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The effect of functional relaxation on the quality of life in patients with periprosthetic joint infection - a randomized controlled trial

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Title

The effect of functional relaxation on the quality of life in patients with periprosthetic joint infection - a randomized 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 multicenter 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 randomized 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 therapy will be implemented as a group therapy. Functional relaxation (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 functional relaxation 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 (MCS) and Physical Component Summary (PCS) of quality of life assessed by the SF-36 health survey 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 to patient initiatives, caregivers, surgeons, and other researchers.
- **Trial registration:** DRKS00028881, 28.04.2022, German Clinical Trials register (<https://www.drks.de>)

Strength and limitations of this study:

- This study will provide the first multisite, randomized-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 pilot data and hence, the calculation of the required sample size.
- Another limitation might be loss to follow-up and the challenge to handle missing data with the Markov chain Monte Carlo method

Keywords

Periprosthetic joint infection, adjunct therapy, psychological burden, functional relaxation, psychosomatic intervention

Administrative information

Title {1}	The effect of functional relaxation on the quality of life in patients with prosthetic joint infection - a randomized controlled trial
Trial registration {2a and 2b}.	DRKS00028881, 28.04.2022, German Clinical Trials register (https://www.drks.de)
Protocol version {3}	17.03.2022, Version 2
Funding {4}	No external funding is received for this study
Author details {5a}	¹ Department for Trauma Surgery, University Medical Center Regensburg ² Department for Psychosomatic Medicine, Regensburg
Name and contact information for the trial sponsor {5b}	University Hospital Regensburg, represented by Sabine Lange MBA, Administrative Director, Franz-Josef-Strauß-Allee 11, 93053 Regensburg, Germany

Role of sponsor {5c}	The sponsor does not have any role in study design, data collection, analysis or interpretation, nor in decision to submit the report for publication
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Introduction

Background and rationale {6a}

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 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 two 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 wellbeing 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 to 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].

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2
3 Thus, it is hypothesized that providing the patients with an easy method useful for self-
4 regulation, stress management, the reduction of anxiety and coping with fears, results
5 in a clinically relevant increase of quality of life scores after adjunct functional relaxation
6 therapy, associated with shorter length of stay, reduced pain and less limitations in the
7 execution of daily tasks.
8
9

10 11 12 **Objectives {7}**

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14 The objective of this trial is to examine the effect of functional relaxation therapy on the
15 quality of life in patients with periprosthetic joint infection.
16

17 18 **Trial design {8}**

19 This is a prospective, parallel two-armed randomized controlled trial (Figure 1). All
20 patients presenting in the participating centers with verified PJI (according to the
21 European Bone and Joint Infection Society (EBJIS) consensus for diagnosis [20] will
22 be assessed for eligibility. In the recruitment period of 30 months, a total of n=490
23 patients will be screened. Here, it is expected that n=270 patients meet the inclusion
24 criteria and are willing to participate in the trial. Then, a clinical baseline assessment
25 will be conducted, and demographics, treatment characteristics (as specified under
26 1.5), the SF-36 quality of life scores and daily steps will be recorded. A web-based
27 randomization will be used to determine the treatment arm with an allocation ratio of
28 1:1, stratified by center (n=135 patients in each group). The participants will not be
29 informed of the treatment allocation. The functional relaxation group as well as the
30 control group will be held continually three times a week and patients will be
31 consecutively allocated after individual randomization. Each session will take place as
32 a group therapy, whereby each group will consist of 3-8 patients. One session will have
33 a duration of 45 min. A manual to guide the sessions was already created in previous
34 clinical trials and the sessions will be held by a physiotherapist certified in functional
35 relaxation, and previously trained on the manual. Patients will participate in the session
36 during their stationary time in the hospital, sessions will also take place as an outpatient
37 procedure. After completion of 12 sessions in 12 weeks, procedures will be the same
38 for both study groups. Follow-up examinations will be performed at the treating center
39 after 3 months, 6 months, and 12 months. During the examination, the SF-36, the
40 Parker mobility score, the number of daily steps as measured with an accelerometer
41 (actibelt®), pain medication and concomitant medications will be assessed. Also, any
42 signs of a reinfection will be documented. Treatment success will be determined by the
43 primary endpoints, the MCS and PCS of the SF-36 after 6 months. Key secondary
44 endpoints will be the SF-36 scores MCS and PCS after 12 months, consumption of
45 pain medication, mobility measured by the Parker mobility score and the physical
46 activity measured by the daily steps.
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56
57 --- Figure 1---
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Methods and analysis

Study setting {9}

The study will be carried out in level 1 trauma centers (n=4) in Germany.

Eligibility criteria {10}

Key inclusion criteria: Patients with verified prosthetic joint infection (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 (DAIR) approach or with an arthrodesis, as well as patients with a Girdlestone situation will be excluded.

Who will take informed consent? {26a}

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. 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 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 functional relaxation 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 {26b}

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

Interventions

Explanation for the choice of comparators {6b}

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3 Functional relaxation will be compared to a placebo relaxation technique as carried out
4 by previous studies. The groups will be guided by an already established manual [15,
5 17, 18]. Previous randomized-controlled trials showed an effectiveness of functional
6 relaxation in other medical conditions with treatment durations of 3 weeks [18], 4 weeks
7 [14], 5 weeks [16], and 10 week [19]. Thus, to ensure the expediency, it was chosen
8 to carry out the intervention once a week with a duration of 45 min for 12 weeks.
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10
11

12 13 **Intervention description {11a}**

14
15 Functional relaxation (FR) originally belongs to the psychodynamically based body-
16 oriented psychotherapy. Intervention techniques consist of small movements of joints,
17 which are performed during expiration accompanied by an exploration of differences
18 of body feelings. Results of clinical studies support the efficacy of FR for diverse
19 disorders and show a significant reduction of pain, anxiety and stress [14–19]. Here,
20 12 weekly sessions with a duration of 45 min each will be held by a physiotherapist
21 certified in FR. The group interventions include 5-10 patients and will be guided by a
22 manual, which was generated during previous studies [15, 17, 18]. The placebo group
23 will receive isotonic exercises, which requires an equivalent amount of motion. Thus,
24 patients will be instructed to hold specific postures for several minutes in a relaxed
25 manner, but without focusing on enhancing bodily awareness as in the treatment
26 group, The experimental treatment and the control treatment will be performed by the
27 same physiotherapist.
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34 **Criteria for discontinuing or modifying allocated interventions {11b}**

35 a) for the individual patients: As guaranteed in the patient information sheet previously
36 to study inclusion, the individual patient will be excluded from study participation, if the
37 patient withdraws his informed consent due to any reasons.
38

39 b) for participating centers: Recruitment and data assessment of the follow-up
40 examinations will be monitored by the Data Safety and Monitoring Board throughout
41 the entire trial period. For recruitment of study patients, we have defined milestones at
42 different time-points. If recruitment at the 50% landmark is below 20% of the total
43 targeted number of patients, the enrolling center will have to be excluded from
44 participating in the trial.
45
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48 c) for the whole trial: If recruitment is not achievable in more than one center, a interim
49 analysis of the achieved effect size and subsequent re-analyses of the required sample
50 size will reveal whether continuation of the trial is still realistic.
51
52
53

54 **Strategies to improve adherence to interventions {11c}**

55 For the total duration of the trial, a telephone line will be opened up, and patients are
56 encouraged to call any time in case that questions regarding the trial procedure occur.
57 Further, to enhance confidentiality, relatives of all participating patients will have the
58 possibility to take part in a certified training course in functional relaxation. Additionally,
59 the trial management will monitor all patient follow-up and will contact patients who
60

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 one 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 permitted or prohibited during the trial {11d}

This trial does not prohibit other treatments.

Provisions for post-trial care {30}

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

Outcomes {12}

Primary efficacy endpoint: Mental Component Summary (MCS) and Physical Component Summary (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 accelerometer (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 {13}

The participant timeline is given in Table 1.

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	Age, sex, admission date, BMI, prior hospitalization, ASA score, CCI Index, comorbidities Localization, type of prosthesis, previous no. of debridement, duration of symptoms, inflammatory

	Baseline-assessment	<p>markers (leucocyte count, CRP; PCT; Urea, GFR INR, D-dimer, Hb), blood culture results</p> <p>Type of surgical treatment, intraoperative culture results, identified pathogen, intraoperative histology results, wound closure</p> <p>Antibiotics administered, pain medication, concomitant medications</p> <p>Number of daily steps, Parker mobility score</p> <p>SF-36 scores</p> <p>Duration of hospital stay</p>
3 months after the intervention	<p>Follow-up 1</p> <p>Clinical assessment including quality of life and physical activity evaluation</p>	<p>Duration of hospital stay</p> <p>Adverse side effects (if any)</p> <p>Suspicion of reinfection</p> <p>Number of daily steps, Parker mobility score, pain medication and concomitant medications</p> <p>SF-36 scores</p>
6 months after the intervention	<p>Follow-up 2</p> <p>Clinical assessment including quality of life and physical activity evaluation</p>	<p>Adverse side effects (if any)</p> <p>Suspicion of reinfection</p> <p>Number of daily steps, Parker mobility score, pain medication and concomitant medications</p> <p>SF-36 scores</p>
12 months after the intervention	<p>Follow-up 3</p> <p>Clinical assessment including quality of life and physical activity evaluation</p>	<p>Adverse side effects (if any)</p> <p>Suspicion of reinfection</p> <p>Number of daily steps, Parker mobility score, pain medication and concomitant medications</p> <p>SF-36 scores</p>

Sample size {14}

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 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 4 points in the control group and about 10 points in the experimental group ($\Delta=6$) 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 ($\Delta=6$, $SD=15$) with a power of $1-\beta=80\%$ at a two-sided significance level $\alpha=0.025$, 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% (e.g. 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 randomized. Based on previous studies conducted in the University Hospital Regensburg, it is assumable 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 Version 9.4.

Recruitment {15}

All patients admitted to the participating centers will be screened for potential recruitment. A daily 24-h report of all PJI patients 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.

Assignment of interventions: allocation

Sequence generation {16a}

A web-based randomization (<http://www.randomizer.net/>) will be used to determine the treatment arm with an allocation ratio of 1:1, stratified by center, reinfection (yes/no) and type of surgical procedure (one-staged exchange, two-staged exchange). The randomization tool will be administered by the Center for Clinical Studies. To minimize

1
2
3 bias *block randomization* with varying block sizes concealed to the investigator will be
4 employed to avoid selection bias. After inclusion of a patient by signing the informed
5 consent, responsible personnel (investigator and study nurse) have to use the
6 individual log-in for the online platform to randomize the patient. All randomizations will
7 be logged and documented within the system and predefined users like the study
8 monitor will be automatically informed about the randomization.
9

10 **Concealment mechanism {16b}**

11
12 The investigator will not be able to access the allocation sequence and randomization
13 table.
14

15 **Implementation {16c}**

16 Allocation will occur via REDCap.
17

18 **Assignment of interventions: Blinding**

19 **Who will be blinded {17a}**

20
21 Patients will be blinded using a single-masked procedure. The participants will not be
22 informed of the treatment allocation, instead all patients will be told that they receive a
23 complementary relaxation technique in order to first, enhance credibility and second,
24 ensure compatibility with the informed consent.
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30 **Procedure for unblinding if needed {17b}**

31 No unblinding procedure is planned.
32
33
34
35

36 **Data collection and management**

37 **Plans for assessment and collection of outcomes {18a}**

38
39 Quality of life, pain medication consumption and physical activity were selected as
40 outcomes to appropriately capture the health status of patients affected with PJI. The
41 SF-36 shows good reliability and validity and is the most widely use quality of life
42 questionnaire worldwide. No other appropriate questionnaire assessing quality of life
43 specifically for this indication exists and the SF-36 was chosen to ensure the
44 comparability with the literature. Due to its structure with separate summary scores for
45 the mental and physical domain, the instrument is sensitive to reflect changes in quality
46 of life due to a relaxation intervention [27]. Patient-reported outcome measures will be
47 administered in a standardized way across trial sites and routinely screened to avoid
48 missing data.
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53 Further, the Parker mobility score [28], the number of daily steps as measured with an
54 accelerometer (actibelt®), pain medication and concomitant medications will be
55 assessed after 3 months, 6 months, and 12 months. An over view of the collected
56 outcomes at each timepoint is given in Table 1.
57
58
59
60

Plans to promote participant retention and complete follow-up {18b}

Please see section “Strategies to improve adherence to interventions {11c}” as these also applied to participant retention.

