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NEUROCANTRIAL: Study Protocol for a Randomized Controlled Trial of a Pain Neuroscience Education Program in Adults with Cancer Pain

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NEUROCANTRIAL: Study Protocol for a Randomized Controlled Trial of a Pain Neuroscience Education Program in Adults with Cancer Pain

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ABSTRACT

Introduction

Pain, which comprises some characteristics related to its typification and variation, is the second most frequent symptom reported in patients with cancer. The incorporation of educational modalities into pain intervention processes has been suggested. The present study aims to examine the effectiveness of pain neuroscience education (PNE) in relation to pain, biopsychosocial variables, and functional capacity compared with conventional management.

Methods

This protocol involves a single-blind controlled clinical trial comparing two groups. The first group will receive conventional treatment in addition to PNE, participants will undergo an intervention of nine sessions, each lasting 30 minutes. Specifically, these sessions will teach the biological and physiological elements using metaphors that will enable the adoption of these pain-related concepts. The second group will receive conventional treatment. For this study, a sample size calculation was performed based on the medical histories of 80 adults presenting with oncologic pain. After the baseline assessment process, randomization, allocation concealment, and masking will be performed at different stages to establish follow-up and an analysis plan that will be applied throughout the protocol period to treat each group.

Ethical considerations

This protocol complies with all ethical considerations of the Declaration of Helsinki and the regulations in effect in the country. Moreover, it was approved by the Ethics and Bioethics

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Committee of the Universidad Santiago de Cali and the participating clinic. The authors commit to presenting the study's results.

Clinical trial registration

NCT05581784

Strengths and limitations of this study

- Patients from a pain medicine and palliative care unit will be recruited in accordance with their applicability in clinical practice.
- This study will involve the development of educational material according to the theoretical references for addressing the patient.
- Functional capacity measurements, such as a 6-minute walk distance and manual pressure strength, which can determine the effect of this intervention on patients, will be included.

Keywords: Pain; Neoplasms; Cancer Pain; Pain Management; Health Education

INTRODUCTION

According to the International Association for the Study of Pain, pain is defined as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage (1). Notably, it is one of the most frequently reported impairments caused by toxicity, surgery, radiation, etc. following cancer treatment (2). Moreover, it is strongly associated with a decreased quality of life and increased self-perceived disability (3). In particular, cancer pain poses a difficulty owing to the complexity of the disease and the subjective experience of pain. In addition to local pain mechanisms of tissue (nociceptive pain) and nerve (neuropathic pain) involvements, some mechanisms are characterized by altered processing without clear evidence of persistent tissue damage (nociplastic pain) (4).

Pain is a common symptom reported by patients with cancer. A previous meta-analysis reported pain in 59%, 64%, and 33% of patients undergoing cancer treatment, in patients with advanced or terminal disease, and after curative treatment, respectively. In addition, it is one of the most feared and annoying symptoms among these patients (5,6). Another study reported that 5%–10% of cancer survivors have severe chronic pain that significantly impairs their function (7). A study of patients with breast cancer reported pain in 25.3%, 18.7%, 15.4%, and 40.6% of patients, with neuropathic, nociceptive, nociplastic, and mixed pain predominating, respectively (8). Notably, this etiology of cancer pain is variable and can be attributed to postoperative syndromes. In addition, adjuvant therapies can have adverse effects. For example, chemotherapy can cause symmetrical painful numbness and burning and tingling in the hands and feet. It can also cause osteoporosis, osteonecrosis, arthralgia, and myalgia (7,9). Radiotherapy can have serious side effects caused by ionizing radiation, the induction of reactive oxygen species production, and damage to DNA and regulatory proteins in cells. This leads to apoptosis and increased inflammation in exposed and adjacent cells due to radiation-induced bystander effects, potentially leading to plexopathies and osteoradionecrosis (10,11). Further, the maintenance therapy used, such as

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that involving aromatase inhibitors, may cause arthralgia and myalgia (12).
Relevant literature in oncology has evidence that the quality of life and survival are associated with early and effective palliative care that includes pain management. Although improvements have been observed, undertreatment of pain remains a problem in a considerable number of patients with cancer (13). In the future, studies are required to evaluate these new treatment approaches (14) that include educational aspects within the intervention process. Accordingly, pain neuroscience education (PNE) describes how the nervous system interprets information from tissues via peripheral sensitization, central sensitization, synaptic activity, and cortical processing (15). This innovative educational approach is effective in changing beliefs about pain and improving pain management strategies and health outcomes in a variety of adult populations with chronic pain (16-18).
Regarding previous studies on PNE in cancer, a quasi-experimental study entitled "Pain Neuroscience Education in cancer survivors with persistent pain: A pilot study," was conducted by Pas R in 2020 (19) with the aim of describing the innovative educational component of PNE. The study demonstrated a significant decrease in pain intensity ($p = 0.001$) compared with baseline. Another study entitled "Effect of perioperative PNE in patients with post-mastectomy persistent pain: a retrospective, propensity score-matched study," which was conducted by Manfuku in 2021 (20), compared conventional biomedical education (BME) ($n = 51$) with PNE ($n = 51$) and reported scores based on the brief pain inventory (BPI) questionnaire. The study results showed that scores for catastrophizing and central sensitization improved with a statistically significant difference between PNE and BME (all, $p < 0.05$), and effect sizes for BPI intensity were moderate ($r = 0.31$). Furthermore, a study by Groef (21) entitled "EduCan trial: A study protocol for a randomized controlled trial on the effectiveness of pain neuroscience education after breast cancer surgery on pain, and physical, emotional, and work-related functioning" aimed to investigate the effectiveness of the PNE intervention for the treatment and prevention of pain and for improvement in physical, emotional, and work-related functioning after breast cancer surgery compared with biomedical education. However, no results from this study have been published to date.

Therefore, the present study aims to examine the effectiveness of PNE in relation to pain, biopsychosocial variables, and functional capacity compared with conventional management. This will be assessed through a single-blind randomized controlled clinical trial.

METHODS AND ANALYSIS

Trial design and context

A randomized controlled parallel-group clinical trial will be conducted with blinding of the researchers. The recruitment will be conducted between November 2022 and March 2024 at the clinical medicine and palliative care unit of a tertiary level clinic in the city of Cali and the Health Department of the University of Santiago de Cali, Colombia.

This proposed quantitative experimental controlled clinical trial will be conducted in accordance with the SPIRIT guidelines for clinical trial protocols (22) and CONSORT guidelines for clinical trials (23). This trial is registered with ClinicalTrials.gov Identifier: NCT05581784.

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Eligibility criteria

The study will include male patients diagnosed with stage III and IV prostate cancer and female patients diagnosed with stage IV genitourinary cancer according to the TNM staging system (24).

Inclusion criteria:

- Patients with a life expectancy of >3 months based on the Karnofsky Scale, Eastern Cooperative Oncology Group Scale, Palliative Prognostic Score, or Palliative Prognostic Index.
- Those who provide informed consent.
- Those with the level of education of high school and those who completed 11 years of education.
- Those who are able to establish communication with the team.
- Those presenting with scores demonstrating preserved cognitive function on a Montreal Cognitive Assessment (MoCA) scale with a minimum score of 25.
- Those who are able to stand upright and walk independently or with external assistance.

Exclusion criteria:

- Patients with surgeries scheduled in the next 3 months.
- Those with impairment of visual and auditory sensory systems (deafness or blindness).
- Those with acute traumatic injury.
- Those with uncontrolled arrhythmias or heart disease.
- Those with severe acute respiratory failure or uncontrolled respiratory pathology.
- Those with recent fractures in the last month.

Participant selection, recruitment, and consent

Participants were identified from the lists of patients in the pain medicine and palliative care ward and selected according to the abovementioned selection criteria. The initial examination and evaluation were carried out by a member of the research team, and potentially eligible participants were approached and recruited by the attending physician after consultation. All eligible patients received a document with information and explanations about the study. Participants were then asked to fill out a separate informed consent form that was previously approved by all institutions involved in the study. After their approval, an evaluation process was conducted to determine the baseline before randomization and assignment to one of the study groups. The flow chart of the study is shown in Figure 1.

Figure 1. Flow chart of the study

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Sample size

To calculate the sample size, we will use the results of the preliminary study by Manfuku (20) who used an educational intervention in cancer patients with pain to determine the process of self-care and medication management in cancer. Manfuku used the BPI as the main measure of pain intensity. Based on an assumption of a mean of 0.51 (±1) in group 1 and 1.69 (±2.2) in group 2, with a difference of −1.18, i.e., assuming pain intensity as the main variable, a power of 90% and an alpha type error of 5% was determined. Overall, 33 patients must be enrolled in each group, and to adjust for a 20% loss, 40 patients are required for each group.

Allocation and randomization

To reduce selection bias, random number randomization with a computer-generated 1:1 assignment in permuted blocks of four to eight patients will be performed. An external researcher will randomly assign patients to one of the two treatment groups after obtaining informed consent and performing a baseline assessment. In order to allocate each patient to the experimental or control group, two strata randomization (age groups, <60 years and older patients) will be also performed to reduce potential confounders and selection bias. Furthermore, the research team members performing the statistical analysis will be blinded.

Masking

To ensure a reduction in information bias during patient follow-up, the principal investigator is blinded. In addition, the post-interventional examinations are self-managed by people who depend on a physiotherapist and carried out for others by an external person trained and specialized in this field. This is done in such a way that the assessor is unaware of the patient's assignment, and the patient is asked not to reveal the group to which they have been assigned at any time. To further reduce the bias, both the therapist conducting the assessment and the therapist conducting the intervention program will be different people.

Intervention group

The intervention group will undergo an intervention based on PNE, which is an educational model for teaching pain biology and physiology. It has been recognized as a compelling approach for managing chronic pain that adopts elements of user-based learning through the use of metaphors and examples (25). In addition, PNE is aimed at changing the understanding of what pain really is, the effects it has, and the biological processes that guide it. It refers to a theoretical framework for pain treatments, and the main goal of the approach is to change the conceptualization of pain as an indicator of tissue damage or pathology, progressively leading to a change in attitudes and the initiation of movements and activities in everyday life (26).

This model is based on various educational interventions (18) and has been defined using the following terms: Explaining Pain (27), Therapeutic Neuroscience Education, and PNE. (28).

Notably, PNE is increasingly used as part of physiotherapy treatment in patients with chronic, non-disciplinary, and neuropathic pain. A comprehensive biopsychosocial clinical

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assessment is recommended before PNE to adequately explain the neurophysiology of pain and biopsychosocial interactions, while ensuring that this process is patient-centered (26).
In this regard, the present clinical trial will conduct nine sessions over a period of 10 weeks, each lasting 30–40 minutes. These sessions will be scheduled weekly. The content of the session will include elements based on the book illustrations explaining pain, the second edition of the Spanish version (27), and its content will correspond to http://www.paininmotion.be/ (29), Louw's manual (30), and the explanation of pain in patients with cancer (6). For the organization of material corresponding to this intervention, some phases will be generated.
The sessions will be based on a guide with nine chapters organized as follows:

- Chapter 1, entitled "Living with Pain," conceptualizes the importance of pain as a defense system and functioning of the organism. Patients will reflect on what their life was like with pain and learn strategies that can help them in the process.
- In Chapter 2, entitled "Pain System," patients learn to understand that although pain is defined as a sensation, ultimately it is not, and rather becomes a perception. This in turn includes what is thought, felt, and believed about the situation.
- In Chapter 3, entitled "Alarm System," patients understand how the alarm system is activated via a detailed process involving neurons, synapses, conduction to the medulla, and processing at the cortical level in the presence of pain.
- Chapter 4, entitled "Extra Sensitivity Altered Alert System," aims to make the patient aware that their nerve cells become more sensitive in the presence of injury or pathology. This process is influenced by factors external to the injury, such as stress, fear, and the perception of pain itself, causing the tissues or organs surrounding the injury to trigger the alarm system as if it were a loudspeaker, leading to hypersensitivity.
- In Chapter 5, entitled "Pain Defenders," patients experience a new sense of pain. The pain can be compared to a big wolf or wild animal attacking the individual, wherein the individual's systems are activated to protect them from the threat and thus the brain makes survival-related decisions.
- In Chapter 6, entitled "Your Fatigue, Anxiety, and Stress," patients understand the function of cortisol and its effect on the sympathetic, parasympathetic, immune, and endocrine nervous systems. Additionally, they understand why living with the constant threat of chronic and persistent pain activates their systems to produce stress-related chemicals, which in turn cause them to experience related symptoms, such as depression, mood swings, changes in appetite, memory problems, weight gain, insomnia, fatigue, and anxiety.
- Chapter 7, entitled "Current Treatment Models," aims to make the patient recognize their fear as a powerful motivator that could help them find new strategies to understand their pain and its treatment, making them consider that they own this process and that they are the owners of their own decisions.
- In Chapter 8, titled "Goals and Achievements," patients understand that pain stems from sensations and that receptors transmit these sensations. Ideally, patients can be made aware at this point that there is evidence that education, knowledge, and understanding include strategies to help them improve and that exercise is important to turn off the alarm system.

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- In Chapter 9, entitled "Emphasis and Pain Differentiation," the patient understands that pain does not mean there is damage and that their pain can be classified according to some characteristics as follows: nociceptive, nociplastic, and neuropathic.

Control intervention

The pharmacological treatment and indications will be evaluated by a doctor specialized in palliative care and pain. In particular, pharmacological treatment will be considered for both groups. Patients will be instructed to follow protocols established by the clinic: use of nonsteroidal anti-inflammatory drugs in the first instance for mild pain; tramadol at a maximum dose of 400 mg, codeine, or tapentadol for moderate pain; and opioids based on availability and use in Colombia, including morphine, oxycodone, hydromorphone, methadone, fentanyl (parenteral and transdermal use), and buprenorphine (transdermal use) for severe pain.

The PNE group will also be advised pharmacological modulation by the attending physician.

Community and expert participation

To organize the chapters, we worked with patients who served on the board of a foundation working for palliative care in the city of Cali and cancer experts for decision-making in consolidating the chapters as well as the feelings and concerns that arise while explaining them.

Results

The measures of outcomes to be included were based on the pain assessment guideline by IMMPACT recommendations (31) as well as from the reports generated when working with patients with cancer (11).

As the primary outcome, the impact of pain is assessed using the BPI, and all secondary outcome measures are presented in Table 1. In particular, an assessment at baseline and 10 weeks after the intervention is considered. BPI is a self-administered questionnaire containing two dimensions: one related to pain intensity and the other to the effect of pain on the patient's activities of daily living. This is rated on a 10-point scale. Higher scores indicate more severe pain (32).

The Visual Analog Pain Scale is used to measure pain intensity on a 10-cm line (total score: 0–10; 0 = no pain and 10 = severe pain). Higher scores indicate a worse result (33).

