# CLINICAL STUDY PROTOCOL

## EFFICACY & SAFETY OF PIROXICAM PLUS COUNTERIRRITANT GEL COMPARED WITH OTHERS TOPICAL NON-STEROID ANTI INFLAMMATION DRUGS IN MANAGING MUSCULOSKELETAL PAIN : A RANDOMIZED CLINICAL STUDY

**NO. PROTOCOL : CT_CTPPXM001_PRT_V003/IX/2025**

**Approved on 08 September 2025**

**Clinical Research Team**

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**Supported by:**

**PT Taisho Pharmaceutical Indonesia TBK**

**2025**

**History of CT_CTPPXM001 protocol changes as follows:**

| Protocol Version | Description |
|---|---|
| CT_CTPPXM001_PRT_V001/II/2025 | This is the first protocol that was reviewed by Clinical Research Team, TPI and TPI's consultant |
| CT_CTPPXM001_PRT_V002/VI/2025 | Protocol V001 has been revised to refer to BPOM RI Letter about Additional data and Protocol revision No. B-RG.01.06.32.323.5.2025.1759 on May 29th 2025. The revisions that applied in the PRT V002 are:<br>- The tittle of clinical study<br>- The clinical study background and justification of the study<br>- The study objective<br>- The study design<br>- The inclusion criteria<br>- The sample size<br>- The investigational products<br>- The study schedule |
| CT CTPPXM001 PRT V003/IX/2025 | Protocol V002 has been revised to refer to the discussion with BPOM RI on Aug 9th 2025.<br>The clinical study was conducted with the main aim of developing education and health standards in Indonesia. Thus, the concept of clinical study will be an Investigator Initiated Trial (IIT).<br><br>Add secondary objective point :<br>- Time (in days) musculoskeletal pain symptoms dissapear. |

| **Changes to this protocol have been reviewed and acknowledged by:** | | |
|---|---|---|
| **Sponsor**<br>**PT Taisho Pharmaceutical Indonesia** | | **Clinical Research Team** |
| **08 September 2025**<br>**dr. Ardini Kartasasmita**<br>**Medical Manager** | **08 September 2025**<br>**Aryani Pratami Dewi**<br>**Head of Regulatory Affairs and Medical** | **08 September 2025**<br>**dr. Erica Kholinne, Sp. OT (K), Ph.d**<br>**Principal Investigator** |

**PROTOCOL SIGNATURE PAGE**

**Clinical Research Team:**

**I agree to conduct the study in accordance with this Protocol and in compliance with all applicable Health Authority requirements, Good Clinical Practice and National Laws.**

| Name & Position | | Signature & Date of Signature |
|---|---|---|
| **dr. Erica Kholinne, Sp.OT (K), Ph.D**<br>**Principal Investigator** | | **Signature:**<br><br>**Date: 8 September 2025** |

## 1. GENERAL INFORMATION

| | |
|---|---|
| Clinical Study Tittle | : Efficacy and safety of Piroxicam Plus Counterirritant gel compared with others Topical Non Steroid Anti Inflammation Drugs in Managing Musculoskeletal Pain: a randomized clinical study. |
| Clinical Study Phase | : Phase III |
| Protocol Number | : CT_CTPPXM001_V003/IX/2025 |
| Protocol Date Version | : V003- 08 September 2025 |
| Principal Investigator | : dr. Erica Kholinne, Sp.OT (K), Ph.D |
| Sub-Investigator | : 1) dr. Astuti Pitarini, Sp.OT (K)<br>2) dr. A. Andi Kurniawan, Sp.KO Subsp. ALK (K)<br>3) dr. Wawan Budisusilo, Sp.KO<br>4) dr. Marion Cinta Kuntjoro, Sp.KFR |
| Sites | : Sports Medicine Clinic<br>1) Klinik Utama Eminence<br>2) St. Carolus Sports Clinic by Eminence |
| Sponsor | : PT Taisho Pharmaceutical Indonesia TBK<br>Millenium Centennial Center 8th Floor,Jalan Jend.Sudirman Kav. 25 Jakarta |
| Monitoring | : The monitoring of this clinical study will be conducted by certified Clinical Research Associates that appointed by Sponsor |

## 2. CLINICAL STUDY BACKGROUND

### 2.1 Piroxicam Plus Counterirritant gel

In 1972, an innovator topical analgesic product was introduced to the Indonesian market. Counterpain® is one of the topical analgesic products that is known not only in Indonesia, but also in other Southeast Asian countries such as Malaysia, Philippines, and Thailand. Counterpain® as an innovator product in Indonesia has several variants, namely Counterpain® cream helps with a warm sensation that relieve muscle pain, Counterpain® Cool with a cool sensation can be used for cooling during exercise and Counterpain® PXM effectively relieves inflammation in musculoskletal and joint.

There are many topical preparations containing non-steroidal anti-inflammatory drugs, namely diclofenac, ketoprofen and also piroxicam. Piroxicam preparations that are registered as innovator products in Indonesia :

- Feldene® gel which only contains Piroxicam as an active substance and
- Counterpain® PXM which contains Piroxicam, and Counterirritant: methyl salicylate, menthol and eugenol as active substances.

Counterpain® PXM was first registered and obtained marketing authorization in Indonesia in 2004 by Bristoll Myers Squibb (BMS). The registration process was completed by providing research data of Counterpain PXM-Thailand clinical study in 1995 as supporting data.

The pharmacokinetic parameters of piroxicam 0.5% topical gel were taken from data were determined in 20 healthy volunteers (6 women and 14 men) following application of multiple doses (20 mg piroxicam daily) over 14 days. 21 blood samples were drawn from each patient beginning just before application of the first dose, with the final sample taken 14 days after application of the last dose. Plasma concentrations of piroxicam were determined by high-performance liquid chromatography using UV detection at 340nm. There was considerable interindividual variation in piroxicam half-lives with a mean of 79 hours. Mean piroxicam plasma concentrations at steady-state were between 300 and 400 ng/ml, which is about 5% of those observed after equivalent doses of oral or intramuscular piroxicam. No adverse experiences were reported during the study period. Thus, the results of this study confirm the minimal systemic absorption of piroxicam during multiple-dose application of the 0.5% topical gel and the excellent tolerability of this mode of piroxicam therapy.

A study that conducted in 1995, with its tittle "The study of efficacy and safety of anti inflammatory and analgesic cream in the treatment of musculoskeletal pain" described that the standard piroxicam gel 0.5 % versus the test drug, piroxicam and analgesic cream containing methylsalicylate, eugenol and menthol are equally effective and well tolerated in the treatment of musculoskeletal pain. It was interesting to note that most of patients prefer to have the warm feeling after application as it indicates that the medication was working.

Another study that conducted in 1995, with its tittle "A double-blind randomized study to evaluate the safety and effectiveness of 0.5% Piroxicam gel compared to Counterpain Plus (combination of 0.5% piroxicam gel, 10% methyl salicylate, 5.4% menthol and 1.36% eugenol) in patients with mild osteoarthritis. As conclusion that both Counterpain Plus and Piroxicam gel are equally effective in gradual relief of the knee joint pain that assessed by Visual Analog Scale or Verbal Rating Scale. Both also equally effective help restore the patient's functional ability.

The last study that executed in 1995 with its tittle "Comparative study of the clinical effects of Counterpain Plus and Feldene Gel on knee arthrosis", found that there was no difference between the terms of biographic data, stage of degeneration, Moberg's functional scores and severity of pain between the groups at pre-trial and the end of the study. Counterpain Plus and Feldene gel have comparable clinical effects on the treatment of knee arthrosis.

In 2009, Taisho Pharmaceutical Holdings acquired the commercial rights of Counterpain in Indonesia. The distribution permit for the Counterpain® PXM product was transferred to PT Taisho Pharmaceutical Indonesia thereafter. Counterpain® PXM as a topical non-steroid anti inflamation drugs (NSAID) Plus Counterirritant such as methyl salicylate, eugenol and menthol, can be used to help relieve musculoskeletal pain and inflamation such as osteoarthritis, acute post-traumatic disorders: tendinitis, tenosynovitis, periarthritis, strain, sprain, muscle tense and low back pain, this indication is approved by BPOM RI in 2011.

There are no recent clinical studies in 2000 onwards that examine the efficacy of Piroxicam plus Counterirritant gel in the treatment of musculoskeletal pain compare with others topical NSAIDs such as Diclofenac gel or Ketoprofen gel.

### 2.2 Justification to conduct clinical study

Acute musculoskeletal pain describes conditions like a sprained ankle or a muscle pull. These usually get better over two or three weeks without treatment, but can be very painful while they

last. Topical non-steroidal anti-inflammatory drugs (NSAIDs) are applied to unbroken skin where it hurts as gels, creams, sprays, or plasters. Topical NSAIDs penetrate the skin, enter tissues or joints, and reduce processes causing pain in the tissue. Drug levels in the blood with topical NSAIDs are very much lower than with the same drug taken by mouth. This minimises the risk of harmful effects.

The review from Cochrane in 2019, "Topical NSAIDs for acute musculoskeletal pain in adults", formulations of topical diclofenac, ibuprofen, ketoprofen, piroxicam, and indomethacin demonstrated significantly higher rates of clinical success (more participants with at least 50% pain relief) than matching topical placebo (moderate or high quality data). From the 42 clinical studies data that taken into the systematic reviews, 15 studies are discussed about Diclofenac, and only 3 studies discussed about efficacy of Piroxicam gel in musculoskletal pain. None of those data explained about Piroxicam gel plus Counteriiritant.

Another review from Global Pain Faculty "The burden of musculoskeletal pain and the role of topical non-steroidal anti-inflammatory drugs (NSAIDs) in its treatment. Ten underpinning statements from a global pain faculty", published on Current Medical Research and Opinion, 2021, presents the conclusions of a detailed discussion on the role of topical NSAIDs during a round table Global Pain Faculty meeting held in Amsterdam in 2019 and subsequent discussions online. The document considers the place of topical therapies alongside other pharmacological and non-pharmacological treatments and presents the evidence for the benefits and harms of topical NSAIDS including indicators of efficacy for three main topical NSAIDs– diclofenac, ibuprofen and ketoprofen – based on almost 15,000 participants in randomized controlled trials for acute and chronic musculoskeletal pain. Randomized controlled trial evidence suggests that adverse events for active topical NSAIDs are similar to placebo. In this review, there is no discussion about effectiveness of Piroxicam gel especially Piroxicam gel plus Counterirritant in musculoskeletal pain.

