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Research Article

Resource-Oriented Case Management to Implement Recommendations for Patients With Chronic Pain and Frequent Use of Analgesics (RELIEF) – Study Protocol of a Cluster-Randomized Controlled Trial

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Background: Chronic non-cancer pain (CNCP) is a frequent reason for consulting a general practitioner. German guidelines underline its biopsychosocial etiology, the relevance of self-care and nonpharmacological therapy options, and comprehensive assessment for individualized treatment and monitoring of pain medication use. A case management program was developed in project RELIEF (Resource-oriented case management to implement recommendations for patients with chronic pain and frequent use of analgesics in general practices) to support the implementation of pain management guideline recommendations in general practice regarding assessment and monitoring, patient and practice team education, promotion of self-care strategies, and rational pharmacotherapy.
Objective: The aim is to effectively reduce pain-related disability in patients with chronic non-cancer pain and improve associated outcomes.
Methods: Following the assessment of its feasibility, the program will now be tested in a cluster-randomized controlled trial with general practices and adult patients with CNCP, pain-related disability, and analgesic use located in Baden-Württemberg, Germany. The intervention comprises a software-supported medical pain history, structured appointments, e-learning for practice teams, educational material for patients, and a toolbox with additional resources. Participating practices will recruit eligible patients via a screening questionnaire. The primary outcome will be measured by the German version of the Pain Disability Index. Outcome evaluation data will be collected by

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digital questionnaires to be completed by participants. Descriptive statistics will summarize demographics and baseline characteristics. A mixed-methods process evaluation will use digitally provided surveys and telephone interviews to assess intervention mechanisms regarding pain-related self-efficacy, patient activation, medication use, non-pharmacological treatment options, and intervention fidelity.
Results: Recruitment will take place between January and April 2026. The targeted maximum sample size is 28 practices and 252 patients. The intervention period will start with completed patient recruitment. It is expected that eligible patients will benefit from improved medication management, intensified use of nonpharmacological treatment strategies, and a reduction of pain-related disabilities.
Conclusions: This study will provide valuable information regarding the potential effects of the intervention.

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Introduction

The prevalence of chronic pain in German primary care is approximately 20% [1]. According to current definitions, pain is classified as chronic if it persists for a period of more than three months or recurs [2][3]. A distinction is made between chronic primary pain (no sufficient explanation based on detectable tissue damage, as in fibromyalgia, nonspecific lower back, or psychosomatic pain disorders) and chronic secondary pain conditions attributable to manifest organ or tissue lesions such as those occurring in the context of degenerative or inflammatory joint and spinal disorders, or neuropathic damage [3].

The understanding of the pathogenesis of chronic pain has evolved significantly in recent years. There is a consensus that chronic pain is always sustained by a biopsychosocial interaction. Since comorbid mental health conditions such as depression, anxiety disorders, or post-traumatic stress disorder are often present [4], effective treatment strategies vary depending on the individual's specific needs. Depending on prevailing comorbidities or factors, different treatment strategies are effective. Comprehensive diagnostics are therefore essential for developing a tailored treatment plan.

According to guidelines, the treatment of chronic non-cancer-related pain requires a holistic therapeutic approach. Non-pharmacological and non-invasive interventions—including education, physical and occupational therapy, and cognitive behavioral therapy—form the foundation of this treatment. Analgesics should be used only for a limited time and in a supportive capacity until conservative measures take effect [5]. Nevertheless, approximately two-thirds of patients with chronic pain use analgesics [6]. Of particular concern is the uncontrolled self-medication with over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs), which occurs in 72 percent of affected individuals in Germany [6], since a long-term use of NSAIDs is associated with an increased risk of cardiovascular events, gastrointestinal lesions, and renal insufficiency. At the same time, the prescription of opioids for non-cancer-related pain is observed in Germany, although there is no sign of an opioid epidemic so far [7]. This practice is concerning due to a lack of evidence regarding long-term

efficacy as well as high rates of side effects such as dependence, cognitive deficits, and constipation [8].

When using analgesics, precise medication management and strict adherence to follow-up examinations are essential. Classified at the highest evidence level, the German S3 guideline for the long-term use of opioids in chronic, non-cancer-related pain (LONTS) outlines evidence-based recommendations for safe opioid management [9][10]. However, these are often not adequately followed in clinical practice. These shortcomings in pain management lead to avoidable patient suffering and place a heavy burden on the healthcare system: patients with pain-related functional limitations have a fivefold increase in physician consultations and a sixfold increase in days of work disability [11].

In Germany, outpatient care for patients with chronic pain (CNCP) is primarily provided by general practitioners (GPs) and specialists in orthopedics, neurology, or rheumatology. Only 10% of those affected receive specialized pain therapy or multimodal treatment approaches [12]. Given their central role as gatekeepers and their long-term relationships with patients, general practitioners play a key role as care coordinators and main prescribers of medication. To lower the barriers to implementing structured pain management in everyday practice, a case management program was conceptualized as part of the RELIEF project. This program focuses on four core areas: assessment and monitoring, education (practice team and patients), promotion of self-management skills, and rational pharmacotherapy.

The RELIEF program aims to measurably reduce pain-related impairment in daily life and improve pain intensity and quality of life among patients with chronic non-cancer pain. A concurrent process evaluation will be conducted to assess intervention mechanisms and perceived outcomes. The focus will be on pain-related self-efficacy, patient activation, medication use, non-pharmacological treatment options, and intervention fidelity. Program feasibility and acceptability were successfully tested in an uncontrolled pilot study involving six general practices and 39 patients [13]. Subsequently, intervention components and study procedures were adapted regarding study design, sample size, some educational content, number of structured monitoring appointments, study-related documentation, and data collection format. Effectiveness will now be evaluated in a large-scale randomized controlled trial.

Aim of the study

This confirmatory cluster-randomized controlled trial will be conducted in general practices in Baden-Württemberg, Germany, with the aim of evaluating the effectiveness of the RELIEF case-management program regarding the primary outcome, the German version of the Pain Disability Index (PDI-G) [14], at the end of follow-up (T1).

