be expected after 6 months in the control group in this study. Our pilot data showed an improvement within the subscale PCS of 3.4 (SD 15) and within the subscale MCS of 4.6 (SD 10) points. Further, according to literature, a supplementary psychosomatic intervention led to an average effect size of 0.4

Table 1 Overview of study visits, procedures per time points and items to be recorded.

Time points of visits	Procedure per time points	Items to be recorded on CRF
During recruitment period	Eligibility screening Clinical confirmation of PJI according to the EBJIS consensus for diagnosis[20] Informed consent Baseline assessment	Age, sex, admission date, BMI, prior hospitalisation, ASA score, CCI, comorbidities Localisation, type of prosthesis, previous number of debridement, duration of symptoms, inflammatory markers (leucocyte count, CRP; PCT; Urea, GFR INR, D-dimer, Hb), blood culture results Type of surgical treatment, intraoperative culture results, identified pathogen, intraoperative histology results, wound closure Antibiotics administered, pain medication, concomitant medications Number of daily steps, Parker mobility score SF-36 scores Duration of hospital stay
3 months after the intervention	Follow-up 1 Clinical assessment including quality of life and physical activity evaluation	Duration of hospital stay Adverse side effects (if any) Suspicion of reinfection Number of daily steps, Parker mobility score, pain medication and concomitant medications SF-36 scores
6 months after the intervention	Follow-up 2 Clinical assessment including quality of life and physical activity evaluation	Adverse side effects (if any) Suspicion of reinfection Number of daily steps, Parker mobility score, pain medication and concomitant medications SF-36 scores
12 months after the intervention	Follow-up 3 Clinical assessment including quality of life and physical activity evaluation	Adverse side effects (if any) Suspicion of reinfection Number of daily steps, Parker mobility score, pain medication and concomitant medications SF-36 scores

BMI, Body Mass Index; CCI, Charlson-Comorbidity Index; CRF, case report form; CRP, C-reactive protein; EBJIS, European Bone and Joint Infection Society; FR, Functional relaxation; GFR, Glomerular filtration rate; Hb, Hemoglobin; INR, International Normalized Ratio; MCS, mental component summary; PCS, physical component summary; PCT, Procalcitonin; PJI, periprosthetic joint infection; SF-36, 36-Item Short Form Health Survey.

across several indications.[21–25] Expressed in terms of a mean difference, an effect size of d=0.4 with an estimated SD=15 underlies a mean difference of 6 points. Based on both assumptions, we expect a mean change from baseline to 6 months follow-up of about four points in the control group and about 10 points in the experimental group (Δ=6) for both SF-36 subscales, PCS and MCS with a conservative estimate of the SD=15. The expected improvement of quality of life for the subscales PCS and MCS in the experimental group is also in line with the minimum clinically important difference (MID) reported as 10 points after joint replacement.[26]

Sample size calculation

To detect an effect size of 0.4 (Δ=6, SD=15) with a power of 1−β=80% at a two-sided significance level α=0.025, a total of 242 patients (n=121 per group, ratio 1:1) need to be available for analysis for the primary estimand. An early drop-out rate of 5% (eg, withdrawal of informed consent before start of therapy, no information about the clinical outcome) of the patients is assumable passed on previous studies conducted in the University Hospital Regensburg. We further expect about 5% of the patients who cannot be used for the analysis of the primary estimand due reasons like violations of essential inclusion or exclusion criteria or death within the first 6 months. Thus, with the assumption of 10% drop-outs, a total of n=270 patients (n=135 per group) need to be randomised.

Based on previous studies conducted at the University Hospital Regensburg, assuming that 45% of the screened patients are not eligible or willing to participate, a total of n=490 patients need to be screened. Sample size calculations were performed using SAS V.9.4.

Recruitment

All patients admitted to the participating centres will be screened for potential recruitment. A daily 24hours report of all patients with PJI will be extracted from the hospital electronic database. Based on this extract, the written and electronic medical records of potential participants will be screened for eligibility by the study team. Eligible participants will be approached in person on the ward. All of the information required for ensuring participant eligibility is obtained as part of clinical routine care.