A study that published in 2018, with its title "Relative efficacy and safety of topical non-steroidal anti-inflammatory drugs for osteoarthritis: a systematic review and network meta-analysis of randomised controlled trials and observational studies", showed that systematic review and network meta-analysis of RCTs and observational studies and have ranked the topical NSAIDs (including salicylate) based on the results. Among all available topical NSAIDs, diclofenac patches were most effective for pain relief and piroxicam gel was the best option to improve function.

By referring to above data from comprehensive review studies and meta-analyses studies, it can be seen that diclofenac gel has more clinical studies data compared to piroxicam gel, so the use of diclofenac gel for the treatment of musculoskeletal pain can be traced with the support of an adequate clinical data whereas this data becomes the basis for selecting standard topical drugs for musculoskeletal pain.

For this reason, a clinical study will be conducted to compare the effectiveness of Piroxicam plus Counterirritant gel with others topical Non Steroid Anti Inflammation Drugs such as Piroxicam gel and Diclofenac gel in the adult population with musculoskeletal pain. This clinical data will be used as a standard treatment in management of musculoskeletal pain.

The clinical study will be conducted with the concept of Investigator Initiated Trial (IIT) with the purpose to developing education and health standards in Indonesia, the result of study will be the source to develop a standard guidance in management of musculoskeletal pain using

topical non steroid anti inflammation drugs especially in Eminence and general in all sports medicine clinic in Indonesia.

## 3. COMPLIANCE WITH GCP

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with Indonesian National Agency for Drug and Food Control Guidance (Pedoman Cara Uji Klinik yang Baik - CUKB). The principal investigator shall conduct this study after agreeing with the sponsor on the content of the protocol of this study and the case report form and compliance with them.

## 4. STUDY OBJECTIVES

The objectives of this study is to demonstrate the equivallency of efficacy and safety in reducing muskuloskeletal pain between Piroxicam plus Counterirritant gel versus Piroxicam gel and Diclofenac gel, applied for $6 \pm 1$ days in Indonesian population.

Justification:
Piroxicam plus Counteriiritant, Piroxicam, Diclofenac are considered as topical Non-Steroid Anti Inflammantory Drugs (NSAIDs). Diclofenac more common to use as a standard topical treatment since they have more clinical studies data than others topical NSAIDs. To demonstrate that Piroxicam plus Counterirritant has the same efficacy with Piroxaicam, Diclofenac, the dedicated clinical study need to be conducted.

## 5. STUDY DESIGN

This is a Phase 3, Randomized Control Trial, Multi centre, Single-blind, and Parallel group of $6 \pm 1$ days duration of data collection after topical application to compare the efficacy and safety of standard treatment of musculosceletal pain in adult populations.
Justification :

- Phase 3 (Confirmatory study)
  The study is conducted to demonstrate whether or not a product offers a treatment benefit to adult participants with musculoskeletal pain between test drug (Piroxicam plus Counterirritant) and commonly used NSAID topical products, Piroxicam gel, Diclofenac gel
- Randomized Control Trial (RCT)
  Participants are randomly assigned to different treatment or control groups to minimize bias and allow for causal inference.
- Multi centre
  The study will be conducted in 2 sites
- Single-blind
  To keep this study maintain the integrity of the data, the investigational product will be given a white sticker to cover all over the tube of investigational products. On top of the tube, there is a study label with unique code to differentiate the test drug and comparator drug. With this procedure, participants will not know which products that assigned to them. Therefore participants can be blinded.
- Parallel

The study in which two groups of participants receive Piroxicam plus Counterirritant gel or Piroxicam gel, or Diclofenac gel . Participants are assigned to one of the treatment arms at the beginning of the trial and continue in that arm throughout the length of the trial. Assignment to a group usually is randomized.

**5.1 Primary End-Point:**

The primary end-point is the difference of musculoskeletal pain reduction $\geq$ 3 scores , of the response to treatment that can be seen through Brief Pain Inventory (BPI) scores.

Justification:

- The Brief Pain Inventory (BPI) scores.

It is a medical questionnaire that is used to assess pain. It has also been validated for pain assessment chronicle. There are 9 questions related to the pain experienced by the participants. The pain assessment will be given in the form of a score, namely a score of 0 - 10.

Score 0 : No Pain
Score 1 – 3 : Mild Pain
Score 4 – 6 : Moderate Pain
Score 7 – 10 : Severe Pain

The difference BPI scale $\geq$ 3 , from initial scale of pain to the end of treatment will be captured as the primary efficacy endpoint.

The selection of difference more than equal to 3 was chosen because if the participant has moderate pain at the beginning of the treatment, then at the end of the treatment there is a decrease in pain to mild pain. This can be seen that the treatment is effective in dealing with musculoskeletal pain.

**5.2 Secondary End-Point:**

1) In data related to safety assessment, the number of participants who experienced adverse events (including serious adverse events) with each symptom present will be recorded and causality of adverse events and serious adverse events assesses with the help of Naranjo's algorithm

Justification:

At the 1st visit, participants will bring home Participant's Diary. Participants need to fill in if they experienced with others symptoms after get the treatment. Also they need to file the rescue medication that they consume during the study timeline. On the 2nd visit and last visit the Investigator will ask about the diary and confirmed the symptoms and medication. When there is safety report, the Investigator will fill in the Safety Form from BPOM RI (Form Kuning MESO) and assess the safety events with the help of Naranjo's algorithm.

The type of symptoms and the number of participants who have symptoms and including side effects will be recorded and become data related to product safety.

2) Investigator Assessment on Participants motions, through Range of Motion (ROM) and Muscle test.

Justification:

One of the symptoms that must be assessed when there is musculoskeletal pain is the range of motion and muscle movement to perform an activity. Therefore, an assessment for the examination of the range of motion and muscle strength carried out by the examining doctor is needed to determine the effect of the treatment carried out in the success of performing the activity.

The effectiveness of the treatment will be seen from the progress in the range of motion that can be performed by the participant at the end of the treatment compared to the beginning of the treatment according to scientific standards.

Range of motion (ROM) or motion arc in this study will be measured using a universal goniometer following standardized procedures to ensure accuracy and reproducibility. Each joint will be assessed in a consistent anatomical position—either supine, seated, or standing—depending on the specific joint involved (e.g., seated for elbow, supine for knee). The Principal Investigator or Sub-Investigator will perform three consecutive measurements for each motion (e.g., flexion, extension), and the average value will be recorded. Key movements assessed will include knee flexion-extension, ankle dorsiflexion-plantarflexion, elbow flexion-extension, and lumbar spine flexion or fingertip-to-floor distance for back pain. The same assessor will conduct all measurements at each time point to minimize inter-rater variability. Any limitations due to pain, guarding, or compensatory movements will be noted. ROM data will be recorded on standardized forms and used to evaluate treatment effectiveness by comparing baseline to post-treatment values against established minimal clinically important difference (MCID) thresholds.

In this study, the minimal clinically important difference (MCID) for joint range of motion (ROM) will be used to define clinically meaningful improvements in mobility following treatment. Based on validated references, the MCID values applied are ≥ 10° for knee flexion/extension (Mizner et al., 2005) and elbow flexion-extension arc (Picha et al., 2020), ≥ 5° for ankle dorsiflexion/plantarflexion (Cleland et al., 2013), and either ≥ 10% change or ≥5 cm improvement for lumbar spine mobility, depending on the measurement method used (Stratford et al., 1994). These thresholds represent the minimum degree of change perceived as beneficial by patients and are appropriate benchmarks for evaluating functional recovery in musculoskeletal pain conditions.

3) Assessment to investigate scales on thermal sensation, thermal comfort, and thermal acceptance using ASHRAE 7-point scale quistionnaire and completed with time starting the thermal sensation.

Definition:
Thermal comfort is the condition of mind that expresses satisfaction with the thermal environment and is assessed by subjective evaluation.
Thermal sensation is assessed to determine whether a specific thermal condition can be considered comfortable or not. The most prominent scale used for the assessment of thermal sensation is the ASHRAE 7-point scale, which consists of seven verbal anchors: “cold”, “cool”, “slightly cool”, “neutral”, “slightly warm”, “warm”, and “hot”.
Thermal acceptance, refers to the degree to which a temperature range or condition is considered acceptable or tolerable by individuals.
The number of thermal sensations felt related to the product will be the result related to the participant's acceptance of the sensation.

4) Assessment to investigate the disapperance time of musculoskletal pain (in days).

Definition:
To know the medication given is effective or not, we need to evaluate the musculoskeletal pain score. One of the result that can be seen is the disappearance time of musculoskletal pain.

## 6. PARTICIPANTS

In selecting participants, Investigator shall carefully examine whether or not it is appropriate to ask for participation in the study, paying attention to matters including dependence on the principal investigator or other personnel, from the perspective of protection of human rights.

Among patients who have “Target Disease,” those who meet “Inclusion Criteria” and do not meet any of “Exclusion Criteria” will be examined.

### 6.1 Target Populations

Participants who were diagnosed with acute musculoskeletal pain will be recruited in this study.

The acute musculoskeletal pain caused by arthritis such as osteoarthritis (OA) with Grade 0 until III Kellgren-Lawrence (KL) grading, or musculosceletal disorders such as ankle sprain, patella tendinitis, tennis elbow, and back pain as mentioned in topical NSAIDs indication that approved by BPOM RI.

Diagnosis criteria were made by history taking, physical examination and radiologic evaluation if necessary.

Justification:

Acute musculoskeletal pain is defined as pain arising from the musculoskeletal system (muscles, bones, joints, ligaments, and tendons) that is sudden in onset and relatively short-lived.

- Subject with musculoskletal pain caused by Osteoarthritis, Grade 0 – Grade III Kellgren-Lawrence

  Grade 0 : No radiographic evidence of osteoarthritis.

  Grade 1 (Doubtful) : Possible osteophytes (bone spurs) and doubtful joint space narrowing.

  Grade 2 (Minimal) : Definite osteophytes and possible joint space narrowing.

  Grade 3 (Moderate) : Moderate joint space narrowing, multiple osteophytes, some sclerosis (increased bone density), and possible bone deformity.
- Subject with musculoskletal pain caused by musculoskletal disorder, such as :

  Ankle sprain is a common injury that occurs when the ligaments in the ankle are stretched or torn due to a sudden twisting or rolling motion of the foot.