Outcomes and hypotheses

Primary outcome

Change in pain-related disability at baseline (T0) and follow-up (T1) will be measured as the primary outcome with the German version of the Pain Disability Index (PDI-G), a 7-item questionnaire used to assess the impact of self-reported pain-related disability, independent of pain localization or pain-related

diagnosis. The items refer to 7 domains of life: family and home responsibilities, work, recreation, social activities, sexuality, self-care, and vital activities. Patients rate each item on a numeric rating scale between 0 and 10 (no disability to maximum disability). The sum of the ratings can score between 0 and 70. Higher scores reflect greater interference of pain with daily activities. A score of 33 is considered 50% pain-related disability (percentile rank) [14]. In patients with chronic back pain, a change of 8.5 to 9.5 points (improvement or deterioration) is regarded as a minimal clinically important change [15]. Generally, scores can be considered clinically relevant when patients with a baseline score of $\leq$27 decrease by a minimum of 7 points, patients with a baseline score between 28 and 42 decrease by a minimum of 15 points, and patients with a baseline score $\geq$ 43 decrease by a minimum of 20 points [16]. However, for this study, based on findings in the pilot study [13], a change of 8.5 points is regarded as minimal clinically important regardless of the baseline score. The PDI-G proved high internal consistency (Cronbach's alpha 0.8–0.9), good construct validity, and change sensitivity [14].

Secondary outcomes

According to the assumed effect mechanisms, a range of secondary outcomes (see Table 1) will be determined at the end (T1) of the study via online-based questionnaires. All variables will also be measured at baseline (T0).

Domain	Variable (Instrument)	
Symptom Burden	• Pain intensity (numerical rating scale from 0–10)	
	• Quality of life (SF-12 questionnaire)	
	• Number of sick days in working patients (last 6 months)	
Medication use	• Frequency of on-demand medication (measured by a patient-reported item on an ordinal scale)	
Behavior / cognitions	• Patient Activation Measure (PAM-13D)	
	• Pain-related self-efficacy (FESS scale)	
	• Avoidance-Endurance (Avoidance-Endurance Screening Instrument)	
	• Pain Catastrophizing (Pain Catastrophizing Scale)	
	• Physical Activity (measured by one non-validated, self-developed questionnaire item)	
	• Use of relaxation techniques (measured by one non-validated, self-developed questionnaire item)	
	• Use of topical applications (measured by one non-validated, self-developed questionnaire item)	
Satisfaction with pain treatment	• Overall satisfaction with pain treatment (one self-developed item) • Satisfaction with pain treatment by the general practice (one self-developed item)	

Table 1. Secondary outcome measures

SF-12 questionnaire [17]*; PAM-13D* [18]*; FESS scale* [19]*; Avoidance-Endurance Screening Instrument*[20]*; Pain Catastrophizing Scale* [21].

Besides primary and secondary outcomes, descriptive variables will be determined at the patient level to describe the sample and to allow subgroup

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analyses (see Table 2). Most descriptive variables will be collected only once at T0 or at the defined times of CareCockpit data export (see Figure 1), respectively. However, the substance group and scheme of pain medication will be assessed at T0 and T1 to describe medication changes during the study period.

Patient-reported descriptive variables collected in the intervention and control group	Time and method of measurement
Socio-demographics: Age, sex, work, educational level, living situation, care degree, receipt of reduced-earning-capacity pension	T0 (online survey)
Pain duration	T0 (online survey)
Pain localization	T0 (online survey)
Pain intensity (scale from 0–10)	T0 (online survey)
Patient-reported pain medication (substance groups)	T0 + T1 (online survey)
Patient-reported pain medication scheme (permanently, on demand, or permanently and on demand) (T0 + T1)	T0 + T1 (online survey)
Patient-reported increase/reduction/discontinuation/start of pain medication per substance group	T1 (online survey)
Patient-reported descriptive variables collected in the intervention group only	
Type of side effects (if opioids, gabapentinoids, or antidepressants are taken)	Pain assessment (CareCockpit)
Likelihood of neuropathic pain (Pain Detect)	Pain assessment (CareCockpit)
Depression (PHQ-9)	Pain assessment (CareCockpit)
Anxiety (GAD-2)	Pain assessment (CareCockpit)
Sleep disorder	Pain assessment (CareCockpit)
Post-Traumatic Stress Disorder	Pain assessment (CareCockpit)
Somatic Disorder (SSD12)	Pain assessment (CareCockpit)
Assumed causes of pain	Pain assessment (CareCockpit)
Factors causing/increasing pain	Pain assessment (CareCockpit)
Type of self-care activities	Pain assessment (CareCockpit)
Type of therapists involved in pain treatment	Pain assessment (CareCockpit)
Healthcare professional-reported descriptive variables reported in the intervention group	
Healthcare professional-reported pain medication (substance groups)	Study appointment 2 (CareCockpit)
Healthcare professional-reported pain medication (increase, reduction, start, or discontinuation per substance group)	Study appointments 3–5 (CareCockpit)

Table 2: Descriptive variables collected via an online questionnaire in the intervention and control group

Pain Detect [22]; *PHQ-9* [23]; *GAD-2* [24]; *SSD12* [25]

Study population

Inclusion and exclusion criteria

Only adults with the ability to give informed consent and to actively participate will be included in the trial. Eligible practices will be general practices offering care to patients of all statutory health insurance providers and will be located in the federal state of Baden-Württemberg. One general practitioner and one medical assistant will commit to participation in the trial. Eligible general practitioners hold a certified specialization in general practice or internal medicine. Medical assistants are eligible if they are 18 years of age or older and have completed an additional qualification as a care assistant in general practice (VERAH) or an equivalent qualification. All practices not meeting the inclusion criteria will not be eligible to participate.

To be eligible for inclusion in the trial, patients must be 18 years of age or older, suffering from CNCP for at least 3 months, and using analgesics or co-analgesics (NSAIDs, Coxibs, ASS—in an analgesic dosage—triptans, paracetamol, opioids, gabapentin, pregabalin, or antidepressants) due to CNCP in the last 4 weeks. Further inclusion criteria are an at least moderate pain-related disability (at least 4 points on a scale from 0–10) in at least 2 out of 7 defined domains of life, the ability to consent, and the ability to participate actively in the program and the process evaluation (this includes sufficient cognitive abilities and access to the internet). Patients with cognitive limitations, inability to consent, inability to actively participate, cancer-related pain, or who are in palliative care will be excluded.