Data management {19}

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 (CDMS). All data management activities will comply with rules according to the EU-GDPR, including pseudonymized 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 computerized 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 stored for at least 10 years.

Confidentiality {27}

Data will be collected pseudonymized and stored on a server at the University hospital clinic Regensburg with strictly controlled access for ensuring confidentiality. All analysis 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 {33}

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

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

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,

1
2
3 the primary endpoints SF-36 physical and mental component score at 6 months after
4 randomization will be analysed. The occurrence of the intercurrent events therapy
5 discontinuation, recurrence of the infection and amputation will be disregarded
6 (Treatment policy strategy). The summary measure will comprise the following
7 methods: The point estimates for both treatment arms will be presented as mean and
8 standard deviation accompanied by the corresponding 97.5% confidence interval and
9 will be compared between functional relaxation therapy and the control intervention.
10 To test the null hypothesis $H_0: \mu_{\text{diff}}=0$ at a two-sided significance level of 0.025 an
11 analysis of covariance (ANCOVA) with the respective component score at month 6 as
12 dependent variable, treatment arm and center as fixed factor, the physiotherapist as a
13 random factor and component score at baseline, sex, age and number of previous
14 surgeries as additional covariates will be used. Results will be presented using
15 estimated marginal means of the difference between both groups accompanied by
16 corresponding 97.5%-confidence intervals. The study will be considered as successful
17 if at least one component score shows a significant difference between both treatment
18 arms. Two-sided alpha will be set at 0.025 to adjust for multiple testing.

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21
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23 The secondary estimand is based on the composite policy strategy. The endpoint is
24 the defined as a responder endpoint, while a patient is counted as a responder if either
25 $\Delta\text{MCS}>10$ and/or $\Delta\text{PCS}>10$ (corresponds to the MID). A patient experiencing one of
26 the intercurrent events, therapy non-adherence (≤ 3 therapy sessions), recurrence of
27 the infection and amputation will be defined as non-responder independently of the
28 SF-36 scores at month 6. The summary measure will be the difference in the
29 proportions of both treatment arms.

30
31
32 Both estimands will provide a reliable answer to the question if functional relaxation
33 therapy provides an additional clinically relevant benefit for higher quality of life after
34 surgical treatment of prosthetic joint infection.

35
36
37 Statistical analyses of the secondary endpoints will be carried out in an exploratory
38 manner without any multiplicity adjustments. Descriptive safety analyses will be
39 provided.

40 41 **Interim analyses {21b}**

42
43 If recruitment is not achievable in more than one center, an interims analysis of the
44 achieved effect size and subsequent re-analyses of the required sample size will be
45 performed to evaluate whether continuation of the trial is realistic.

46 47 **Methods for additional analyses (e.g. subgroup analyses) {20b}**

48
49 Depending on the results of the primary endpoint, subgroup analyses based on age,
50 sex and therapy adherence will be performed.

51 52 **Methods in analysis to handle protocol non-adherence and any statistical** 53 **methods to handle missing data {20c}**

54
55 We expect no more than 10% missing values regarding primary endpoints, which are
56 considered to be missing completely at random (MCAR) or missing at random (MAR).
57 To account for missing values regarding primary endpoints, multiple imputation using
58 the Markov chain Monte Carlo (MCMC) method will be used. The MCMC imputation
59 model will include the SF-36 measures at 3 months and if available at 12 months as
60 well as the baseline patient characteristics age, sex, BMI, smoking status, ASA score,

CCI, localization of the prosthesis (knee or hip), type of surgical procedure and revision rate. A sensitivity analysis using an ANCOVA approach on ranks will be used to explore the robustness of inference from the initial model.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

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 upon a reasonable request for a period of five years.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

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

To ensure adherence to the intervention scheme and quality of the performance of each recruiting center, 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 randomization, blinding, and the intervention performance using the mandatory documentation during monitoring visits at the centers.

Composition of the data monitoring committee, its role and reporting structure {21a}

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 specializes in monitoring of non-commercial 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 center in order to ensure each center'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 summarized in a report that will be forwarded to the PI. Monitoring will follow a risk-based approach and the study is assessed a low-risk trial. Thus, 100% source data

1
2
3 verification focuses on informed consent, inclusion/exclusion criteria, the primary
4 endpoints, randomization, and adverse and intercurrent events. All other aspects of
5 the trial will be subjected to a 20% source data verification. In addition to the pre-trial
6 visit, on-site monitoring is scheduled five times during the recruitment period with an
7 interval of 6 months. After the milestone “last patient out” is achieved, one additional
8 close-out visit will be planned.
9

10 **Adverse event reporting and harms {22}**

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12 The occurrence of adverse and intercurrent events will be coded using the Medical
13 Dictionary for Regulatory Activities (MedDRA) terminology and documented in an
14 eCRF throughout the follow-up period by each participating center and recorded
15 centrally at the Center for Clinical Studies of the University Hospital Regensburg. The
16 safety assessments will be summarized by the statistician and safety reports will be
17 forwarded to the independent Data Safety and Monitoring Board (DSMB)
18
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20 **Frequency and plans for auditing trial conduct {23}**

21
22 Besides the pre-trial monitoring visit, Interims visits of study sites for the purpose of
23 quality assurance and data monitoring will take place every six months. In addition,
24 the PI will have weekly meetings with the research staff monitoring for any concerns.
25 The DSMB will meet regularly biannually.
26
27

28 **Plans for communicating important protocol amendments to relevant parties**

29 **(e.g. trial participants, ethical committees) {25}**

30
31 Any protocol amendments require external approval from the Ethics Committee of the
32 University Hospital Regensburg. Modifications will only be made with the authorisation
33 of the study team as well as the DSMB. In case of any modifications the written
34 participant information and consent form will be updated and signed again by all
35 participants.
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39 **Dissemination plans {31a}**

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41 The data collected during this study will be presented at international meetings and
42 conferences. Data from this study will be published open-access in a peer-reviewed
43 journal. The statistical analysis plan will be made available as an amendment of the
44 primary paper. Individual deidentified participant data (including data dictionaries) will
45 be shared through Zenodo, a European open access data repository. Data and
46 documents will be made available to interested researchers upon a reasonable request
47 for a period of five years. Patient representatives ("Forschungspartner") from the
48 Rheuma-Liga (<https://www.rheuma-liga.de/>) were involved in the in the sense of
49 participatory research in the conceptualisation of the study. These will participate
50 during the whole research process. Further, focus group discussion will be held twice
51 at University Hospital Regensburg, first to present the research strategy and
52 preliminary results as well as to evaluate whether additional endpoints are of interest
53 from the patient's perspective. Second it will be evaluated how patient-oriented,
54 complementary treatment concepts can be established in daily clinical practice and
55 medical aftercare. Regularly meetings with the project partners will take place every 3
56 months.
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3 Additionally, invitations to functional relaxation courses and preliminary results will be
4 distributed to patients via the German Association for medical relaxation methods
5 (<https://www.dgaehat.de/>).

6 After data analysis, a symposium will be organised which will be open to the public. In
7 the format of posters and talks with subsequent fishbowl discussions detailed
8 information regarding the state of art in the diagnosis and treatment of PJI will be
9 provided in order to shape the direction of future research and outline possibilities to
10 enhance the quality of life of infection patients
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14 15 Discussion

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17 In this prospective, parallel two-armed randomized controlled trial it will be evaluated
18 whether an adjunct functional relaxation therapy results in a clinically relevant increase
19 of the quality of life in patients with periprosthetic joint infection.

20 The ensure the novelty of this research, the databases Clinicaltrials.gov, Deutsches
21 Register Klinischer Studien, ICTRP search portal, Cochrane CENTRAL, Cochrane
22 library and MEDLINE were searched on the 9th of February 2022 covering all
23 publication dates resulting in no registered trials associated with adjunct relaxation
24 therapies or psychological interventions in patients with PJI. Hence, implementing a
25 body-oriented psychotherapy intervention in clinical practice and evaluating its effect
26 may pave the way for an integral approach in orthopaedic and trauma surgery shifting
27 the focus towards a biopsychosocial model of recovery [29]. Further, the clinical trial
28 will promote a multidisciplinary treatment approach, which has been shown to be
29 beneficial for PJI patients [30, 31].
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34 A major strength of the present trial is the implementation of participatory research. An
35 active involvement of affected patients, and their (caring) relatives, can increase the
36 relevance and quality of clinical trials improving both the methodology and outcomes
37 of the research [32, 33]. Thus, by involving patient representatives in the planning and
38 design phase of the clinical trial, the perspective of those affected could already be
39 incorporated into the identification of priority research questions, the selection of the
40 intervention and primary endpoints, and subsequently, the development of the
41 research design.
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46 A potential pitfall might be the calculated sample size. As no similar interventions have
47 been performed in PJI patients [13], assumptions for the expected effect size are solely
48 based on the literature reporting a supplementary psychosomatic intervention across
49 several indications [21–25]. However, the feasibility of recruitment was assured by
50 analysis of patient data using hospital data management. Further, in preparation for
51 the proposal of this trial, semi-structured interviews were conducted in the University
52 Hospital Regensburg (unpublished data) suggesting a high willingness to participate
53 in the trial. Nevertheless, if recruitment is not achievable in more than one center, a
54 interim analysis of the achieved effect size and subsequent re-analyses of the
55 required sample size will be calculated to evaluate the proceeding of the trial.
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Trial status

Latest protocol version 2, 17 March 2022, recruitment is scheduled to begin by October 2022

Abbreviations

CCI: Charlson-Comorbidity Index

DAIR: debridement, antibiotics and implant retention

DSMB: Data Safety and Monitoring Board

EBJIS: European Bone and Joint Infection Society

eCRF: electronic case report form

FR: Functional relaxation

MCMC: Markov chain Monte Carlo

MCS: Mental Component Summary Score

MedDRA: Medical Dictionary for Regulatory Activities

PCS: Physical Component Summary Score

PJI: Periprosthetic joint infection

Declarations

Ethics approval and consent to participate {24}

The project is conducted in conformity with the "Declaration of Helsinki". 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.

Consent for publication {32}

A consent to publish is not applicable as no data that would identify a participant will be published.

Availability of data and materials {29}

Data will be stored on a server at the University hospital clinic Regensburg with strictly controlled access (researchers only) for ensuring confidentiality. The deidentified data collected during this study will be shared through Zenodo, a European open access data repository.

Competing interests {28}

The authors declare that they have no competing interests.

Funding {4}

No external funding is received for this study.

Authors' contributions {31b}

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

Acknowledgements

We thank the German Rheumatism League Federal Association e.V. (<https://www.rheuma-liga.de/>) for their support of this trial. Further we thank Florian Zeman from the Center for Clinical Studies, University Hospital Regensburg for his support on the statistical part of the study protocol.