  Patellar tendinitis, also known as jumper's knee, is an inflammation of the patellar tendon, which connects the kneecap (patella) to the shinbone (tibia).

  Tennis elbow, also known as lateral epicondylitis, is a condition characterized by pain on the outer side of the elbow, specifically near the bony prominence (lateral epicondyle). It's typically caused by overuse or repetitive motions of the forearm muscles, which can lead to tiny tears and inflammation in the tendons that attach these muscles to the elbow.

  Back pain, also known as dorsalgia, refers to pain experienced in the back, from the base of the neck to the top of the buttocks.

### 6.2 Inclusion criteria

- Outpatient in a health care setting.
- Between the ages of 18 - 60 years of either sex.
- Patients diagnosed with musculoskeletal pain as described in the target population.
- Patient can read and understand how to fill out the assessment form and diary.
- Patients gave written consent to participate in the study independently.

### 6.3 Exclusion criteria

- Patient who has osteoarthritis with Grade IV Kellgren-Lawrence (KL) grading.
- Patients who underwent any of the following treatments:
  - Paracentesis and drainage of joint

- Intraarticular injection (joint protection agents, local anesthetic, etc.)
- Nerve block (including trigger points)

- Patients are being treated with an analgesic opioids for their musculosceletal pain.
- Patients being treated with anti coagulant therapy such as warfarin, clopidogrel.
- Patients being treated with oral corticosteroids 3 days before and until signed the informed consent.
- Patients being treated using rigid orthoses those requiring such treatment
- Patients with neuropsychiatric disorders including depression, dementia, schizophrenia, and anxiety neurosis
- Patients with Grade 3 hypertension (systolic blood pressure ≥ 180 mmHg and diastolic blood pressure ≥ 110 mmHg regardless of the use of an antihypertensive drugs)
- Patients with acute peptic ulcer
- Patients with bronchial asthma or those with current or previous aspirin-induced asthma (asthmatic attacks induced by NSAIDs and other relevant drugs)
- Patients with a history of hypersensitivity or allergy to NSAIDs
- Patients with serious hepatic disease, renal disease, cardiac disease, hematologic disease, or malignancy
- Patients with a history of dermatitis requiring treatment with topical agents
- Patients with dermatitis or wounds at the application site of the study drug
- Pregnant women, women who may be pregnant, women who wish to become pregnant during the study, or nursing women
- Patients considered by the Investigator to be inappropriate as participants of this study

### 6.4 Withdrawal Criteria

- Any clinical adverse event, serious illness, or other medical condition identified by the investigator or treating doctor that suggests continued participation is not in the subject's best interest.
- A voluntary decision by the patient to withdraw from the study.
- If the subject was found to have entered the study in violation of the protocol or if the patient was uncooperative during the study.
- Any subject who required the use of an unacceptable concomitant medication—defined as a medication that interfered with the study—will be addressed with justification from the investigator.

### 6.5 Preparation of Consent Form and Other Written Information for Patients

The principal investigator prepares the consent form and other written information for patients that are used to obtain the consent of participants to participate in the study and revise them as necessary, in cooperation with the sponsor. The principal investigator submits the prepared or revised documents concerned to the sponsor and obtains prior approval of the institutional review board.

#### 6.5.1 Matters That Should be Included in Consent Form and Other Written Information for Patients

The consent form and other written information for patients must include the following matters at least.

- That the study involves research.

- Study objectives
- Names and contacts of the investigators
- Study methods
- Anticipated advantages for physical and mental health of participants resulting from the study drugs (if such advantages are not expected, to that effect) and anticipated disadvantages to participants
- Presence or absence of other therapeutic methods for the patients concerned and the important benefits and risks anticipated in association with these therapeutic methods
- Anticipated duration of participation in the study
- That participation in the study is voluntary and the participants can reject to participate or stop participating in the study any time. That the participants will neither be treated unfairly due to such rejection or withdrawal nor lose the benefits they should have received for the reason of not participating in the study
- That monitors, people in charge of audit, institutional review boards and other personnel and the regulatory agency can view the source documents related to the medical care That subject confidentiality will be protected in such viewing That, by signing the consent form, participants agree to the viewing
- That subject confidentiality will be protected when the study results are published
- Consultation service at the study site participants should make inquires to or contact when they wish to have further information regarding the study and their rights or when any health hazard associated with the study occurs
- Compensation and treatment participants can receive when health hazards associated with the study occur
- Anticipated number of participants participating in the study
- That any information that may influence the intention of participants to continue to participate in the study is promptly provided to participants if such information was obtained
- Conditions or reasons for terminating the participation of certain participants in the study
- Details of the expense of participants, if any
- Details of the payment in cash, etc. to participants, if any
- Rules that participants should follow
- Matters regarding the institutional review boards that investigate and deliberate the adequacy of this study, including the types of institutional review boards, etc. and the matters investigated and deliberated by each institutional review board

### 6.5.2 Timing and Method of Informed Consent

Investigator provides sufficient explanation to  before conducting the study, using the consent form and other written information for patients, confirms that the participants fully understood the explanation, and then obtains written voluntary consent of the participants themselves to the participation in the study. Investigator who provided the

explanation and the subject write down their names and place their seals on or sign and date the consent form.

Investigator gives a copy of the consent form and other written information for patients to the participants who agreed to participate in the study and records it. The above receipt of documents can be recorded in a column for receipt prepared in the medical record or the consent form. The original consent form is retained at the designated area at each study site.

Investigator enters the date of consent in the case report form.

### 6.5.3 Points for Consideration in Acquisition of Consent

The principal investigator, sub-investigator, or clinical research coordinator shall consider the following points regarding acquisition of consent.

- Participants must be neither forced to participate or continue to participate in the study nor unduly influenced in their decisions.
- In the explanation, any phrases that make or appear to make participants waive their rights or release or appear to release the principal investigator, sub-investigator, CRC, study site, and sponsor from liability must not be used.
- In the explanation, words that are understandable to participants and as non-technical as possible must be used.
- Before consent, participants must be given a chance to ask questions and sufficient time to decide whether to participate in the study. On the above occasion, all the questions must be answered to the satisfaction of the participants.

### 6.5.4 Revision of Consent Form and Other Written Explanation for Patients (provision of new information)

(1) When Investigator obtained new information that may influence the intention of participants to continue to participate in the study or may be related to the consent of the participants (including reports of serious ADRs), Investigator verbally gives the information concerned to the participants immediately and confirms whether or not the participants intend to continue to participate in the study. Investigator also records the information Investigator has given and the result of confirmation in the medical record or other documents.

(2) In cases described in (1), if the principal investigator acknowledges the necessity of revision of the consent form and other written information for patients, principal investigator promptly revises the consent form and other written information for patients based on the information concerned and newly obtains the approval of the institutional review board.

(3) Investigator provides explanation again using the consent form and other written information for patients that were revised according to the rule in (2) to the participants including those who already received the information concerned verbally and obtains their written consent to continuation of participation in the study. However, explanation does not have to be provided to the participants who already completed the study.

## 6.6 Subject Enrollment

A unique subject IDs will be assigned to each participant by the Investigator at 1st visit. This number will serve as the participant's identifier in the study as well in the study database. This subject IDs will be unique across each site and it will be a 5 digit number including last three digits will be the subject ID at each site with hyphen between the site number and the last three digits. Site number will be assigned by Sponsor.

At the start of the study, the principal investigator assigns participant ID to the participants who gave written consent by themselves. Two copies of the screening list of participants that includes the information of the participants who gave consent are prepared. One copy is retained and the other copy is submitted to the sponsor. Regarding the participants who were not enrolled, the reason is recorded.

On the CRFs or other documents submitted to the Sponsor, participants should not be identified by their names, but by their assigned subject IDs only. If subject names are included on copies of documents submitted to the Sponsor, the names must be obliterated and the assigned subject ID added to each of the documents.

## 6.7 Sample Size

Assumptions
- Outcome : Pain score
- Standard deviation ($\sigma$) : 1.81
- Clinically meaningful margin ($\Delta$ or $\delta$) : 1.0
- Power : 80% ($Z_{1}$-$\beta$ = 0.84)
- Significance level ($\alpha$) : 0.05

Reference standard deviation from Kocak AO, Dogruyol S, Akbas I, Menekse TS, Gur STA, Kocak MB, Cekmen B, Orun S, Cakir Z. Comparison of topical capsaicin and topical piroxicam in the treatment of acute trauma-induced pain: A randomized double-blind trial. Am J Emerg Med. 2020 Sep;38(9):1767-1771. doi: 10.1016/j.ajem.2020.05.104. Epub 2020 Jun 2. PMID: 32739846.

For **equivalence trials with 3 groups**, you typically plan for **pairwise equivalence testing**:
- Diclofenac vs. Piroxicam
- Diclofenac vs. PXM plus Counterirritant
- Piroxicam vs. PXM plus Counterirritant

This means you must **adjust α** to account for **multiple comparisons**, commonly using **Bonferroni correction**:

Adjusted $\alpha = 0.05 / 3 = 0.0167 \rightarrow Z_{1}\text{-}\alpha/2 \approx$ **2.39**

**Sample Size Formula and Calculation**

Using the formula for equivalence trials:

$n = ((Z_{1}\text{-}\alpha/2 + Z_{1}\text{-}\beta) \times \sigma / \Delta)^2$

Substituting the values:

$n = ((2.39 + 0.84) \times 1.81 / 1.0)^2$

$n = (4.059 \times 1.81)^2 = (7.35)^2 = 54.0$

Sample size per group (rounded): 54
Total sample size for 3 groups: 162

With 10% dropout:
Total = 162 / (1 - 0.10) ≈ 180 participants
Recommended: 60 participants per group

The clinical study will be recruited in total 180 subjects, which means 60 subjects per arm.

Justification:

- We used the reference from Kocak et al. because: The study used topical piroxicam, which is the main active ingredient in Counterpain PXM. The study was randomized, double-blind, and controlled, and reported the standard deviation of pain scores in full—a parameter that is essential for sample size calculations. To date, we have not found any publications comparing diclofenac gel directly with topical piroxicam, with standard deviations appropriate for use in statistical calculations. So, even though the comparator was capsaicin, this reference was chosen because it is quite representative in terms of pain type and study design.

## 6.8 Study Drugs

The specific information about Study Drugs will be described in the Study Drugs Handling Manual.