Secondary measures

Central sensitization

The Central Sensitization Inventory is used for determining central sensitization. This scale is used to identify patients with symptoms related to central sensitization and has two sections: Section A comprises 25 questions about central sensitization syndrome symptoms,

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and Section B assesses the patient's condition in relation to their diagnosis. The patient answers the 25 questions in Section A with a score of 0–4. The total score is between 0 and 100. Scores of >40 indicate central sensitization (34).

Catastrophizing

The Pain Catastrophizing Scale is a 13-item self-administered questionnaire measuring three items of perceived pain intensity (rumination, magnification, and feeling helpless). Participants indicate the extent to which they agree with statements about their pain as 0, strongly disagree; 1, to a mild degree; 2, to a moderate degree; 3, to a great extent; and 4, all the time. It has three subscales that score rumination, magnification, and helplessness. All subscale scores are added to give a total score from 0 to 52. Higher scores indicate that the participant thinks more about the pain and feels helpless (35).

Kinesiophobia

The Tampa Scale is used to assess the fear of pain and movement. It comprises 11 items that are answered on a 4-point Likert scale. Total scores for each scale range from 11 to 44, with higher scores indicating a greater fear of pain and movement (36).

Depression

The Beck Depression Inventory will be used to assess the state of depression. It contains 21 categories measuring physical, emotional, cognitive, and motivational symptoms, and each category is scored between 0 and 3. The patient is then asked to select the most appropriate category. The score increases progressively from no symptoms to severe symptoms (0–10 points, no depression; 11–17 points, mild depression; 18–23 points, moderate depression; ≥24: severe depression) (37).

Neuropathic pain

The DN4 scale will be used to assess neuropathic pain, and it scores 4 questions out of 10 to determine the presence of neuropathic pain (38).

Cognitive function

The MoCA assessment will be used for assessing cognitive impairment, and it consists of 19 items and 8 cognitive domains that assess skills such as visuo-spatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation; it can have a maximum score of 30, with 25 or 26 being the cut-off points for cognitive impairment (39).

Quality of life

The widely used questionnaire European Organization for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30) is used to assess the quality of life and includes five functional scales (physical, role, cognitive, emotional, and social functioning), a global quality of life scale, three symptom scales (fatigue, nausea, and pain), and six individual items (loss of appetite, diarrhea, dyspnea, constipation, insomnia, and economic impact). On the functional and global quality of life scales, a higher score indicates better health. On symptom scales, a higher score indicates a higher symptom burden (40).

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Sleep quality

The Pittsburgh Sleep Quality Index is one of the most reliable tests for defining sleep quality and its disorders. It contains a total of 19 questions. Questions are grouped into seven scoring areas, each ranging from 0–3 points (41).

Functional capacity

A 6-minute walk test is used to determine exercise tolerance and functional status. The distance covered in meters in the last 6 minutes is measured (42,43).

The Timed Get-up-and-Go test was developed as a predictor of falls and as a measure of functional capacity. In this test, the participant sits in a chair, stands up, walks for 3 m, and sits down again. The test runtime is calculated (44).

Manual grip strength

This is a marker of nutritional status as well as the morbidity and mortality associated with the pathological lesion. It will be measured using a dynamometer to establish the value of grip strength in kilograms (45).

Table 1. Description of the measurements

VARIABLES	DIMENSIONS	INDICATOR	VALUE
Sociodemographic features	Age	How many years old	• Age: ≥45 years
	Sex	Female or male	• Female or male
	Educational level	Level of schooling	• Incomplete elementary school education, complete elementary school education, incomplete high school education, complete high school education, technical education, technological college-level education, university-level education, and postgraduate
	Provenance	Urban or rural	• Rural or urban
	Affiliation regimen	Subsidized, contributory, or linked	• Contributory, subsidized, linked, or specialized
	Diagnostic period	Months	Months after the diagnosis
	Pharmacological treatment	Medication use	Use of medications and dosage

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	Adjuvant treatment	Presence of adjuvant treatment	Chemotherapy or radiotherapy Frequency of administration
Physical measurements	Vital signs	Vital sign parameters	Heart rate Oxygen (O_2) saturation Respiratory frequency Blood pressure
Impact of pain	Brief pain questionnaire	BPI	1–22 items to evaluate the degree of pain and its severity based on pain history
Presence of pain	Numerical assessment of pain	Numerical pain indicator	Numerical: score from 1 to 10 in pain Categorical: None, mild, moderate, or severe
Cognitive Function	Cognitive dimensions	Score range 0–30	Score on the MoCA test Categorical: Normal, mild impairment, moderate impairment, or severe impairment
Depression	Beck Index	Presence of 0–21 items	Numerical: Score obtained in the test Categorical: None, Mild, Moderate, and Severe
Kinesiophobia	Tampa Scale	11 items Score range from 1–4	Numerical: 1–4 Categorical: None, Mild, Moderate, and Severe
Catastrophizing	Catastrophizatio n scale	13 items Score range from 1–4	Three factors: rumination, magnification, and hopelessness (scored from 1 to 4)
Central sensitization	Central sensitization inventory	25 points Score range 1–4.	This evaluates 25 pain-related symptoms, with scores from 0 to 100 Categorical: Yes or No
Neuropathic pain	Scale DN4	Score range 0–10 points	This evaluates four questions with possibility to score up to 10 points in order to determine the presence of neuropathic pain Categorical: Yes or No
Quality of sleep	Pittsburgh Sleep Quality Index.	Score range 0–21 points	Categorical: Good, Fair, or Poor

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Quality of life	EORTC QLQ-C30	30 questions Score range 1–4	Assessment of the quality of life of patients with cancer
Functional capacity	TC6M 6-minute walk test.	Meters traveled	Meter indicator Heart rate Borg: Dyspnea; Fatigue
	Timed Get-up-and-Go test	Time in seconds	Time in seconds
	Manual dynamometry	Force in kilograms	Force in kilograms

Data analysis

A statistical analysis will be performed based on the following steps:
A flowchart will be prepared to describe the process of patient recruitment and follow-up throughout the study based on the 2010 CONSORT Declaration. The flowchart will include the number of patients and reasons for exclusion, the number of patients randomized and assigned to the study units, and the losses and interruptions in the interventions within the groups (22).
An exploratory analysis will be performed to assess the data behavior and the key assumptions required for the application of a particular test (normality, linearity, or homoscedasticity); in addition, the presence of errors and biases in the data collected, the presence of anomalies, and all missing data will be assessed.
The sociodemographic and clinical variables will be analyzed in addition to those related to the patients' baseline oncological process at inclusion in the study by plotting their baseline characteristics according to the measurement scale of each variable using measures of central tendency, dispersion, frequency tables, and 95% confidence intervals. This analysis will be performed for each group and then subjected to homogeneity hypothesis tests based on the nature of each variable.
A univariate analysis of each described variable will then be performed considering the results before and after the intervention. In addition, we will perform a bivariate analysis to determine the correlation between dependent and independent variables and a multivariate analysis to examine the interaction and relationships between them.
Pain scores on the pain rating scale, quality of life scores, and physical function test scores will be considered as the primary outcomes; the difference in their mean values between groups will be analyzed using the Student's t-test, and the difference within each group will be analyzed using the paired t-test. The interpretation of effect size will be performed using the Cohen's D index or coefficient, which classifies effect size as small (0.2–0.49), moderate (0.5–0.8), or large (>0.8).
A multivariate analysis will be performed using linear regression for the dependent variables, such as pain, cognitive function, depression, kinesiophobia, catastrophizing, pain impact, central sensitization, neuropathic pain, sleep quality, quality of life, and physical function. If the criteria of normality, homoscedasticity, and independence of the variable are not met, the possibility of transforming the variable will be evaluated. Once the

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regression has been performed, we will assess whether the model represents or resembles the observed data. To control for potential confounders, the variables previously considered as confounders will be adjusted, such as pharmacological dose, presence of adjuvant treatment, and previous hospitalizations for pain. In addition, the possibility of a change in the effect between these variables will be assessed.
The analysis will be carried out according to the protocol based on the specification for who completed the intervention, but the analysis will also be estimated based on the intention to treat the whole group.

Data security and management

Participant data will be stored in a secure database in accordance with ethical considerations and good health practices. Each patient will be assigned an identifier to protect confidentiality. The information will be reviewed to determine the validity of the data. The data will then undergo additional checks to ensure that the information encrypted matches the information received.

Test monitoring

A pilot study will be initiated to determine the dosage for the different questionnaires to be used and the time and response capacity of the patients.

The material used during the intervention will be tested and reviewed by experts as well as patient representatives to verify the understanding of each of the constructed chapters.

Ethics and diffusion

In this research, all participants will be provided with reasonable information about the objectives, methods, possible conflicts of interest, estimated benefits, foreseeable risks, and inconveniences arising from this investigation. Participants sign an informed consent form that clearly explains the procedure to be performed, the nature of the procedures, the benefits and risks they face, their ability to choose freely, and that everything will be performed without coercion. It will also be made clear that if the individual does not agree to participate, they can withdraw their consent at any time.
This project was submitted on October 8, 2021 for approval and review by the Ethics and Bioethics Committee of the University of Santiago de Cali, and it was approved in minutes 16 of October 8, 2021. It was also submitted to the ethics committee at the Clínica de Occidente, Angiografía de Occidente and was approved in the minutes of November 25, 2021.

Patient and public involvement

Due to the characteristics of the intervention, work was done prior to its development on the validation of the content provided in the manual with some patients with similar characteristics to verify that the content included in each of the chapters is consistent and is understood by the patients. At the end of each session, questions are asked about the main

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concepts of each of the chapters. The manual developed will be available for consultation, and public dissemination sessions of the results will be held open to the public with the aim of publicizing the results.

Dissemination of results

The research team is committed to the full publication of the results of this study. The results will be reported according to CONSORT guidelines and are intended to be published in high profile journals. In the research, there is a component related to social acquisition and knowledge dissemination, and these results are expected to be presented to patient representatives and the various palliative care committees.

Contributorship statement

Ordoñez- Mora LT: Research idea, development of the intervention material, construction of materials and methods, statistical validation, review and approval of the manuscript.

Rosero ID: Development of the intervention material, construction of materials and methods, statistical validation, review and approval of the manuscript.

Morales-Osorio MA: Development of the intervention material, construction of materials and methods, statistical validation, review and approval of the manuscript.

Guil R: Construction of materials and methods, statistical validation, review and approval of the manuscript.

Quintero Jordan G: Development of the intervention material, review and approval of the manuscript.

Agudelo Jimenez J: Construction of materials and methods, statistical validation, review and approval of the manuscript.

Gonzalez Ruiz K: Construction of materials and methods, statistical validation, review and approval of the manuscript.

Avila-Valencia JC: Construction of materials and methods, statistical validation, review and approval of the manuscript.

Competing interests: Competing interests are not declared.

Conflict of interest: No conflicts of interest are declared by the authors or the funding entity.

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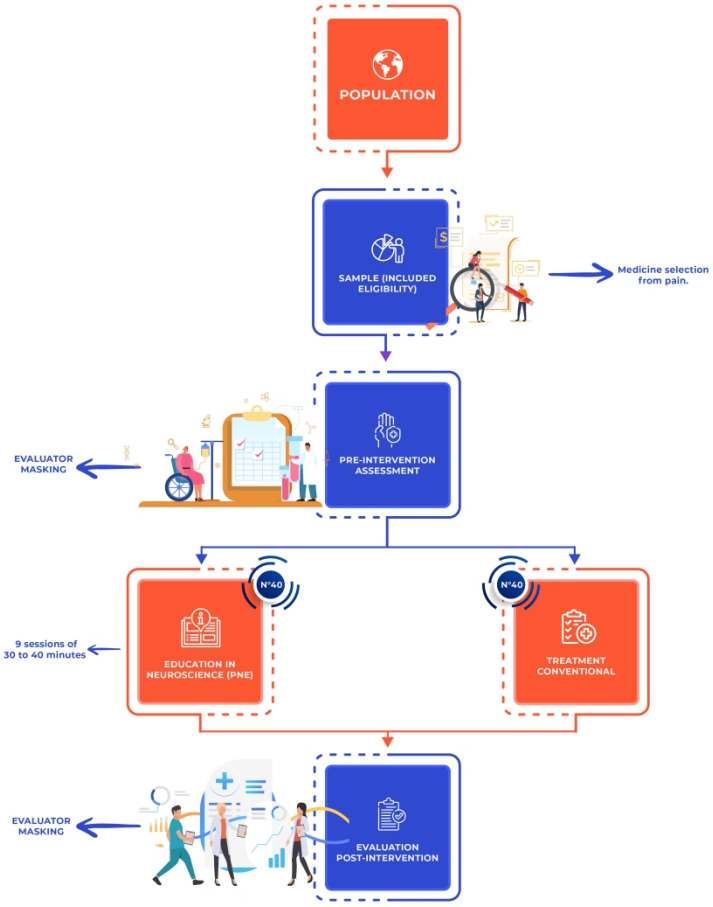

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17

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Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	13
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	2
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	4

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		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	5
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5

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Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12

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Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
Data monitoring: interim analysis	#21b	Description 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	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	na
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	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	12

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Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	18
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	12
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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NEUROCANTRIAL: Study Protocol for a Randomized Controlled Trial of a Pain Neuroscience Education Program in Adults with Cancer Pain

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NEUROCANTRIAL: Study Protocol for a Randomized Controlled Trial of a Pain Neuroscience Education Program in Adults with Cancer Pain

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ABSTRACT

Introduction:

Pain is the second most frequent symptom reported in cancer patients among the main reasons for consultation. The incorporation of educational modalities in pain intervention processes has been suggested. This study aims to examine the efficacy of neuroscience pain education (PNE) in relation to pain, biopsychosocial variables, and functional capacity in comparison with conventional treatment. It is hypothesized that an intervention based on neuroscience-based pain education (PNE) achieves better outcomes than conventional management, in terms of pain, biopsychosocial variables, and functional capacity in adults with oncologic pain.

Methods

This will be a single-blind, controlled clinical trial in which two groups will be compared using changes in pain as the primary measure. The first group will receive conventional treatment in addition to PNE, and participants will undergo an intervention of nine sessions (1 session per week, for a total of nine weeks), each lasting 30–40 minutes. Specifically, these sessions will teach biophysiological elements using metaphors that allow the adoption of these concepts related to pain. The second group will receive conventional treatment (pharmacological treatment). For this study, a sample size calculation was made based on the background, where 80 adults with oncologic pain were required. An initial evaluation will be made to establish the baseline characteristics, and then, according to the randomization, the assignment to the PNE group or the control group will be made, and the two groups will be

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summoned again. Ten weeks later, for the -intervention evaluation, the statistical analysis plan will be established by protocol and by intention-to-treat.

Ethical considerations

This protocol complies with all ethical considerations. It also was approved by the Ethics and Bioethics Committee of the University and the participating clinic. The authors commit to presenting the study's results.