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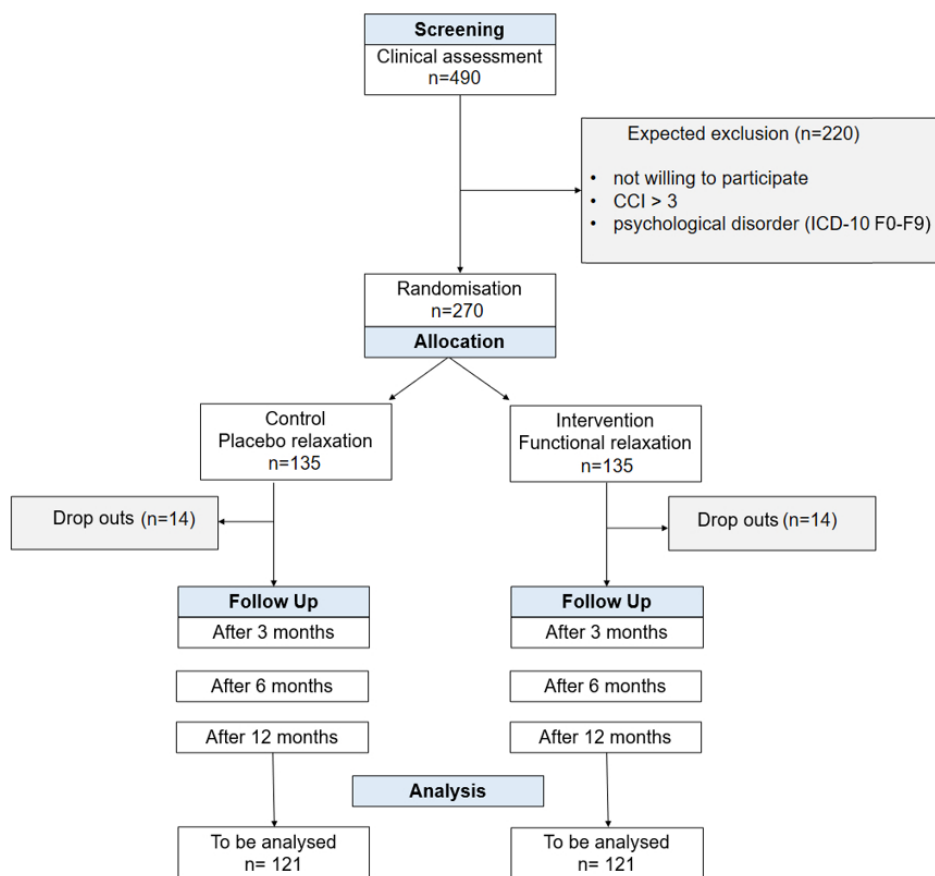
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Figure Legends

Figure 1: Schematic overview of the trial flow.



Schematic overview of the trial flow.

77x71mm (300 x 300 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym p. 1, section "Title"
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry p. 2, section "Administrative information"
	2b	All items from the World Health Organization Trial Registration Data Set p. 2, section "Administrative information"
Protocol version	3	Date and version identifier p. 2, section "Administrative information"
Funding	4	Sources and types of financial, material, and other support p. 2, section "Administrative information"/ p. 16, section "Declarations"
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors p. 2, section "Administrative information"
	5b	Name and contact information for the trial sponsor p. 2, section "Administrative information"
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities p. 2, section "Administrative information"
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) p. 12, section "Oversight and monitoring"

Introduction

1			
2	Background and	6a	Description of research question and justification for undertaking the
3	rationale		trial, including summary of relevant studies (published and
4			unpublished) examining benefits and harms for each intervention
5			p. 2, section “Background”
6			
7		6b	Explanation for choice of comparators
8			p. 5, section “Interventions”,
9			
10	Objectives	7	Specific objectives or hypotheses
11			p. 3, section “Objectives”
12			
13			
14	Trial design	8	Description of trial design including type of trial (eg, parallel group,
15			crossover, factorial, single group), allocation ratio, and framework (eg,
16			superiority, equivalence, noninferiority, exploratory)
17			p. 3, section “Trial design”
18			
19			
20	Methods: Participants, interventions, and outcomes		
21			
22	Study setting	9	Description of study settings (eg, community clinic, academic hospital)
23			and list of countries where data will be collected. Reference to where
24			list of study sites can be obtained
25			p. 4, section “Methods”, subsection “Study setting”
26			
27			
28	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility
29			criteria for study centres and individuals who will perform the
30			interventions (eg, surgeons, psychotherapists)
31			p. 4, section “Methods”, subsection “Eligibility criteria”
32			
33	Interventions	11a	Interventions for each group with sufficient detail to allow replication,
34			including how and when they will be administered
35			p. 5, section “Interventions”
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38		11b	Criteria for discontinuing or modifying allocated interventions for a
39			given trial participant (eg, drug dose change in response to harms,
40			participant request, or improving/worsening disease)
41			p. 5, section “Interventions”
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43			
44		11c	Strategies to improve adherence to intervention protocols, and any
45			procedures for monitoring adherence (eg, drug tablet return,
46			laboratory tests)
47			p. 6, section “Interventions”
48			
49		11d	Relevant concomitant care and interventions that are permitted or
50			prohibited during the trial
51			p. 6, section “Interventions”
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2	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
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9			p. 6, section “Interventions”
10			
11	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
12			
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15			p. 7, section “Interventions”
16			
17	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
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21			p. 8, section “Interventions”
22			
23	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
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26			p. 8, section “Interventions”

Methods: Assignment of interventions (for controlled trials)

Allocation:

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31	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
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38			p. 9, section “Assignment of interventions: allocation”
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40	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
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45			p. 9, section “Assignment of interventions: allocation”
46			
47	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
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50			p. 9, section “Assignment of interventions: allocation”
51			
52	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
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56			p. 9, section “Assignment of interventions: blinding”
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- 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
- p. 9, section "Assignment of interventions: blinding"**

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Methods: Data collection, management, and analysis

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- Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
- p. 9, section "Data collection and management"**
- 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
- p. 10, section "Data collection and management"**
- Data management 19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
- p. 10, section "Data collection and management"**
- Statistical methods 20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
- p. 11, section "Statistical methods"**
- 20b Methods for any additional analyses (eg, subgroup and adjusted analyses)
- p. 12, section "Statistical methods"**
- 20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
- p. 12, section "Statistical methods"**

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Methods: Monitoring

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- Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
- p. 13, section "Oversight and monitoring"**

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2		21b	Description of any interim analyses and stopping guidelines, including
3			who will have access to these interim results and make the final
4			decision to terminate the trial
5			p. 12, section “Statistical methods”
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7	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and
8			spontaneously reported adverse events and other unintended effects
9			of trial interventions or trial conduct
10			p. 13, section “Oversight and monitoring”
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13	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and
14			whether the process will be independent from investigators and the
15			sponsor
16			p. 13, section “Oversight and monitoring”
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19	Ethics and dissemination		
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21	Research ethics	24	Plans for seeking research ethics committee/institutional review board
22	approval		(REC/IRB) approval
23			p. 15, section “Declarations”
24			
25	Protocol	25	Plans for communicating important protocol modifications (eg,
26	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties
27			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,
28			regulators)
29			p. 13, section “Oversight and monitoring”
30			
31			
32	Consent or assent	26a	Who will obtain informed consent or assent from potential trial
33			participants or authorised surrogates, and how (see Item 32)
34			p. 4, section “Methods”
35			
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37		26b	Additional consent provisions for collection and use of participant data
38			and biological specimens in ancillary studies, if applicable
39			p. 5, section “Methods”,
40			
41	Confidentiality	27	How personal information about potential and enrolled participants will
42			be collected, shared, and maintained in order to protect confidentiality
43			before, during, and after the trial
44			p. 11, section “Data collection and management”
45			
46			
47	Declaration of	28	Financial and other competing interests for principal investigators for
48	interests		the overall trial and each study site
49			p. 16, section “Declarations”
50			
51	Access to data	29	Statement of who will have access to the final trial dataset, and
52			disclosure of contractual agreements that limit such access for
53			investigators
54			p. 16, section “Declarations”
55			
56			
57			
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60			

1			
2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation
4			p. 6, section “Interventions”,
5			
6	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
7	policy		participants, healthcare professionals, the public, and other relevant
8			groups (eg, via publication, reporting in results databases, or other
9			data sharing arrangements), including any publication restrictions
10			p. 14, section “Dissemination plans”
11			
12		31b	Authorship eligibility guidelines and any intended use of professional
13			writers
14			p. 16, section “Declarations”
15			
16		31c	Plans, if any, for granting public access to the full protocol, participant-
17			level dataset, and statistical code
18			p. 12, section “Statistical methods
19			”
20			
21			
22	Appendices		
23			
24	Informed consent	32	Model consent form and other related documentation given to
25	materials		participants and authorised surrogates
26			p. 16, section “Declarations”
27			
28			
29	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
30	specimens		specimens for genetic or molecular analysis in the current trial and for
31			future use in ancillary studies, if applicable
32			p. 11, section “Data collection and management”
33			

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons [“Attribution-NonCommercial-NoDerivs 3.0 Unported”](https://creativecommons.org/licenses/by-nc-nd/3.0/) license.

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The effect of functional relaxation on the quality of life in patients with periprosthetic joint infection: Protocol for a randomized controlled trial

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Title

The effect of functional relaxation on the quality of life in patients with periprosthetic joint infection: Protocol for a randomized 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 multicenter 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 randomized 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 therapy will be implemented as a group therapy. Functional relaxation (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 functional relaxation 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 (MCS) and Physical Component Summary (PCS) of quality of life assessed by the SF-36 health survey 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 on in congresses.
- **Trial registration:** DRKS00028881, 28.04.2022, German Clinical Trials register (<https://www.drks.de>)

Strength and limitations of this study:

- This study will provide the first multisite, randomized-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 loss to follow-up and the challenge to handle missing data with the Markov chain Monte Carlo method

Keywords

Periprosthetic joint infection, adjunct therapy, psychological burden, functional relaxation, psychosomatic intervention

Administrative information

Title {1}	The effect of functional relaxation on the quality of life in patients with prosthetic joint infection - a randomized controlled trial
Trial registration {2a and 2b}.	DRKS00028881, 28.04.2022, German Clinical Trials register (https://www.drks.de)
Protocol version {3}	17.03.2022, Version 2
Funding {4}	No external funding is received for this study
Author details {5a}	¹ Department for Trauma Surgery, University Medical Center Regensburg ² Department for Psychosomatic Medicine, Regensburg

Name and contact information for the trial sponsor {5b}	University Hospital Regensburg, represented by Sabine Lange MBA, Administrative Director, Franz-Josef-Strauß-Allee 11, 93053 Regensburg, Germany
Role of sponsor {5c}	The sponsor does not have any role in study design, data collection, analysis or interpretation, nor in decision to submit the report for publication

Introduction

Background and rationale

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 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 two 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 wellbeing 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 to 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

1
2
3 during expiration accompanied by an exploration of differences of body feelings.
4 Results of previous clinical studies support the efficacy of FR for diverse disorders and
5 show a significant reduction of pain, anxiety and stress [14–19].
6

7 Thus, it is hypothesized that providing the patients with an easy method useful for self-
8 regulation, stress management, the reduction of anxiety and coping with fears, results
9 in a clinically relevant increase of quality of life scores after adjunct functional relaxation
10 therapy, associated with shorter length of stay, reduced pain and less limitations in the
11 execution of daily tasks.
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15 16 **Objectives**

17 The objective of this trial is to examine the effect of functional relaxation therapy on the
18 quality of life in patients with periprosthetic joint infection.
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25 **Methods and analysis**