### 6.8.1 Test Drug : Counterpain® PXM

- Active Ingredients : Piroxicam plus Counterirritant (Methyl Salicylate, Eugenol and Menthol)
- Dose :
  Adults : Refer to product's leaflet as follow: no occlusive dress should be employed. Apply gel to the affected area three times daily leaving no residual material on the skin. 1 gram of gel ( ~ 3 cm) applied to the affected area.
  The affected areas are:
    - The arms: hand, wrist, elbow, shoulder sinistra or dextra
    - The legs: feet, ankle, knee sinistra or dextra
    - Upper back or Lower back

  3 times daily means:
    - application one time in morning (06.00 – 11.00),
    - one time in afternoon (11.01 – 17.00),
    - one time in evening (17.01 – 23.00).

  Aplication of gel will use dosing cards that provided in this clinical study.
- Method of administration: external use only.
- Every visit, participants will get 2 tubes and in total are 6 tubes for 6 $\pm$ 1 days application.

Justification:
The dosage for use refers to the Counterpain® PXM leaflet which has been approved by BPOM RI.
Refer to Counterpain® PXM data that 1 gram equal to 3 cm.

| Counterpain PXM dalam gram | Setara dengan ukuran (cm) | Setara dengan assay Piroxicam (mg) | Kandungan zat Counterirritant didalamnya | | |
|---|---|---|---|---|---|
| | | | Methyl Salicylate | Menthol | Eugenol |
| 1 gram Counterpain PXM | 3 cm | Mengandung Piroxicam 4.7 - 5.1 mg | Methyl Salicylate 97.2 - 119.17 mg | Menthol 48.5 - 55.9 mg | Eugenol 12.5 - 14.7. mg |

1. 1 GRAM

Foto ukuran dalam cm yang setara dengan 1 gram Counterpain PXM

### 6.8.2 Comparator Drug : Hotin® DCL

- Active Ingredients : Diclofenac Diethylamine 11.6 mg (Diclofenac Sodium 10 mg)
- Dose : Refer to the product's leaflet : no occlusive dress should be employed. Apply the required amount of cream on the affected area three times a day and rub gently. The amount of cream needed depends on the extent of the painful area. The affected area are :
    - In the arms: hand, wrist, elbow, shoulder sinistra or dextra
    - In the legs: feet, ankle, knee sinistra or dextra
    - Upper back or Lower back

  3 times daily means :
    - application one time in morning (06.00 – 11.00),
    - one time in afternoon (11.01 – 17.00),
    - one time in evening (17.01 – 23.00).

  Aplication of gel will use dosing card that provided in this clinical study.
- Method of administration: external use only.
- Every visit, participants will get 2 tubes and in total are 6 tubes for 6 $\pm$ 1 days application

Justification:
The dosage for use refers to the HOTIN DCL® leaflet which has been approved by BPOM RI

### 6.8.3 Comparator Drug : Pirofel® gel

- Active Ingredients : Piroxicam 0.5%
- Dose :

Adults : Refer to product's leaflet as follow : no occlusive dress should be employed. Apply gel to the affected area three times daily leaving no residual material on the skin. 1 gram of gel applied to the affected area.
The affected area are :

- In the arms: hand, wrist, elbow, shoulder sinistra or dextra
- In the legs: feet, ankle, knee sinistra or dextra
- Upper back or Lower back

3 times daily means :

- application one time in morning (06.00 – 11.00),

- one time in afternoon (11.01 – 17.00),
- one time in evening (17.01 – 23.00).

Aplication of gel will use dosing card that provided in this clinical study.

- Method of administration: external use only.
- Every visit, participants will get 2 tubes and in total are 6 tubes for 6 ± 1 days application.

Justification:
The dosage for use refers to the Pirofel® gel leaflet which has been approved by BPOM RI.

**Dosing Card**


**6.9 Study Drugs Labelling**

A label is needed for the study drug used.
Investigational products will be given to Participants in tube only, no individual box.
All Investigational Products tubes will be covered by white sticker, leaving only the tip of the tube containing the batch number and expiration date information. On top of the white sticker will be a study drug label that have specific code and number.
Below is the labelling process for investigational products :

The packaging label from investigational products will be covered by a white secured sticker. Only the bottom side (tail) which contains the batch number information is left open.

Clinical study label will be put on the top of white sticker.


Final label on the tube


Every tube will be numbered with drug number sequentially, as detailed:

| Test drug (Yellow sticker) | Comparator drug (Orange Sticker) | Comparator drug (Brown Sticker) |
|---|---|---|
| C001 | H001 | P001 |
| C002 | H002 | P002 |
| C003 | H003 | P003 |
| etc. until the last of stock | etc. until the last of stock | etc. until the last of stock |

- Initial “C” for study drug and 3 digits number
- Initial “H” for comparator drug and 3 digits number
- Initial “P” for comparator drug and 3 digits number

### 6.10 Rescue Medication

Rescue medication can be given to patient who have given informed consent. The rescue medication given is only if the subject can not bear the pain and to help reduce pain and per investigator advise. The rescue medication is a drug specifically provided for this study. The use of rescue medication will be recorded. The dosage of rescue medication will be determined by the Investigator.

- Active Ingredients : Paracetamol 600 mg
- Brand name : Sumagesic
- Dose : 1 tablets maximum 3 dose per 24 hours or refer to Investigator advise.
- Method of administration: Oral.

### 6.11 Storage Method

Please keep under 30° C, protect and avoid direct light. Kept until 1 month after the product opens.

### 6.12 Dispensing, Storage, Management, and Collection Procedures

The Study Drug Handling Manual will be provided and completed to ensure the study drugs are prepared, shipped, stored, dispensed, and returned to comply with regulations.

The Investigational Products will be relabelled in Sponsor Technical Operations Plant Site. After the Sponsor ensures the quality of the product, the study drug will be relabeled, which means that this drug is used explicitly for clinical studies.
The sponsor will deliver the study drug from the Technical Operations plant to each research site by courier, where it can monitor the temperature of the study drug delivery below 30°C.
The Study Coordinator from each research site will ensure the storage of study drugs.
During the study, the distribution of study drug participants will be prescribed by the Investigator based on randomization and dispensed to the participants by the Sports Therapist during the recovery program.

Use GraphPad QuickCalcs (https://www.graphpad.com/quickcalcs/randomize1/) to generate a random allocation list, ensuring equal numbers for each treatment group:

- Group A: Piroxicam + Counterirritant
- Group B: Piroxicam
- Group C: Diclofenac

Each eligible participant will be assigned a unique subject ID upon enrollment. The study coordinator will match the subject ID to a treatment group based on the pre-generated list. All tubes will be labeled with a sticker displaying only the randomization code to maintain blinding of both participants and investigators. The tube will then be dispensed to the participant according to the assigned code. Only the investigator will have access to the full randomization list.

At the end of the study period, all study drugs will be returned by the participants to each site. This return process will be assisted by each Study Coordinator. An then be sent to Technical Operations for destruction.

### 6.13 Adherence of study drug

The dose of study drugs used during treatment period is checked based on the diary. If AE is occurred to the subject, Investigator can reduce or stop the dose of study drugs.

### 6.14 Unacceptable Concomitant Medication

As explained in the clinical data and pharmacokinetics and pharmacodynamics of Paracetamol, the drugs mentioned below are known to have interactions with Paracetamol. For this reason, it is not acceptable to get the following treatment:

- Opioid Analgesics
- Oral Non Steroid Anti Inflammation Drugs
  Caution is recommended when analgesic products are used in combination because of possible increases in adverse events (e.g. nephrotoxicity, gastrointestinal lesions, bleeding).
- Alcohol
- Anticoagulants – Oral, Injection: Piroxicam is highly protein bound. There is therefore a possibility of interaction with such drugs as coumarin anticoagulants

## 7 STUDY PLAN

### 7.7.1 Group Composition

The following 2 groups are examined. The participants are allocated to these groups at the ratio of 1:1 that will be randomized.

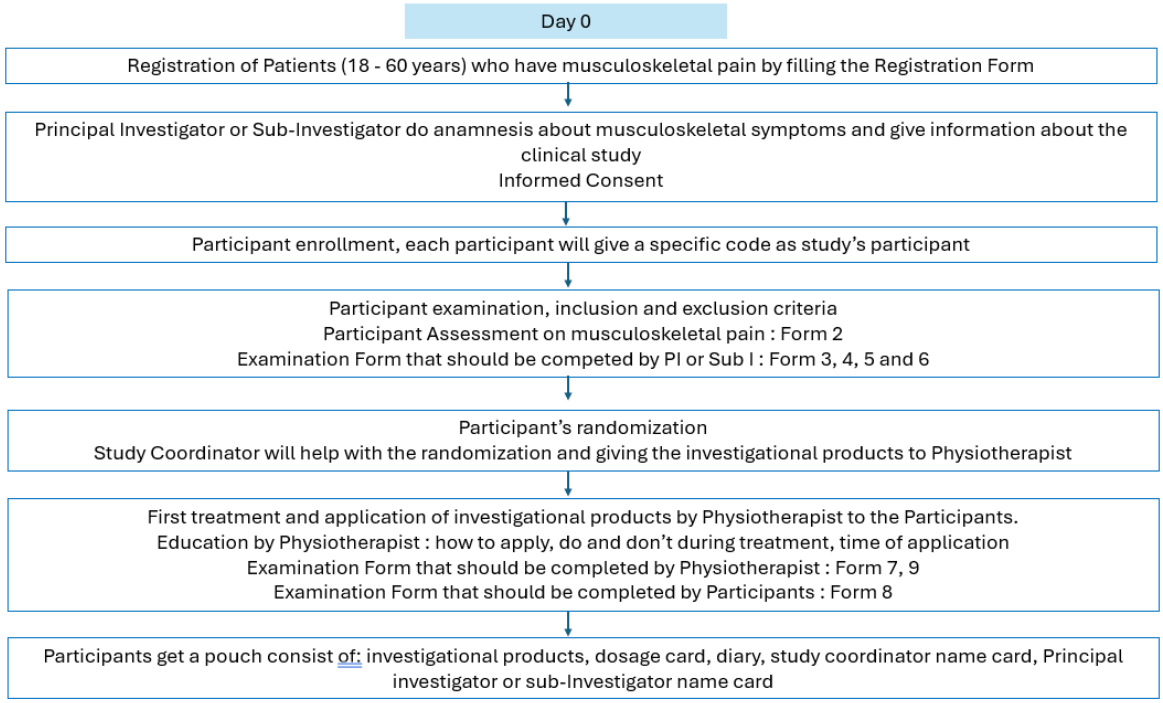
- Test drug group : Piroxicam plus Counterirritant Gel
- Comparator group : Diclofenac diethylamine Gel
- Comparator group : Piroxicam Gel

### 7.7.2 Study period and process

The study period for each participant is defined as “the period from the day of consent to the end of study (the day on which final tests and observation are finished or the day of discontinuation of the study).