Clinical trial registration

NCT05581784

Strengths and limitations of this study

- Patients from a pain medicine and palliative care unit will be recruited in accordance with their applicability in clinical practice.
- This study will involve the development of educational material according to the theoretical references for addressing the patient.
- Functional capacity measurements, such as a 6-minute walk distance and manual pressure strength, which can determine the effect of this intervention on patients, will be included.

Limitations:

- The calculated sample may not be reached due to difficulties in obtaining patients.
- There may be losses associated with comorbidities due to the stage of the cancer and adjuvant processes.

Keywords: Pain; Neoplasms; Cancer Pain; Pain Management; Health Education

INTRODUCTION

In 2021, about 5,562 new cases of cancer were reported in Colombia, of which breast cancer was the second most frequent type of cancer in women (16.3% of new cases), followed by uterus cancer (13.7% of new cases), while in men, the second type of cancer with the highest number of new cases was prostate cancer (14.5% new cases) (1), observing an increase in cases as age increases. In turn, pain is a common symptom reported by cancer patients. A previous meta-analysis reported pain in 59%, 64% and 33% of patients undergoing cancer treatment, in patients with advanced or terminal disease and after curative treatment, respectively (2).

According to the International Association for the Study of Pain, pain is defined as an unpleasant sensory and emotional experience associated with, or resembling, actual or potential tissue damage (3). In particular, it is one of the most frequent alterations caused by toxicity, surgery, radiation, among others, after cancer treatment (4). Oncologic pain poses a difficulty due to the complexity of the disease and the subjective experience of pain. In addition, during cancer treatment, pain mechanisms may appear due to different causes, the first one possibly due to tissue involvement (nociceptive pain) and the second one to nerve

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damage (neuropathic pain), and at other times some mechanisms are characterized by altered processing without clear evidence of persistent tissue damage (non-disciplinary pain) (5). In addition, it is closely related to decreased quality of life and increased self-perceived disability (6).

Pain is one of the most feared and annoying symptoms among these patients (2,7). Another study reported that 5%–10% of cancer survivors have severe chronic pain that significantly impairs their function (8). A study of patients with breast cancer reported pain in 25.3%, 18.7%, 15.4%, and 40.6% of them, with neuropathic, nociceptive, nociplastic, and mixed pain predominating, respectively (9). Notably, this etiology of cancer pain is variable and can be attributed to postoperative syndromes. In addition, adjuvant therapies can have adverse effects. For example, chemotherapy can cause symmetrical painful numbness and burning and tingling in hands and feet. It can also cause osteoporosis, osteonecrosis, arthralgia, and myalgia (8,10). Radiotherapy can have serious side effects caused by ionizing radiation, the induction of reactive oxygen species production, and damage to DNA and regulatory proteins in cells. This leads to apoptosis and increased inflammation in exposed and adjacent cells due to radiation-induced bystander effects, potentially leading to plexopathies and osteoradionecrosis (11,12). Likewise, the maintenance therapy used, such as that involving aromatase inhibitors, may cause arthralgia and myalgia (13).

The relevant literature in oncology shows that quality of life and survival rate are associated with early and effective palliative care, including pain management, establishing recommendations for the inclusion of interventions oriented to non-pharmacological approaches such as education (14). Future studies are required to evaluate these new treatment approaches (15) that include educational aspects within the intervention process. Accordingly, pain neuroscience education (PNE) describes how the nervous system interprets information from tissues via peripheral sensitization, central sensitization, synaptic activity, and cortical processing (16). This innovative educational approach is effective in changing beliefs about pain and improving pain management strategies and health outcomes in a variety of adult populations with chronic pain (17-19).
Regarding previous studies on PNE in cancer, a quasi-experimental study was conducted by Pas R (20) with the aim of describing the innovative educational component of PNE. The study showed a significant decrease in pain intensity ($p = 0.001$) compared with baseline. Another study conducted by Manfuku (21), compared conventional biomedical education (BME) ($n = 51$) with PNE ($n = 51$) and reported scores based on the brief pain inventory (BPI) questionnaire. The findings show that scores for catastrophizing and central sensitization improved with a statistically significant difference between PNE and BME (all, $p < 0.05$), and effect sizes for BPI intensity were moderate ($r = 0.31$). Furthermore, a study carried out by Groef (22) aimed to investigate the effectiveness of PNE intervention for the treatment and prevention of pain and for improvement in physical, emotional, and work-related functioning after breast cancer surgery, compared with biomedical education. The results of this protocol were recently published by Dams (23) finding that patients who received PNE after 6 months of breast cancer surgery showed a decreased sensitivity to pressure pain in the trunk, compared with the biomedical education group. However, no significant differences were found between the types of education received.

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The present study aims to examine the effectiveness of PNE in relation to pain, biopsychosocial variables, and functional capacity compared with conventional management in people with prostate, uterine, and breast cancer. This will be assessed through a single-blind randomized controlled clinical trial. It is hypothesized that an intervention based on neuroscience-based pain education (PNE) achieves better outcomes than conventional management in terms of pain, biopsychosocial variables, and functional capacity in adults with oncologic pain.

METHODS AND ANALYSIS

Trial design and context

A randomized controlled parallel-group clinical trial will be conducted with blinding of the researchers. The recruitment will be conducted between February 2023 and March 2024 at the clinical medicine and palliative care unit of a tertiary level clinic in the city of Cali and the Health Department of the University of Santiago de Cali, Colombia.

This proposed quantitative experimental controlled clinical trial will be conducted in accordance with the SPIRIT guidelines for clinical trial protocols (24) and CONSORT guidelines for clinical trials (25) and outcomes extension (26). This trial is registered with ClinicalTrials.gov Identifier: NCT05581784.

Eligibility criteria

The study will include male patients diagnosed with stage III and IV prostate cancer and female patients diagnosed with stage III and IV uterine and breast cancer according to the TNM staging system stands for Tumour, Node, Metastasis (27). Includes persons with an initial pain rating of 3 as assessed with VAS.

Inclusion criteria:

- Patients with a life expectancy of >3 months based on the Karnofsky Scale, Eastern Cooperative Oncology Group Scale, Palliative Prognostic Score, or Palliative Prognostic Index.
- Those who provide informed consent.
- Those who are able to establish communication with the team.
- Those presenting with scores demonstrating preserved cognitive function on a Montreal Cognitive Assessment (MoCA) scale with a minimum score of 25.
- Those who are able to stand upright and walk independently or with external assistance.

Exclusion criteria:

- Patients with surgeries scheduled in the next 3 months.
- Those with impairment of visual and auditory sensory systems (deafness or blindness).
- Those with acute traumatic injury.
- Those with uncontrolled arrhythmias or heart disease.
- Those with severe acute respiratory failure or uncontrolled respiratory pathology.

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- Those with recent fractures in the last month.
- Patients diagnosed with previous rheumatic diseases (before a cancer diagnosis).

Participant selection, recruitment, and consent

Participants will be identified from the lists of patients in the pain medicine and palliative care ward and selected according to the abovementioned selection criteria. The initial examination and evaluation were carried out by a member of the research team, and potentially eligible participants were approached and recruited by the attending physician after consultation. All eligible patients received a document with information and explanations about the study. Participants were then asked to fill out a separate informed consent form that was previously approved by all institutions involved in the study. After their approval, an evaluation process was conducted to determine the baseline before randomization and assignment to one of the study groups. The second assessment was performed at 10 weeks. The flow chart of the study is shown in Figure 1 and Appendix 1.

Figure 1. Flow chart of the study

Sample size

To calculate the sample size, we used the results of the preliminary study by Manfuku (21) who used an educational intervention in cancer patients with pain to determine the process of self-care and medication management in cancer. Manfuku used the BPI as the main measure of pain intensity. The Gpower 3.1 program was used based on an assumption of a mean of 0.51 (±1) in group 1 and 1.69 (±2.2) in group 2, with a difference of −1.18, i.e. (t test), assuming pain intensity as the main variable, a power of 90% and an alpha type error of 5% and one-tailed adjustment was determined. Overall, 37 patients must be enrolled in each group, and to adjust for a 10% loss, 41 patients are required for each group.

Allocation and randomization

To reduce selection bias, random number randomization with a computer-generated 1:1 assignment in permuted blocks of four to eight patients will be performed. An external researcher will randomly assign patients to one of the two treatment groups after obtaining informed consent and performing a baseline assessment. In order to allocate each patient to the experimental or control group, two strata randomization (age groups, <60 years and older patients) will be also performed to reduce potential confounders and selection bias. Furthermore, the research team members performing the statistical analysis will be blinded.

Blinding

To ensure a reduction in information bias during patient follow-up, the principal investigator is blinded. In addition, the post-interventional examinations are self-managed by people who depend on a physiotherapist and carried out for others by an external person trained and

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specialized in this field. This is done in such a way that the assessor is unaware of the patient's assignment, and the patient is asked not to reveal the group to which they have been assigned at any time. To further reduce the bias, both the therapist conducting the assessment and the therapist conducting the intervention program will be different people.

Intervention group

The intervention group will undergo an intervention based on PNE, which is an educational model for teaching pain biopsychosocial. It has been recognized as a compelling approach for managing chronic pain that adopts elements of user-based learning through the use of metaphors and examples (28). In addition, PNE is aimed at changing the understanding of what pain really is, the effects it has, and the biological processes that guide it. It refers to a theoretical framework for pain treatments, and the main goal of the approach is to change the conceptualization of pain as an indicator of tissue damage or pathology, progressively leading to a change in attitudes and the initiation of movements and activities in everyday life (29). This model is based on various educational interventions (19) and has been defined using the following terms: Explaining Pain (30), Therapeutic Neuroscience Education, and PNE. (31). Notably, PNE is increasingly used as part of physiotherapy treatment in patients with chronic, non-disciplinary, and neuropathic pain. A comprehensive biopsychosocial clinical assessment is recommended before PNE to adequately explain the neurophysiology of pain and biopsychosocial interactions, while ensuring that this process is patient-centered (29).

The clinical trial will comprise nine sessions over a period of 10 weeks, each lasting 30–40 minutes. These sessions will be scheduled weekly. Interventions will be scheduled on an individual or group basis (if possible). Supporting slides will be used to explain the content, and questions will be allowed throughout the sessions.

The content of the sessions will include elements based on book illustrations explaining pain, the second edition of the Spanish version (27) whose content will correspond to http://www.paininmotion.be/ (32); Louw's manual (33), and the explanation of pain in patients with cancer (7) which will be adapted from the use of examples and metaphors. For the organization of material corresponding to this intervention, some phases will be generated.

The sessions will be based on a guide with nine chapters organized as follows:

- Chapter 1, entitled "Living with Pain," conceptualizes the importance of pain as a defense system and functioning of the organism. Patients will reflect on what their life was like with pain and learn strategies that can help them in the process.
- In Chapter 2, entitled "Pain System," patients learn to understand that although pain is defined as a sensation, ultimately it is not, and rather becomes a perception. This in turn includes what is thought, felt, and believed about the situation.
- In Chapter 3, entitled "Alarm System," patients understand how the alarm system is activated via a detailed process involving neurons, synapses, conduction to the medulla, and processing at the cortical level in the presence of pain.
- Chapter 4, entitled "Extra Sensitivity Altered Alert System," aims to make the patient aware that their nerve cells become more sensitive in the presence of injury or pathology. This process is influenced by factors external to the injury, such as stress, fear, and the perception of pain itself, causing the tissues or organs surrounding the

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injury to trigger the alarm system as if it were a loudspeaker, leading to hypersensitivity.

- In Chapter 5, entitled "Pain Defenders," patients experience a new sense of pain. The pain can be compared to a big wolf or wild animal attacking the individual, wherein the individual's systems are activated to protect them from the threat and thus the brain makes survival-related decisions.
- In Chapter 6, entitled "Your Fatigue, Anxiety, and Stress," patients understand the function of cortisol and its effect on the sympathetic, parasympathetic, immune, and endocrine nervous systems. Additionally, they understand why living with the constant threat of chronic and persistent pain activates their systems to produce stress-related chemicals, which in turn cause them to experience related symptoms, such as depression, mood swings, changes in appetite, memory problems, weight gain, insomnia, fatigue, and anxiety.
- Chapter 7, entitled "Current Treatment Models," aims to make the patient recognize their fear as a powerful motivator that could help them find new strategies to understand their pain and its treatment, making them consider that they own this process and that they are the owners of their own decisions.
- In Chapter 8, titled "Goals and Achievements," patients understand that pain stems from sensations and that receptors transmit these sensations. Ideally, patients can be made aware at this point that there is evidence that education, knowledge, and understanding include strategies to help them improve and that exercise is important to turn off the alarm system.
- In Chapter 9, entitled "Emphasis and Pain Differentiation," the patient understands that pain does not mean there is damage and that their pain can be classified according to some characteristics as follows: nociceptive, nociplastic, and neuropathic.

Control intervention

The pharmacological treatment and indications will be evaluated by a doctor specialized in palliative care and pain. In particular, pharmacological treatment will be considered for both groups. Patients will be instructed to follow protocols established by the clinic: use of nonsteroidal anti-inflammatory drugs in the first instance for mild pain; tramadol at a maximum dose of 400 mg, codeine, or tapentadol for moderate pain; and opioids based on availability and use in Colombia, including morphine, oxycodone, hydromorphone, methadone, fentanyl (parenteral and transdermal use), and buprenorphine (transdermal use) for severe pain.

The PNE group will also be advised pharmacological modulation by the attending physician.

Community and expert participation

To organize the chapters, we worked with patients who served on the board of a foundation working for palliative care in the city of Cali and cancer experts for decision-making in consolidating the chapters as well as the feelings and concerns that arise while explaining them.

Outcomes

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The measures of outcomes to be included were based on the pain assessment guideline by IMMPACT recommendations (34) as well as from the reports generated when working with patients with cancer (12).

As the primary outcome, the impact of pain is assessed using the BPI, and all secondary outcome measures are presented in Table 1. In particular, an assessment at baseline and 10 weeks after the intervention is considered. BPI is a self-administered questionnaire containing two dimensions: one related to pain intensity and the other to the effect of pain on the patient's activities of daily living. This is rated on a 10-point scale. Higher scores indicate more severe pain (35).

The Visual Analog Pain Scale is used to measure pain intensity on a 10-cm line (total score: 0–10; 0 = no pain and 10 = severe pain). Higher scores indicate a worse result (36).

Secondary measures

Central sensitization

The Central Sensitization Inventory is used to identify patients with symptoms related to central sensitization and has two sections: Section A comprises 25 questions about central sensitization syndrome symptoms, and Section B assesses the patient's condition in relation to their diagnosis. The patient answers the 25 questions in Section A with a score of 0–4. The total score is between 0 and 100. Scores of >40 indicate central sensitization (37).

Catastrophizing

The Pain Catastrophizing Scale is a 13-item self-administered questionnaire measuring three items of perceived pain intensity (rumination, magnification, and feeling helpless). Participants indicate the extent to which they agree with statements about their pain as 0, strongly disagree; 1, to a mild degree; 2, to a moderate degree; 3, to a great extent; and 4, all the time. It has three subscales that score rumination, magnification, and helplessness. All subscale scores are added to give a total score from 0 to 52. Higher scores indicate that the participant thinks more about the pain and feels helpless (38).