26 **Trial design**

27 This is a prospective, parallel two-armed randomized controlled trial (Figure 1). All
28 patients presenting in the participating centers with verified PJI (according to the
29 European Bone and Joint Infection Society (EBJIS) consensus for diagnosis [20] will
30 be assessed for eligibility. In the recruitment period of 30 months, a total of n=490
31 patients will be screened. Here, it is expected that n=270 patients meet the inclusion
32 criteria and are willing to participate in the trial. Then, a clinical baseline assessment
33 will be conducted, and demographics, treatment characteristics (as specified under
34 1.5), the SF-36 quality of life scores and daily steps will be recorded. A web-based
35 randomization will be used to determine the treatment arm with an allocation ratio of
36 1:1, stratified by center (n=135 patients in each group). The participants will not be
37 informed of the treatment allocation. The functional relaxation group as well as the
38 control group will be held continually three times a week and patients will be
39 consecutively allocated after individual randomization. Each session will take place as
40 a group therapy, whereby each group will consist of 3-8 patients. One session will have
41 a duration of 45 min. A manual to guide the sessions was already created in previous
42 clinical trials and the sessions will be held by a physiotherapist certified in functional
43 relaxation, and previously trained on the manual. Patients will participate in the session
44 during their stationary time in the hospital, sessions will also take place as an outpatient
45 procedure. After completion of 12 sessions in 12 weeks, procedures will be the same
46 for both study groups. Follow-up examinations will be performed at the treating center
47 after 3 months, 6 months, and 12 months. During the examination, the SF-36, the
48 Parker mobility score, the number of daily steps as measured with an accelerometer
49 (actibelt®), pain medication and concomitant medications will be assessed. Also, any
50 signs of a reinfection will be documented. Treatment success will be determined by the
51 primary endpoints, the MCS and PCS of the SF-36 after 6 months. Key secondary
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1
2
3 endpoints will be the SF-36 scores MCS and PCS after 12 months, consumption of
4 pain medication, mobility measured by the Parker mobility score and the physical
5 activity measured by the daily steps.
6

7
8 --- Figure 1---

9 10 **Study setting**

11
12 The study will be carried out in level 1 trauma centers (n=4) in Germany.
13
14

15 16 **Eligibility criteria**

17 Key inclusion criteria: Patients with verified prosthetic joint infection (PJI) aged 18 or
18 older will be recruited. Written informed consent and surgical treatment including a
19 one-staged exchange, or a two-staged exchange is a prerequisite for participation.

20 Key exclusion criteria: Patients diagnosed with a concomitant psychological disorder
21 (ICD-10 F0-F9) or a Charlson-Comorbidity Index (CCI) > 3 will be excluded. Further,
22 patients surgically treated with a debridement, antibiotics and implant retention (DAIR)
23 approach or with an arthrodesis, as well as patients with a Girdlestone situation will be
24 excluded.
25
26

27 28 **Who will take informed consent?**

29
30 Participants will be approached on the hospital ward and given verbal explanation of
31 the study by a study researcher. A written participant information and consent form will
32 be provided. Participants will be informed that their decision whether or not to
33 participate in the study will not impact their access to routine care and that they can
34 discontinue the participation in the study at any time. Participants will be given the
35 opportunity to read, discuss and ask questions. Those willing to participate will sign the
36 consent form.
37
38

39 40 **Patient and Public Involvement**

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

50 Additionally, invitations to functional relaxation courses and preliminary results will be
51 distributed to patients via the German Association for medical relaxation methods
52 (<https://www.dgaehat.de/>).
53
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56 57 **Additional consent provisions for collection and use of participant data and 58 biological specimens**

59
60 Not applicable as biologic specimens are not collected for this study.

Interventions

Explanation for the choice of comparators

Functional relaxation will be compared to a placebo relaxation technique as carried out by previous studies. The groups will be guided by an already established manual [15, 17, 18]. Previous randomized-controlled trials showed an effectiveness of functional relaxation in other medical conditions with treatment durations of 3 weeks [18], 4 weeks [14], 5 weeks [16], and 10 week [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 description

Functional relaxation (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 discontinuing or modifying allocated interventions

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 centers: 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 center will have to be excluded from participating in the trial.

c) for the whole trial: If recruitment is not achievable in more than one center, a 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 to interventions

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 functional relaxation. 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 one 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 permitted or prohibited during the trial

This trial does not prohibit other treatments.

Provisions for post-trial care

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

Outcomes

Primary efficacy endpoint: Mental Component Summary (MCS) and Physical Component Summary (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 accelerometer (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 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.

Participant timeline

The participant timeline is given in Table 1.

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 hospitalization, ASA score, CCI Index, comorbidities Localization, type of prosthesis, previous no. 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	Adverse side effects (if any)

	Clinical assessment including quality of life and physical activity evaluation	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

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 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 4 points in the control group and about 10 points in the experimental group ($\Delta=6$) 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 ($\Delta=6$, $SD=15$) with a power of $1-\beta=80\%$ at a two-sided significance level $\alpha=0.025$, 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% (e.g. 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 randomized. Based on previous studies conducted in the University Hospital Regensburg, it is assumable 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 Version 9.4.

Recruitment

All patients admitted to the participating centers will be screened for potential recruitment. A daily 24-h report of all PJI patients 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.

Assignment of interventions: allocation

Sequence generation

A web-based randomization (<http://www.randomizer.net/>) will be used to determine the treatment arm with an allocation ratio of 1:1, stratified by center, reinfection (yes/no) and type of surgical procedure (one-staged exchange, two-staged exchange). The randomization tool will be administered by the Center for Clinical Studies. To minimize bias *block randomization* 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 randomize the patient. All randomizations will be logged and documented within the system and predefined users like the study monitor will be automatically informed about the randomization.

Concealment mechanism

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

Implementation

Allocation will occur via REDCap.

Assignment of interventions: 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

Plans for assessment and collection 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

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2
3 SF-36 shows good reliability and validity and is the most widely use quality of life
4 questionnaire worldwide. No other appropriate questionnaire assessing quality of life
5 specifically for this indication exists and the SF-36 was chosen to ensure the
6 comparability with the literature. Due to its structure with separate summary scores for
7 the mental and physical domain, the instrument is sensitive to reflect changes in quality
8 of life due to a relaxation intervention [27]. Patient-reported outcome measures will be
9 administered in a standardized way across trial sites and routinely screened to avoid
10 missing data.
11
12

13
14 Further, the Parker mobility score [28], the number of daily steps as measured with an
15 accelometer (actibelt®), pain medication and concomitant medications will be
16 assessed after 3 months, 6 months, and 12 months. An over view of the collected
17 outcomes at each timepoint is given in Table 1.
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22 **Plans to promote participant retention and complete follow-up**

23 Please see section “Strategies to improve adherence to interventions {11c}” as these
24 also applied to participant retention.
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28

29 **Data management**

30 For study data collection, a web-based electronic case report form (eCRF) will be setup
31 within an FDA 21 CFR Part 11 and ICH E6(R2) compliant clinical database
32 management system (CDMS). All data management activities will comply with rules
33 according to the EU-GDPR, including pseudonymized data storage.
34
35

36 Each investigator is responsible to review and ensure the accuracy, completeness,
37 and timeliness of the data reported in the patient’s data entered in the eCRF and will
38 provide his/her signature and date of signature on the eCRF pages. During the study,
39 field monitors will review the eCRF entries by remote, and if necessary, by onsite
40 source data verification in order to ensure accuracy, completeness and plausibility of
41 data entered. In addition, a central statistical monitoring approach will be applied to
42 improve data quality and site performances. Data entered into the study database will
43 be systematically and periodically checked by senior data management staff for
44 completeness, for omissions, and values requiring further clarifications using
45 computerized and manual procedures. Any errors or omissions are entered on Data
46 Query Forms, which are forwarded to the study site for resolution. Quality control audits
47 of all key safety and efficacy data in the database are made prior to locking the
48 database. After study completion, all electronic study data will be transferred to an
49 auditable and system-independent accessible standard data format (CDISC) and
50 stored for at least 10 years.
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58 **Confidentiality**

59 Data will be collected pseudonymized and stored on a server at the University hospital
60 clinic Regensburg with strictly controlled access for ensuring confidentiality. All

analysis 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 randomization 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 standard deviation accompanied by the corresponding 97.5% confidence interval and will be compared between functional relaxation therapy and the control intervention. To test the null hypothesis $H_0: \mu_{\text{diff}}=0$ at a two-sided significance level of 0.025 an analysis of covariance (ANCOVA) with the respective component score at month 6 as dependent variable, treatment arm and center 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%-confidence intervals. 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 $\Delta\text{MCS}>10$ and/or $\Delta\text{PCS}>10$ (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 functional relaxation 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 center, an interim analysis of the

1
2
3 achieved effect size and subsequent re-analyses of the required sample size will be
4 performed to evaluate whether continuation of the trial is realistic.

6 **Methods for additional analyses (e.g. subgroup analyses)**

7
8 Depending on the results of the primary endpoint, subgroup analyses based on age,
9 sex and therapy adherence will be performed.

10 **Methods in analysis to handle protocol non-adherence and any statistical** 11 **methods to handle missing data**

12
13 We expect no more than 10% missing values regarding primary endpoints, which are
14 considered to be missing completely at random (MCAR) or missing at random (MAR).
15 To account for missing values regarding primary endpoints, multiple imputation using
16 the Markov chain Monte Carlo (MCMC) method will be used [29]. The MCMC
17 imputation model will include the SF-36 measures at 3 months and if available at 12
18 months as well as the baseline patient characteristics age, sex, BMI, smoking status,
19 ASA score, CCI, localization of the prosthesis (knee or hip), type of surgical procedure
20 and revision rate. A sensitivity analysis using an ANOVA approach on ranks will be
21 used to explore the robustness of inference from the initial model.
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28 **Plans to give access to the full protocol, participant level-data and statistical** 29 **code**

30
31 Data from this study will be published open-access in a peer-reviewed journal. The
32 statistical analysis plan will be made available as an amendment of the primary paper.
33 Individual deidentified participant data (including data dictionaries) will be shared
34 through Zenodo, a European open access data repository. Data and documents will
35 be made available to interested researchers upon a reasonable request for a period of
36 five years.
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39

40 ***Oversight and monitoring***

41 **Composition of the coordinating center and trial steering committee**

42
43 Each recruiting treatment center will be represented by a cooperating investigator, who
44 is responsible for coordination, performance of recruitment, randomization,
45 performance of patient-blinded interventions and follow-up examinations at the
46 referring center.
47
48

49
50 To ensure adherence to the intervention scheme and quality of the performance of
51 each recruiting center, an independent Data Safety and Monitoring Board (DSMB) has
52 been established, consisting of three experienced surgeons and researchers in the
53 field of orthopaedic and trauma surgery, who are not involved in conductance or design
54 of the trial and are not part of any of the involved medical institutions. The Board's
55 responsibility will be monitoring and verifying the proper conduct of the study with
56 respect to randomization, blinding, and the intervention performance using the
57 mandatory documentation during monitoring visits at the centers.
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60

Composition of the data monitoring committee, its role and reporting structure

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 specializes in monitoring of non-commercial 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 center in order to ensure each center'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 summarized in a report that will be forwarded to the PI. Monitoring will follow a risk-based approach and the study is assessed a low-risk trial. Thus, 100% source data verification focuses on informed consent, inclusion/exclusion criteria, the primary endpoints, randomization, 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 (MedDRA) terminology and documented in an eCRF throughout the follow-up period by each participating center and recorded centrally at the Center for Clinical Studies of the University Hospital Regensburg. The safety assessments will be summarized by the statistician and safety reports will be forwarded to the independent Data Safety and Monitoring Board (DSMB).

Frequency and plans for auditing trial conduct

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

Plans for communicating important protocol amendments to relevant parties

(e.g. trial participants, ethical committees)

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

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3 primary paper. Individual deidentified participant data (including data dictionaries) will
4 be shared through Zenodo, a European open access data repository. Data and
5 documents will be made available to interested researchers upon a reasonable request
6 for a period of five years. Patient representatives ("Forschungspartner") from the
7 Rheuma-Liga (<https://www.rheuma-liga.de/>) were involved in the in the sense of
8 participatory research in the conceptualisation of the study. These will participate
9 during the whole research process. Further, focus group discussion will be held twice
10 at University Hospital Regensburg, first to present the research strategy and
11 preliminary results as well as to evaluate whether additional endpoints are of interest
12 from the patient's perspective. Second it will be evaluated how patient-oriented,
13 complementary treatment concepts can be established in daily clinical practice and
14 medical aftercare. Regularly meetings with the project partners will take place every 3
15 months.

