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, 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 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 analgesics use located in Baden-Württemberg, Germany. The intervention comprises

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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 Pain Disability Index German version. Outcome evaluation data will be collected by digitalized 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 takes place between January and April 2026. Targeted maximum sample size is 28 practices and 252 patients. The intervention period will start with completed recruitment. It is expected that eligible patients will benefit from improved medication management, intensified use of nonpharmacological treatment strategies and reduction of pain-related disabilities.
Conclusions: This study will provide valuable information regarding 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 over 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, unspecific 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 bio-psycho-social interaction. Since comorbid mental health conditions such as depression, anxiety disorders, or Posttraumatic 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 for 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 a safe opioid management [9][10]. However, these often are 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 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 orthopaedics, 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 6 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 to evaluate 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 of pain-related disability at baseline (T0) and follow-up (T1) will be measured as 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 from 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 – 10 (no disability - maximum disability). The sum of the ratings can score between 0 – 70. Higher scores reflect higher interference of pain regarding daily activities. A score of 33 is considered as 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 minimal clinically important change [15]. Generally, scores can be considered clinically relevant when patients with a baseline score of $\leq$27 decrease minimal 7 points, patients with a baseline score between 28 and 42 decrease minimal 15 points, and patients with a baseline score $\geq$ 43 decrease minimal 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 (SF12 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)
Behaviour / cognitions	• Patient Activation Measure (PAM13-D)
	• Pain-related self-efficacy (FESS scale)
	• Avoidance-Endurance (Avoidance-Endurance-Screening-Instrument)
	• Pain Catastrophizing (Pain-Catastrophising-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

SF12 questionnaire) [17]*; (PAM13-D)* [18]*; FESS scale)* [19]*; Avoidance-Endurance-Screening-Instrument)*[20]*; Pain-Catastrophising-Scale)* [21]*;*

Beside primary and secondary outcomes, descriptive variables will be determined on patient level in order to describe the sample and to allow subgroup analyses (see Table 2). Most descriptive variables will only be collected once at T0 or at the defined times of CareCockpit data export (see figure 1) respectively. However, substance group and scheme of pain medication will be assessed at T0 and T1 in order 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–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)
Likeliness 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)

Patient-reported descriptive variables collected in the intervention and control group	Time and method of measurement
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)
Health care professional-reported descriptive variables reported in the intervention group	
Health care professional reported pain medication (substance groups)	Study appointment 2 (CareCockpit)
Health care professional reported pain medication (increase, reduction, start, 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 adult persons with ability to give informed consent and to actively participate will be included into 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 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 will be 18 years of age or older, suffering from chronic non-cancer pain for at least 3 months and using analgesics or co-analgesics (NSAID, Coxibe, ASS - in an analgetic dosage -, triptans, paracetamol, opioids, gabapentin, pregabalin or antidepressants) due to chronic non-cancer pain in the last 4 weeks. Further inclusion criteria are an at least moderate pain-related disability (at least 4 points on 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, patients with cancer-related pain, and patients 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 1000 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 to be interested in participation 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 identify patients in their practice receiving opioids due to chronic non-cancer pain using the filter options of their practice software and ask them to fill in a screening questionnaire. In addition, each practice will hand out the screening questionnaire to adult patients entering the practice from a defined date on until a total of 150 questionnaires are returned. Practice teams will inform the study center about how many patients who receive opioids were filtered, screened and included.

The recruitment target for each practice is 9 patients. The practice team will consecutively invite all eligible patients of which ideally at least 2 take opioids to participate in the study by handing out the information material. Factors indicating a likely benefit from the program for example might be a need or desire for pain education, need of support in fostering non-medical treatment options, ineffectiveness of pain medication, or complex aetiology of pain with strong psychosocial influences. The specific reasons for their choices will be explored as part of the process evaluation. For each patient who declines participation, another selected patient will be invited.

The practice team will be asked to add some information on 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 centre for evaluation purposes regarding the prevalence of patients in a primary care setting 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 participating at any time without specification of 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. In case this consent is not given, all data obtained from the respective patient that have not been included in analyses yet 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. A 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 a 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 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 are necessary incentives 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 then can 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 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 computed-generated randomization list using permuted block sizes. The randomization list will be securely stored at the Institute of Medical Biometry. Allocation will be concealed from study participants and the researchers conducting the study until baseline data collection

is completed. 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.

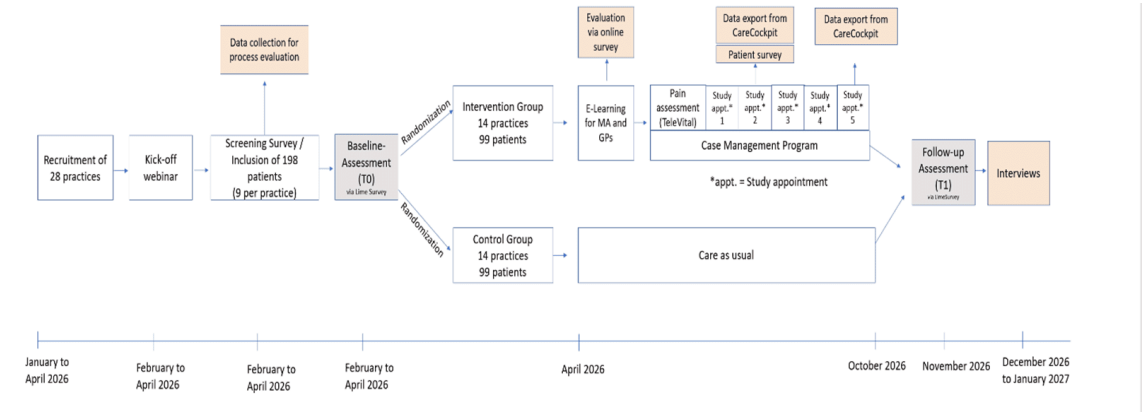

Figure 1. Study design and course of the study

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] and 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 efficacy of analgesics and patient adherence with long-term opioid analgesic treatment [27].