Kinesiophobia

The Tampa Scale is used to assess the fear of pain and movement. It comprises 11 items that are answered on a 4-point Likert scale. Total scores for each scale range from 11 to 44, with higher scores indicating a greater fear of pain and movement (39).

Depression

The Beck Depression Inventory will be used to assess the state of depression. It contains 21 categories measuring physical, emotional, cognitive, and motivational symptoms, and each category is scored between 0 and 3. The patient is then asked to select the most appropriate category. The score increases progressively from no symptoms to severe symptoms (0–10 points, no depression; 11–17 points, mild depression; 18–23 points, moderate depression; ≥24: severe depression) (40).

Neuropathic pain

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The DN4 scale will be used to assess neuropathic pain, and it scores 4 questions out of 10 will be used to determine the symptomatology related to neuropathic pain (41).

Cognitive function

The MoCA assessment will be used for assessing cognitive impairment, and it consists of 19 items and 8 cognitive domains that assess skills such as visuo-spatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation; it can have a maximum score of 30, with 25 or 26 being the cut-off points for cognitive impairment (42).

Quality of life

The widely used questionnaire European Organization for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30) is used to assess the quality of life and includes five functional scales (physical, role, cognitive, emotional, and social functioning), a global quality of life scale, three symptom scales (fatigue, nausea, and pain), and six individual items (loss of appetite, diarrhea, dyspnea, constipation, insomnia, and economic impact). On the functional and global quality of life scales, a higher score indicates better health. On symptom scales, a higher score indicates a higher symptom burden (43).

Sleep quality

The Pittsburgh Sleep Quality Index is one of the most reliable tests for defining sleep quality and its disorders. It contains a total of 19 questions. Questions are grouped into seven scoring areas, each ranging from 0–3 points (44).

Functional capacity

A 6-minute walk test is used to determine exercise tolerance and functional status. The distance covered in meters in the last 6 minutes is measured (45,46).

The Timed Get-up-and-Go test was developed as a predictor of falls and as a measure of functional capacity. In this test, the participant sits in a chair, stands up, walks for 3 m, and sits down again. The test runtime is calculated (47).

Manual grip strength

This is a marker of nutritional status as well as the morbidity and mortality associated with the pathological lesion. It will be measured using a dynamometer to establish the value of grip strength in kilograms (48).

Pharmaceuticals

The establishment of the baseline of the drugs used for pain, as well as the type, dose, and frequency of consumption will be generated.

Table 1. Description of the measurements

VARIABLES	DIMENSIONS	INDICATOR	VALUE

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Sociodemographic features	Age Sex Educational level Provenance Affiliation regimen	How many years old Female or male Level of schooling Urban or rural Subsidized, contributory, or linked	• Age: ≥40 years • Female or male • Incomplete elementary school education, complete elementary school education, incomplete high school education, complete high school education, technical education, technological college-level education, university-level education, and postgraduate • Rural or urban • Contributory, subsidized, linked, or specialized
	Diagnostic period	Months	Months after the diagnosis
	Pharmacological treatment	Medication use	Use of medications and dosage
	Adjuvant treatment	Presence of adjuvant treatment	Chemotherapy or radiotherapy Frequency of administration
Physical measurements	Vital signs	Vital sign parameters	Heart rate Oxygen (O_2) saturation Respiratory frequency Blood pressure
Impact of pain	Brief pain questionnaire	BPI	1–22 items to evaluate the degree of pain and its severity based on pain history
Presence of pain	Numerical assessment of pain	Numerical pain indicator	Numerical: score from 1 to 10 in pain Categorical: None, mild, moderate, or severe
Cognitive Function	Cognitive dimensions	Score range 0–30	Score on the MoCA test Categorical: Normal, mild impairment, moderate impairment, or severe impairment
Depression	Beck Index	Presence of 0–21 items	Numerical: Score obtained in the test

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			Categorical: None, Mild, Moderate, and Severe
Kinesiophobia	Tampa Scale	11 items Score range from 1–4	Numerical: 1–4 Categorical: None, Mild, Moderate, and Severe
Catastrophizing	Catastrophization scale	13 items Score range from 1–4	Three factors: rumination, magnification, and hopelessness (scored from 1 to 4)
Central sensitization	Central sensitization inventory	25 points Score range 1–4.	This evaluates 25 pain-related symptoms, with scores from 0 to 100 Categorical: Yes or No
Neuropathic pain	Scale DN4	Score range 0–10 points	This evaluates four questions with possibility to score up to 10 points in order to determine the presence of neuropathic pain Categorical: Yes or No
Quality of sleep	Pittsburgh Sleep Quality Index.	Score range 0–21 points	Categorical: Good, Fair, or Poor
Quality of life	EORTC QLQ-C30	30 questions Score range 1–4	Assessment of the quality of life of patients with cancer
Functional capacity	TC6M 6-minute walk test.	Meters traveled	Meter indicator Heart rate Borg: Dyspnea; Fatigue
	Timed Get-up-and-Go test	Time in seconds	Time in seconds
	Manual dynamometry	Force in kilograms	Force in kilograms

Data analysis

A statistical analysis will be performed based on the following steps:
A flowchart will be prepared to describe the process of patient recruitment and follow-up throughout the study based on the CONSORT Declaration. The flowchart will include the number of patients and reasons for exclusion, the number of patients randomized and

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assigned to the study units, and the losses and interruptions in the interventions within the groups (24).

An exploratory analysis will be performed to assess the data behavior and the key assumptions required for the application of a particular test (normality, linearity, or homoscedasticity); in addition, the presence of errors and biases in the data collected, the presence of anomalies, and all missing data will be assessed.

The sociodemographic and clinical variables will be analyzed in addition to those related to the patients' baseline oncological process at inclusion in the study by plotting their baseline characteristics according to the measurement scale of each variable using measures of central tendency, dispersion, frequency tables, and 95% confidence intervals. This analysis will be performed for each group and then subjected to homogeneity hypothesis tests based on the nature of each variable.

A univariate analysis of each described variable will then be performed considering the results before and after the intervention. In addition, we will perform a bivariate analysis to determine the correlation between dependent and independent variables and a multivariate analysis to examine the interaction and relationships between them.

Pain scores on the Pain Rating Scale will be considered the primary outcomes and quality of life scores and physical function test scores are secondary variables; the difference in their mean values between groups will be analyzed using the Student's t-test, and the difference within each group will be analyzed using the paired t-test. The interpretation of effect size will be performed using the Cohen's D index or coefficient, which classifies effect size as small (0.2–0.49), moderate (0.5–0.8), or large (>0.8).

A multivariate analysis will be performed using linear regression for the dependent variables, such as pain, cognitive function, depression, kinesiophobia, catastrophizing, pain impact, central sensitization, neuropathic pain, sleep quality, quality of life, and physical function. If the criteria of normality, homoscedasticity, and independence of the variable are not met, the possibility of transforming the variable will be evaluated. Once the regression has been performed, we will assess whether the model represents or resembles the observed data. To control for potential confounders, the variables previously considered as confounders will be adjusted, such as pharmacological dose, presence of adjuvant treatment, and previous hospitalizations for pain. In addition, the possibility of a change in the effect between these variables will be assessed.

The analysis will be carried out according to the protocol based on the specification for who completed the intervention, but the analysis will also be estimated based on the intention to treat the whole group.

Data security and management

Participant data will be stored in a secure database in accordance with ethical considerations and good health practices. Each patient will be assigned an identifier to protect confidentiality. The information will be reviewed to determine the validity of the data. The data will then undergo additional checks to ensure that the information encrypted matches the information received.

Test monitoring

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A pilot study will be initiated to determine the dosage for the different questionnaires to be used and the time and response capacity of the patients.

The material used during the intervention will be tested and reviewed by experts as well as patient representatives to verify the understanding of each of the constructed chapters.

Ethics and diffusion

In this research, all participants will be provided with reasonable information about the objectives, methods, possible conflicts of interest, estimated benefits, foreseeable risks, and inconveniences arising from this investigation. Participants sign an informed consent form that clearly explains the procedure to be performed, the nature of the procedures, the benefits and risks they face, their ability to choose freely, and that everything will be performed without coercion. It will also be made clear that if the individual does not agree to participate, they can withdraw their consent at any time.
This project was submitted on October 8, 2021 for approval and review by the Ethics and Bioethics Committee of the University of Santiago de Cali, and it was approved in minutes 16 of October 8, 2021. It was also submitted to the ethics committee at the Clínica de Occidente, Angiografía de Occidente and was approved in the minutes of November 25, 2021.

Patient and public involvement

Due to the characteristics of the intervention, work was done prior to its development on the validation of the content provided in the manual with some patients with similar characteristics to verify that the content included in each of the chapters is consistent and is understood by the patients. At the end of each session, questions are asked about the main concepts of each of the chapters. The manual developed will be available for consultation, and public dissemination sessions of the results will be held open to the public with the aim of publicizing the results.

Dissemination of results

The research team is committed to the full publication of the results of this study. The results will be reported according to CONSORT guidelines and are intended to be published in high profile journals. In the research, there is a component related to social acquisition and knowledge dissemination, and these results are expected to be presented to patient representatives and the various palliative care committees.

Contributorship statement

Ordoñez- Mora LT: Research idea, development of the intervention material, construction of materials and methods, statistical validation, review and approval of the manuscript.

Rosero ID: Development of the intervention material, construction of materials and methods, statistical validation, review and approval of the manuscript.

Morales-Osorio MA: Development of the intervention material, construction of materials and methods, statistical validation, review and approval of the manuscript.

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Guil R: Construction of materials and methods, statistical validation, review and approval of the manuscript.

Quintero Jordan G: Development of the intervention material, review and approval of the manuscript.

Agudelo Jimenez J: Construction of materials and methods, statistical validation, review and approval of the manuscript.

Gonzalez Ruiz K: Construction of materials and methods, statistical validation, review and approval of the manuscript.

Avila-Valencia JC: Construction of materials and methods, statistical validation, review and approval of the manuscript.

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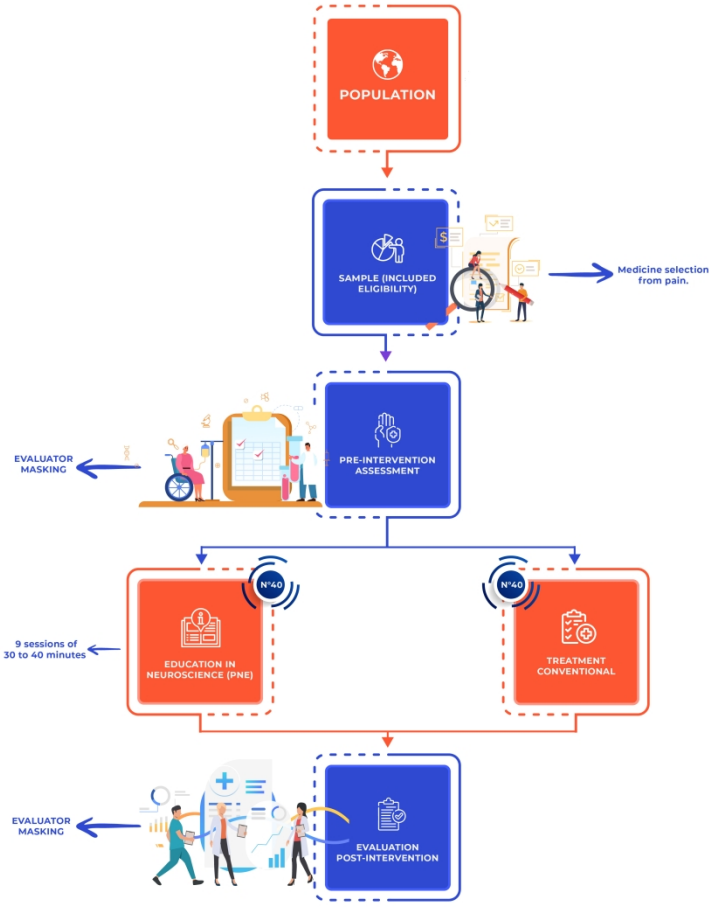

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Appendix 1. Diagram for recruiting and conducting interventions and evaluations according to SPIRIT Guidelines

STUDY PERIOD					
	Enrolment	Allocation	Post-Allocation		Close-out
Timepoint	$-t_1$	0	t_1	t_2	t_3
ENROLMENT					
Eligibility screen	X				
Informed consent	X				
Demographic characteristic	X				
Allocation		X			
INTERVENTIONS:					
PNE interventions					
Control (usual care)					
ASSESSMENTS:					
Baseline		X			
Primary pain measures		X		X	
Secondary variables		X		X	
Statistical Analysis					X

t1 Initial evaluation
t2 After 10 weeks

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17

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Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	13
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	2
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	4

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		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	5
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5

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Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12

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Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
Data monitoring: interim analysis	#21b	Description 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	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	na
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	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	12

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Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	18
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	12
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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NEUROCANTRIAL: Study Protocol for a Randomized Controlled Trial of a Pain Neuroscience Education Program in Adults with Cancer Pain

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NEUROCANTRIAL: Study Protocol for a Randomized Controlled Trial of a Pain Neuroscience Education Program in Adults with Cancer Pain

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ABSTRACT

Introduction

Pain is the second most frequent symptom reported in cancer patients among the main reasons for consultation. The incorporation of educational modalities in pain intervention processes has been suggested. This study aims to examine the efficacy of neuroscience pain education (PNE) in relation to pain, biopsychosocial variables, and functional capacity in comparison with conventional treatment. It is hypothesized that an intervention based on neuroscience-based pain education (PNE) achieves better outcomes than conventional management, in terms of pain, biopsychosocial variables, and functional capacity in adults with oncologic pain.

Methods and analysis

This will be a single-blind, controlled clinical trial in which two groups will be compared using changes in pain as the primary measure. The first group will receive conventional treatment in addition to PNE, and participants will undergo an intervention of nine sessions (1 session per week, for a total of nine weeks), each lasting 30–40 minutes. Specifically, these sessions will teach biophysiological elements using metaphors that allow the adoption of these concepts related to pain. The second group will receive conventional treatment (pharmacological treatment). For this study, a sample size calculation was made based on the background, where 80 adults with oncologic pain were required. An initial evaluation will be made to establish the baseline characteristics, and then, according to the randomization, the assignment to the PNE group or the control group will be made, and the two groups will be

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summoned again. Ten weeks later, for the -intervention evaluation, the statistical analysis plan will be established by protocol and by intention-to-treat.

Ethics and dissemination

This protocol complies with all ethical considerations. It also was approved by the Ethics and Bioethics Committee of the University and the participating clinic. The authors commit to presenting the study's results.