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

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

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32 In this prospective, parallel two-armed randomized controlled trial it will be evaluated
33 whether an adjunct functional relaxation therapy results in a clinically relevant increase
34 of the quality of life in patients with periprosthetic joint infection.

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36 The ensure the novelty of this research, the databases Clinicaltrials.gov, Deutsches
37 Register Klinischer Studien, ICTRP search portal, Cochrane CENTRAL, Cochrane
38 library and MEDLINE were searched on the 9th of February 2022 covering all
39 publication dates resulting in no registered trials associated with adjunct relaxation
40 therapies or psychological interventions in patients with PJI. Hence, implementing a
41 body-oriented psychotherapy intervention in clinical practice and evaluating its effect
42 may pave the way for an integral approach in orthopaedic and trauma surgery shifting
43 the focus towards a biopsychosocial model of recovery [30]. Further, the clinical trial
44 will promote a multidisciplinary treatment approach, which has been shown to be
45 beneficial for PJI patients [31, 32].
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49 A major strength of the present trial is the implementation of participatory research. An
50 active involvement of affected patients, and their (caring) relatives, can increase the
51 relevance and quality of clinical trials improving both the methodology and outcomes
52 of the research [33, 34]. Thus, by involving patient representatives in the planning and
53 design phase of the clinical trial, the perspective of those affected could already be
54 incorporated into the identification of priority research questions, the selection of the
55 intervention and primary endpoints, and subsequently, the development of the
56 research design.
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3 A potential pitfall might be the calculated sample size. As no similar interventions have
4 been performed in PJI patients [13], assumptions for the expected effect size are solely
5 based on the literature reporting a supplementary psychosomatic intervention across
6 several indications [21–25]. However, the feasibility of recruitment was assured by
7 analysis of patient data using hospital data management. Further, in preparation for
8 the proposal of this trial, semi-structured interviews were conducted in the University
9 Hospital Regensburg (unpublished data) suggesting a high willingness to participate
10 in the trial. Nevertheless, if recruitment is not achievable in more than one center, a
11 interim analysis of the achieved effect size and subsequent re-analyses of the
12 required sample size will be calculated to evaluate the proceeding of the trial.
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17 **Trial status**

18 Latest protocol version 2, 17 March 2022, recruitment is scheduled to begin by
19 October 2022
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24 **Abbreviations**

25 CCI: Charlson-Comorbidity Index
26 DAIR: debridement, antibiotics and implant retention
27 DSMB: Data Safety and Monitoring Board
28 EBJIS: European Bone and Joint Infection Society
29 eCRF: electronic case report form
30 FR: Functional relaxation
31 MCMC: Markov chain Monte Carlo
32 MCS: Mental Component Summary Score
33 MedDRA: Medical Dictionary for Regulatory Activities
34 PCS: Physical Component Summary Score
35 PJI: Periprosthetic joint infection
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44 **Declarations**

45 **Ethics approval and consent to participate**

46 The project is conducted in conformity with the "Declaration of Helsinki". Approval from
47 the Ethical Committee of the University Hospital Regensburg was received (file
48 number: 21-2226-101). Written, informed consent to participate will be obtained from
49 all participants.
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54 **Consent for publication**

55 A consent to publish is not applicable as no data that would identify a participant will
56 be published.
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Availability of data and materials

Data will be stored on a server at the University hospital clinic Regensburg with strictly controlled access (researchers only) for ensuring confidentiality. The deidentified data collected during this study will be shared through Zenodo, a European open access data repository.

Competing interests

The authors declare that they have no competing interests.

Funding

No external funding is received for this study.

Authors' contributions

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

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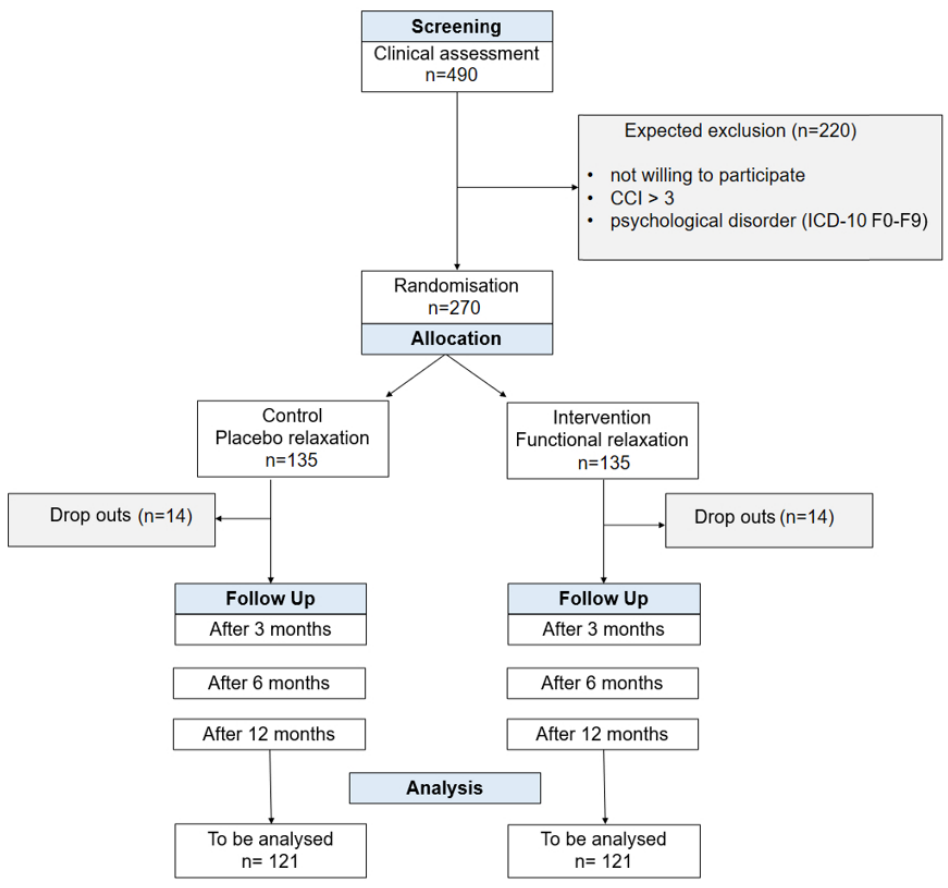
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7 **Figure Legends**

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9 Figure 1: Schematic overview of the trial flow.
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For peer review only



Schematic overview of the trial flow.

77x71mm (300 x 300 DPI)

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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym p. 1, section "Title"
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry p. 2, section "Administrative information"
	2b	All items from the World Health Organization Trial Registration Data Set p. 2, section "Administrative information"
Protocol version	3	Date and version identifier p. 2, section "Administrative information"
Funding	4	Sources and types of financial, material, and other support p. 2, section "Administrative information"/ p. 16, section "Declarations"
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors p. 2, section "Administrative information"
	5b	Name and contact information for the trial sponsor p. 2, section "Administrative information"
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities p. 2, section "Administrative information"
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) p. 12, section "Oversight and monitoring"

Introduction

1			
2	Background and	6a	Description of research question and justification for undertaking the
3	rationale		trial, including summary of relevant studies (published and
4			unpublished) examining benefits and harms for each intervention
5			p. 2, section “Background”
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7		6b	Explanation for choice of comparators
8			p. 5, section “Interventions”,
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10	Objectives	7	Specific objectives or hypotheses
11			p. 3, section “Objectives”
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14	Trial design	8	Description of trial design including type of trial (eg, parallel group,
15			crossover, factorial, single group), allocation ratio, and framework (eg,
16			superiority, equivalence, noninferiority, exploratory)
17			p. 3, section “Trial design”
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19			
20	Methods: Participants, interventions, and outcomes		
21			
22	Study setting	9	Description of study settings (eg, community clinic, academic hospital)
23			and list of countries where data will be collected. Reference to where
24			list of study sites can be obtained
25			p. 4, section “Methods”, subsection “Study setting”
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28	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility
29			criteria for study centres and individuals who will perform the
30			interventions (eg, surgeons, psychotherapists)
31			p. 4, section “Methods”, subsection “Eligibility criteria”
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33	Interventions	11a	Interventions for each group with sufficient detail to allow replication,
34			including how and when they will be administered
35			p. 5, section “Interventions”
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38		11b	Criteria for discontinuing or modifying allocated interventions for a
39			given trial participant (eg, drug dose change in response to harms,
40			participant request, or improving/worsening disease)
41			p. 5, section “Interventions”
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44		11c	Strategies to improve adherence to intervention protocols, and any
45			procedures for monitoring adherence (eg, drug tablet return,
46			laboratory tests)
47			p. 6, section “Interventions”
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49		11d	Relevant concomitant care and interventions that are permitted or
50			prohibited during the trial
51			p. 6, section “Interventions”
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2	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
3			p. 6, section “Interventions”
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11	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
12			p. 7, section “Interventions”
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17	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
18			p. 8, section “Interventions”
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23	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
24			p. 8, section “Interventions”
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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31	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
32			p. 9, section “Assignment of interventions: allocation”
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40	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
41			p. 9, section “Assignment of interventions: allocation”
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47	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
48			p. 9, section “Assignment of interventions: allocation”
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52	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
53			p. 9, section “Assignment of interventions: blinding”
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- 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
- p. 9, section "Assignment of interventions: blinding"**

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Methods: Data collection, management, and analysis

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- Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
- p. 9, section "Data collection and management"**
- 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
- p. 10, section "Data collection and management"**
- Data management 19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
- p. 10, section "Data collection and management"**
- Statistical methods 20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
- p. 11, section "Statistical methods"**
- 20b Methods for any additional analyses (eg, subgroup and adjusted analyses)
- p. 12, section "Statistical methods"**
- 20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
- p. 12, section "Statistical methods"**

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Methods: Monitoring

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- Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
- p. 13, section "Oversight and monitoring"**

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2		21b	Description of any interim analyses and stopping guidelines, including
3			who will have access to these interim results and make the final
4			decision to terminate the trial
5			p. 12, section “Statistical methods”
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7	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and
8			spontaneously reported adverse events and other unintended effects
9			of trial interventions or trial conduct
10			p. 13, section “Oversight and monitoring”
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13	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and
14			whether the process will be independent from investigators and the
15			sponsor
16			p. 13, section “Oversight and monitoring”
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19	Ethics and dissemination		
20			
21	Research ethics	24	Plans for seeking research ethics committee/institutional review board
22	approval		(REC/IRB) approval
23			p. 15, section “Declarations”
24			
25	Protocol	25	Plans for communicating important protocol modifications (eg,
26	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties
27			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,
28			regulators)
29			p. 13, section “Oversight and monitoring”
30			
31			
32	Consent or assent	26a	Who will obtain informed consent or assent from potential trial
33			participants or authorised surrogates, and how (see Item 32)
34			p. 4, section “Methods”
35			
36			
37		26b	Additional consent provisions for collection and use of participant data
38			and biological specimens in ancillary studies, if applicable
39			p. 5, section “Methods”,
40			
41	Confidentiality	27	How personal information about potential and enrolled participants will
42			be collected, shared, and maintained in order to protect confidentiality
43			before, during, and after the trial
44			p. 11, section “Data collection and management”
45			
46			
47	Declaration of	28	Financial and other competing interests for principal investigators for
48	interests		the overall trial and each study site
49			p. 16, section “Declarations”
50			
51	Access to data	29	Statement of who will have access to the final trial dataset, and
52			disclosure of contractual agreements that limit such access for
53			investigators
54			p. 16, section “Declarations”
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2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation
4			p. 6, section “Interventions”,
5			
6	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
7	policy		participants, healthcare professionals, the public, and other relevant
8			groups (eg, via publication, reporting in results databases, or other
9			data sharing arrangements), including any publication restrictions
10			p. 14, section “Dissemination plans”
11			
12			
13		31b	Authorship eligibility guidelines and any intended use of professional
14			writers
15			p. 16, section “Declarations”
16			
17			
18		31c	Plans, if any, for granting public access to the full protocol, participant-
19			level dataset, and statistical code
20			p. 12, section “Statistical methods
21			
22			
23	Appendices		
24	Informed consent	32	Model consent form and other related documentation given to
25	materials		participants and authorised surrogates
26			p. 16, section “Declarations”
27			
28			
29	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
30	specimens		specimens for genetic or molecular analysis in the current trial and for
31			future use in ancillary studies, if applicable
32			p. 11, section “Data collection and management”
33			

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons [“Attribution-NonCommercial-NoDerivs 3.0 Unported”](https://creativecommons.org/licenses/by-nc-nd/3.0/) license.