The participants considered as a complete visit after the 3rd visit examination on 6 ± 1 days visit.

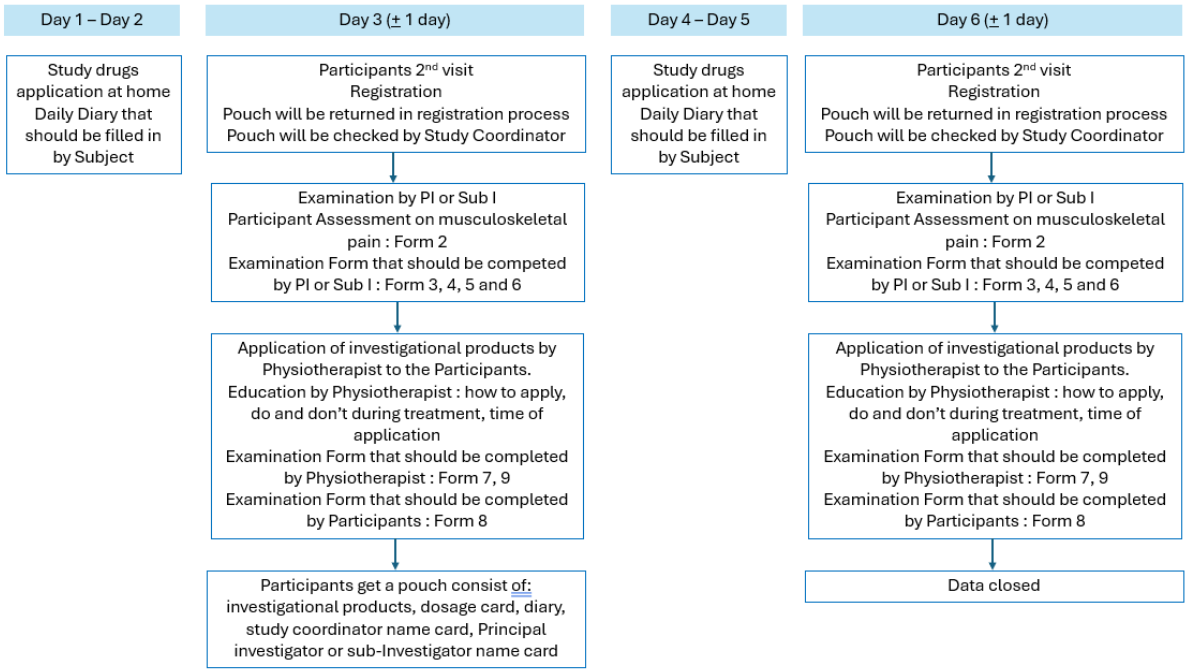
- 1st visit consider as Day 0
- 2nd visit is on Day 3 ± 1 days
- 3rd visit is on Day 6 ± 1 days




The study's flow in Day 0 :

1) The registration officers will receive participants who register at the Eminence clinic and ask about symptoms related to the participant's visit. If the Participant complains of pain, the patient will be asked to fill out a registration form.
2) The Principal Investigator or Sub Investigator will ask some questions (anamnesis) about the symptoms and explain about a clinical study that is conducted in the clinic. The PI or Sub-I will ask the Participant's willingness to join the research and explain regarding informed consent. If the Participant agrees, an informed consent will be signed.
3) The participants are asked to complete the Individual Assessement of Pain.
    a. Form 2 : Pemeriksaan Inventerisasi Rasa Nyeri Singkat
4) The examination was carried out by conducting anamnesis, physical examination to confirmation the musculoskletal pain, range of motion and muscle test and confirmation related to the inclusion and exclusion criteria. If needed a radiologic examination will be conducted.
5) In the examination, the PI or Sub-I should complete some Forms :
    a. Form 3 : Pemeriksaan Awal Rasa Nyeri
    b. Form 4 : Pemeriksaan Indikator Rasa Nyeri Non Verbal
    c. Form 5 : Pemeriksaan Rentang Gerak
    d. Form 6 : Pemeriksaan Kekuatan Otot
6) The PI or Sub-I will provide a diagnosis and therapy appropriate to the diagnosis.

7) Randomization of participants is carried out helped by Study Coordinator. The administration of therapeutic drugs according to the randomization list by a physiotherapist. The physiotherapist will provide information related to how to apply topical drugs to participants and provide the first dose of the investigational product in the therapy room.
    a. Form 7 : Pemberian aplikasi obat topikal by Physiotherapist
    b. Form 8 : Sensasi Termal by Participant
8) Each participant will get physical therapy program refered to standard protocol and diagnosis
9) Each participant will be given a pouch containing 2 tubes of investigational products, 3 dosing cards, 4 strips of rescue medications, a participant diary, a study coordinator business card and a PI or Sub-I business card.




The study's flow in Day 1 - Day 3 (± 1 day)

1) Participants will continue topical medication sessions at home. The Study Coordinator will assist with daily reminders for topical medication administration and diary completion. Participants will be asked to return to the study site on day 4 ± 1 day with carrying the left over tubes and rescue medications, dosing cards, diary and put inside the pouch.
2) The participant will do the re-registration to registration officer and send back the pouch that will be given to the Fisiotherapist.
3) The examinations will remains same as Day 0 from poin 2 until 5.
4) The physiotherapist will provide information related to how to apply topical drugs to participants and applied the dose of the investigational product in the therapy room.
5) The administration of therapeutic drugs according to the randomization list by a physiotherapist. The physiotherapist will provide information related to how to apply topical drugs to participants and provide the dose of the investigational product in the therapy room.
    - Form 7 : Pemberian aplikasi obat topikal by Physiotherapist

- Form 8 : Sensasi Termal by Participant

6) Each participant will be given a pouch containing 2 tubes of investigational products, 3 dosing cards, 4 strips of rescue medications, a participant diary, a study coordinator business card and a PI or Sub-I business card.
7) Participants will continue topical medication sessions at home. The Study Coordinator will assist with daily reminders for topical medication administration and diary completion. Participants will be asked to return to the study site on day 8 $\pm$ 1 with carrying the left over tubes and rescue medications, dosing cards, diary and put inside the pouch.

The study's flow in Day 5 - Day 6 ($\pm$ 1 day)

1) Participants will continue topical medication sessions at home. The Study Coordinator will assist with daily reminders for topical medication administration and diary completion. Participants will be asked to return to the study site on day 6 $\pm$ 1 day with carrying the left over tubes and rescue medications, dosing cards, diary and put inside the pouch.
2) The participant will do the re-registration to registration officer and send back the pouch that will be given to the Fisiotherapist.
3) The examinations will remains same as Day 0 from poin 2 until 5.
4) The PI or Sub-I will give information that this is the last day of the study and the investigational drugs application last dose will be given by the physiotherapist.
5) The administration of therapeutic drugs according to the randomization list by a physiotherapist. The physiotherapist will provide information related to how to apply topical drugs to participants and provide the last dose of the investigational product in the therapy room.
   - Form 7 : Pemberian aplikasi obat topikal by Physiotherapist
   - Form 8 : Sensasi Termal by Participan
6) End of Study.

### 7.7.3 Ensuring Safety of Participants

Basic Points

1) The Principal Investigator is responsible for all the medical decisions related to the study.
2) The Principal Investigator ensures that sufficient medical care for all the AEs related to the study is provided to participants during their participation in the study and after that.
3) The sponsor is responsible for continuously assessing the safety of study drugs.
4) The sponsor promptly notifies all Principal Investigators involved in the study of the information that may adversely affect the safety of participants, influence the conduct of the study, or require changes in the approval of the continuation of the study by the institutional review board (IRB)/EC.

## 7.8 CRITERIA AND PROCEDURE FOR DISCONTINUATION FOR PARTICIPANTS

### 7.8.1 Discontinuation Criteria

Investigator discontinues the study when a subject meets the following criteria.

1. When continuation of the study is difficult due to worsening of the target disease of this study or symptoms caused by the target disease
2. When a significant or persisting noncompliance with the protocol that makes it difficult to ensure safety or influences efficacy assessment was detected

3. When a subject is found not to meet the inclusion criteria for participants of this study or to meet the exclusion criteria
4. When it is difficult to continue the study or a subject requests for discontinuation due to onset of AEs
5. When a subject requests for discontinuation (not in relation to AEs)
6. When a subject stops visiting the site, making it difficult to continue the study
7. Other cases in which Investigator considers it difficult to continue the study

### 7.8.2 Discontinuation Procedures

When any event corresponding to "Discontinuation Criteria" occurs during the study treatment, Investigator discontinues the administration of study drugs, performs the observation and tests specified in " Schedule and Efficacy and Safety Endpoints," and enter the results, discontinuation day, and reason for discontinuation in case report form.
Appropriate treatment including alternative therapies is provided after discontinuation.
When the study is discontinued due to occurrence of a safety problem in the subject concerned, appropriate measures are taken and the problem is addressed in accordance with " Ensuring Safety of Participants."
When a subject stops visiting the site, Investigator asks a subject to visit the site and efforts are made to perform the observation and tests specified in "Schedule, Efficacy and Safety Endpoints."
If the designated observation and tests cannot be performed, Investigator promptly conducts follow-up investigation on the course after the latest observation and AEs over the phone, by letter, or other possible methods and enters the result in case report form. When confirmation was made with a person other than the subject for a compelling reason, the reason and the relationship of this person with the subject are entered in case report form.