Allocation

Sequence generation

A web-based randomisation (http://www.randomizer.net/) will be used to determine the treatment arm with an allocation ratio of 1:1, stratified by centre, reinfection (yes/no) and type of surgical procedure (one-staged exchange, two-staged exchange). The randomisation tool will be administered by the Center for Clinical Studies. To minimise bias *block randomisation* with varying block sizes concealed to the investigator will be employed to avoid selection bias. After inclusion of a patient by signing the informed consent, responsible personnel (investigator and study nurse) have to use the individual log-in for the online platform to randomise the patient. All randomisations will be logged and documented within the system and predefined users like the study monitor will be automatically informed about the randomisation.

Concealment mechanism

The investigator will not be able to access the allocation sequence and randomisation table.

Implementation

Allocation will occur via REDCap.

Blinding

Who will be blinded?

Patients will be blinded using a single-masked procedure. The participants will not be informed of the treatment allocation, instead all patients will be told that they receive a complementary relaxation technique in order to first, enhance credibility and second, ensure compatibility with the informed consent.

Procedure for unblinding if needed

No unblinding procedure is planned.

Data collection and management

Assessment of outcomes

Quality of life, pain medication consumption and physical activity were selected as outcomes to appropriately capture the health status of patients affected with PJI. The SF-36 shows good reliability and validity and is the most widely use quality of life questionnaire worldwide. No other appropriate questionnaire assessing quality of life specifically for this indication exists and the SF-36 was chosen to ensure the comparability with the literature. Due to its structure with separate summary scores for the mental and physical domain, the instrument is sensitive to reflect changes in quality of life due to a relaxation intervention.[27] Patient-reported outcome measures will be administered in a standardised way across trial sites and routinely screened to avoid missing data.

Further, the Parker mobility score,[28] the number of daily steps as measured with an accelometer (actibelt), pain medication and concomitant medications will be assessed after 3 months, 6 months, and 12 months. An overview of the collected outcomes at each time point is given in table 1.

Data management

For study data collection, a web-based electronic case report form (eCRF) will be setup within an FDA 21 CFR Part 11 and ICH E6(R2) compliant clinical database management system. All data management activities will comply with rules according to the EU-GDPR, including pseudonymised data storage.

Each investigator is responsible to review and ensure the accuracy, completeness and timeliness of the data reported in the patient's data entered in the eCRF and will provide his/her signature and date of signature on the eCRF pages. During the study, field monitors will

review the eCRF entries by remote, and if necessary, by onsite source data verification in order to ensure accuracy, completeness and plausibility of data entered. In addition, a central statistical monitoring approach will be applied to improve data quality and site performances. Data entered into the study database will be systematically and periodically checked by senior data management staff for completeness, for omissions and values requiring further clarifications using computerised and manual procedures. Any errors or omissions are entered on Data Query Forms, which are forwarded to the study site for resolution. Quality control audits of all key safety and efficacy data in the database are made prior to locking the database. After study completion, all electronic study data will be transferred to an auditable and system-independent accessible standard data format (CDISC) and storage for at least 10 years.

Confidentiality

Data will be collected pseudonymised and stored on a server at the University Hospital Clinic Regensburg with strictly controlled access for ensuring confidentiality. All analyses will be conducted with deidentified data.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use

Not applicable as this type of data will not be collected.