Measures and materials for recruitment

a) Recruitment of practices

General practices will be recruited via the PraCMan practice network, which currently comprises about 1,000 practices in Baden-Württemberg; via the network of general practices trained in performing research (FoPraNet), currently comprising about 70 trained research-ready practices; and via the email distribution list of the German Association of General Practitioners (Hausärzteverband) Baden-Württemberg.

An invitation to participate in the trial and a flyer with basic information about the study will be sent to the practices by postal or electronic mail, together with a declaration of interest form. If a practice declares that it is interested in participating in the study, the informational material and consent forms for the participating physician and the participating medical assistant will be sent. In case the recruitment target is not met, a reminder will be issued.

b) Recruitment of patients

To identify eligible patients, all participating practices will be asked to hand out a screening questionnaire to adult patients entering the practice from a defined date on to identify patients with CNCP and use of analgesics. Practices will use a provided template to check screening questionnaires against the inclusion criteria. In addition, practices will identify patients receiving opioids due to CNCP using filter options of their practice software and ask approximately 10 of them to fill in the screening questionnaire with the aim of including patients with opioid use and CNCP. Each practice will hand out a total of 150 questionnaires. To prevent selection bias and exclusion of more complex patients, practice teams will inform the study center about how many patients who receive opioids were filtered, screened, and included. Reasons for non-recruitment, including patient refusal, will be documented by the practice teams on the screening questionnaire. All eligible patients identified in the screening survey will be invited consecutively to participate in the study by handing out the information material. The recruitment target for each practice is 9 patients.

The practice teams will be asked to add some information to the screening questionnaires of all patients meeting the inclusion criteria (regardless of whether they agree to participate in the study or not) by checking the patient file. The practice team will de-identify all questionnaires (also of patients without chronic pain) by cutting the lines for name and birthdate and send them to the study center for evaluation purposes regarding patient characteristics and the prevalence of patients who meet the inclusion criteria without their GP being aware of it.

Process of obtaining informed consent

Before the start of the trial, participating patients will be informed verbally and in writing about the nature and scope of the planned study, in particular about possible benefits for their health and possible risks. Their consent is documented by signing the informed consent form. All participants will be informed that their participation is voluntary and that they can withdraw their consent to participate at any time without specifying reasons and without any disadvantages for their treatment. In the event of withdrawal from the study, the practice team will notify the study center, and patients will be asked to consent that already collected data may remain in the analysis. If this consent is not given, all data obtained from the respective patient that have not yet been included in analyses will be destroyed.

Financial compensation

GPs in the intervention group will receive financial compensation for participation in the kick-off webinar and per patient for study appointments 1, 2, 3, 4, and 5. Practices will issue an invoice via a standardized form, and the respective amount will be transferred to the specified bank account. Financial compensation for GPs in the intervention group is necessary because the intervention causes a considerably higher workload compared to usual care. It is also common in routine care for comparable programs to receive additional remuneration. Therefore, the payment of compensation for effort represents a realistic scenario.

Medical assistants in the intervention group will receive financial compensation for participation in the kick-off webinar, for conducting a screening survey, and for completing the e-learning. Medical assistants will issue an invoice via a

standardized form. The compensation is necessary because conducting the screening survey represents an additional workload for medical assistants and the e-learning will probably be completed in their free time. The compensation is a necessary incentive to ensure intervention adherence.

GPs in the control group will receive financial compensation for participation in the kick-off webinar and for each patient completing the T0 and T1 questionnaires. They will issue an invoice via a standardized form. Medical assistants in the control group will receive financial compensation for participation in the kick-off webinar and for conducting the screening survey and will issue an invoice via a standardized form. Financial compensation in the control group is a necessary incentive to motivate the practice teams to complete data collection even though they do not benefit from an intervention. Practice teams in the control group will be given the opportunity to complete the e-learning and to receive the educational material after trial completion.

At the end of the intervention period, all participating patients with completed T0 and T1 surveys will receive a small gift (value €2). In addition, practice teams in the control group can then receive the educational booklet for their patients and have access to the e-learning.

Methods and conduct of the study

Study Design

A multi-center, prospective, confirmatory, two-armed, non-blinded, cluster-randomized controlled trial with practices as the unit of randomization will be conducted (see Figure 1). Cluster randomization was chosen to avoid contamination between patients within practices. Randomization will be conducted by the Institute of Medical Biometry and carried out in a 1:1 ratio, meaning that the intervention and control groups will be assigned the same number of practices. Practices will be randomized by an independent statistician according to a computer-generated randomization list using permuted block sizes. The randomization list will only include practice numbers 01 to 28 and be securely stored at the Institute of Medical Biometry. Allocation will be concealed from study participants and the researchers conducting the study until the screening survey and baseline data collection (T0) are completed. Outcome assessors will not be able to identify practices. An accompanying process evaluation will be conducted which involves qualitative and quantitative methods. Reporting will follow the CONSORT extension for cluster-randomized trials [26]. Figure 1 describes the study design and course.

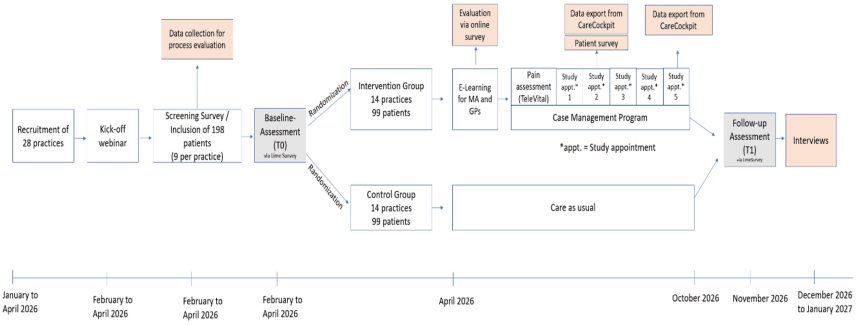

Figure 1. Study design and course of the study

Orange boxes refer to data collection for the process evaluation.