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The effect of functional relaxation on the quality of life in patients with periprosthetic joint infection: Protocol for a randomized controlled trial

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Title

The effect of functional relaxation on the quality of life in patients with periprosthetic joint infection: Protocol for a randomized 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 multicenter 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 randomized 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 therapy will be implemented as a group therapy. Functional relaxation (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 functional relaxation 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 (MCS) and Physical Component Summary (PCS) of quality of life assessed by the SF-36 health survey 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 on in congresses.
- **Trial registration:** DRKS00028881, 28.04.2022, German Clinical Trials register (<https://www.drks.de>)

Strength and limitations of this study:

- This study will provide the first multisite, randomized-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 loss to follow-up and the challenge to handle missing data with the Markov chain Monte Carlo method

Keywords

Periprosthetic joint infection, adjunct therapy, psychological burden, functional relaxation, psychosomatic intervention

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 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 two 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 wellbeing 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 to 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

1
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3 increased risk of infection after joint replacement, higher odds of adverse events, and
4 worse clinical outcomes [7, 8]. Also, the prevalence for developing psychological
5 disorders after surgery has been highlighted [9]. A few studies indicate the beneficial
6 effect of psychological support and the efficacy of relaxation therapy in patients
7 undergoing total knee replacement [10–12]. However, concerning PJI, a gap in the
8 literature was identified by a recent review screening 4,213 articles for the treatment of
9 PJI finding none, which evaluated psychological interventions [13].
10
11

12 Functional relaxation (FR) originally belongs to the psychodynamically based body-
13 oriented psychotherapy, frequently applied in the field of psychosomatic medicine.
14 Intervention techniques consist of small movements of joints, which are performed
15 during expiration accompanied by an exploration of differences of body feelings.
16 Results of previous clinical studies support the efficacy of FR for diverse disorders and
17 show a significant reduction of pain, anxiety and stress [14–19].
18
19

20 Thus, it is hypothesized that providing the patients with an easy method useful for self-
21 regulation, stress management, the reduction of anxiety and coping with fears, results
22 in a clinically relevant increase of quality of life scores after adjunct functional relaxation
23 therapy, associated with shorter length of stay, reduced pain and less limitations in the
24 execution of daily tasks.
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30 **Objectives**

31 The objective of this trial is to examine the effect of functional relaxation therapy on the
32 quality of life in patients with periprosthetic joint infection.
33
34
35

36 **Methods and analysis**

37 **Trial design**

38 This is a prospective, parallel two-armed randomized controlled trial (Figure 1). All
39 patients presenting in the participating centers with verified PJI (according to the
40 European Bone and Joint Infection Society (EBJIS) consensus for diagnosis [20] will
41 be assessed for eligibility. In the recruitment period of 30 months, a total of n=490
42 patients will be screened. Here, it is expected that n=270 patients meet the inclusion
43 criteria and are willing to participate in the trial. Then, a clinical baseline assessment
44 will be conducted, and demographics, treatment characteristics (as specified under
45 1.5), the SF-36 quality of life scores and daily steps will be recorded. A web-based
46 randomization will be used to determine the treatment arm with an allocation ratio of
47 1:1, stratified by center (n=135 patients in each group). The participants will not be
48 informed of the treatment allocation. The functional relaxation group as well as the
49 control group will be held continually three times a week and patients will be
50 consecutively allocated after individual randomization. Each session will take place as
51 a group therapy, whereby each group will consist of 3-8 patients. One session will have
52 a duration of 45 min. A manual to guide the sessions was already created in previous
53 clinical trials and the sessions will be held by a physiotherapist certified in functional
54 relaxation, and previously trained on the manual. Patients will participate in the session
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3 during their stationary time in the hospital, sessions will also take place as an outpatient
4 procedure. After completion of 12 sessions in 12 weeks, procedures will be the same
5 for both study groups. Follow-up examinations will be performed at the treating center
6 after 3 months, 6 months, and 12 months. During the examination, the SF-36, the
7 Parker mobility score, the number of daily steps as measured with an accelerometer
8 (actibelt®), pain medication and concomitant medications will be assessed. Also, any
9 signs of a reinfection will be documented. Treatment success will be determined by the
10 primary endpoints, the MCS and PCS of the SF-36 after 6 months. Key secondary
11 endpoints will be the SF-36 scores MCS and PCS after 12 months, consumption of
12 pain medication, mobility measured by the Parker mobility score and the physical
13 activity measured by the daily steps.
14
15
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17

18 --- Figure 1---
19

20 **Study setting**

21 The study will be carried out in level 1 trauma centers (n=4) in Germany, located in
22 Bavaria (University Hospital Regensburg, Caritas-Hospital St. Josef Regensburg,
23 Hospital Barmherzige Brüder Regensburg, Innklinikum Altötting).
24
25
26
27

28 Administrative information are shown in Supplementary file 1.
29

30 **Eligibility criteria**

31 Key inclusion criteria: Patients with verified prosthetic joint infection (PJI) aged 18 or
32 older will be recruited. Written informed consent and surgical treatment including a
33 one-staged exchange, or a two-staged exchange is a prerequisite for participation.
34
35

36 Key exclusion criteria: Patients diagnosed with a concomitant psychological disorder
37 (ICD-10 F0-F9) or a Charlson-Comorbidity Index (CCI) > 3 will be excluded. Further,
38 patients surgically treated with a debridement, antibiotics and implant retention (DAIR)
39 approach or with an arthrodesis, as well as patients with a Girdlestone situation will be
40 excluded.
41
42
43

44 **Informed consent**

45 Participants will be approached on the hospital ward and given verbal explanation of
46 the study by a study researcher. A written participant information and consent form will
47 be provided (Supplementary file 2). Participants will be informed that their decision
48 whether or not to participate in the study will not impact their access to routine care
49 and that they can discontinue the participation in the study at any time. Participants will
50 be given the opportunity to read, discuss and ask questions. Those willing to participate
51 will sign the consent form.
52
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54

55 **Patient and Public Involvement**

56 Patient representatives ("Forschungspartner") from the Rheuma-Liga
57 (<https://www.rheuma-liga.de/>) were involved in the in the sense of participatory
58 research in the conceptualisation of the study. These will participate during the whole
59 research process. Further, focus group discussion will be held twice at University
60

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3 Hospital Regensburg, first to present the research strategy and preliminary results as
4 well as to evaluate whether additional endpoints are of interest from the patient's
5 perspective. Second it will be evaluated how patient-oriented, complementary
6 treatment concepts can be established in daily clinical practice and medical aftercare.
7 Regular meetings with the project partners will take place every 3 months.
8 Additionally, invitations to functional relaxation courses and preliminary results will be
9 distributed to patients via the German Association for medical relaxation methods
10 (<https://www.dgaehat.de/>).
11
12
13

14 **Additional consent provisions for collection and use of participant data and** 15 **biological specimens**

16 Not applicable as biologic specimens are not collected for this study.
17
18
19
20

21 **Interventions**

22 **Choice of comparators**

23 Functional relaxation will be compared to a placebo relaxation technique as carried out
24 by previous studies. The groups will be guided by an already established manual [15,
25 17, 18]. Previous randomized-controlled trials showed an effectiveness of functional
26 relaxation in other medical conditions with treatment durations of 3 weeks [18], 4 weeks
27 [14], 5 weeks [16], and 10 week [19]. Thus, to ensure the expediency, it was chosen
28 to carry out the intervention once a week with a duration of 45 min for 12 weeks.
29
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32
33

34 **Intervention**

35 Functional relaxation (FR) originally belongs to the psychodynamically based body-
36 oriented psychotherapy. Intervention techniques consist of small movements of joints,
37 which are performed during expiration accompanied by an exploration of differences
38 of body feelings. Results of clinical studies support the efficacy of FR for diverse
39 disorders and show a significant reduction of pain, anxiety and stress [14–19]. Here,
40 12 weekly sessions with a duration of 45 min each will be held by a physiotherapist
41 certified in FR. The group interventions include 5-10 patients and will be guided by a
42 manual, which was generated during previous studies [15, 17, 18]. The placebo group
43 will receive isotonic exercises, which requires an equivalent amount of motion. Thus,
44 patients will be instructed to hold specific postures for several minutes in a relaxed
45 manner, but without focusing on enhancing bodily awareness as in the treatment
46 group. The experimental treatment and the control treatment will be performed by the
47 same physiotherapist.
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55 **Criteria for discontinuation**

56 a) for the individual patients: As guaranteed in the patient information sheet previously
57 to study inclusion, the individual patient will be excluded from study participation, if the
58 patient withdraws his informed consent due to any reasons.
59
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3 b) for participating centers: Recruitment and data assessment of the follow-up
4 examinations will be monitored by the Data Safety and Monitoring Board throughout
5 the entire trial period. For recruitment of study patients, we have defined milestones at
6 different time-points. If recruitment at the 50% landmark is below 20% of the total
7 targeted number of patients, the enrolling center will have to be excluded from
8 participating in the trial.
9

10
11 c) for the whole trial: If recruitment is not achievable in more than one center, a interim
12 analysis of the achieved effect size and subsequent re-analyses of the required sample
13 size will reveal whether continuation of the trial is still realistic.
14
15

16 17 **Strategies to improve adherence**

18
19 For the total duration of the trial, a telephone line will be opened up, and patients are
20 encouraged to call any time in case that questions regarding the trial procedure occur.
21 Further, to enhance confidentiality, relatives of all participating patients will have the
22 possibility to take part in a certified training course in functional relaxation. Additionally,
23 the trial management will monitor all patient follow-up and will contact patients who
24 missed a follow up appointment. Also, the dates for follow-up visits are set at the end
25 of the previous appointment and patients are reminded of the appointment one week
26 before the scheduled appointment by phone or email. A 14-day window, defined as 7
27 days before and 7 days after the due date, will be available to complete the follow-up
28 visits.
29
30
31

32 **Relevant concomitant care prohibited during the trial**

33
34 This trial does not prohibit other treatments.
35

36 **Provisions for post-trial care**

37
38 After the completion of the 12 sessions (either functional relaxation or a placebo
39 intervention), follow up visits will take place after 3 months, 6 months, and 12 months.
40
41

42 **Outcomes**

43
44 Primary efficacy endpoint: Mental Component Summary (MCS) and Physical
45 Component Summary (PCS) of quality of life assessed by the SF-36 health survey
46 after 6 months.
47

48
49 Key secondary endpoint(s): SF-36 scores after 12 months, consumption of pain
50 medication, mobility measured by the Parker mobility score and the physical activity
51 measured by daily steps with an accelerometer (actibelt®).
52

53
54 Quality of life, pain medication consumption and physical activity were selected as
55 outcomes to appropriately capture the health status of patients affected with PJI. The
56 SF-36 shows good reliability and validity and is the most widely use quality of life
57 questionnaire worldwide. No other appropriate questionnaire assessing quality of life
58 specifically for this indication exists and the SF-36 was chosen to ensure the
59 comparability with the literature. Due to its structure with separate summary scores for
60

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.