## 7.9 STUDY, EFFICACY AND SAFETY ENDPOINTS SCHEDULE

| | 1st Visit | | 2nd Visit | | 3rd Visit | Data Input & Locked | Note |
|---|---|---|---|---|---|---|---|
| Days | Day 0 | Day 1 - Day 2 | Day 3 ± 1 day | Day 4 - Day 5 | Day 6 ± 1 day | Day 7 - Day 15 | |
| Informed consent | X | | | | | | PI, Subject |
| Inclusion and Exclusion Criteria | X | | | | | | PI, Sub I |
| Medical Examination | X | | X | | X | | PI, Sub I |
| Randomization | X | | | | | | Study Coordinator |
| Dispense Study Drugs | X | | | | | | PI, Sub I, Study Coordinator , Physiotherapist |
| Recovery Treatment : - Aplication of Study Drugs to affected site - Physiotherapy and exercise based on diagnosis and treatment from PI, Sub-I | X | | X | | X | | PI, Sub PI, Study Coordinator, Physiotherapist |
| Primary and Secondary endpoint assessement | X | | X | | X | | PI, Sub-I, Physiotherapist |
| Application of Study Drugs at home | | X | | X | | | Subject |
| Subject's diary | X | X | X | X | X | | Subject |
| Concomitant medication | X | X | X | X | X | | PI, Sub PI, Subject |
| Rescue medication | X | X | X | X | X | | PI, Sub PI, Subject |
| Adverse events | X | X | X | X | X | | PI, Sub PI, Subject |
| Study drugs and Diary returned | | | | | X | | Registration officer, Physiotherapist |
| Data input | X | | X | | X | X | Study Coordinator |
| Data locked | | | | | | X | Study Coordinator |
| Monitoring | | | X | | X | X | CRA |

### 7.9.1 Primary Endpoint

The assessment of primary endpoint wil be assessed through form 2, Inventerisasi Rasa Nyeri Singkat on 1st Visit, 2nd Visit and 3rd Visit.
The primary end-point is the difference BPI scale $\geq$ 3 , from initial scale of pain to the end of treatment will be captured as the primary efficacy endpoint.

### 7.9.2 Secondary Endpoint

The assessment of secondary endpoints will be assessed through :

- Form 3 : Pemeriksaan nyeri awal pasien
- Form 4 : Pemeriksan indikator rasa nyeri non verbal
- Form 5 : Pemeriksaan rentang gerak
- Form 6 : Pemeriksaan kekuatan otot

By Principal Investigator or Sub Investigator on 1st Visit, 2nd Visit and 3rd Visit.

- Form 8 : thermal sensation, thermal comfort, and thermal acceptance and time of thermal sensation.

By Participant on 1st Visit, 2nd Visit and 3rd Visit.

- Adverse events symptoms, concomitant medication, rescue medication that will be described in the Diary Participant.

By Participant on Day 0 until study is completed.

## 7.10 STATISTICAL ANALYSIS

### 7.4.1 Analysis Sets

In the efficacy analysis, the **Per Protocol Set (PPS)** will be used as the primary analysis set, while the **Full Analysis Set (FAS)** will serve as the secondary analysis set. For safety analysis, the **Safety Analysis Set** will be used. The definitions are as follows:

- **Per Protocol Set (PPS):**
  The PPS includes participants who do not have any major protocol violations (such as not meeting inclusion/exclusion criteria or poor compliance), and who have completed the required assessments of the primary endpoint as specified in the protocol.
- **Full Analysis Set (FAS):**
  The FAS includes all participants who received at least one dose of the study drug and had at least one post-baseline assessment for efficacy endpoints. This set reflects the intention-to-treat principle.
- **Safety Analysis Set:**
  The Safety Analysis Set includes all participants who received at least one dose of the study drug and had at least one post-baseline safety assessment. All safety data, including adverse events and rescue medication use, will be analyzed in this set.

### 7.4.2 Statistical Analysis Plan

The statistical analysis will be performed after data finalization and database lock, following the predefined analysis sets (PPS, FAS, and Safety Analysis Set). All analyses will be conducted using standard statistical software (e.g., SPSS, SAS, or R), with the level of statistical significance set at $\mathbf{p < 0.05}$, unless otherwise adjusted.

**Efficacy Analysis**

- **Primary Endpoint (Pain Score using Brief Pain Inventory):**
  - **Test**: **Analysis of Covariance (ANCOVA)** adjusting for baseline BPI score

  - **Equivalence testing**: Pairwise comparisons using **two one-sided t-tests (TOST)** to assess whether the difference in mean change from baseline falls within the equivalence margin (±1.0)
  - **Assumptions**: Normality and homogeneity of variance will be checked. If violated, non-parametric equivalent (e.g., **Wilcoxon rank-sum test**) will be used.
- **Secondary Endpoints:**
  - **Range of Motion (ROM) and Muscle Strength:**
    - **Test**: **Repeated Measures ANOVA** or **mixed-effects model**, depending on data completeness and correlation structure
    - If non-normal: **Friedman test** or **Wilcoxon signed-rank test** for within-group, **Kruskal-Wallis test** for between-group comparisons.
  - **Thermal Sensation, Comfort, and Acceptance (ASHRAE Scale):**
    - **Test**: **Chi-square test** or **Fisher's exact test** for categorical comparisons
    - **Ordinal regression** may be used to explore patterns of thermal perception across groups.
  - **Responding Analysis (pain reduction ≥3 points):**
    - **Test**: **Chi-square test** for group-wise comparison of response rates
    - **Risk difference** and **number needed to treat (NNT)** will be calculated.

**Safety Analysis**

- **Adverse Events (AEs) and Adverse Drug Reactions (ADRs):**
  - **Test**: **Chi-square test** or **Fisher's exact test** for comparing incidence across groups
  - Descriptive statistics for type, severity, onset, and duration
  - **Severity grading** and **causality assessment** using **Naranjo's algorithm.**
- **Rescue Medication Use:**
  - **Test**: **Poisson regression** or **negative binomial regression** if data are overdispersed
  - Summarized as a mean number of doses used per participant and compared between groups.

**Demographic and Baseline Characteristics**

- **Continuous Variables** (e.g., age, BMI):
  - **Test**: **One-way ANOVA** or **Kruskal-Wallis test** (if non-normal distribution)
- **Categorical Variables** (e.g., sex, diagnosis):
  - **Test**: **Chi-square test** or **Fisher's exact test** as appropriate

**Missing Data Handling**

- **Primary Analysis** will be based on the **Per Protocol Set**, with sensitivity analysis using **Full Analysis Set (FAS)**under **intention-to-treat (ITT)** principles.
- **Multiple imputation** will be considered for missing primary endpoint data if the proportion of missing data exceeds 5%.

## 7.11 COMPLIANCE WITH AND DEVIATION FROM PROTOCOL OR CHANGES AND REVISION OF PROTOCOL

### 7.11.1 Compliance with and Deviation from or Changes in Protocol

Investigator must not deviate from or change the protocol unless the Principal Investigator obtains prior written agreement with the sponsor and written approval by the institutional review board (IRB)/EC. However, this does not apply when the deviation or change is medically inevitable, for example, deviation or change for avoiding urgent risk to participants, or when the change does not affect the conduct of the study (for example, change in phone numbers).

1) Investigator can deviate from or change the protocol without prior written agreement with the sponsor and prior approval by the institutional review board (IRB)/EC for medically compelling reasons, for example, to avoid urgent risk to participants. In such cases, the Principal Investigator notifies the sponsor of the details of the deviation or change and its reason. The Principal Investigator also discusses the revision of the protocol with the sponsor and reaches an agreement. The approval of draft revision by the institutional review board (IRB)/EC is obtained as soon as possible.
2) The Principal Investigator promptly submits the report of all the changes in the study that significantly affect the conduct of the study or increase the risk to participants to the sponsor and the institutional review board (IRB)/EC.
3) Investigator records all the actions that deviate from the protocol. Among the actions deviate from the protocol, the Principal Investigator prepares the documents that include the reasons, immediately submits them to the sponsor, and retains a copy only for the actions for medically compelling reasons including avoidance of urgent risk to participants.

### 7.11.2 Revision of Protocol

The protocol and case report form are revised by the following procedures.

1) When the sponsor considers the revision necessary, the sponsor provides the Principal Investigator the draft revision of the protocol and case report form and other necessary materials and information.
2) The sponsor gives the Principal Investigator time necessary for him or her to sufficiently review the materials and information including the draft revision of the protocol provided in accordance with the previous clause and discuss with the sponsor.
3) After discussing with the Principal Investigator, the sponsor reaches an agreement with the Principal Investigator on the details of the revised protocol and case report form and compliance with the revised protocol. The sponsor and the Principal Investigator each sign, and date the written agreement to prove the above agreement. Similar processes are followed when the protocol and case report form are corrected at the direction of the institutional review board (IRB)/EC, within the range accepted by the sponsor.
4) The sponsor promptly submits the revised protocol and case report form and promptly obtains the approval by the institutional review board (IRB)/EC. For changes in the protocol related to administrative matters (for example, changes in monitors or changes in phone numbers, etc.), addition or deletion of other study sites, and changes in the Principal Investigator or other personnel at other study sites, the sponsor notifies the Principal Investigator of the details of the changes.

### 7.11.3 Completion or Discontinuation and Interruption of Study

#### 7.11.3.1 Completion of Study

The completion day of the study for each subject is defined as “the day on which observation of all items specified in the protocol is completed or discontinuation day for the subject” and the completion day of the study for each study site as “the latest day among the study completion days for the participants enrolled at the study site concerned.”

After: the study treatment and observation specified in the protocol were completed for the last subject at the study site concerned, the Principal Investigator promptly notifies the institutional review board (IRB)/EC and the sponsor of the completion of the study in writing and reports the outline of the study results based on the report he or she prepared to the institutional review board (IRB)/EC and the sponsor.

#### 7.11.3.2 Discontinuation or Interruption of Entire Study

Criteria for Discontinuation or Interruption of Entire Study

The sponsor promptly discusses the discontinuation or interruption of the study with the medical expert when the following criteria are met and continuation of the study at all the study sites is considered difficult or meaningless.

1) When “unexpected” serious AEs (diseases, disorders, deaths) occur
2) When information indicating that the tendencies in occurrence of “expected” significant AEs including number of incidents, frequency, and conditions for occurrence cannot be predicted based on the investigator’s brochure was obtained
3) When information indicating that the tendencies in occurrence of ADRs including number of incidents, frequency, and conditions for occurrence markedly changed for the worse was obtained
4) When information indicating or not indicating the superiority of the test drug to the comparator was obtained
5) When other information affecting the continuation of the study was obtained
    a. Procedures for Discontinuation or Interruption of Entire Study
    b. The entire study is discontinued or interrupted by the following procedures.
6) When the entire study is discontinued or interrupted, the sponsor promptly notifies all the Principal Investigators involved in the study and the regulatory agency to that effect and the detailed reasons in writing.
7) When the sponsor decides the discontinuation or interruption of the entire study and notifies Principal Investigators of the decision, Principal Investigators promptly notifies the institutional review boards (IRB)/EC to that effect in writing and explains the details of the discontinuation or interruption to the institutional review board (IRB)/EC.
8) When the Principal Investigators are notified of the discontinuation or interruption of the entire study, they promptly notify the participants receiving study treatment to that effect and take appropriate measures including switching to other therapies.