Statistical methods

Statistical methods for primary and secondary outcomes

Primary estimand: Within the population of all randomised patients defined by the inclusion and exclusion criteria with at least one assessment of the SF-36 at any point of time, the primary endpoints, SF-36 physical and mental component score at 6 months after randomisation, will be analysed. The occurrence of the intercurrent events therapy discontinuation, recurrence of the infection and amputation will be disregarded (treatment policy strategy). The summary measure will comprise the following methods: The point estimates for both treatment arms will be presented as mean and SD accompanied by the corresponding 97.5% CI and will be compared between FR therapy and the control intervention. To test the null hypothesis H_0: $\mu_{diff}=0$ at a two-sided significance level of 0.025 an analysis of covariance with the respective component score at month 6 as dependent variable, treatment arm and centre as fixed factor, the physiotherapist as a random factor and component score at baseline, sex, age and number of previous surgeries as additional covariates will be used. Results will be presented using estimated marginal means of the difference between both groups accompanied by corresponding 97.5% CIs. The study will be considered as successful if at least one component score shows a significant difference between both treatment arms. Two-sided alpha will be set at 0.025 to adjust for multiple testing.

The secondary estimand is based on the composite policy strategy. The endpoint is defined as a responder endpoint, while a patient is counted as a responder if either ΔMCS>10 and/or ΔPCS>10 (corresponds to the MID). A patient experiencing one of the intercurrent events, therapy non-adherence (≤3 therapy sessions), recurrence of the infection and amputation will be defined as non-responder independently of the SF-36 scores at month 6. The summary measure will be the difference in the proportions of both treatment arms.

Both estimands will provide a reliable answer to the question if FR therapy provides an additional clinically relevant benefit for higher quality of life after surgical treatment of prosthetic joint infection.

Statistical analyses of the secondary endpoints will be carried out in an exploratory manner without any multiplicity adjustments. Descriptive safety analyses will be provided.

Interim analyses

If recruitment is not achievable in more than one centre, an interim analysis of the achieved effect size and subsequent re-analyses of the required sample size will be performed to evaluate whether continuation of the trial is realistic.

Methods for additional analyses

Depending on the results of the primary endpoint, subgroup analyses based on age, sex and therapy adherence will be performed.

Methods to handle missing data

We expect no more than 10% missing values regarding primary endpoints, which are considered to be missing completely at random or missing at random. To account for missing values regarding primary endpoints, multiple imputation using the Markov chain Monte Carlo (MCMC) method will be used.[29] The MCMC imputation model will include the SF-36 measures at 3 months and if available at 12 months as well as the baseline patient characteristics age, sex, Body Mass Index, smoking status, ASA score, CCI, localisation of the prothesis (knee or hip), type of surgical procedure and revision rate. A sensitivity analysis using an analysis of variance (ANOVA) approach on ranks will be used to explore the robustness of inference from the initial model.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee

Each recruiting treatment centre will be represented by a cooperating investigator, who is responsible for coordination, performance of recruitment, randomisation, performance of patient-blinded interventions and follow-up examinations at the referring centre.

To ensure adherence to the intervention scheme and quality of the performance of each recruiting centre, an independent Data Safety and Monitoring Board (DSMB) has been established, consisting of three

experienced surgeons and researchers in the field of orthopaedic and trauma surgery, who are not involved in conductance or design of the trial and are not part of any of the involved medical institutions. The Board's responsibility will be monitoring and verifying the proper conduct of the study with respect to randomisation, blinding and the intervention performance using the mandatory documentation during monitoring visits at the centres.

Composition of the data monitoring committee

Quality assurance will consist of a combination of remote monitoring and on-site monitoring. Remote monitoring will be done by the data manager and will focus on data flow and accuracy in completing the eCRF. If performance is below a pre-defined quality threshold, additional on-site monitoring visits will be scheduled. On-site monitoring will be commissioned to the CRO multi-service-monitoring, which specialises in monitoring of non-commercial Investigator-Initiated Trials (IITs) since 2000. The monitors are qualified according to ICH-GCP and DIN ISO 14155 and adhere to the CRO's SOPs MON 002, 003, 007 and 008.

On-site monitoring starts with a pre-trial visit of each centre in order to ensure each centre's capability to comply with the study protocol and with the recruitment of the adequate number of patients. The findings of the pre-trial monitoring visit will be summarised in a report that will be forwarded to the PI. Monitoring will follow a risk-based approach, and the study is assessed as a low-risk trial. Thus, 100% source data verification focuses on informed consent, inclusion/exclusion criteria, the primary endpoints, randomisation and adverse and intercurrent events. All other aspects of the trial will be subjected to a 20% source data verification. In addition to the pre-trial visit, on-site monitoring is scheduled five times during the recruitment period with an interval of 6 months. After the milestone 'last patient out' is achieved, one additional close-out visit will be planned.