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 hospitalization, ASA score, CCI Index, comorbidities Localization, type of prosthesis, previous no. 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

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 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 4 points in the control group and about 10 points in the experimental group ($\Delta=6$) 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 ($\Delta=6$, $SD=15$) with a power of $1-\beta=80\%$ at a two-sided significance level $\alpha=0.025$, 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% (e.g. 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

1
2
3 the first 6 months. Thus, with the assumption of 10% drop-outs, a total of n=270
4 patients (n=135 per group) need to be randomized.

5 Based on previous studies conducted at the University Hospital Regensburg,
6 assuming that 45% of the screened patients are not eligible or willing to participate, a
7 total of n=490 patients need to be screened. Sample size calculations were performed
8 using SAS Version 9.4.
9

10 **Recruitment**

11
12 All patients admitted to the participating centers will be screened for potential
13 recruitment. A daily 24-h report of all PJI patients will be extracted from the hospital
14 electronic database. Based on this extract, the written and electronic medical records
15 of potential participants will be screened for eligibility by the study team. Eligible
16 participants will be approached in person on the ward. All of the information required
17 for ensuring participant eligibility is obtained as part of clinical routine care.
18
19

20 **Allocation**

21 **Sequence generation**

22
23 A web-based randomization (<http://www.randomizer.net/>) will be used to determine the
24 treatment arm with an allocation ratio of 1:1, stratified by center, reinfection (yes/no)
25 and type of surgical procedure (one-staged exchange, two-staged exchange). The
26 randomization tool will be administered by the Center for Clinical Studies. To minimize
27 bias *block randomization* with varying block sizes concealed to the investigator will be
28 employed to avoid selection bias. After inclusion of a patient by signing the informed
29 consent, responsible personnel (investigator and study nurse) have to use the
30 individual log-in for the online platform to randomize the patient. All randomizations will
31 be logged and documented within the system and predefined users like the study
32 monitor will be automatically informed about the randomization.
33
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35
36

37 **Concealment mechanism**

38
39 The investigator will not be able to access the allocation sequence and randomization
40 table.
41

42 **Implementation**

43 Allocation will occur via REDCap.
44

45 **Blinding**

46 **Who will be blinded**

47
48 Patients will be blinded using a single-masked procedure. The participants will not be
49 informed of the treatment allocation, instead all patients will be told that they receive a
50 complementary relaxation technique in order to first, enhance credibility and second,
51 ensure compatibility with the informed consent.
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54
55

56 **Procedure for unblinding if needed**

57
58 No unblinding procedure is planned.
59
60

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 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 [27]. Patient-reported outcome measures will be administered in a standardized 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 accelerometer (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 timepoint 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 (CDMS). All data management activities will comply with rules according to the EU-GDPR, including pseudonymized 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 computerized 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 stored for at least 10 years.

Confidentiality

Data will be collected pseudonymized and stored on a server at the University hospital clinic Regensburg with strictly controlled access for ensuring confidentiality. All

analysis 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 in- 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 randomization 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 standard deviation accompanied by the corresponding 97.5% confidence interval and will be compared between functional relaxation therapy and the control intervention. To test the null hypothesis $H_0: \mu_{\text{diff}}=0$ at a two-sided significance level of 0.025 an analysis of covariance (ANCOVA) with the respective component score at month 6 as dependent variable, treatment arm and center 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%-confidence intervals. 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 the defined as a responder endpoint, while a patient is counted as a responder if either $\Delta\text{MCS}>10$ and/or $\Delta\text{PCS}>10$ (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 functional relaxation 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 center, 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 (MCAR) or missing at random (MAR). 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, BMI, smoking status, ASA score, CCI, localization of the prosthesis (knee or hip), type of surgical procedure and revision rate. A sensitivity analysis using an ANOVA approach on ranks will be used to explore the robustness of inference from the initial model.

Oversight and monitoring

Composition of the coordinating center and trial steering committee

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

To ensure adherence to the intervention scheme and quality of the performance of each recruiting center, 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 randomization, blinding, and the intervention performance using the mandatory documentation during monitoring visits at the centers.

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 specializes in monitoring of non-commercial IITs since 2000. The monitors are

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3 qualified according to ICH-GCP and DIN ISO 14155 and adhere to the CRO's SOPs
4 MON 002, 003, 007, and 008.
5

6 On-site monitoring starts with a pre-trial visit of each center in order to ensure each
7 center's capability to comply with the study protocol and with the recruitment of the
8 adequate number of patients. The findings of the pre-trial monitoring visit will be
9 summarized in a report that will be forwarded to the PI. Monitoring will follow a risk-
10 based approach and the study is assessed a low-risk trial. Thus, 100% source data
11 verification focuses on informed consent, inclusion/exclusion criteria, the primary
12 endpoints, randomization, and adverse and intercurrent events. All other aspects of
13 the trial will be subjected to a 20% source data verification. In addition to the pre-trial
14 visit, on-site monitoring is scheduled five times during the recruitment period with an
15 interval of 6 months. After the milestone "last patient out" is achieved, one additional
16 close-out visit will be planned.
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19 **Adverse event reporting and harms**

21 The occurrence of adverse and intercurrent events will be coded using the Medical
22 Dictionary for Regulatory Activities (MedDRA) terminology and documented in an
23 eCRF throughout the follow-up period by each participating center and recorded
24 centrally at the Center for Clinical Studies of the University Hospital Regensburg. The
25 safety assessments will be summarized by the statistician and safety reports will be
26 forwarded to the independent Data Safety and Monitoring Board (DSMB).
27
28

29 **Frequency and plans for auditing trial conduct**

31 Besides the pre-trial monitoring visit, Interims visits of study sites for the purpose of
32 quality assurance and data monitoring will take place every six months. In addition,
33 the PI will have weekly meetings with the research staff monitoring for any concerns.
34 The DSMB will meet regularly biannually.
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38 **Plans for communicating important protocol amendments to relevant parties**

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

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

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

11 After data analysis, a symposium will be organised which will be open to the public. In
12 the format of posters and talks with subsequent fishbowl discussions detailed
13 information regarding the state of art in the diagnosis and treatment of PJI will be
14 provided in order to shape the direction of future research and outline possibilities to
15 enhance the quality of life of infection patients
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18 19 20 **Discussion**

21
22 In this prospective, parallel two-armed randomized controlled trial it will be evaluated
23 whether an adjunct functional relaxation therapy results in a clinically relevant increase
24 of the quality of life in patients with periprosthetic joint infection.
25

26 To ensure the novelty of this research, the databases Clinicaltrials.gov, Deutsches
27 Register Klinischer Studien, ICTRP search portal, Cochrane CENTRAL, Cochrane
28 library and MEDLINE were searched on the 9th of February 2022 covering all
29 publication dates resulting in no registered trials associated with adjunct relaxation
30 therapies or psychological interventions in patients with PJI. Hence, implementing a
31 body-oriented psychotherapy intervention in clinical practice and evaluating its effect
32 may pave the way for an integral approach in orthopaedic and trauma surgery shifting
33 the focus towards a biopsychosocial model of recovery [30]. Further, the clinical trial
34 will promote a multidisciplinary treatment approach, which has been shown to be
35 beneficial for PJI patients [31, 32].
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39 A major strength of the present trial is the implementation of participatory research. An
40 active involvement of affected patients, and their (caring) relatives, can increase the
41 relevance and quality of clinical trials improving both the methodology and outcomes
42 of the research [33, 34]. Thus, by involving patient representatives in the planning and
43 design phase of the clinical trial, the perspective of those affected could already be
44 incorporated into the identification of priority research questions, the selection of the
45 intervention and primary endpoints, and subsequently, the development of the
46 research design.
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51 A potential pitfall might be the calculated sample size. As no similar interventions have
52 been performed in PJI patients [13], assumptions for the expected effect size are solely
53 based on the literature reporting a supplementary psychosomatic intervention across
54 several indications [21–25]. However, the feasibility of recruitment was assured by
55 analysis of patient data using hospital data management. Further, in preparation for
56 the proposal of this trial, semi-structured interviews were conducted in the University
57 Hospital Regensburg (unpublished data) suggesting a high willingness to participate
58 in the trial. Nevertheless, if recruitment is not achievable in more than one center, a
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interims 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.

Trial status

Latest protocol version 2, 17 March 2022, recruitment is scheduled to begin by October 2022

Abbreviations

CCI: Charlson-Comorbidity Index

DAIR: debridement, antibiotics and implant retention

DSMB: Data Safety and Monitoring Board

EBJIS: European Bone and Joint Infection Society

eCRF: electronic case report form

FR: Functional relaxation

MCMC: Markov chain Monte Carlo

MCS: Mental Component Summary Score

MedDRA: Medical Dictionary for Regulatory Activities

PCS: Physical Component Summary Score

PJI: Periprosthetic joint infection

Declarations

Ethics approval and consent to participate

The project is conducted in conformity with the "Declaration of Helsinki". 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.

Consent for publication

A consent to publish is not applicable as no data that would identify a participant will be published.

Availability of data and materials

Data will be stored on a server at the University hospital clinic Regensburg with strictly controlled access (researchers only) for ensuring confidentiality. The deidentified data collected during this study will be shared through Zenodo, a European open access data repository.

Competing interests

The authors declare that they have no competing interests.

Funding

No external funding is received for this study.

Authors' contributions

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

Acknowledgements

We thank the German Rheumatism League Federal Association e.V. (<https://www.rheuma-liga.de/>) for their support of this trial. Further we thank Florian Zeman from the Center for Clinical Studies, University Hospital Regensburg for his support on the statistical part of the study protocol.

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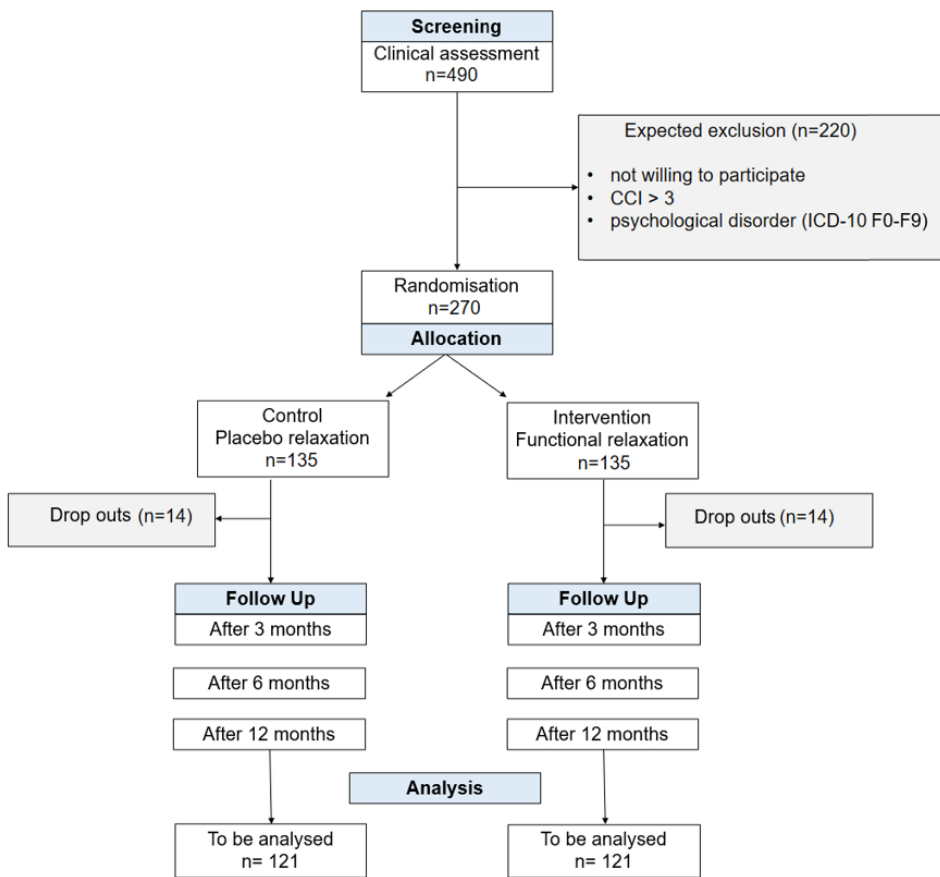
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Figure Legends

Figure 1: Schematic overview of the trial flow.