Intervention components of the case-management program

The intervention has been described in detail in our pilot protocol [13]. Following the pilot study, adaptations have been integrated into the five key components for the RCT: 1) The RELIEF module for the case management software "CareCockpit" facilitates and documents assessment and monitoring in a streamlined way to accommodate general practice care routines; 2) The number of scheduled structured appointments with GPs or medical assistants has been increased from 3 to 5; 3) The online training on chronic pain management for GPs and medical assistants now includes content specifically related to headaches; 4) Amended educational materials for patients now include content related to headaches; 5) The digital toolbox with resources for patients and practice teams was supplemented with additional information on triptans and the DIRE Score (Diagnosis, Intractability, Risk, and Efficacy), which supports primary care physicians in predicting the efficacy of analgesics and patient adherence with long-term opioid analgesic treatment [27].

After enrollment into the study, patients complete a pain assessment via a browser-based application (TeleVital App) at home on their own digital device (smartphone, tablet, computer, etc.). It is expected that this will take patients 30 to 60 minutes, depending on individual characteristics. The assessment focuses on various aspects of pain and mental comorbidities. During the structured study appointment 1, the patient and GP will discuss the patient's specifications in the assessment, and open pain history taking will take place. For this purpose, GPs or medical assistants will perform a manual import of the assessment data into the CareCockpit software, an established case management software currently used by about 1,000 general practices in Baden-Württemberg for the case management program PraCMan. This is a care model for patients with multimorbidity insured by AOK Baden-Württemberg (for further information, see www.hausarzt-bw.de/pracman).

The data import will only be started when the patient is present in the practice to ensure that GPs are able to react immediately to critical information such as severe depression. Practice teams will receive the data in two versions: the original version with all items and patients' responses and, in addition, a summary of the assessment. At the end of study appointment 1, educational material on chronic pain (a booklet and links to educational videos) will be

handed out to patients, and the date for study appointment 2 will be set for about 2-4 weeks later.

During study appointment 2, patients and GPs and/or medical assistants will reflect on the provided educational material and agree on treatment goals related to daily activities (for instance, to be able to do some gardening) and self-care activities such as physical activity or relaxation techniques. If necessary, medication is prescribed and/or therapies outside the general practice are initiated (for instance, physiotherapy, multimodal pain therapy, psychotherapy, rehabilitation, etc.) and monitoring activities are planned. A treatment plan containing all this information will be issued by the responsible GP via the CareCockpit software, and the date for study appointment 3 will be set for 4-6 weeks later.

During study appointment 3, practice teams will check whether activities could be applied as planned. If necessary, the treatment plan will be adapted. A telephone monitoring will be conducted 4 weeks and 12 weeks after study appointment 3 by medical assistants following a checklist in the CareCockpit software (study appointments 4 and 5). The activities performed during study appointments will be briefly documented by the practice teams via a standardized form in the CareCockpit module. The intervention period will end with a follow-up assessment (T1) 2 weeks after study appointment 5.

GPs and medical assistants in the intervention group will complete a standardized e-learning on chronic pain management with 4 modules covering the pathogenesis of chronic pain, self-care activities (relaxation techniques, physical activity, external applications), analgesics, and interprofessional and interdisciplinary pain therapy. The e-learning is to be completed before the first patient receives study appointment 1, and completion certificates will be sent to the study center for documentation purposes. In case of delays, reminders will be sent to the practice teams and a deadline will be set. GPs will receive 10 CME points for completing the e-learning. A website with a toolbox containing useful links and information on chronic pain will be provided by the study center. If practice teams in the control group are interested in completing the e-learning modules, a link can only be requested after completion of the intervention period. Control group practices may also request the patient information material after the intervention period. Table 3 summarizes the planned course of the case management program.

When	What	Who	Where
Week 0 (Start case management program)	T0 and pain assessment (LimeSurvey, TeleVital)	Patient	At home
Week 2	Study appointment 1	GP	At practice
	Reading educational material	Patient	At home
Week 5-6	Study appointment 2	GP	At practice
	Applying treatment plan	Patient	At home
Week 10-12	Study appointment 3	MA	At practice
	Applying treatment plan	Patient	At home
Week 16	Study appointment 4	MA	Telephone
	Applying treatment plan	Patient	At home
Week 24	Study appointment 5	MA	Telephone
Week 26 (End of case management program)	T1 assessment	Patient	At home

Table 3: Course of the case management program

GP = general practitioner, MA = medical assistant

Data collection

Data collection for the pain assessment and for outcome and process evaluation has been described in detail in a previously elaborated data protection concept and comprises the following steps:

Patients receive a weblink from their GP practice leading to the browser-based TeleVital App. Patients complete the assessment via the TeleVital App on their own digital device. The data will be stored on the TeleVital Server located at the University Hospital Heidelberg. Data from the TeleVital App will be transferred to the CareCockpit Software installed in the GP practice. The data import will be initiated manually by the practice team at the next patient contact. Thus, practice teams will receive the assessment data only when the patient is present in the practice. Practice teams will use the assessment data for the purpose of diagnostics and treatment.

Patient-reported outcomes and the sociodemographic data of GPs and medical assistants will be collected before (T0) and after (T1) in the intervention group and the control group by online questionnaires which participants will complete at home. The survey tool LimeSurvey will be used for this purpose. Completion of T0 and T1 is considered to take less than 10 minutes for practice teams and approximately 30 minutes for patients. Data will be stored on secure servers of the University of Heidelberg. Only the study team of the Department of Primary Care and Health Services Research will have access to the original survey data. After download of the complete data set, data will be stored on secure servers of

University Hospital Heidelberg and deleted from LimeSurvey. In the intervention group, parts of the outcomes will be collected via the pain assessment, which will be transferred to the study center via the CareCockpit software in anonymized form to avoid redundant data collection.

Process evaluation

Data for the process evaluation will be collected at various points in time in order to assess intervention mechanisms and intervention fidelity. During patient recruitment, practice teams will be asked to send the de-identified screening questionnaires used to identify eligible patients to the study center for evaluation purposes. The e-learning for GPs and medical assistants in the intervention group will be hosted on the platform Moodle on the server of the aQua Institute, Göttingen. Upon completing the e-learning, participants will be asked to fill in a short online survey to evaluate the modules regarding several aspects such as subjective knowledge increase, appropriateness of required time, and usability of the platform. The survey will be conducted anonymously via the survey tool LimeSurvey hosted at the server of the University of Heidelberg. Completion of the e-learning will not be possible without filling out the evaluation form. A copy of the certificate of completion will be sent to the study center for documentation purposes.