Adverse event reporting and harms

The occurrence of adverse and intercurrent events will be coded using the Medical Dictionary for Regulatory Activities terminology and documented in an eCRF throughout the follow-up period by each participating centre and recorded centrally at the Center for Clinical Studies of the University Hospital Regensburg. The safety assessments will be summarised by the statistician and safety reports will be forwarded to the independent DSMB.

Frequency and plans for auditing trial conduct

Besides the pre-trial monitoring visit, interim visits of study sites for the purpose of quality assurance and data monitoring will take place every 6 months. In addition, the PI will have weekly meetings with the research stuff monitoring for any concerns. The DSMB will meet regularly biannually.

Plans for communicating important protocol amendments to relevant parties

Any protocol amendments require external approval from the Ethics Committee of the University Hospital Regensburg. Modifications will only be made with the authorisation of the study team as well as the DSMB. In case of any modifications, the written participant information and consent form will be updated and signed again by all participants.

Dissemination plans

The data collected during this study will be presented at international meetings and conferences. Data from this study will be published open-access in a peer-reviewed journal. The statistical analysis plan will be made available as an amendment of the primary paper. Individual deidentified participant data (including data dictionaries) will be shared through Zenodo, a European open access data repository. Data and documents will be made available to interested researchers on a reasonable request for a period of 5 years. Patient representatives ('Forschungspartner') from the Rheuma-Liga (https://www.rheuma-liga.de/) were involved in the sense of participatory research in the conceptualisation of the study. These will participate during the whole research process. Further, focus group discussion will be held twice at University Hospital Regensburg, first to present the research strategy and preliminary results as well as to evaluate whether additional endpoints are of interest from the patient's perspective. Second, it will be evaluated how patient-oriented, complementary treatment concepts can be established in daily clinical practice and medical aftercare. Regularly meetings with the project partners will take place every 3 months.

Additionally, invitations to FR courses and preliminary results will be distributed to patients via the German Association for medical relaxation methods (https://www.dgaehat.de/).

After data analysis, a symposium will be organised, which will be open to the public. In the format of posters and talks with subsequent fishbowl discussions, detailed information regarding the state of art in the diagnosis and treatment of PJI will be provided in order to shape the direction of future research and outline possibilities to enhance the quality of life of infection patients

DISCUSSION

In this prospective, parallel two-armed randomised controlled trial, it will be evaluated whether an adjunct FR therapy results in a clinically relevant increase of the quality of life in patients with PJI.

The ensure the novelty of this research, the databases Clinicaltrials.gov, Deutsches Register Klinischer Studien, ICTRP search portal, Cochrane CENTRAL, Cochrane library and MEDLINE were searched on 9 February 2022 covering all publication dates resulting in no registered trials associated with adjunct relaxation therapies or

psychological interventions in patients with PJI. Hence, implementing a body-oriented psychotherapy intervention in clinical practice and evaluating its effect may pave the way for an integral approach in orthopaedic and trauma surgery shifting the focus towards a biopsychosocial model of recovery.[30] Further, the clinical trial will promote a multidisciplinary treatment approach, which has been shown to be beneficial for PJI patients.[31 32]

A major strength of the present trial is the implementation of participatory research. An active involvement of affected patients, and their (caring) relatives, can increase the relevance and quality of clinical trials improving both the methodology and outcomes of the research.[33 34] Thus, by involving patient representatives in the planning and design phase of the clinical trial, the perspective of those affected could already be incorporated into the identification of priority research questions, the selection of the intervention and primary endpoints, and subsequently, the development of the research design.