### 7.11.4 Discontinuation or Interruption at Study Sites

#### 7.11.4.1 Criteria for Discontinuation or Interruption at Study Sites

When the following criteria are met, the sponsor assesses whether or not the study can be continued at all or part of the study sites.

1) When the protocol needs to be changed and some study sites cannot respond to the change
2) When the sponsor cannot approve an instruction for correction based on the opinion of the institutional review board (IRB)/EC

3) When the institutional review board (IRB)/EC instructed to discontinue the study
4) When some study sites violated GCP, the protocol, or study contract significantly or continuously

#### 7.11.4.2 Procedures for Discontinuation or Interruption at Study Sites

The study is discontinued or interrupted at study sites by the following procedures.

1) When the Principal Investigator discontinued or interrupted the study, he or she promptly explains the discontinuation or interruption in detail in writing to the sponsor and the institutional review board (IRB)/EC.
2) When the institutional review board (IRB)/EC decided discontinuation or interruption of the study and notifies to that effect, the Principal Investigator promptly notifies the sponsor.

## 7.12 DIRECT ACCESS TO SOURCE DOCUMENTATION

### 7.12.1 Direct Access to Source Documents, etc.

The Principal Investigator accepts the monitoring and audit by the sponsor and inspection by the institutional review board (IRB)/EC and the regulatory agency and provides all the study-related records including source documents for direct access.

### 7.12.2 Method of Direct Access

If necessary, the study site and sponsor can have access to clinical study documents. The justification for opening access to clinical study documents will be discussed by the study site and the sponsor. Any access to clinical study documents requires prior Sponsor approval.

## 7.13 QUALITY CONTROL AND QUALITY ASSURANCE OF STUDY

The sponsor responsibly performs the quality assurance based on the standard operating procedures and maintains quality control system in order to assure that the study is conducted and data are generated, recorded, and reported in compliance with the protocol, the pharmaceutical affairs law, and GCP.

The sponsor will ensure that the reporting of adverse events that occur in this study will be reported to the the institutional review board (IRB)/EC and also BPOM RI in accordance with regulations applied in Indonesia.

### 7.13.1 Quality Control of Study

The sponsor applies quality control at each step of the handling of data in order to assure the reliability of all the study-related data and their appropriate processing.

The monitors assigned by the sponsor perform monitoring (including direct access to the study-related record such as source documents) according to the standard operating procedures and confirm that the study is being conducted appropriately at study sites in compliance with the protocol, the standard operating procedures, and Good Clinical Practice.

### 7.13.2 Quality Assurance of Study

The sponsor assures the quality of the study by establishing an audit department that is independent of the department that implements the study. In order to assure the quality of the study, the personnel in charge of audit performs audit at appropriate timing at the sponsor as well as at study sites and other facilities involved in the study as necessary, in accordance with the standard operating procedures of the sponsor.

## 7.14 ETHICAL IMPLEMENTATION OF STUDY

### 7.14.1 Review of Study

This study is reviewed by the institutional review board (IRB)/EC selected by each study site as to whether or not its implementation is appropriate from the perspective of ethical, scientific, and medical adequacy.

### 7.14.2 Continued Review of Study

The adequacy of continued implementation of this study at a particular study site is reviewed once a year or more frequently, or in the following cases.

1) When the sponsor notified the Principal Investigator of serious and unexpected ADRs or other events
2) When the Principal Investigator reported serious AEs or other events
3) When the Principal Investigator reported a revision of consent form and other written information for patients
4) When the Principal Investigator submitted the overview of the current status of the study for the review regarding continuation of the study
5) Other cases in which the Principal Investigator considers that the review regarding continuation of the study is necessary

The Principal Investigator requests the opinion of the institutional review board (IRB)/EC regarding the adequacy of continuation of the study at the study site concerned.

### 7.14.3 Matters Related to Protection of Privacy and Personal Information of Participants

In order to protect the privacy and personal information of participants, participants are identified by subject IDs.

In the preparation and handling of case report forms and the monitoring, audit, and other tasks performed by the sponsor, as well as when the study results are published, attention is paid to protection of privacy and personal information of participants.

## 7.15 STORAGE OF RECORD

### 7.15.1 Investigator

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor.

### 7.15.2 Institutional Review Board (IRB)/EC

The institutional review board (IRB) /EC is an independent body constituted of medical, scientific and non- scientific member, whose responsibility is to ensure safeguard the rights, safety, and well-being of all trial participants.

The institutional review board (IRB) /EC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after

completion of the trial and make them available upon request from the regulatory authority(ies).

### 7.15.3 Sponsor

1) The sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor.
2) When the storage of the documents that should be stored by the Principal Investigator or the institutional review board (IRB) /EC becomes unnecessary, the sponsor notifies the institutional review board (IRB) /EC to that effect through Investigator.

## 7.16 MONETARY PAYMENT

The sponsor pays the cost of this study based on the contract with each study site.

## 7.17 INSURANCE

The sponsor takes necessary measures including issued guarantee letter in order to compensate for the treatment of health hazards of participants caused by the study and other losses.

## 7.18 COMPENSATION FOR HEALTH HAZARDS

1) When any health hazard occurs to a subject in this study, the study site and the sponsor respond to it for the subject or his or her bereaved family in the following manner.
2) The study site makes all possible efforts to treat the health hazard.
3) If neither intention nor negligence of the sponsor was involved and no other parties have liability for the health hazard caused by the study, the sponsor provides compensation based on its compensation system. However, if the health hazard was proven to be the results of the subject's own intention or significant negligence, the compensation is reduced or not provided. If a health hazard that newly occurred is causally unrelated to the study, it is not compensated.
4) If intention or negligence of the sponsor, the study site, a party commissioned by the sponsor or the study site to carry out study-related tasks, or other parties was involved in the health hazard caused by the study, the party that is legally responsible for this health hazard provides the compensation.
5) Adverse event that happened during observation and treatment period will be monitored by investigator and sponsor. The cost for theadverse event related to the study will be compensated by sponsor.

## 7.19 HANDLING OF PUBLICATION

The sponsor is free to use the information obtained in this study for the purposes including the application for marketing approval related to the test drug.

**References:**

1. J.B. Fourtillan and J. Girault. Piroxicam Plasma Concentrations Following Repeated
Topical Application of a Piroxicam 0.5% Gel. Drug Invest. 4 (5): 435-440, 1992.

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9. Picha KJ, Harding JL, George SZ. Clinically important differences in range of motion and strength for patients with musculoskeletal disorders of the upper extremity. J Hand Ther. 2020;33(3):403–412. doi:10.1016/j.jht.2020.01.007
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13. Leaflet Counterpain PXM. Indonesia
14. Leaflet Hotin DCL. Indonesia
15. Leaflet Pirofel. Indonesia

**Appendix 1**

**FORMULIR PEMERIKSAAN**

| Jenis Formulir | Diisi oleh |
|---|---|
| Formulir 2, Inventerisasi Rasa Nyeri Singkat | Pasien |
| Formulir 3, Pemeriksaan Awal Nyeri Pasien | Dokter Pemeriksa |
| Formulir 4, Pemeriksaan Indikator Rasa Nyeri Non – Verbal | Dokter Pemeriksa |
| Formulir 5, Pemeriksaan Rentang Gerak | Dokter Pemeriksa |
| Formulir 6, Pemeriksaan Kekuatan Otot | Dokter Pemeriksa |
| Formulir 7, Pemberian aplikasi obat topikal | Fisioterapis |
| Formulir 8, Sensasi Termal | Pasien |
| Formulir 9, Program Fisioterapi & Latihan | Fisioterapis |

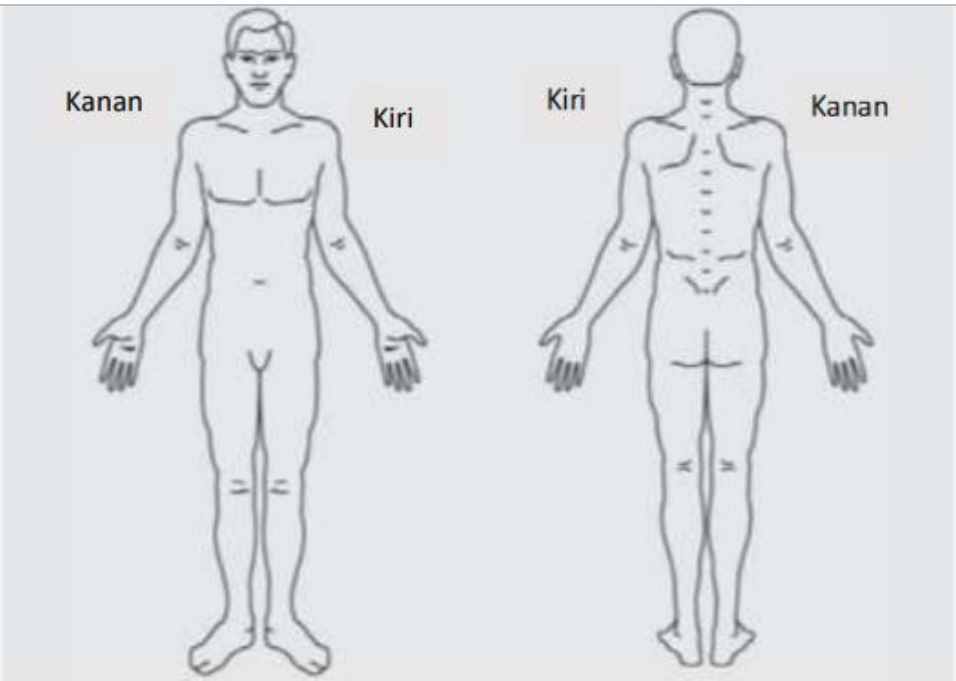
**FORMULIR PASIEN**

**FORMULIR PEMERIKSAAN 2**

| **INVENTERISASI RASA NYERI SINGKAT** | | |
|---|---|---|
| Nama | : | |
| Tanggal | : | |
| Waktu | : | |
| Kunjungan ke | : | |

**Isilah pertanyaan dibawah ini sesuai dengan kondisi yang Anda rasakan hari ini. Lingkari yang paling mendekati kondisi Anda.**

| | | | |
|---|---|---|---|
| **1** | **Sepanjang hidup kita, kebanyakan dari kita mengalami rasa sakit dari waktu ke waktu (seperti sakit kepala ringan, terkilir, dan sakit gigi).**<br><br>**Pernahkah Anda merasakan sakit selain rasa sakit biasa tersebut hari ini?** | **:** | **Ya**<br><br>**Tidak** |
| **2** | Pada diagram, arsir area di mana Anda merasakan sakit. Beri tanda X pada area yang sangat sakit | | |




**3** Nilai rasa sakit Anda dengan melingkari salah satu angka yang sangat menggambarkan rasa sakit Anda yang TERBURUK di 24 jam terakhir.