As part of the intervention, patients will receive a booklet and links to educational videos containing information about chronic pain from the practice teams. The booklet will contain a link to an anonymous online questionnaire focusing on the usefulness of the provided educational material and the patients' experiences with study appointments 1 and 2. Patients will be asked to complete the questionnaire within 4 weeks after study appointment 2.

All participating GPs and medical assistants will be invited to report their experiences during the intervention period in a telephone interview. All patients completing at least three study appointments will be invited to a telephone interview. Depending on the response rate, a purposive sample of patients will be drawn. Written information will be provided and written informed consent to participate will be obtained using agreement forms. The interview guides will focus on aspects regarding the perceived applicability and effects of the case management program, unexpected effects, intervention fidelity, and impulses regarding potentially necessary adaptations with regard to a broader implementation of the case management program. All interviews will be recorded and transcribed via NoScribe (GitHub, Inc.). Transcripts will be pseudonymized and stored on secure servers at the Department of Primary Care and Health Services Research, University Hospital Heidelberg. All audio files will be deleted after transcription and data analysis have been completed.

Time Schedule

Figure 1 and Table 3 give an overview of the course of the study and the time schedule. The intervention period is expected to end in October 2026, and data collection is expected to be completed in January 2027.

Benefit-Risk-Assessment

Benefit

It is expected that patients in the intervention group will benefit from intensified care, which involves more, longer, and better-structured contacts with the

practice team compared to patients in the control group. Patients in the intervention group will also receive more information about chronic pain via the educational materials and conversations with the practice teams. It is also assumed that patients will benefit from more individualized care because their GPs will receive more information about their pain situation via the digital pain assessment compared to GPs in the control group.

GPs and medical assistants in the intervention group are expected to benefit from the provided training and tools, which will enable them to implement holistic, guideline-based pain management in their practices. It is assumed that the feeling of being able to offer good care to patients with chronic pain will result in higher work satisfaction. Furthermore, GPs will benefit from case payments and the continuing medical education credits they will receive for completion of the e-learning.

Risks

A burden for GPs and medical assistants will derive from the additional time needed for the case management program, the study procedures, and participation in the process evaluation. The assessment comprises a screening of mental illnesses. If a mental illness is detected, GPs are responsible for delivering or organizing appropriate care for the concerned patients. This may also be associated with a considerable additional workload. Some elements of the case management program can be delegated to medical assistants, for example, reflecting on the educational material or setting treatment targets. Thus, medical assistants will be more involved in the care of patients with chronic pain than usual, which may result in an additional mental or time burden. Patients will be asked to provide detailed information about their pain history, mental condition, and personal goals and receive comprehensive information about chronic pain. This may possibly provoke negative, stressful emotions. Participation in the case management program will require additional appointments and therefore be associated with an additional time burden for patients as well.

The CareCockpit documentation requires an assessment by the practice teams regarding how helpful or burdensome each of the study appointments was perceived by patients. A data export after study appointment 2 will provide information regarding adverse events or unexpected burden.

Assessment

The study team believes that the benefits clearly outweigh the risks. The intensified care and more individualized treatment are expected to improve chronic pain management. Potential burdens are offset by the long-term benefits of improved patient care, increased satisfaction, and better outcomes. Our experiences in the previously conducted pilot study underline these assumptions.

Stop criteria

Patients will drop out if they are diagnosed with a cancerous disease or if they withdraw their consent to participate in the trial. Practices will drop out if the responsible GP withdraws consent to participate. The principal investigator will stop the trial if serious harms are observed or reported.

Statistical Design and Process Evaluation

The Institute of Medical Biometry, University Hospital Heidelberg, Germany, will perform analyses of clinical data, including baseline characterization of patients and outcome assessment.

Analysis Set and estimands

The analysis will be performed based on the full analysis set (FAS) based on all patients enrolled in a randomized practice. The randomization is conducted at the practice level. Group allocation will be assessed according to the intention-to-treat (ITT) principle, meaning patients will be analyzed according to the randomization of their respective practice.

Primary estimand:

- Treatment: Intervention with case management program versus Standard of Care
- Population: The target population is defined through the in- and exclusion criteria.
- Variable: The variable of interest is the PDI-G at T1.

Intercurrent events: Possible intercurrent events are death and discontinuation of the intervention program in the intervention group. Death will be handled using the hypothetical strategy, reflecting what the outcome would have been if the patient had not died, as death is considered unrelated to the disease and independent of the assigned treatment (intervention and standard of care). Since the exclusion of deceased patients would alter the randomized sample, potentially introduce selection bias, and restrict the target population, the hypothetical strategy is preferred to maintain the intended estimand and ensure that the treatment effect is estimated for the full population. Discontinuation of the intervention program cannot be directly measured and is therefore addressed using a treatment policy strategy, reflecting the effect of assignment to the intervention under real-world conditions where non-adherence is expected. The variable ‘all study appointments completed’ (yes/no) will be used as an indirect indicator of treatment discontinuation and will be considered when handling missing values. No further intercurrent events are expected.

Population-level summary: The summary measure is the difference in means.

General considerations

A statistical analysis plan will be finalized prior to the final analysis and databank closure. All analyses will be performed in R version 4.4.0 or higher in a validated environment. The final analysis will be done as soon as the database has been declared to be complete and accurate and has been locked. Descriptive statistics will be provided to summarize the demographics and baseline characteristics of all participants. In general, continuous variables will be described using the number of observations, mean, standard deviation, median, Q1, Q3, minimum, maximum, 95% confidence intervals, and, if existing, number of missing values. For categorical variables, absolute and relative frequencies will be given, with missing values being reported as a separate category. A CONSORT flow diagram will be created to display the progress of all participants through the trial. This includes the number of patients assessed for eligibility and the number of patients excluded because they did not meet inclusion criteria, declined to participate, or for any other reason.