A potential pitfall might be the calculated sample size. As no similar interventions have been performed in patients with PJI,[13] assumptions for the expected effect size are solely based on the literature reporting a supplementary psychosomatic intervention across several indications.[21–25] However, the feasibility of recruitment was assured by analysis of patient data using hospital data management. Further, in preparation for the proposal of this trial, semi-structured interviews were conducted in the University Hospital Regensburg (unpublished data) suggesting a high willingness to participate in the trial. Nevertheless, if recruitment is not achievable in more than one centre, a interim analysis of the achieved effect size and subsequent re-analyses of the required sample size will be calculated to evaluate the proceeding of the trial.

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Contributors All authors (NW, TL, VA and MR) contributed to the conception of the study and the protocol development. NW and MR wrote the study protocol. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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REFERENCES

1 Rupp M, Lau E, Kurtz SM, *et al*. Projections of primary TKA and THA in Germany from 2016 through 2040. *Clin Orthop Relat Res* 2020;478:1622–33.
2 Slifka KJ, Yi SH, Reddy SC, *et al*. 287. The attributable mortality of prosthetic joint infection after primary hip and knee arthroplasty among medicare beneficiaries, 2005–2012. *Open Forum Infect Dis* 2018;5:S118.
3 Knebel C, Menzemer J, Pohlig F, *et al*. Peri-prosthetic joint infection of the knee causes high levels of psychosocial distress: a prospective cohort study. *Surg Infect* 2020;21:877–83.
4 Walter N, Rupp M, Hierl K, *et al*. Long-term patient-related quality of life after knee periprosthetic joint infection. *JCM* 2021;10:907.
5 Lueck E, Schlaepfer TE, Schildberg FA, *et al*. The psychological burden of a two-stage exchange of infected total hip and knee arthroplasties. *J Health Psychol* 2022;27:470–80.
6 Moore AJ, Blom AW, Whitehouse MR, *et al*. Deep prosthetic joint infection: a qualitative study of the impact on patients and their experiences of revision surgery. *BMJ Open* 2015;5:e009495.
7 Browne JA, Sandberg BF, D'Apuzzo MR, *et al*. Depression is associated with early postoperative outcomes following total joint arthroplasty: a nationwide database study. *J Arthroplasty* 2014;29:481–3.
8 Buller LT, Best MJ, Klika AK, *et al*. The influence of psychiatric comorbidity on perioperative outcomes following primary total hip and knee arthroplasty; a 17-year analysis of the national hospital discharge survey database. *J Arthroplasty* 2015;30:165–70.
9 Nickinson RSJ, Board TN, Kay PR. Post-operative anxiety and depression levels in orthopaedic surgery: a study of 56 patients undergoing hip or knee arthroplasty. *J Eval Clin Pract* 2009;15:307–10.
10 Eymir M, Unver B, Karatosun V. Relaxation exercise therapy improves pain, muscle strength, and kinesiophobia following total knee arthroplasty in the short term: a randomized controlled trial. *Knee Surg Sports Traumatol Arthrosc* 2022;30:2776-2785.
11 Lim YC, Yobas P, Chen H-C. Efficacy of relaxation intervention on pain, self-efficacy, and stress-related variables in patients following total knee replacement surgery. *Pain Manag Nurs* 2014;15:888–96.
12 Tristaino V, Lantieri F, Tornago S, *et al*. Effectiveness of psychological support in patients undergoing primary total hip or knee arthroplasty: a controlled cohort study. *J Orthop Traumatol* 2016;17:137–47.
13 Kunutsor SK, Beswick AD, Peters TJ, *et al*. Health care needs and support for patients undergoing treatment for prosthetic joint infection following hip or knee arthroplasty: a systematic review. *PLoS One* 2017;12:e0169068.
14 Lahmann C, Nickel M, Schuster T, *et al*. Functional relaxation and guided imagery as complementary therapy in asthma: a randomized controlled clinical trial. *Psychother Psychosom* 2009;78:233–9.
15 Lahmann C, Loew TH, Tritt K, *et al*. Efficacy of functional relaxation and patient education in the treatment of somatoform heart disorders: a randomized, controlled clinical investigation. *Psychosomatics* 2008;49:378–85.
16 Lahmann C, Röhricht F, Sauer N, *et al*. Functional relaxation as complementary therapy in irritable bowel syndrome: a randomized, controlled clinical trial. *J Altern Complement Med* 2010;16:47–52.
17 Loew TH, Sohn R, Martus P, *et al*. Functional relaxation as a somatopsychotherapeutic intervention: a prospective controlled study. *Altern Ther Health Med* 2000;6:70–5.
18 Loew TH, Tritt K, Siegfried W, *et al*. Efficacy of 'functional relaxation' in comparison to terbutaline and a 'placebo relaxation' method in patients with acute asthma. A randomized, prospective, placebo-controlled, crossover experimental investigation. *Psychother Psychosom* 2001;70:151–7.
19 Lahmann C, Gebhardt M, Sattel H, *et al*. A randomized controlled trial on functional relaxation as an adjunct to psychoeducation for stress. *Front Psychol* 2017;8:1553.
20 McNally M, Sousa R, Wouthuyzen-Bakker M, *et al*. The EBJIS definition of periprosthetic joint infection. *Bone Joint J* 2021;103-B:18–25.