After enrolment 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.). The assessment focusses on various aspects of pain and mental comorbidities. During the structured study appointment

1, patient and GP will discuss the patients' 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 1000 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 on 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 appointment 4 and 5). The activities performed during study appointments will briefly be 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.

Participating GPs and medical assistants will complete an e-learning on chronic pain management with 4 modules covering the pathogenesis of chronic pain, self-care activities (relaxation technics, physical activity, external applications), analgesics and interprofessional and interdisciplinary pain therapy. The e-learning should be completed before the first patient receives study appointment 1. 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 team. 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 (Lime Survey, TeleVital)	Patient	At home
Week2	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 by online questionnaires which participants will complete at home. The survey tool LimeSurvey will be used for this purpose. Data will be stored on secure servers of the University 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 centre for evaluation purposes. The e-learning for GPs and medical assistants will be hosted on the platform Moodle on the server of the aQua Institute, Göttingen. After 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 Lime Survey hosted at the server of the University Heidelberg.

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 focussing on the usefulness of the provided educational material and the patients' experiences with study appointment 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 3 study appointments will

be invited to a telephone interview. Depending on the response rate, a purposive sample of patients will be drawn. A 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 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 to 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 continuous 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 to deliver or organize appropriate care for the concerned patients. This may also be associated with 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 also for patients.

The CareCockpit documentation requires an assessment by the practice teams regarding how helpful or burdening each of the study appointments were 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. The 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 (IMBI), 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). 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 data bank closure. All analysis 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 demographics and baseline characteristics of all participants. In general, continuous variables will be described using number of observations, mean, standard deviation, median, Q1, Q3, minimum, maximum, 95% confidence intervals and, if existing, number of missing. 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 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 dependent variable. The model will include treatment group, age, sex, PDI-G at T0 as fixed effects and practice as 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 random effect. If meaningful, graphical presentations (e.g., boxplots) will be provided. Furthermore, the treatment effect will be assessed descriptively within relevant subgroups.

Handling missing values

Missing values of the primary endpoint PDI-G will be replaced on 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. Missing values for scores measured by validated instruments will be imputed if necessary and will be described in the SAP. Other secondary endpoints (for instance medication intake) will not be imputed.

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 interclass correlation coefficient (ICC) is assumed to be 0.05. The coefficient of variation (COV) of 0.28 is estimated from the pilot study. The average cluster size is expected to be 7. A power of 90% was chosen to ensure a sufficient 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 drop-out rate of 20% on patient level, 9 patients per practice will be recruited, resulting in a total of 198 participants. To account for an additional 20% drop-out rate at the practice level, 14 practices per arm will be randomized. The sample size was calculated with PASS version 24.0.06.

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 Lime Survey hosted on secure servers of the 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 as well as the pain assessment completed by patients will be transferred to the study centre (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 the period of 10 years after conclusion of the study. The participating general practices commit to retaining the study data for a period of 10 years and to securely destroy them thereafter. Pseudonymization keys for patient data will only be available to the responsible GP or medical assistant. Pseudonymisation 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 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 has 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 as 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].

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 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.

The described combination of intervention components for patients with CNCP in German primary care has a still 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 design, conduct, analysis, and reporting of trial; including any authority over these activities	23
	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	23
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	7a	Sources of funding and other support (e.g., supply of drugs)	23

Section / Topic	No	SPIRIT 2025 checklist item description	Reported on page no.
interest	7b	Financial and other conflicts of interest for principal investigators and steering committee members	23
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 summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2,3,4
	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, physiotherapists)	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

Section / Topic	No	SPIRIT 2025 checklist item description	Reported on page no.
	15b	Criteria for discontinuing or modifying 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
Participant timeline	18	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
Sample size	19	How sample size was determined, including all assumptions supporting the sample size calculation	16
Recruitment	20	Strategies for achieving adequate participant enrolment 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 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

Section / Topic	No	SPIRIT 2025 checklist item description	Reported on page no.
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 description of the similarity of interventions	n/a
	24c	If blinded, circumstances under which unblinding is permissible, and 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 where data collection forms can be accessed, if not in the protocol	11, 12
	25b	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	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

Section / Topic	No	SPIRIT 2025 checklist item description	Reported on page no.
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 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 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
	32b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	19

Section / Topic	No	SPIRIT 2025 checklist item description	Reported on page no.
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

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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.

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 into secondary use for research purposes in further pain management related studies.

Potential Competing Interests

The principal investigator Cornelia Straßner is member of the guideline commission of the German Society of General Practice and Family Medicine (DEGAM). All authors declare no conflict of interest.

Grant information

The project RELIEF is exclusively funded by the German Federal Ministry of Research, Technology and aerospace (former 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 would be submitted to this committee for approval. The funder had no role in design, conception, conduct, analysis, and reporting of this trial. The funder receives regular interim and yearly reports about the progress of the study.

Acknowledgements

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 to the intervention development. MW provided expertise to 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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Potential competing interests: The principal investigator Cornelia Straßner is member of the guideline commission of the German Society of General Practice and Family Medicine (DEGAM). All authors declare no conflict of interest.