Primary outcome

The confirmatory analysis corresponds to the primary estimand and will be performed based on the ITT set. The following hypotheses will be tested in the primary analysis:

$$H_0 : P_I - P_C = 0 \; vs. \; H_1 : P_I - P_C \neq 0,$$

where P_I is the mean difference between T0 and T1 in the intervention group and P_C is the mean difference between T0 and T1 in the control group. The superiority of the intervention group over the control group will be evaluated using a mixed linear regression model with the PDI-G score at T1 as the dependent variable. The model will include treatment group, age, sex, and PDI-G at T0 as fixed effects and practice as a random effect. A Wald test of the treatment effect estimate will be used to assess the statistical significance.

Sensitivity analyses regarding the primary estimand and the imputation method will be performed (e.g., replacing missing values by last observation carried forward, variation of variables in the imputation method). Further sensitivity analyses (e.g., best- and worst-case scenarios) will be performed and described in more detail in the SAP. Supplementary analyses regarding the primary endpoint include a complete case analysis.

Secondary outcomes

All secondary outcomes will be evaluated descriptively by group. Descriptive p-values for the corresponding effects will be reported along with 95% confidence intervals (CIs). For continuous variables, a t-test or Mann–Whitney U test will be applied, as appropriate. For categorical or binary variables, a chi-squared test will be used. In addition, linear mixed models will be calculated for the scores measured at T1, with treatment group, age, sex, and score value at baseline as fixed effects and practice as a random effect. If meaningful, graphical presentations (e.g., boxplots) will be provided. Furthermore, the treatment effect will be assessed descriptively within relevant subgroups. Potential inter-practice variability may be explored descriptively, including possible differences in practice characteristics and their association with treatment effects. Details will be specified in the statistical analysis plan.

Handling missing values

Missing values of the primary endpoint PDI-G will be replaced at the item level using multiple imputation based on predictive mean matching using the variables age, sex, practice, and pain intensity at baseline, and the variable ‘all study appointments completed’ (yes/no) as potential predictors. Missing scores and differences can then be calculated using the imputed items. Treatment discontinuation is considered an intercurrent event (ICE) and will be handled according to a treatment policy strategy. Data will be included in the analysis as observed. The variable ‘all study appointments completed’ (yes/no) is directly related to this ICE and is therefore included in the imputation model. Its inclusion is necessary to adequately reflect the missing data mechanism and to ensure consistency with the treatment policy strategy. Missing values for scores measured by validated instruments (secondary endpoints) will also be imputed if necessary. The corresponding imputation methods will be specified in detail in the statistical analysis plan as a prespecified approach. Other secondary endpoints, such as medication intake, and descriptive outcomes (e.g., physical

activity) will not be imputed, as these variables are not considered suitable for imputation given their nature. Missing values for these endpoints will be described and handled descriptively. This approach ensures a consistent and transparent missing data strategy across all endpoints.

Sample size calculation

The sample size calculation is based on the primary efficacy endpoint, the PDI-G score at T1, and was informed by insights gained in the pilot study [13]. The calculation assumes a two-sample t-test. A clinically relevant effect difference of 8.5 points in the PDI-G score is expected. The standard deviation of 14 is estimated from the pilot study.

The significance level is set to α = 5% (two-sided) and the power to 90%. The intraclass correlation coefficient (ICC) is assumed to be 0.05, which represents a conservative estimate. This value was chosen conservatively, as an ICC of approximately 0.03 is commonly assumed in comparable cluster-randomized trials. In the pilot study, no between-practice variance was observed, corresponding to an estimated ICC of 0. However, ICC estimates derived from small pilot studies are inherently unstable. Therefore, an ICC of 0.05 was assumed to account for potential clustering effects in the main trial. The coefficient of variation (COV) of 0.28 is estimated from the pilot study. In the pilot study, almost all practices recruited between seven and eight patients. Sensitivity calculations demonstrated that reasonable variations in the coefficient of variation had only a negligible impact on the required sample size. The average cluster size is expected to be 7. A power of 90% was chosen to ensure a sufficiently high probability of detecting the clinically relevant effect, considering potential variability introduced by the cluster study design. Under these assumptions, 11 practices per arm (22 in total) are required. To account for an expected dropout rate of 20% at the patient level, 9 patients per practice will be recruited, resulting in a total of 198 participants. To account for an additional 20% dropout rate at the practice level, 14 practices per arm will be randomized. The sample size was calculated with PASS version 24.0.06. The anticipated ICC and average cluster size were specified as input parameters, and PASS automatically derived the corresponding design effect (DEFF) to adjust the required sample size for the clustered study design. Thus, while the calculation is based on a two-sample t-test framework, the loss of statistical efficiency due to clustering was fully accounted for through the DEFF adjustment. This approach follows standard methodology for sample size calculation in cluster-randomized trials. The primary analysis will be conducted using a linear mixed model including a random effect for cluster to account for the hierarchical data structure and within-cluster correlation. Sensitivity analyses will be specified in further detail in the statistical analysis plan.

Process evaluation

Analysis of the qualitative data collected in the process evaluation will use an inductive approach based on the themes covered in the interview guide (including unintended effects). Data management will be done in MAXQDA (Verbi Software). Written surveys will be conducted digitally through the survey tool LimeSurvey hosted on secure servers of Heidelberg University. All quantitative survey data and data from free-text fields will be analyzed descriptively using SPSS and visualized in Excel (Microsoft). In addition, data entered by the practice teams into the CareCockpit software to document

activities performed during the study appointments (including information about changes in pain medication as well as the pain assessment completed by patients) will be transferred to the study center (see Figure 1) in pseudonymized form and analyzed within the scope of the process evaluation. All data will be deidentified before analysis. All process evaluation data will be triangulated for classification of perceived intervention and program effects as well as program fidelity.

Data management and data protection

Data generated in this study will be pseudonymized and stored on secure servers at the Department of Primary Care and Health Services Research, University Hospital Heidelberg, Germany, for a period of 10 years after the conclusion of the study. The participating general practices commit to retaining the study data for a period of 10 years and to securely destroying them thereafter. Pseudonymization keys for patient data will only be available to the responsible GP or medical assistant. Pseudonymization keys for data referring to GPs and medical assistants will only be available to the RELIEF study team. Personal data will be anonymized as soon as possible according to the research purpose.