Clinical trial registration

NCT05581784

Strengths and limitations of this study

- Patients from a pain medicine and palliative care unit will be recruited in accordance with their applicability in clinical practice.
- This study will involve the development of educational material according to the theoretical references for addressing the patient.
- Functional capacity measurements, such as a 6-minute walk distance and manual pressure strength, which can determine the effect of this intervention on patients, will be included.

Limitations:

- The calculated sample may not be reached due to difficulties in obtaining patients.
- There may be losses associated with comorbidities due to the stage of the cancer and adjuvant processes.

Keywords: Pain; Neoplasms; Cancer Pain; Pain Management; Health Education

INTRODUCTION

In 2021, about 5,562 new cases of cancer were reported in Colombia, of which breast cancer was the second most frequent type of cancer in women (16.3% of new cases), followed by uterus cancer (13.7% of new cases), while in men, the second type of cancer with the highest number of new cases was prostate cancer (14.5% new cases) (1), observing an increase in cases as age increases. In turn, pain is a common symptom reported by cancer patients. A previous meta-analysis reported pain in 59%, 64% and 33% of patients undergoing cancer treatment, in patients with advanced or terminal disease and after curative treatment, respectively (2).

According to the International Association for the Study of Pain, pain is defined as an unpleasant sensory and emotional experience associated with, or resembling, actual or potential tissue damage (3). In particular, it is one of the most frequent alterations caused by toxicity, surgery, radiation, among others, after cancer treatment (4). Oncologic pain poses a difficulty due to the complexity of the disease and the subjective experience of pain. In addition, during cancer treatment, pain mechanisms may appear due to different causes, the first one possibly due to tissue involvement (nociceptive pain) and the second one to nerve

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damage (neuropathic pain), and at other times some mechanisms are characterized by altered processing without clear evidence of persistent tissue damage (non-disciplinary pain) (5). In addition, it is closely related to decreased quality of life and increased self-perceived disability (6). In addition, it is closely related to the decrease in quality of life and the increase in self-perceived disability.

Pain is one of the most feared and annoying symptoms among these patients (2,7). A study reported that 5%–10% of cancer survivors have severe chronic pain that significantly impairs their function (8). A study of patients with breast cancer reported pain in 25.3%, 18.7%, 15.4%, and 40.6% of them, with neuropathic, nociceptive, nociplastic, and mixed pain predominating, respectively (9). Notably, this etiology of cancer pain is variable and can be attributed to postoperative syndromes. In addition, adjuvant therapies can have adverse effects. For example, chemotherapy can cause symmetrical painful numbness and burning and tingling in hands and feet. It can also cause osteoporosis, osteonecrosis, arthralgia, and myalgia (8,10). Radiotherapy can have serious side effects caused by ionizing radiation, the induction of reactive oxygen species production, and damage to DNA and regulatory proteins in cells. This leads to apoptosis and increased inflammation in exposed and adjacent cells due to radiation-induced bystander effects, potentially leading to plexopathies and osteoradionecrosis (11,12). Likewise, the maintenance therapy used, such as that involving aromatase inhibitors, may cause arthralgia and myalgia (13).

To control the adverse effects mentioned above the relevant literature in oncology shows that quality of life and survival rate are associated with early and effective palliative care, including pain management, establishing recommendations for the inclusion of interventions oriented to non-pharmacological approaches such as education (14). Future studies are required to evaluate these new treatment approaches (15) that include educational aspects within the intervention process. Accordingly, pain neuroscience education (PNE) describes how the nervous system interprets information from tissues via peripheral sensitization, central sensitization, synaptic activity, and cortical processing (16). This innovative educational approach is effective in changing beliefs about pain and improving pain management strategies and health outcomes in a variety of adult populations with chronic pain (17-19).

Regarding previous studies on PNE in cancer, a quasi-experimental study was conducted by Pas R (20) with the aim of describing the innovative educational component of PNE. The study showed a significant decrease in pain intensity ($p = 0.001$) compared with baseline. Another study conducted by Manfuku (21), compared conventional biomedical education (BME) ($n = 51$) with PNE ($n = 51$) and reported scores based on the brief pain inventory (BPI) questionnaire. The findings show that scores for catastrophizing and central sensitization improved with a statistically significant difference between PNE and BME (all, $p < 0.05$), and effect sizes for BPI intensity were moderate ($r = 0.31$). Furthermore, a study carried out by Groef (22) aimed to investigate the effectiveness of PNE intervention for the treatment and prevention of pain and for improvement in physical, emotional, and work-related functioning after breast cancer surgery, compared with biomedical education. The results of this protocol were recently published by Dams (23) finding that patients who received PNE after 6 months of breast cancer surgery showed a decreased sensitivity to pressure pain in the trunk, compared with the biomedical education group. However, no significant differences were found between the types of education received.

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The present study aims to examine the effectiveness of PNE in relation to pain, biopsychosocial variables, and functional capacity compared with conventional management in people with prostate, uterine, and breast cancer. This will be assessed through a single-blind randomized controlled clinical trial. It is hypothesized that an intervention based on neuroscience-based pain education (PNE) achieves better outcomes than conventional management in terms of pain, biopsychosocial variables, and functional capacity in adults with oncologic pain.

METHODS AND ANALYSIS

Trial design and context

A randomized controlled parallel-group clinical trial will be conducted with blinding of the researchers. The recruitment will be conducted between February 2023 and March 2024 at the clinical medicine and palliative care unit of a tertiary level clinic in the city of Cali and the Health Department of the University of Santiago de Cali, Colombia.

This proposed quantitative experimental controlled clinical trial will be conducted in accordance with the SPIRIT guidelines for clinical trial protocols (24) and CONSORT guidelines for clinical trials (25) and outcomes extension (26). This trial is registered with ClinicalTrials.gov Identifier: NCT05581784.

Patient and public involvement in the trial design

During the initial preparation and setup of the trial. We consulted with a patient diagnosed with breast cancer, along with a representative from the Palliative Care Unit. The patient's perspective offered valuable insight into the challenges and anxieties faced during cancer treatment. Simultaneously, the representative of the Palliative Care Unit played a crucial role in shaping the study framework and provided guidance on the assessment of work-related functional outcomes.

Due to the characteristics of the intervention, work was done prior to its development on the validation of the content provided in the manual with some patients with similar characteristics to verify that the content included in each of the chapters is consistent and is understood by the patients. At the end of each session, questions are asked about the main concepts of each of the chapters. The manual developed will be available for consultation, and public dissemination sessions of the results will be held open to the public with the aim of publicizing the results.

Eligibility criteria

The study will include male patients diagnosed with stage III and IV prostate cancer and female patients diagnosed with stage III and IV uterine and breast cancer according to the TNM staging system stands for Tumour, Node, Metastasis (27). Includes persons with an initial pain rating of 3 as assessed with VAS.

Inclusion criteria:

- Patients with a life expectancy of >3 months based on the Karnofsky Scale, Eastern Cooperative Oncology Group Scale, Palliative Prognostic Score, or Palliative Prognostic Index.

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- Those who provide informed consent.
- Those who are able to establish communication with the team, please note that the sessions will be conducted in Spanish and a proficiency in the language is required.
- Those presenting with scores demonstrating preserved cognitive function on a Montreal Cognitive Assessment (MoCA) scale with a minimum score of 25.
- Those who are able to stand upright and walk independently or with external assistance.

Exclusion criteria:

- Patients with surgeries scheduled in the next 3 months.
- Those with impairment of visual and auditory sensory systems (deafness or blindness).
- Those with acute traumatic injury.
- Those with uncontrolled arrhythmias or heart disease.
- Those with severe acute respiratory failure or uncontrolled respiratory pathology.
- Those with recent fractures in the last month.
- Patients diagnosed with previous rheumatic diseases (before a cancer diagnosis).

Participant selection, recruitment, and consent

Participants will be identified from the lists of patients in the pain medicine and palliative care ward and selected according to the abovementioned selection criteria. The initial examination and evaluation were carried out by a member of the research team, and potentially eligible participants were approached and recruited by the attending physician after consultation. All eligible patients received a document with information and explanations about the study. Participants were then asked to fill out a separate informed consent form that was previously approved by all institutions involved in the study. After their approval, an evaluation process was conducted to determine the baseline before randomization and assignment to one of the study groups. The second assessment will take place immediately following the intervention. The flow chart of the study is shown in Figure 1 and Appendix 1.

Figure 1. Flow chart of the study

Sample size

To calculate the sample size, we used the results of the preliminary study by Manfuku (21) who used an educational intervention in cancer patients with pain to determine the process of self-care and medication management in cancer. Manfuku used the BPI as the main measure of pain intensity. The Gpower 3.1 program was used based on an assumption of a mean of 0.51 (±1) in group 1 and 1.69 (±2.2) in group 2, with a difference of −1.18, i.e. (t test), assuming pain intensity as the main variable, a power of 90% and an alpha type error of 5% and one-tailed adjustment was determined. Overall, 37 patients must be enrolled in each group, and to adjust for a 10% loss, 41 patients are required for each group.

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Allocation and randomization

To reduce selection bias, random number randomization with a computer-generated 1:1 assignment in permuted blocks of four to eight patients will be performed. An external researcher will randomly assign patients to one of the two treatment groups after obtaining informed consent and performing a baseline assessment. In order to allocate each patient to the experimental or control group, two strata randomization (age groups, <60 years and older patients) will be also performed to reduce potential confounders and selection bias. Furthermore, the research team members performing the statistical analysis will be blinded.

Blinding

To ensure a reduction in information bias during patient follow-up, the principal investigator is blinded. In addition, the post-interventional examinations are self-managed by people who depend on a physiotherapist and carried out for others by an external person trained and specialized in this field. This is done in such a way that the assessor is unaware of the patient's assignment, and the patient is asked not to reveal the group to which they have been assigned at any time. To further reduce the bias, both the therapist conducting the assessment and the therapist conducting the intervention program will be different people.

Intervention group

The intervention group will undergo an intervention based on PNE, which is an educational model for teaching pain biopsychosocial. It has been recognized as a compelling approach for managing chronic pain that adopts elements of user-based learning through the use of metaphors and examples (28). In addition, PNE is aimed at changing the understanding of what pain really is, the effects it has, and the biological processes that guide it. It refers to a theoretical framework for pain treatments, and the main goal of the approach is to change the conceptualization of pain as an indicator of tissue damage or pathology, progressively leading to a change in attitudes and the initiation of movements and activities in everyday life (29).
This model is based on various educational interventions (19) and has been defined using the following terms: Explaining Pain (30), Therapeutic Neuroscience Education, and PNE. (31). Notably, PNE is increasingly used as part of physiotherapy treatment in patients with chronic, non-disciplinary, and neuropathic pain. A comprehensive biopsychosocial clinical assessment is recommended before PNE to adequately explain the neurophysiology of pain and biopsychosocial interactions, while ensuring that this process is patient-centered (29).

The clinical trial will comprise nine sessions over a period of 10 weeks, each lasting 30–40 minutes. These sessions will be scheduled weekly. Interventions will be scheduled on an individual or group basis (if possible). Supporting slides will be used to explain the content, and questions will be allowed throughout the sessions.
The content of the sessions will include elements based on book illustrations explaining pain, the second edition of the Spanish version (27) whose content will correspond to http://www.paininmotion.be/ (32); Louw's manual (33), and the explanation of pain in patients with cancer (7) which will be adapted from the use of examples and metaphors. For the organization of material corresponding to this intervention, some phases will be generated.
The sessions will be based on a guide with nine chapters organized as follows:

- Chapter 1, entitled "Living with Pain," conceptualizes the importance of pain as a defense system and functioning of the organism. Patients will reflect on what their life was like with pain and learn strategies that can help them in the process.
- In Chapter 2, entitled "Pain System," patients learn to understand that although pain is defined as a sensation, ultimately it is not, and rather becomes a perception. This in turn includes what is thought, felt, and believed about the situation.
- In Chapter 3, entitled "Alarm System," patients understand how the alarm system is activated via a detailed process involving neurons, synapses, conduction to the medulla, and processing at the cortical level in the presence of pain.
- Chapter 4, entitled "Extra Sensitivity Altered Alert System," aims to make the patient aware that their nerve cells become more sensitive in the presence of injury or pathology. This process is influenced by factors external to the injury, such as stress, fear, and the perception of pain itself, causing the tissues or organs surrounding the injury to trigger the alarm system as if it were a loudspeaker, leading to hypersensitivity.
- In Chapter 5, entitled "Pain Defenders," patients experience a new sense of pain. The pain can be compared to a big wolf or wild animal attacking the individual, wherein the individual's systems are activated to protect them from the threat and thus the brain makes survival-related decisions.
- In Chapter 6, entitled "Your Fatigue, Anxiety, and Stress," patients understand the function of cortisol and its effect on the sympathetic, parasympathetic, immune, and endocrine nervous systems. Additionally, they understand why living with the constant threat of chronic and persistent pain activates their systems to produce stress-related chemicals, which in turn cause them to experience related symptoms, such as depression, mood swings, changes in appetite, memory problems, weight gain, insomnia, fatigue, and anxiety.
- Chapter 7, entitled "Current Treatment Models," aims to make the patient recognize their fear as a powerful motivator that could help them find new strategies to understand their pain and its treatment, making them consider that they own this process and that they are the owners of their own decisions.
- In Chapter 8, titled "Goals and Achievements," patients understand that pain stems from sensations and that receptors transmit these sensations. Ideally, patients can be made aware at this point that there is evidence that education, knowledge, and understanding include strategies to help them improve and that exercise is important to turn off the alarm system.
- In Chapter 9, entitled "Emphasis and Pain Differentiation," the patient understands that pain does not mean there is damage and that their pain can be classified according to some characteristics as follows: nociceptive, nociplastic, and neuropathic.

Control intervention

The pharmacological treatment and indications will be evaluated by a doctor specialized in palliative care and pain. In particular, pharmacological treatment will be considered for both groups. Patients will be instructed to follow protocols established by the clinic: use of nonsteroidal anti-inflammatory drugs in the first instance for mild pain; tramadol at a maximum dose of 400 mg, codeine, or tapentadol for moderate pain; and opioids based on availability and use in Colombia, including morphine, oxycodone, hydromorphone,

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methadone, fentanyl (parenteral and transdermal use), and buprenorphine (transdermal use) for severe pain.

The PNE group will also be advised pharmacological modulation by the attending physician.

Community and expert participation

To organize the chapters, we worked with patients who served on the board of a foundation working for palliative care in the city of Cali and cancer experts for decision-making in consolidating the chapters as well as the feelings and concerns that arise while explaining them. Our approach also involved leveraging the expertise of professionals to validate the protocols, along with consulting a patient to gather pertinent information.

Outcomes

The measures of outcomes to be included were based on the pain assessment guideline by IMMPACT recommendations (34) as well as from the reports generated when working with patients with cancer (12).

As the primary outcome, the impact of pain is assessed using the BPI, and all secondary outcome measures are presented in Table 1. In particular, an assessment at baseline and 10 weeks after the intervention is considered. BPI is a self-administered questionnaire containing two dimensions: one related to pain intensity and the other to the effect of pain on the patient's activities of daily living. This is rated on a 10-point scale. Higher scores indicate more severe pain (35).