21 Kamenov K, Twomey C, Cabello M, *et al*. The efficacy of psychotherapy, pharmacotherapy and their combination on functioning and quality of life in depression: a meta-analysis. *Psychol Med* 2017;47:414–25.
22 Rehse B, Pukrop R. Effects of psychosocial interventions on quality of life in adult cancer patients: meta analysis of 37 published controlled outcome studies. *Patient Educ Couns* 2003;50:179–86.
23 de la Torre-Luque A, Gambara H, López E, *et al*. Psychological treatments to improve quality of life in cancer contexts: a meta-analysis. *Int J Clin Health Psychol* 2016;16:211–9.
24 Mowla F, Khanjari S, Haghani S. Effect of the combination of benson's relaxation technique and brief psychoeducational intervention on religious coping, sense of coherence, and quality of life of family caregivers. *J Educ Health Promot* 2020;9:117.
25 Sima R-M, Pleș L, Socea B, *et al*. Evaluation of the SF-36 questionnaire for assessment of the quality of life of endometriosis patients undergoing treatment: a systematic review and meta-analysis. *Exp Ther Med* 2021;22:1283.
26 Escobar A, Quintana JM, Bilbao A, *et al*. Responsiveness and clinically important differences for the WOMAC and SF-36 after total knee replacement. *Osteoarthritis Cartilage* 2007;15:273–80.
27 Ellert U, Kurth B-M. Methodische Betrachtungen zu den Summenscores des SF-36 anhand der erwachsenen bundesdeutschen Bevölkerung. [Methodological views on the SF-36 summary scores based on the adult German population]. In: *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. 47, 2004: 1027–32.
28 Parker MJ, Palmer CR. A new mobility score for predicting mortality after hip fracture. *J Bone Joint Surg Br* 1993;75:797–8.
29 van Ravenzwaaij D, Cassey P, Brown SD. A simple introduction to markov chain monte-carlo sampling. *Psychon Bull Rev* 2018;25:143–54.
30 Ring D. Editorial comment: comprehensive orthopaedic care. *Clin Orthop Relat Res* 2018;476:694–5.
31 Walter N, Rupp M, Baertl S, *et al*. The role of multidisciplinary teams in musculoskeletal infection. *Bone Joint Res* 2022;11:6–7.
32 Walter N, Rupp M, Baertl S, *et al*. Periprosthetic joint infection : patients benefit from a multidisciplinary team approach. *Bone Joint Res* 2022;11:8–9.
33 Staniszewska S, Haywood KL, Brett J, *et al*. Patient and public involvement in patient-reported outcome measures: evolution not revolution. *Patient* 2012;5:79–87.
34 Mitteilungen Der DRL. *Z Rheumatol* 2016;75:236.