Data processing

In this study, data will be processed at two departments of the University Hospital Heidelberg: The Department of Primary Care and Health Services Research (responsible persons: PD Dr. med. Cornelia Straßner and Dr. sc.hum. Regina Poß-Doering) and the Institute of Medical Biometry (responsible persons: Alexandra Balzer and Dr. sc. hum. Manuel Feißt). The original data will be processed at the Department of Primary Care and Health Services Research, and cleaned datasets will be transferred to the Institute of Medical Biometry for further analysis. Patient names and all other confidential information are subject to medical confidentiality and the provisions of the General Data Protection Regulation (GDPR) and the State and Federal Data Protection Act (LDSG and BDSG). Patient data may only be passed on in pseudonymized form. Third parties do not have access to original documents.

Audio and image recordings

Audio recordings obtained from telephone interviews with patients, general practitioners, and medical assistants as part of the process evaluation will be deleted after transcription is completed. All transcripts will be anonymized prior to analysis. No image recordings will be taken.

Withdrawal of consent

Consent may be withdrawn by study participants at any time, without providing reasons and without any disadvantages.

Deleting and anonymizing data

If a participant withdraws from the study, any data material already collected will be destroyed, or the study participants will be asked whether they agree to the use of the data for analysis.

Dissemination

After completion of the trial, all collected data will be analyzed, and publications regarding the findings in the process and the outcome evaluation will be prepared and submitted to open-access peer-reviewed journals. Findings will also be presented at scientific meetings and conferences. Through the dissemination channels of the partnering self-help organization, findings will also be published in lay language to inform affected patients.

Study status

Recruitment of participating general practices started in January 2026 and is still ongoing. The disclosure of the randomization result and thus the group allocation will occur in April and May 2026, respectively, when practices have completed the screening survey and participating patients have completed T0. This will be considered the start of the intervention period. The study center monitors trial conduct and progress continuously in weekly status meetings.

Discussion

Chronic pain is often downplayed and tolerated in older adults as those affected mistakenly consider it a normal part of aging [28]. Older adults might adopt a stoic attitude and resort to ineffective coping strategies based on self-restraint [28][29]. A study from Italy shows that evidence-based methods such as exercise and relaxation [9] are rarely used, while unproductive strategies such as avoidance dominate [30].

The needs and experiences of older adults with chronic pain and their coping strategies [31][32], as well as effective pain self-management interventions, have been explored by other studies [29][33]. The RELIEF case management program comprises innovative elements. GPs, MAs, and patients may benefit from this structured approach and patient activation, which can facilitate open discussion with patients on their needs. Through the structured pain history (including intensity, progression, and psychosocial factors) and the targeted involvement of medical assistants in setting and monitoring goals, patient engagement will be promoted and the practice team will share the workload in team-based care [34] [35].

The RELIEF program addresses well-known coordination challenges in the care of patients with chronic conditions: By embedding educational components directly into the primary care setting, GPs in the intervention group remain informed and can actively refer to the content during the course of treatment [5]. The combination of face-to-face therapy and remote delivery of content has been shown to promote self-management of chronic conditions and complements face-to-face treatment [36]. Adverse effects such as stressful and negative emotions may be triggered by recording detailed information about pain history, mental condition, and personal goals. However, it also has the potential to trigger reflexive processes, behavioral adaptations, and mobilize self-care resources.

Although cluster randomization reduces the risk of contamination, participating practice teams might share knowledge informally in regional professional networks. To mitigate this, control practices can only receive access to the e-learning modules and the patient information material when the intervention

period is completed. The self-reported primary outcome might carry a risk of reporting bias, which cannot be fully excluded. The RELIEF trial is a complex intervention, and interpretability might be limited due to the multiple components included. To avoid difficulty in attributing observed effects to specific components, the process evaluation will investigate in detail with regard to every component.

Participation in the RELIEF trial requires internet access and digital engagement, which could potentially exclude older, socioeconomically disadvantaged, or digitally underserved patients. To mitigate digital exclusion and maintain demographic representativeness, participating patients are allowed to seek support when accessing provided links to questionnaires.

The described combination of intervention components for patients with CNCP in German primary care still has a limited evidence base. Findings in this study are expected to provide clear indications regarding a potential reduction of pain-related disability and other patient-related outcomes and insight into intervention fidelity.

Reporting guidelines

SPIRIT 2025 checklist of items to address in a randomized trial

*protocol**

Section / Topic	No.	SPIRIT 2025 checklist item description	Reported on page no.
Administrative information			
Title and structured summary	1a	Title stating the trial design, population, and interventions, with identification as a protocol	1
	1b	Structured summary of trial design and methods, including items from the World Health Organization Trial Registration Data Set	1, 2
Protocol version	2	Version date and identifier	2
Roles and responsibilities	3a	Names, affiliations, and roles of protocol contributors	1
	3b	Name and contact information for the trial sponsor	23
	3c	Role of trial sponsor and funders in the design, conduct, analysis, and reporting of the trial, including any authority over these activities	20
	3d	Composition, roles, and responsibilities of the coordinating site, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable	20
Open science			
Trial registration	4	Name of trial registry, identifying number (with URL), and date of registration. If not yet registered, name of intended registry	2
Protocol and statistical analysis plan	5	Where the trial protocol and statistical analysis plan can be accessed	19
Data sharing	6	Where and how the individual de-identified participant data (including data dictionary), statistical code, and any other materials will be accessible	19
Funding and conflicts of interest	7a	Sources of funding and other support (e.g., supply of drugs)	20
	7b	Financial and other conflicts of interest for principal investigators and steering committee members	20
Dissemination policy	8	Plans to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., reporting in trial registry, plain language summary, publication)	18
Introduction			
Background and rationale	9a	Scientific background and rationale, including a summary of relevant studies (published and	2, 3, 4