Schematic overview of the trial flow.

77x71mm (300 x 300 DPI)

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Supplementary file 1: Administrative information.

Title	The effect of functional relaxation on the quality of life in patients with prosthetic joint infection - a randomized controlled trial
Trial registration	DRKS00028881, 28.04.2022, German Clinical Trials register (https://www.drks.de)
Protocol version	17.03.2022, Version 2
Funding	No external funding is received for this study
Author details	¹ Department for Trauma Surgery, University Medical Center Regensburg ² Department for Psychosomatic Medicine, Regensburg
Name and contact information for the trial sponsor	University Hospital Regensburg, represented by Sabine Lange MBA, Administrative Director, Franz-Josef-Strauß-Allee 11, 93053 Regensburg, Germany
Role of sponsor	The sponsor does not have any role in study design, data collection, analysis or interpretation, nor in decision to submit the report for publication

Universitätsklinikum Regensburg, 93042 Regensburg
- Klinik / Abteilung / Institut / Zentrum -

Informed consent for the study:

The effect of functional relaxation on the quality of life in patients with periprosthetic joint infection

I. Information about the study

Within the framework of this study, we are investigating the influence of Functional Relaxation on the quality of life of patients with periprosthetic joint infections. Functional Relaxation is a body-oriented psychotherapy method, whereby small movements of the joints, combined with exhalation are performed. With consent, you would participate in 12 sessions (once a week) a'45 minutes at the University Hospital. Each session will be in a group of 2-5 people and will be guided by a certified psychotherapist.

Before the intervention, after 3 months, 6 months and 12 months we would ask you to answer two questionnaires about your health status and quality of life. We would also collect your daily step count during the course of the intervention by means of a sensor.

For further questions about the research project or a demonstration of Functional Relaxation, please contact the principal investigator at any time.

II. Privacy policy

For the purpose of conducting the study, medical findings and personal information (such as age, gender and ethnicity) about you will be collected and written down in your personal file or stored electronically by your study doctor*. Personal data from previous examinations by physicians* may also be added to your patient file at the study site. If necessary, the study physician* may contact your primary care physician* and/or treating physician* to obtain additional medical information about you. Your primary care physician* and/or treating physician* may disclose this information only if authorized by you.

The data important for the study will also be stored in encrypted (pseudo-nymized) form in a password-protected electronic database. Pseudo-nymized means that no name or initials are used, only a numerical or letter code. The data are secured against unauthorized access. Only your study physicians* and their associated team will be able to identify you personally from the encrypted data. Your study data will only be passed on to third parties in anonymized form; this means that it will no longer be possible to assign it to you personally.

Your name and date of birth will be entered on the consent form. It is possible that inspectors* from official monitoring authorities may inspect these documents to verify that the study is being conducted in accordance with regulations. Inspectors are required to keep your personal data confidential.



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4 **SPITZE IN DER MEDIZIN. MENSCHLICH IN DER BEGEGNUNG.**
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7 **The legal basis for processing the personal data concerning you is your voluntary written**
8 **consent in accordance with the DSGVO (pursuant to Art. 6(1)(a) DSGVO in conjunction**
9 **with Art. 9(2)(a) DSGVO) when processing sensitive data. Your consent is voluntary and**
10 **can be revoked at any time without adverse effect for the future.**
11

12 **Without your consent to the processing and disclosure of the data concerning you in**
13 **encrypted form, you cannot participate in the above-mentioned study. Publications in**
14 **journals and public trial registries (e.g. clinicaltrials.gov or EU Clinical Trials Register) or**
15 **presentations of study results will not include any data from which you can be personally**
16 **identified.**
17

18 **Your data will be processed in this study primarily for this purpose. However, it is possible**
19 **that in the course of the investigation and data analysis, further research questions may**
20 **arise that are related to the subject of this study. In this case, your data would also be**
21 **used for this purpose. However, you can explicitly object to this in the consent form.**
22

23 **Your collected data will be stored by the study team for a period of up to 10 years after**
24 **completion or termination of the study. After this period, your data, including the**
25 **characteristics that identify you, will be deleted. After deletion, it is no longer possible to**
26 **draw conclusions about you**
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SPITZE IN DER MEDIZIN. MENSCHLICH IN DER BEGEGNUNG.

I have read and taken note of "I. Information about the study" and "II. Privacy policy". Any queries I may have had were answered satisfactorily by the person responsible for the study and I have had sufficient time to consider my participation in the project.

In the following, I give my consent for the ticked items:

Participation in the study with the knowledge that the investigation and study may be terminated by me at any time.

Processing of my data for study purposes.

In case of withdrawal of my consent:

May all my data collected so far continue to be used for the purposes of this study.

May all my data collected so far - with the exception of biomaterials - be further used for the purposes of this study.

May all my data collected so far also be reused for purposes unrelated to the study in the Clinic and Polyclinic for Trauma Surgery.

Must all data no longer required be deleted immediately.

My consent is voluntary and I can revoke it at any time without giving reasons for the future. The revocation of consent does not affect the lawfulness of the processing carried out on the basis of the consent until the revocation.

(Date, Name & Signature [*Principal Investigator*])

(Date, Name & Signature Participant)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym p. 1, section "Title"
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry Page 1, Abstract"
	2b	All items from the World Health Organization Trial Registration Data Set Supplementary File 2 "Administrative information"
Protocol version	3	Date and version identifier Supplementary File 2 "Administrative information"
Funding	4	Sources and types of financial, material, and other support Supplementary File 2 "Administrative information" p. 15, section "Declarations"
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Supplementary File 2 "Administrative information"
	5b	Name and contact information for the trial sponsor Supplementary File 2 "Administrative information"
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities Supplementary File 2 "Administrative information"
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) Supplementary File 2 "Oversight and monitoring"

Introduction

1			
2	Background and	6a	Description of research question and justification for undertaking the
3	rationale		trial, including summary of relevant studies (published and
4			unpublished) examining benefits and harms for each intervention
5			p. 2, section “Background”
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7		6b	Explanation for choice of comparators
8			p. 5, section “Interventions”,
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10	Objectives	7	Specific objectives or hypotheses
11			p. 3, section “Objectives”
12			
13			
14	Trial design	8	Description of trial design including type of trial (eg, parallel group,
15			crossover, factorial, single group), allocation ratio, and framework (eg,
16			superiority, equivalence, noninferiority, exploratory)
17			p. 3, section “Trial design”
18			
19			
20	Methods: Participants, interventions, and outcomes		
21			
22	Study setting	9	Description of study settings (eg, community clinic, academic hospital)
23			and list of countries where data will be collected. Reference to where
24			list of study sites can be obtained
25			p. 4, section “Methods”, subsection “Study setting”
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28	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility
29			criteria for study centres and individuals who will perform the
30			interventions (eg, surgeons, psychotherapists)
31			p. 4, section “Methods”, subsection “Eligibility criteria”
32			
33	Interventions	11a	Interventions for each group with sufficient detail to allow replication,
34			including how and when they will be administered
35			p. 5, section “Interventions”
36			
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38		11b	Criteria for discontinuing or modifying allocated interventions for a
39			given trial participant (eg, drug dose change in response to harms,
40			participant request, or improving/worsening disease)
41			p. 5, section “Interventions”
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44		11c	Strategies to improve adherence to intervention protocols, and any
45			procedures for monitoring adherence (eg, drug tablet return,
46			laboratory tests)
47			p. 6, section “Interventions”
48			
49		11d	Relevant concomitant care and interventions that are permitted or
50			prohibited during the trial
51			p. 6, section “Interventions”
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2	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
3			p. 6, section “Outcomes”
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11	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
12			p. 7, section “Participant timeline”
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17	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
18			p. 8, section “Sample size”
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23	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
24			p. 9, section “Recruitment”
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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31	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
32			p. 9, section “Allocation”
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40	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
41			p. 9, section “Allocation”
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47	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
48			p. 9, section “Allocation”
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52	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
53			p. 9, section “Allocation”
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- 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
- p. 9, section "Assignment of interventions: blinding"**

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Methods: Data collection, management, and analysis

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- Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
- p. 9, section "Data collection and management"**
- 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
- p. 10, section "Data collection and management"**
- Data management 19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
- p. 10, section "Data collection and management"**
- Statistical methods 20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
- p. 11, section "Statistical methods"**
- 20b Methods for any additional analyses (eg, subgroup and adjusted analyses)
- p. 12, section "Statistical methods"**
- 20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
- p. 12, section "Statistical methods"**

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Methods: Monitoring

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- Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
- p. 13, section "Oversight and monitoring"**

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2		21b	Description of any interim analyses and stopping guidelines, including
3			who will have access to these interim results and make the final
4			decision to terminate the trial
5			p. 11, section “Statistical methods”
6			
7	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and
8			spontaneously reported adverse events and other unintended effects
9			of trial interventions or trial conduct
10			p. 13, section “Oversight and monitoring”
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13	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and
14			whether the process will be independent from investigators and the
15			sponsor
16			p. 13, section “Oversight and monitoring”
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19	Ethics and dissemination		
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21	Research ethics	24	Plans for seeking research ethics committee/institutional review board
22	approval		(REC/IRB) approval
23			p. 15, section “Declarations”
24			
25	Protocol	25	Plans for communicating important protocol modifications (eg,
26	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties
27			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,
28			regulators)
29			p. 13, section “Oversight and monitoring”
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31			
32	Consent or assent	26a	Who will obtain informed consent or assent from potential trial
33			participants or authorised surrogates, and how (see Item 32)
34			p. 4, section “Methods”
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37		26b	Additional consent provisions for collection and use of participant data
38			and biological specimens in ancillary studies, if applicable
39			p. 5, section “Methods”,
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41	Confidentiality	27	How personal information about potential and enrolled participants will
42			be collected, shared, and maintained in order to protect confidentiality
43			before, during, and after the trial
44			p. 10, section “Data management”
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47	Declaration of	28	Financial and other competing interests for principal investigators for
48	interests		the overall trial and each study site
49			p. 15, section “Declarations”
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51	Access to data	29	Statement of who will have access to the final trial dataset, and
52			disclosure of contractual agreements that limit such access for
53			investigators
54			p. 15, section “Declarations”
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2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation
4			p. 6, section “Interventions”,
5			
6	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
7	policy		participants, healthcare professionals, the public, and other relevant
8			groups (eg, via publication, reporting in results databases, or other
9			data sharing arrangements), including any publication restrictions
10			p. 14, section “Dissemination plans”
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12		31b	Authorship eligibility guidelines and any intended use of professional
13			writers
14			p. 16, section “Declarations”
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16		31c	Plans, if any, for granting public access to the full protocol, participant-
17			level dataset, and statistical code
18			p. 12, section “Statistical methods
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23	Appendices		
24	Informed consent	32	Model consent form and other related documentation given to
25	materials		participants and authorised surrogates
26			p. 16, section “Declarations”
27			
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29	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
30	specimens		specimens for genetic or molecular analysis in the current trial and for
31			future use in ancillary studies, if applicable
32			p. 11, section “Data collection and management”
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons [“Attribution-NonCommercial-NoDerivs 3.0 Unported”](https://creativecommons.org/licenses/by-nc-nd/3.0/) license.