The Visual Analog Pain Scale is used to measure pain intensity on a 10-cm line (total score: 0–10; 0 = no pain and 10 = severe pain). Higher scores indicate a worse result (36).

Secondary measures

Central sensitization

The Central Sensitization Inventory is used to identify patients with symptoms related to central sensitization and has two sections: Section A comprises 25 questions about central sensitization syndrome symptoms, and Section B assesses the patient's condition in relation to their diagnosis. The patient answers the 25 questions in Section A with a score of 0–4. The total score is between 0 and 100. Scores of >40 indicate central sensitization (37).

Catastrophizing

The Pain Catastrophizing Scale is a 13-item self-administered questionnaire measuring three items of perceived pain intensity (rumination, magnification, and feeling helpless). Participants indicate the extent to which they agree with statements about their pain as 0, strongly disagree; 1, to a mild degree; 2, to a moderate degree; 3, to a great extent; and 4, all the time. It has three subscales that score rumination, magnification, and helplessness. All subscale scores are added to give a total score from 0 to 52. Higher scores indicate that the participant thinks more about the pain and feels helpless (38).

Kinesiophobia

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The Tampa Scale is used to assess the fear of pain and movement. It comprises 11 items that are answered on a 4-point Likert scale. Total scores for each scale range from 11 to 44, with higher scores indicating a greater fear of pain and movement (39).

Depression

The Beck Depression Inventory will be used to assess the state of depression. It contains 21 categories measuring physical, emotional, cognitive, and motivational symptoms, and each category is scored between 0 and 3. The patient is then asked to select the most appropriate category. The score increases progressively from no symptoms to severe symptoms (0–10 points, no depression; 11–17 points, mild depression; 18–23 points, moderate depression; ≥24: severe depression) (40).

Neuropathic pain

The DN4 scale will be used to assess neuropathic pain, and it scores 4 questions out of 10 will be used to determine the symptomatology related to neuropathic pain (41).

Cognitive function

The MoCA assessment will be used for assessing cognitive impairment, and it consists of 19 items and 8 cognitive domains that assess skills such as visuo-spatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation; it can have a maximum score of 30, with 25 or 26 being the cut-off points for cognitive impairment (42).

Quality of life

The widely used questionnaire European Organization for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30) is used to assess the quality of life and includes five functional scales (physical, role, cognitive, emotional, and social functioning), a global quality of life scale, three symptom scales (fatigue, nausea, and pain), and six individual items (loss of appetite, diarrhea, dyspnea, constipation, insomnia, and economic impact). On the functional and global quality of life scales, a higher score indicates better health. On symptom scales, a higher score indicates a higher symptom burden (43).

Sleep quality

The Pittsburgh Sleep Quality Index is one of the most reliable tests for defining sleep quality and its disorders. It contains a total of 19 questions. Questions are grouped into seven scoring areas, each ranging from 0–3 points (44).

Functional capacity

A 6-minute walk test is used to determine exercise tolerance and functional status. The distance covered in meters in the last 6 minutes is measured (45,46).

The Timed Get-up-and-Go test was developed as a predictor of falls and as a measure of functional capacity. In this test, the participant sits in a chair, stands up, walks for 3 m, and sits down again. The test runtime is calculated (47).

Manual grip strength

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This is a marker of nutritional status as well as the morbidity and mortality associated with the pathological lesion. It will be measured using a dynamometer to establish the value of grip strength in kilograms (48).

Pharmaceuticals

The establishment of the baseline of the drugs used for pain, as well as the type, dose, and frequency of consumption will be generated.

Table 1. Description of the measurements

VARIABLES	DIMENSIONS	INDICATOR	VALUE
Sociodemographic features	Age	How many years old	• Age: ≥40 years • Female or male • Incomplete elementary school education, complete elementary school education, incomplete high school education, complete high school education, technical education, technological college-level education, university-level education, and postgraduate • Rural or urban • Contributory, subsidized, linked, or specialized
	Sex	Female or male	
	Educational level	Level of schooling	
	Provenance	Urban or rural	
	Affiliation regimen	Subsidized, contributory, or linked	
	Diagnostic period	Months	Months after the diagnosis
	Pharmacological treatment	Medication use	Use of medications and dosage
	Adjuvant treatment	Presence of adjuvant treatment	Chemotherapy or radiotherapy Frequency of administration
Physical measurements	Vital signs	Vital sign parameters	Heart rate Oxygen (O_2) saturation Respiratory frequency Blood pressure
Impact of pain	Brief pain questionnaire	BPI	1–22 items to evaluate the degree of pain and its severity based on pain history

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Presence of pain	Numerical assessment of pain	Numerical pain indicator	Numerical: score from 1 to 10 in pain Categorical: None, mild, moderate, or severe
Cognitive Function	Cognitive dimensions	Score range 0–30	Score on the MoCA test Categorical: Normal, mild impairment, moderate impairment, or severe impairment
Depression	Beck Index	Presence of 0–21 items	Numerical: Score obtained in the test Categorical: None, Mild, Moderate, and Severe
Kinesiophobia	Tampa Scale	11 items Score range from 1–4	Numerical: 1–4 Categorical: None, Mild, Moderate, and Severe
Catastrophizing	Catastrophization scale	13 items Score range from 1–4	Three factors: rumination, magnification, and hopelessness (scored from 1 to 4)
Central sensitization	Central sensitization inventory	25 points Score range 1–4.	This evaluates 25 pain-related symptoms, with scores from 0 to 100 Categorical: Yes or No
Neuropathic pain	Scale DN4	Score range 0–10 points	This evaluates four questions with possibility to score up to 10 points in order to determine the presence of neuropathic pain Categorical: Yes or No
Quality of sleep	Pittsburgh Sleep Quality Index.	Score range 0–21 points	Categorical: Good, Fair, or Poor
Quality of life	EORTC QLQ-C30	30 questions Score range 1–4	Assessment of the quality of life of patients with cancer
Functional capacity	TC6M 6-minute walk test.	Meters traveled	Meter indicator Heart rate Borg: Dyspnea; Fatigue
	Timed Get-up-and-Go test	Time in seconds	Time in seconds
	Manual dynamometry	Force in kilograms	Force in kilograms

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Data analysis

A statistical analysis will be performed based on the following steps:
A flowchart will be prepared to describe the process of patient recruitment and follow-up throughout the study based on the CONSORT Declaration. The flowchart will include the number of patients and reasons for exclusion, the number of patients randomized and assigned to the study units, and the losses and interruptions in the interventions within the groups (24).
An exploratory analysis will be performed to assess the data behavior and the key assumptions required for the application of a particular test (normality, linearity, or homoscedasticity); in addition, the presence of errors and biases in the data collected, the presence of anomalies, and all missing data will be assessed.
The sociodemographic and clinical variables will be analyzed in addition to those related to the patients' baseline oncological process at inclusion in the study by plotting their baseline characteristics according to the measurement scale of each variable using measures of central tendency, dispersion, frequency tables, and 95% confidence intervals. This analysis will be performed for each group and then subjected to homogeneity hypothesis tests based on the nature of each variable.
A univariate analysis of each described variable will then be performed considering the results before and after the intervention. In addition, we will perform a bivariate analysis to determine the correlation between dependent and independent variables and a multivariate analysis to examine the interaction and relationships between them.
Pain scores on the Pain Rating Scale will be considered the primary outcomes and quality of life scores and physical function test scores are secondary variables; the difference in their mean values between groups will be analyzed using the Student's t-test, and the difference within each group will be analyzed using the paired t-test. The interpretation of effect size will be performed using the Cohen's D index or coefficient, which classifies effect size as small (0.2–0.49), moderate (0.5–0.8), or large (>0.8).
A multivariate analysis will be performed using linear regression for the dependent variables, such as pain, cognitive function, depression, kinesiophobia, catastrophizing, pain impact, central sensitization, neuropathic pain, sleep quality, quality of life, and physical function. If the criteria of normality, homoscedasticity, and independence of the variable are not met, the possibility of transforming the variable will be evaluated. Once the regression has been performed, we will assess whether the model represents or resembles the observed data. To control for potential confounders, the variables previously considered as confounders will be adjusted, such as pharmacological dose, presence of adjuvant treatment, and previous hospitalizations for pain. In addition, the possibility of a change in the effect between these variables will be assessed.
The analysis will be carried out according to the protocol based on the specification for who completed the intervention, but the analysis will also be estimated based on the intention to treat the whole group.

Data security and management

Participant data will be stored in a secure database in accordance with ethical considerations and good health practices. Each patient will be assigned an identifier to protect confidentiality. The information will be reviewed to determine the validity of the data. The

data will then undergo additional checks to ensure that the information encrypted matches the information received.

Test monitoring

A pilot study will be initiated to determine the dosage for the different questionnaires to be used and the time and response capacity of the patients.

The material used during the intervention will be tested and reviewed by experts as well as patient representatives to verify the understanding of each of the constructed chapters.

Ethics and diffusion

In this research, all participants will be provided with reasonable information about the objectives, methods, possible conflicts of interest, estimated benefits, foreseeable risks, and inconveniences arising from this investigation. Participants sign an informed consent form that clearly explains the procedure to be performed, the nature of the procedures, the benefits and risks they face, their ability to choose freely, and that everything will be performed without coercion. It will also be made clear that if the individual does not agree to participate, they can withdraw their consent at any time.

Dissemination of results

The research team is committed to the full publication of the results of this study. The results will be reported according to CONSORT guidelines and are intended to be published in high profile journals. In the research, there is a component related to social acquisition and knowledge dissemination, and these results are expected to be presented to patient representatives and the various palliative care committees.

Contributorship statement

Ordoñez- Mora LT: Research idea, development of the intervention material, construction of materials and methods, statistical validation, review and approval of the manuscript. **Rosero ID**: Development of the intervention material, construction of materials and methods, statistical validation, review and approval of the manuscript. **Morales-Osorio MA**: Development of the intervention material, construction of materials and methods, statistical validation, review and approval of the manuscript. **Guil R**: Construction of materials and methods, statistical validation, review and approval of the manuscript. **Quintero Jordan G**: Development of the intervention material, review and approval of the manuscript. **Agudelo Jimenez J**: Construction of materials and methods, statistical validation, review and approval of the manuscript. **Gonzalez Ruiz K**: Construction of materials and methods, statistical validation, review and approval of the manuscript. **Avila-Valencia JC**: Construction of materials and methods, statistical validation, review and approval of the manuscript.

Conflict of interest: No conflicts of interest are declared by the authors or the funding entity.

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Ethics Approval:

This project was submitted on October 8, 2021 for approval and review by the Ethics and Bioethics Committee of the University of Santiago de Cali, and it was approved in minutes 16 of October 8, 2021. It was also submitted to the ethics committee at the Clínica de Occidente, Angiografía de Occidente and was approved in the minutes of November 25, 2021.

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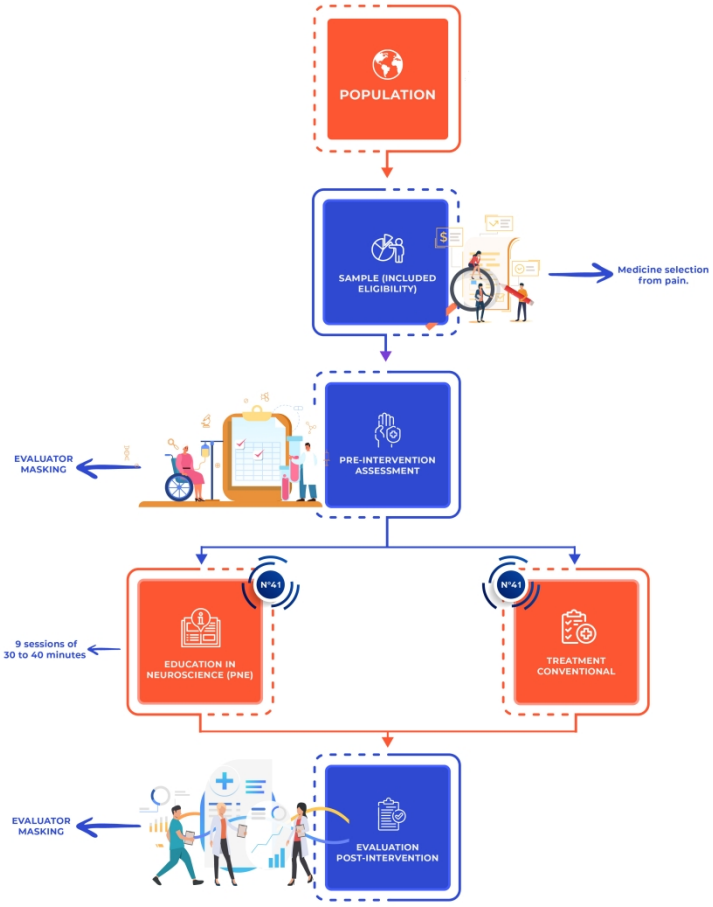

Study flowchart

381x381mm (300 x 300 DPI)

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Appendix 1. Diagram for recruiting and conducting interventions and evaluations according to SPIRIT Guidelines

STUDY PERIOD					
	Enrolment	Allocation	Post-Allocation		Close-out
Timepoint	$-t_1$	0	t_1	t_2	t_3
ENROLMENT					
Eligibility screen	X				
Informed consent	X				
Demographic characteristic	X				
Allocation		X			
INTERVENTIONS:					
PNE interventions					
Control (usual care)					
ASSESSMENTS:					
Baseline		X			
Primary pain measures		X		X	
Secondary variables		X		X	
Statistical Analysis					X

t1 Initial evaluation
t2 After 10 weeks

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17

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Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	13
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	2
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	4

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		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	5
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5

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Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12

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Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
Data monitoring: interim analysis	#21b	Description 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	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	na
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	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	12

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Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	18
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	12
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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BMJ Open

NEUROCANTRIAL: Study Protocol for a Randomized Controlled Trial of a Pain Neuroscience Education Program in Adults with Cancer Pain

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Secondary Subject Heading:	Palliative care, Oncology, Rehabilitation medicine, Medical management
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NEUROCANTRIAL: Study Protocol for a Randomized Controlled Trial of a Pain Neuroscience Education Program in Adults with Cancer Pain

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ABSTRACT

Introduction

Pain is the second most frequent symptom reported in cancer patients among the main reasons for consultation. The incorporation of educational modalities in pain intervention processes has been suggested. This study aims to examine the efficacy of neuroscience pain education (PNE) in relation to pain, biopsychosocial variables, and functional capacity in comparison with conventional treatment. It is hypothesized that an intervention based on neuroscience-based pain education (PNE) achieves better outcomes than conventional management, in terms of pain, biopsychosocial variables, and functional capacity in adults with oncologic pain.