Section / Topic	No.	SPIRIT 2025 checklist item description	Reported on page no.
Administrative information			
		unpublished) examining benefits and harms for each intervention	
	9b	Explanation for choice of comparator	4
Objectives	10	Specific objectives related to benefits and harms	4, 13
Methods: Patient and public involvement, trial design			
Patient and public involvement	11	Details of, or plans for, patient or public involvement in the design, conduct, and reporting of the trial	17, 24
Trial design	12	Description of trial design including type of trial (e.g., parallel group, crossover), allocation ratio, and framework (e.g., superiority, equivalence, non-inferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			
Trial setting	13	Settings (e.g., community, hospital) and locations (e.g., countries, sites) where the trial will be conducted	4
Eligibility criteria	14a	Eligibility criteria for participants	6
	14b	If applicable, eligibility criteria for sites and for individuals who will deliver the interventions (e.g., surgeons, physical therapists)	4
Intervention and comparator	15a	Intervention and comparator with sufficient details to allow replication, including how, when, and by whom they will be administered. If relevant, where additional materials describing the intervention and comparator (e.g., intervention manual) can be accessed	9, 10, 11
	15b	Criteria for discontinuing or modifying an allocated intervention/comparator for a trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	15c	Strategies to improve adherence to intervention/comparator protocols, if applicable, and any procedures for monitoring adherence (e.g., drug tablet return, sessions attended)	8
	15d	Concomitant care that is permitted or prohibited during the trial	n/a
Outcomes	16	Primary and secondary outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome	4, 5
Harms	17	How harms are defined and will be assessed (e.g., systematically, non-systematically)	13

doi.org/10.32388/MZZYA7.2

Section / Topic	No.	SPIRIT 2025 checklist item description	Reported on page no.
Administrative information			
Participant timeline	18	Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12
Sample size	19	How sample size was determined, including all assumptions supporting the sample size calculation	16
Recruitment	20	Strategies for achieving adequate participant enrollment to reach target sample size	7
Methods: Assignment of interventions			
Randomization:			
Sequence generation	21a	Who will generate the random allocation sequence and the method used	14
	21b	Type of randomization (simple or restricted) and details of any factors for stratification. To reduce the predictability of a random sequence, other details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	14, 15, 16
Allocation concealment mechanism	22	Mechanism used to implement the random allocation sequence (e.g., central computer/telephone; sequentially numbered, opaque, sealed containers), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	23	Whether the personnel who will enroll and those who will assign participants to the interventions will have access to the random allocation sequence	9
Blinding	24a	Who will be blinded after assignment to interventions (e.g., participants, care providers, outcome assessors, data analysts)	n/a
	24b	If blinded, how blinding will be achieved and a description of the similarity of interventions	n/a
	24c	If blinded, circumstances under which unblinding is permissible, and the procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	25a	Plans for assessment and collection of trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of trial instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to	11, 12

Section / Topic	No.	SPIRIT 2025 checklist item description	Reported on page no.
Administrative information			
		where data collection forms can be accessed, if not in the protocol	
	25b	Plans to promote participant retention and complete follow-up, including a list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	26	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be accessed, if not in the protocol	16, 17
Statistical methods	27a	Statistical methods used to compare groups for primary and secondary outcomes, including harms	14, 15
	27b	Definition of who will be included in each analysis (e.g., all randomized participants) and in which group	15
	27c	How missing data will be handled in the analysis	16
	27d	Methods for any additional analyses (e.g., subgroup and sensitivity analyses)	15
Methods: Monitoring			
Data monitoring committee	28a	Composition of the data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and funder; conflicts of interest 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	n/a
	28b	Explanation of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Trial monitoring	29	Frequency and procedures for monitoring trial conduct. If there is no monitoring, give an explanation	18, 23
Ethics			
Research ethics approval	30	Plans for seeking research ethics committee/institutional review board approval	23
Protocol amendments	31	Plans for communicating important protocol modifications to relevant parties	23
Consent or assent	32a	Who will obtain informed consent or assent from potential trial participants or authorized proxies, and how	7, 8, 16, 17

Section / Topic	No.	SPIRIT 2025 checklist item description	Reported on page no.
Administrative information			
	32b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	19
Confidentiality	33	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19
Ancillary and post-trial care	34	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	20

Citation: [37]

Statements and Declarations

Trial Registration

German Clinical Trials Register https://www.drks.de/search/de/trial/DRKS00038960 (registered Jan. 26, 2026).

Protocol Version 1, Apr. 20, 2026.

Funding

The project RELIEF is exclusively funded by the German Federal Ministry of Research, Technology and Aerospace (formerly the German Federal Ministry of Education and Research; Funding code 01GY2106) and received ethics approval from the Ethics Committee of the Medical Faculty at University Heidelberg, Germany (S-632/2025). Potentially necessary amendments will be submitted to this committee for approval. The funder had no role in the design, conception, conduct, analysis, or reporting of this trial. The funder receives regular interim and yearly reports about the progress of the study.

Potential Competing Interests

Cornelia Straßner, the principal investigator, is a member of the guideline commission of the German Society of General Practice and Family Medicine (Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin, DEGAM). The other authors declare no competing interests.

Ethics

The study is carried out in accordance with the current version of the Declaration of Helsinki. Before the start of the study, an ethical and legal review was conducted by the ethics committee of Heidelberg University. Participation of patients and subjects is voluntary. Written informed consent will be obtained from all participants prior to participation. The principal investigators are responsible for the successful execution of the study and maintenance of ethical compliance.

Data Availability

Open posting of the statistical analysis plan and data collected and analyzed in this trial is not covered by the study information and the informed consent sheets. All data will be stored on a secure server at the Department of Primary Care and Health Services Research, University Hospital Heidelberg, Germany. De-identified sets of these data can be made available by the corresponding author on reasonable request provided that participants consented to secondary use for research purposes in further pain management-related studies.

Author Contributions

RPD, CS, and SB designed this study and the intervention components and drafted and revised this study protocol. AB and MF provided expertise on the statistical analysis and critically revised the manuscript. RPD, CS, SB, VSW, RS, and MRZ contributed to the development of the educational intervention components. CS and RPD share the project management; SB is a doctoral candidate in RELIEF. JT provided expertise for the intervention development. MW provided expertise for the intervention development and planning of the RCT. All authors provided input and critical feedback and approved the final version of the manuscript.

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Declarations

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