Methods and analysis

This will be a single-blind, controlled clinical trial in which two groups will be compared using changes in pain as the primary measure. The first group will receive conventional treatment in addition to PNE, and participants will undergo an intervention of nine sessions (1 session per week, for a total of nine weeks), each lasting 30–40 minutes. Specifically, these sessions will teach biophysiological elements using metaphors that allow the adoption of these concepts related to pain. The second group will receive conventional treatment (pharmacological treatment). For this study, a sample size calculation was made based on the background, where 80 adults with oncologic pain were required. An initial evaluation will be made to establish the baseline characteristics, and then, according to the randomization, the assignment to the PNE group or the control group will be made, and the two groups will be

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summoned again. Ten weeks later, for the -intervention evaluation, the statistical analysis plan will be established by protocol and by intention-to-treat.

Ethics and dissemination

This protocol complies with all ethical considerations. The authors commit to presenting the study's results. This study was approved by the ethics committees of the Universidad Santiago de Cali, Clínica de Occidente/ Angiografía de Occidente. The authors commit to presenting the study's results.

Clinical trial registration

NCT05581784

Strengths and limitations of this study

- Patients from a pain medicine and palliative care unit will be recruited in accordance with their applicability in clinical practice.
- This study will involve the development of educational material according to the theoretical references for addressing the patient.
- Functional capacity measurements, such as a 6-minute walk distance and manual pressure strength, which can determine the effect of this intervention on patients, will be included.

Limitations:

- The calculated sample may not be reached due to difficulties in obtaining patients.
- There may be losses associated with comorbidities due to the stage of the cancer and adjuvant processes.

Keywords: Pain; Neoplasms; Cancer Pain; Pain Management; Health Education

INTRODUCTION

In 2021, about 5,562 new cases of cancer were reported in Colombia, of which breast cancer was the second most frequent type of cancer in women (16.3% of new cases), followed by uterus cancer (13.7% of new cases), while in men, the second type of cancer with the highest number of new cases was prostate cancer (14.5% new cases) (1), observing an increase in cases as age increases. In turn, pain is a common symptom reported by cancer patients. A previous meta-analysis reported pain in 59%, 64% and 33% of patients undergoing cancer treatment, in patients with advanced or terminal disease and after curative treatment, respectively (2).

According to the International Association for the Study of Pain, pain is defined as an unpleasant sensory and emotional experience associated with, or resembling, actual or potential tissue damage (3). In particular, it is one of the most frequent alterations caused by toxicity, surgery, radiation, among others, after cancer treatment (4). Oncologic pain poses a difficulty due to the complexity of the disease and the subjective experience of pain. In addition, during cancer treatment, pain mechanisms may appear due to different causes, the

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first one possibly due to tissue involvement (nociceptive pain) and the second one to nerve damage (neuropathic pain), and at other times some mechanisms are characterized by altered processing without clear evidence of persistent tissue damage (non-disciplinary pain) (5). In addition, it is closely related to decreased quality of life and increased self-perceived disability (6). In addition, it is closely related to the decrease in quality of life and the increase in self-perceived disability.

Pain is one of the most feared and annoying symptoms among these patients (2,7). A study reported that 5%–10% of cancer survivors have severe chronic pain that significantly impairs their function (8). A study of patients with breast cancer reported pain in 25.3%, 18.7%, 15.4%, and 40.6% of them, with neuropathic, nociceptive, nociplastic, and mixed pain predominating, respectively (9). Notably, this etiology of cancer pain is variable and can be attributed to postoperative syndromes. In addition, adjuvant therapies can have adverse effects. For example, chemotherapy can cause symmetrical painful numbness and burning and tingling in hands and feet. It can also cause osteoporosis, osteonecrosis, arthralgia, and myalgia (8,10). Radiotherapy can have serious side effects caused by ionizing radiation, the induction of reactive oxygen species production, and damage to DNA and regulatory proteins in cells. This leads to apoptosis and increased inflammation in exposed and adjacent cells due to radiation-induced bystander effects, potentially leading to plexopathies and osteoradionecrosis (11,12). Likewise, the maintenance therapy used, such as that involving aromatase inhibitors, may cause arthralgia and myalgia (13).

To control the adverse effects mentioned above the relevant literature in oncology shows that quality of life and survival rate are associated with early and effective palliative care, including pain management, establishing recommendations for the inclusion of interventions oriented to non-pharmacological approaches such as education (14). Future studies are required to evaluate these new treatment approaches (15) that include educational aspects within the intervention process. Accordingly, pain neuroscience education (PNE) describes how the nervous system interprets information from tissues via peripheral sensitization, central sensitization, synaptic activity, and cortical processing (16). This innovative educational approach is effective in changing beliefs about pain and improving pain management strategies and health outcomes in a variety of adult populations with chronic pain (17-19).

Regarding previous studies on PNE in cancer, a quasi-experimental study was conducted by Pas R (20) with the aim of describing the innovative educational component of PNE. The study showed a significant decrease in pain intensity ($p = 0.001$) compared with baseline. Another study conducted by Manfuku (21), compared conventional biomedical education (BME) ($n = 51$) with PNE ($n = 51$) and reported scores based on the brief pain inventory (BPI) questionnaire. The findings show that scores for catastrophizing and central sensitization improved with a statistically significant difference between PNE and BME (all, $p < 0.05$), and effect sizes for BPI intensity were moderate ($r = 0.31$). Furthermore, a study carried out by Groef (22) aimed to investigate the effectiveness of PNE intervention for the treatment and prevention of pain and for improvement in physical, emotional, and work-related functioning after breast cancer surgery, compared with biomedical education. The results of this protocol were recently published by Dams (23) finding that patients who received PNE after 6 months of breast cancer surgery showed a decreased sensitivity to

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pressure pain in the trunk, compared with the biomedical education group. However, no significant differences were found between the types of education received.
The present study aims to examine the effectiveness of PNE in relation to pain, biopsychosocial variables, and functional capacity compared with conventional management in people with prostate, uterine, and breast cancer. This will be assessed through a single-blind randomized controlled clinical trial. It is hypothesized that an intervention based on neuroscience-based pain education (PNE) achieves better outcomes than conventional management in terms of pain, biopsychosocial variables, and functional capacity in adults with oncologic pain.

METHODS AND ANALYSIS

Trial design and context

A randomized controlled parallel-group clinical trial will be conducted with blinding of the researchers. The recruitment will be conducted between February 2023 and March 2024 at the clinical medicine and palliative care unit of a tertiary level clinic in the city of Cali and the Health Department of the University of Santiago de Cali, Colombia.

This proposed quantitative experimental controlled clinical trial will be conducted in accordance with the SPIRIT guidelines for clinical trial protocols (24) and CONSORT guidelines for clinical trials (25) and outcomes extension (26). This trial is registered with ClinicalTrials.gov Identifier: NCT05581784.

Patient and public involvement in the trial design

During the initial preparation and setup of the trial. We consulted with a patient diagnosed with breast cancer, along with a representative from the Palliative Care Unit. The patient's perspective offered valuable insight into the challenges and anxieties faced during cancer treatment. Simultaneously, the representative of the Palliative Care Unit played a crucial role in shaping the study framework and provided guidance on the assessment of work-related functional outcomes.

Due to the characteristics of the intervention, work was done prior to its development on the validation of the content provided in the manual with some patients with similar characteristics to verify that the content included in each of the chapters is consistent and is understood by the patients. At the end of each session, questions are asked about the main concepts of each of the chapters. The manual developed will be available for consultation, and public dissemination sessions of the results will be held open to the public with the aim of publicizing the results.

Eligibility criteria

The study will include male patients diagnosed with stage III and IV prostate cancer and female patients diagnosed with stage III and IV uterine and breast cancer according to the TNM staging system stands for Tumour, Node, Metastasis (27). Includes persons with an initial pain rating of 3 as assessed with VAS.

Inclusion criteria:

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- Patients with a life expectancy of >3 months based on the Karnofsky Scale, Eastern Cooperative Oncology Group Scale, Palliative Prognostic Score, or Palliative Prognostic Index.
- Those who provide informed consent.
- Those who are able to establish communication with the team, please note that the sessions will be conducted in Spanish and a proficiency in the language is required.
- Those presenting with scores demonstrating preserved cognitive function on a Montreal Cognitive Assessment (MoCA) scale with a minimum score of 25.
- Those who are able to stand upright and walk independently or with external assistance.

Exclusion criteria:

- Patients with surgeries scheduled in the next 3 months.
- Those with impairment of visual and auditory sensory systems (deafness or blindness).
- Those with acute traumatic injury.
- Those with uncontrolled arrhythmias or heart disease.
- Those with severe acute respiratory failure or uncontrolled respiratory pathology.
- Those with recent fractures in the last month.
- Patients diagnosed with previous rheumatic diseases (before a cancer diagnosis).

Participant selection, recruitment, and consent

Participants will be identified from the lists of patients in the pain medicine and palliative care ward and selected according to the abovementioned selection criteria. The initial examination and evaluation were carried out by a member of the research team, and potentially eligible participants were approached and recruited by the attending physician after consultation. All eligible patients received a document with information and explanations about the study. Participants were then asked to fill out a separate informed consent form that was previously approved by all institutions involved in the study. After their approval, an evaluation process was conducted to determine the baseline before randomization and assignment to one of the study groups. The second assessment will take place immediately following the intervention. The flow chart of the study is shown in Figure 1 and Appendix 1.

Figure 1. Flow chart of the study

Sample size

To calculate the sample size, we used the results of the preliminary study by Manfuku (21) who used an educational intervention in cancer patients with pain to determine the process of self-care and medication management in cancer. Manfuku used the BPI as the main measure of pain intensity. The Gpower 3.1 program was used based on an assumption of a mean of 0.51 (±1) in group 1 and 1.69 (±2.2) in group 2, with a difference of −1.18, i.e. (t

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test), assuming pain intensity as the main variable, a power of 90% and an alpha type error of 5% and one-tailed adjustment was determined. Overall, 37 patients must be enrolled in each group, and to adjust for a 10% loss, 41 patients are required for each group.

Allocation and randomization

To reduce selection bias, random number randomization with a computer-generated 1:1 assignment in permuted blocks of four to eight patients will be performed. An external researcher will randomly assign patients to one of the two treatment groups after obtaining informed consent and performing a baseline assessment. In order to allocate each patient to the experimental or control group, two strata randomization (age groups, <60 years and older patients) will be also performed to reduce potential confounders and selection bias. Furthermore, the research team members performing the statistical analysis will be blinded.

Blinding

To ensure a reduction in information bias during patient follow-up, the principal investigator is blinded. In addition, the post-interventional examinations are self-managed by people who depend on a physiotherapist and carried out for others by an external person trained and specialized in this field. This is done in such a way that the assessor is unaware of the patient's assignment, and the patient is asked not to reveal the group to which they have been assigned at any time. To further reduce the bias, both the therapist conducting the assessment and the therapist conducting the intervention program will be different people.

Intervention group

The intervention group will undergo an intervention based on PNE, which is an educational model for teaching pain biopsychosocial. It has been recognized as a compelling approach for managing chronic pain that adopts elements of user-based learning through the use of metaphors and examples (28). In addition, PNE is aimed at changing the understanding of what pain really is, the effects it has, and the biological processes that guide it. It refers to a theoretical framework for pain treatments, and the main goal of the approach is to change the conceptualization of pain as an indicator of tissue damage or pathology, progressively leading to a change in attitudes and the initiation of movements and activities in everyday life (29). This model is based on various educational interventions (19) and has been defined using the following terms: Explaining Pain (30), Therapeutic Neuroscience Education, and PNE. (31). Notably, PNE is increasingly used as part of physiotherapy treatment in patients with chronic, non-disciplinary, and neuropathic pain. A comprehensive biopsychosocial clinical assessment is recommended before PNE to adequately explain the neurophysiology of pain and biopsychosocial interactions, while ensuring that this process is patient-centered (29).

The clinical trial will comprise nine sessions over a period of 10 weeks, each lasting 30–40 minutes. These sessions will be scheduled weekly. Interventions will be scheduled on an individual or group basis (if possible). Supporting slides will be used to explain the content, and questions will be allowed throughout the sessions.
The content of the sessions will include elements based on book illustrations explaining pain, the second edition of the Spanish version (27) whose content will correspond to http://www.paininmotion.be/ (32); Louw's manual (33), and the explanation of pain in patients with cancer (7) which will be adapted from the use of examples and metaphors. For

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the organization of material corresponding to this intervention, some phases will be generated.
The sessions will be based on a guide with nine chapters organized as follows:

- Chapter 1, entitled "Living with Pain," conceptualizes the importance of pain as a defense system and functioning of the organism. Patients will reflect on what their life was like with pain and learn strategies that can help them in the process.
- In Chapter 2, entitled "Pain System," patients learn to understand that although pain is defined as a sensation, ultimately it is not, and rather becomes a perception. This in turn includes what is thought, felt, and believed about the situation.
- In Chapter 3, entitled "Alarm System," patients understand how the alarm system is activated via a detailed process involving neurons, synapses, conduction to the medulla, and processing at the cortical level in the presence of pain.
- Chapter 4, entitled "Extra Sensitivity Altered Alert System," aims to make the patient aware that their nerve cells become more sensitive in the presence of injury or pathology. This process is influenced by factors external to the injury, such as stress, fear, and the perception of pain itself, causing the tissues or organs surrounding the injury to trigger the alarm system as if it were a loudspeaker, leading to hypersensitivity.
- In Chapter 5, entitled "Pain Defenders," patients experience a new sense of pain. The pain can be compared to a big wolf or wild animal attacking the individual, wherein the individual's systems are activated to protect them from the threat and thus the brain makes survival-related decisions.
- In Chapter 6, entitled "Your Fatigue, Anxiety, and Stress," patients understand the function of cortisol and its effect on the sympathetic, parasympathetic, immune, and endocrine nervous systems. Additionally, they understand why living with the constant threat of chronic and persistent pain activates their systems to produce stress-related chemicals, which in turn cause them to experience related symptoms, such as depression, mood swings, changes in appetite, memory problems, weight gain, insomnia, fatigue, and anxiety.
- Chapter 7, entitled "Current Treatment Models," aims to make the patient recognize their fear as a powerful motivator that could help them find new strategies to understand their pain and its treatment, making them consider that they own this process and that they are the owners of their own decisions.
- In Chapter 8, titled "Goals and Achievements," patients understand that pain stems from sensations and that receptors transmit these sensations. Ideally, patients can be made aware at this point that there is evidence that education, knowledge, and understanding include strategies to help them improve and that exercise is important to turn off the alarm system.
- In Chapter 9, entitled "Emphasis and Pain Differentiation," the patient understands that pain does not mean there is damage and that their pain can be classified according to some characteristics as follows: nociceptive, nociplastic, and neuropathic.

Control intervention
The pharmacological treatment and indications will be evaluated by a doctor specialized in palliative care and pain. In particular, pharmacological treatment will be considered for

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both groups. Patients will be instructed to follow protocols established by the clinic: use of nonsteroidal anti-inflammatory drugs in the first instance for mild pain; tramadol at a maximum dose of 400 mg, codeine, or tapentadol for moderate pain; and opioids based on availability and use in Colombia, including morphine, oxycodone, hydromorphone, methadone, fentanyl (parenteral and transdermal use), and buprenorphine (transdermal use) for severe pain.

The PNE group will also be advised pharmacological modulation by the attending physician.

Community and expert participation

To organize the chapters, we worked with patients who served on the board of a foundation working for palliative care in the city of Cali and cancer experts for decision-making in consolidating the chapters as well as the feelings and concerns that arise while explaining them. Our approach also involved leveraging the expertise of professionals to validate the protocols, along with consulting a patient to gather pertinent information.

Outcomes

The measures of outcomes to be included were based on the pain assessment guideline by IMMPACT recommendations (34) as well as from the reports generated when working with patients with cancer (12).

As the primary outcome, the impact of pain is assessed using the BPI, and all secondary outcome measures are presented in Table 1. In particular, an assessment at baseline and 10 weeks after the intervention is considered. BPI is a self-administered questionnaire containing two dimensions: one related to pain intensity and the other to the effect of pain on the patient's activities of daily living. This is rated on a 10-point scale. Higher scores indicate more severe pain (35).

The Visual Analog Pain Scale is used to measure pain intensity on a 10-cm line (total score: 0–10; 0 = no pain and 10 = severe pain). Higher scores indicate a worse result (36).

Secondary measures

Central sensitization

The Central Sensitization Inventory is used to identify patients with symptoms related to central sensitization and has two sections: Section A comprises 25 questions about central sensitization syndrome symptoms, and Section B assesses the patient's condition in relation to their diagnosis. The patient answers the 25 questions in Section A with a score of 0–4. The total score is between 0 and 100. Scores of >40 indicate central sensitization (37).

Catastrophizing

The Pain Catastrophizing Scale is a 13-item self-administered questionnaire measuring three items of perceived pain intensity (rumination, magnification, and feeling helpless). Participants indicate the extent to which they agree with statements about their pain as 0, strongly disagree; 1, to a mild degree; 2, to a moderate degree; 3, to a great extent; and 4, all

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the time. It has three subscales that score rumination, magnification, and helplessness. All subscale scores are added to give a total score from 0 to 52. Higher scores indicate that the participant thinks more about the pain and feels helpless (38).

Kinesiophobia

The Tampa Scale is used to assess the fear of pain and movement. It comprises 11 items that are answered on a 4-point Likert scale. Total scores for each scale range from 11 to 44, with higher scores indicating a greater fear of pain and movement (39).

Depression

The Beck Depression Inventory will be used to assess the state of depression. It contains 21 categories measuring physical, emotional, cognitive, and motivational symptoms, and each category is scored between 0 and 3. The patient is then asked to select the most appropriate category. The score increases progressively from no symptoms to severe symptoms (0–10 points, no depression; 11–17 points, mild depression; 18–23 points, moderate depression; ≥24: severe depression) (40).

Neuropathic pain

The DN4 scale will be used to assess neuropathic pain, and it scores 4 questions out of 10 will be used to determine the symptomatology related to neuropathic pain (41).

Cognitive function

The MoCA assessment will be used for assessing cognitive impairment, and it consists of 19 items and 8 cognitive domains that assess skills such as visuo-spatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation; it can have a maximum score of 30, with 25 or 26 being the cut-off points for cognitive impairment (42).

Quality of life

The widely used questionnaire European Organization for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30) is used to assess the quality of life and includes five functional scales (physical, role, cognitive, emotional, and social functioning), a global quality of life scale, three symptom scales (fatigue, nausea, and pain), and six individual items (loss of appetite, diarrhea, dyspnea, constipation, insomnia, and economic impact). On the functional and global quality of life scales, a higher score indicates better health. On symptom scales, a higher score indicates a higher symptom burden (43).

Sleep quality

The Pittsburgh Sleep Quality Index is one of the most reliable tests for defining sleep quality and its disorders. It contains a total of 19 questions. Questions are grouped into seven scoring areas, each ranging from 0–3 points (44).

Functional capacity

A 6-minute walk test is used to determine exercise tolerance and functional status. The distance covered in meters in the last 6 minutes is measured (45,46).

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The Timed Get-up-and-Go test was developed as a predictor of falls and as a measure of functional capacity. In this test, the participant sits in a chair, stands up, walks for 3 m, and sits down again. The test runtime is calculated (47).

Manual grip strength

This is a marker of nutritional status as well as the morbidity and mortality associated with the pathological lesion. It will be measured using a dynamometer to establish the value of grip strength in kilograms (48).

Pharmaceuticals

The establishment of the baseline of the drugs used for pain, as well as the type, dose, and frequency of consumption will be generated.

Table 1. Description of the measurements

VARIABLES	DIMENSIONS	INDICATOR	VALUE
Sociodemographic features	Age	How many years old	• Age: ≥40 years
	Sex	Female or male	• Female or male
	Educational level	Level of schooling	• Incomplete elementary school education, complete elementary school education, incomplete high school education, complete high school education, technical education, technological college-level education, university-level education, and postgraduate
	Provenance	Urban or rural	• Rural or urban
	Affiliation regimen	Subsidized, contributory, or linked	• Contributory, subsidized, linked, or specialized
	Diagnostic period	Months	Months after the diagnosis
	Pharmacological treatment	Medication use	Use of medications and dosage
	Adjuvant treatment	Presence of adjuvant treatment	Chemotherapy or radiotherapy Frequency of administration
Physical measurements	Vital signs	Vital sign parameters	Heart rate Oxygen (O_2) saturation Respiratory frequency

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			Blood pressure
Impact of pain	Brief pain questionnaire	BPI	1–22 items to evaluate the degree of pain and its severity based on pain history
Presence of pain	Numerical assessment of pain	Numerical pain indicator	Numerical: score from 1 to 10 in pain Categorical: None, mild, moderate, or severe
Cognitive Function	Cognitive dimensions	Score range 0–30	Score on the MoCA test Categorical: Normal, mild impairment, moderate impairment, or severe impairment
Depression	Beck Index	Presence of 0–21 items	Numerical: Score obtained in the test Categorical: None, Mild, Moderate, and Severe
Kinesiophobia	Tampa Scale	11 items Score range from 1–4	Numerical: 1–4 Categorical: None, Mild, Moderate, and Severe
Catastrophizing	Catastrophization scale	13 items Score range from 1–4	Three factors: rumination, magnification, and hopelessness (scored from 1 to 4)
Central sensitization	Central sensitization inventory	25 points Score range 1–4.	This evaluates 25 pain-related symptoms, with scores from 0 to 100 Categorical: Yes or No
Neuropathic pain	Scale DN4	Score range 0–10 points	This evaluates four questions with possibility to score up to 10 points in order to determine the presence of neuropathic pain Categorical: Yes or No
Quality of sleep	Pittsburgh Sleep Quality Index.	Score range 0–21 points	Categorical: Good, Fair, or Poor
Quality of life	EORTC QLQ-C30	30 questions Score range 1–4	Assessment of the quality of life of patients with cancer
Functional capacity	TC6M 6-minute walk test.	Meters traveled	Meter indicator Heart rate Borg: Dyspnea; Fatigue

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	Timed Get-up-and-Go test	Time in seconds	Time in seconds
	Manual dynamometry	Force in kilograms	Force in kilograms

Data analysis

A statistical analysis will be performed based on the following steps:

A flowchart will be prepared to describe the process of patient recruitment and follow-up throughout the study based on the CONSORT Declaration. The flowchart will include the number of patients and reasons for exclusion, the number of patients randomized and assigned to the study units, and the losses and interruptions in the interventions within the groups (24).

An exploratory analysis will be performed to assess the data behavior and the key assumptions required for the application of a particular test (normality, linearity, or homoscedasticity); in addition, the presence of errors and biases in the data collected, the presence of anomalies, and all missing data will be assessed.

The sociodemographic and clinical variables will be analyzed in addition to those related to the patients' baseline oncological process at inclusion in the study by plotting their baseline characteristics according to the measurement scale of each variable using measures of central tendency, dispersion, frequency tables, and 95% confidence intervals. This analysis will be performed for each group and then subjected to homogeneity hypothesis tests based on the nature of each variable.

A univariate analysis of each described variable will then be performed considering the results before and after the intervention. In addition, we will perform a bivariate analysis to determine the correlation between dependent and independent variables and a multivariate analysis to examine the interaction and relationships between them.

Pain scores on the Pain Rating Scale will be considered the primary outcomes and quality of life scores and physical function test scores are secondary variables; the difference in their mean values between groups will be analyzed using the Student's t-test, and the difference within each group will be analyzed using the paired t-test. The interpretation of effect size will be performed using the Cohen's D index or coefficient, which classifies effect size as small (0.2–0.49), moderate (0.5–0.8), or large (>0.8).

A multivariate analysis will be performed using linear regression for the dependent variables, such as pain, cognitive function, depression, kinesiophobia, catastrophizing, pain impact, central sensitization, neuropathic pain, sleep quality, quality of life, and physical function. If the criteria of normality, homoscedasticity, and independence of the variable are not met, the possibility of transforming the variable will be evaluated. Once the regression has been performed, we will assess whether the model represents or resembles the observed data. To control for potential confounders, the variables previously considered as confounders will be adjusted, such as pharmacological dose, presence of adjuvant treatment, and previous hospitalizations for pain. In addition, the possibility of a change in the effect between these variables will be assessed.

The analysis will be carried out according to the protocol based on the specification for who completed the intervention, but the analysis will also be estimated based on the intention to treat the whole group.

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Data security and management

Participant data will be stored in a secure database in accordance with ethical considerations and good health practices. Each patient will be assigned an identifier to protect confidentiality. The information will be reviewed to determine the validity of the data. The data will then undergo additional checks to ensure that the information encrypted matches the information received.

Test monitoring

A pilot study will be initiated to determine the dosage for the different questionnaires to be used and the time and response capacity of the patients.

The material used during the intervention will be tested and reviewed by experts as well as patient representatives to verify the understanding of each of the constructed chapters.

Ethics and Dissemination

In this research, all participants will be provided with reasonable information about the objectives, methods, possible conflicts of interest, estimated benefits, foreseeable risks, and inconveniences arising from this investigation. Participants sign an informed consent form that clearly explains the procedure to be performed, the nature of the procedures, the benefits and risks they face, their ability to choose freely, and that everything will be performed without coercion. It will also be made clear that if the individual does not agree to participate, they can withdraw their consent at any time. This study was reviewed and approved by the Ethics and Bioethics Committee of the University of Santiago de Cali on October 8, 2021 according to act N°16. It was also submitted to the ethics committee at the Clínica de Occidente, Angiografía de Occidente and was approved on November 25, 2021.

Dissemination of results

The research team is committed to the full publication of the results of this study. The results will be reported according to CONSORT guidelines and are intended to be published in high profile journals. In the research, there is a component related to social acquisition and knowledge dissemination, and these results are expected to be presented to patient representatives and the various palliative care committees.

Contributorship statement

Ordoñez- Mora LT: Research idea, development of the intervention material, construction of materials and methods, statistical validation, review and approval of the manuscript. **Rosero ID**: Development of the intervention material, construction of materials and methods, statistical validation, review and approval of the manuscript. **Morales-Osorio MA**: Development of the intervention material, construction of materials and methods, statistical validation, review and approval of the manuscript. **Guil R**: Construction of materials and methods, statistical validation, review and approval of the manuscript. **Quintero Jordan G**: Development of the intervention material, review and approval of the manuscript. **Agudelo Jimenez J**: Construction of materials and methods, statistical validation, review and approval of the manuscript. **Gonzalez Ruiz K**: Construction of materials and methods, statistical

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validation, review and approval of the manuscript. **Avila-Valencia JC**: Construction of materials and methods, statistical validation, review and approval of the manuscript.

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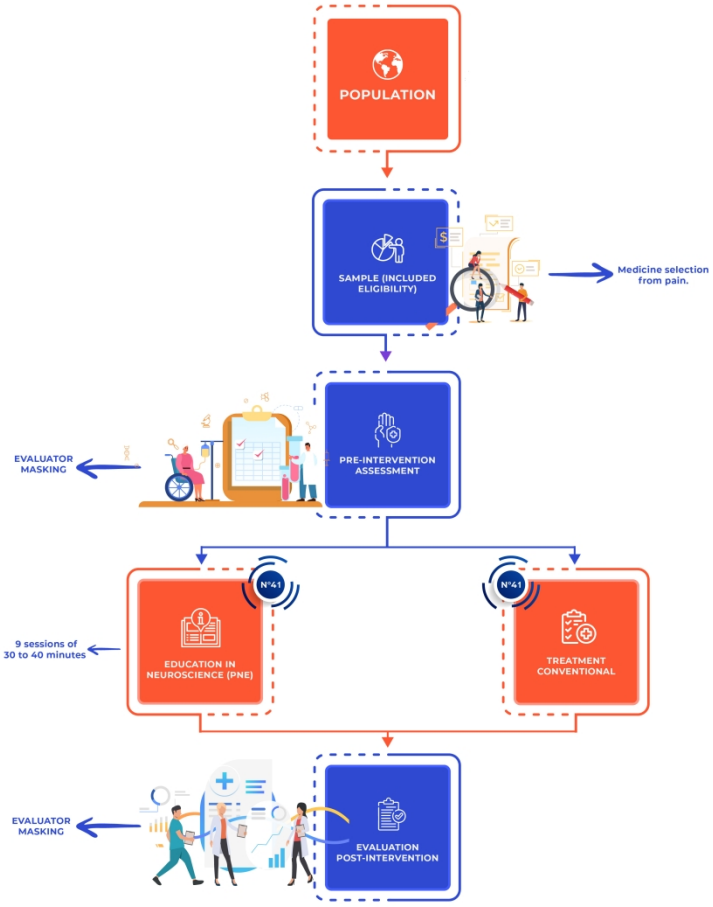

Study flowchart

381x381mm (300 x 300 DPI)

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Appendix 1. Diagram for recruiting and conducting interventions and evaluations according to SPIRIT Guidelines

STUDY PERIOD					
	Enrolment	Allocation	Post-Allocation		Close-out
Timepoint	$-t_1$	0	t_1	t_2	t_3
ENROLMENT					
Eligibility screen	X				
Informed consent	X				
Demographic characteristic	X				
Allocation		X			
INTERVENTIONS:					
PNE interventions					
Control (usual care)					
ASSESSMENTS:					
Baseline		X			
Primary pain measures		X		X	
Secondary variables		X		X	
Statistical Analysis					X

t1 Initial evaluation
t2 After 10 weeks

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17

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Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	13
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	2
Objectives	#7	Specific objectives or hypotheses	3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	4

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		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	5
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5

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Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12

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Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
Data monitoring: interim analysis	#21b	Description 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	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	na
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	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	12

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Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	18
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	12
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

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