0 1 2 3 4 5 6 7 8 9 10

Tidak ada rasa sakit — Rasa sakitnya luar biasa seperti yang bisa Anda bayangkan

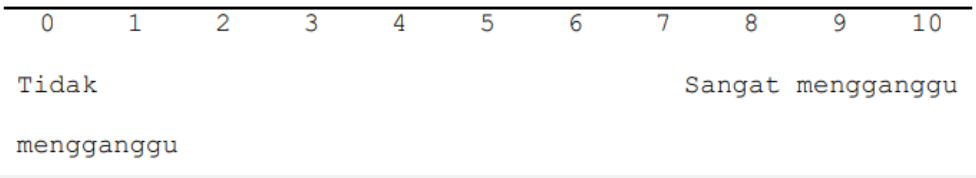
**4** Nilai rasa sakit Anda dengan melingkari salah satu angka yang sangat menggambarkan rasa sakit Anda yang PALING RINGAN di 24 jam terakhir

0 1 2 3 4 5 6 7 8 9 10

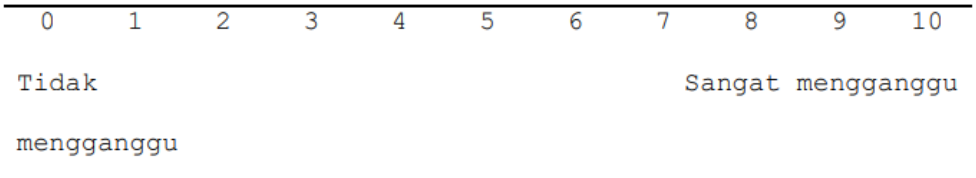
Tidak ada rasa sakit — Rasa sakitnya luar biasa seperti yang bisa Anda bayangkan

| | | | |
|---|---|---|---|
| **5** | Nilai rasa sakit Anda dengan melingkari salah satu angka yang sangat menggambarkan rasa sakit Anda RATA-RATA.<br><br>0 1 2 3 4 5 6 7 8 9 10<br>Tidak ada rasa sakit — Rasa sakitnya luar biasa seperti yang bisa Anda bayangkan | | |
| **6** | Nilai rasa sakit Anda dengan melingkari salah satu angka yang menggambarkan rasa sakit yang sedang Anda rasakan SEKARANG.<br><br>0 1 2 3 4 5 6 7 8 9 10<br>Tidak ada rasa sakit — Rasa sakitnya luar biasa seperti yang bisa Anda bayangkan | | |
| **7** | Pengobatan atau perawatan apa yang Anda terima untuk rasa sakit Anda? | : | |
| **8** | Dalam 24 jam terakhir, seberapa banyak rasa sakit tersebut berkurang setelah menerima pengobatan atau perawatan? Lingkari salah satu persentase yang sangat menggambarkan RASA LEGA yang Anda rasakan.<br><br>0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%<br>Tidak berkurang sama sekali — Sepenuhnya Hilang | | |
| **9** | Lingkari salah satu angka yang menggambarkan bagaimana, selama 24 jam terakhir, rasa sakit menganggu Anda dalam : | | |

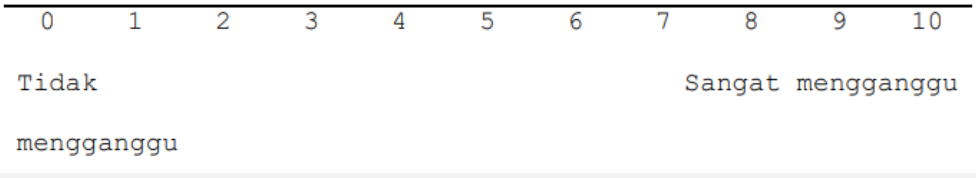
A. Kegiatan sehari-hari:



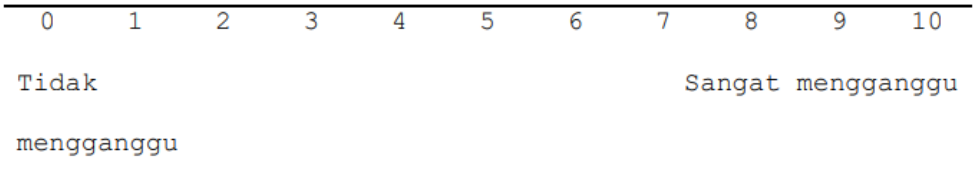

B. Suasana hati:



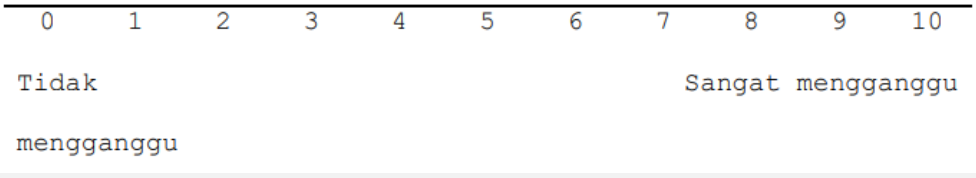

C. Kemampuan berjalan:



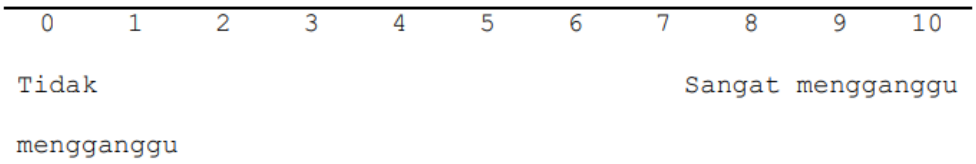

D. Pekerjaan biasa (termasuk bekerja di luar rumah dan pekerjaan rumah):



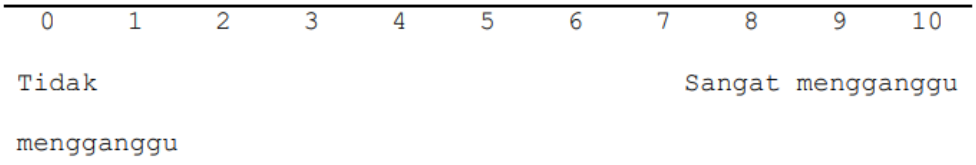

E. Hubungan dengan orang lain:



F. Tidur:



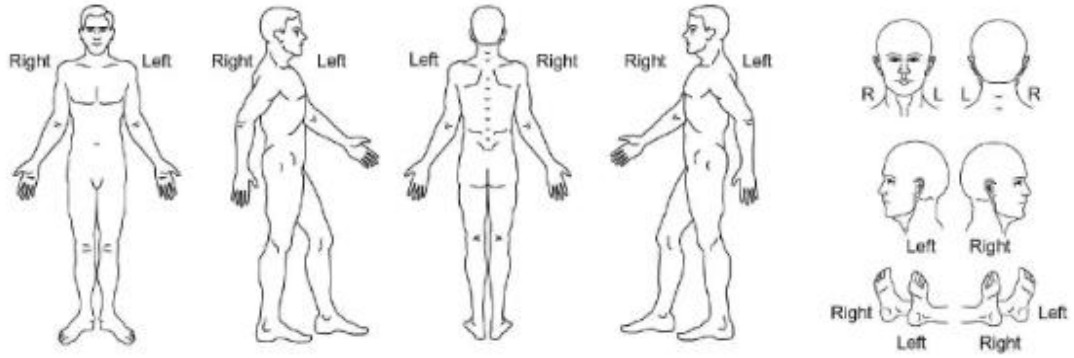

G. Kesenangan hidup:




**Paraf Pasien: _____ Tanggal : _____**

## FORMULIR DOKTER PEMERIKSA

| FORMULIR PEMERIKSAAN 3 | | |
|---|---|---|
| PEMERIKSAAN AWAL RASA NYERI | | |
| Nama | : | |
| Tanggal | : | |
| Waktu | : | |
| Kunjungan ke | : | |

| | |
|---|---|
| 1 | Lokasi rasa nyeri<br>  <br> |
| 2 | Pemeriksaan intensitas dan karakter rasa nyeri<br>1. Serangan dan pola sementara :<br>• Kapan Anda mulai merasakan sakit?<br>• Seberapa sering rasa sakit itu muncul?<br>• Apakah ada perubahan dalam intensitasnya?<br>2. Lokasi<br>• Dimana Anda merasakan sakitnya?<br>• Apakah dirasakan lebih dari satu titik?<br>3. Keterangan<br>• Bagaimana rasa sakit yang Anda rasakan?<br>• Bagaimana cara Anda menjelaskan rasa sakit tersebut? |

| | | |
|---|---|---|
| | 4. Intensitas<br>Dalam skala 0 hingga 10, dengan 0 berarti tidak sakit sama sekali dan 10 berarti rasa sakit terburuk yang dapat Anda bayangkan,<br>• Berapa skalanya saat ini?<br>• Berapa skalanya ketika Anda sedang merasa sangat kesakitan?<br>• Berapa skalanya ketika Anda merasa sakitnya di saat terbaik?<br><br>5. Faktor yang memperburuk dan meringankan –<br>• Apa yang meringankan rasa nyeri Anda?<br>• Apa yang memperburuk rasa nyeri Anda?<br><br>6. Perawatan sebelumnya –<br>• Jenis pengobatan apa yang pernah Anda lakukan untuk meringankan rasa nyeri Anda?<br>• Apakah pengobatan itu efektif?<br><br>7. Efek –<br>• Bagaimana rasa nyeri tersebut mempengaruhi fungsi fisik dan sosial Anda? | |
| 3 | Pemeriksaan psikososial | |
| 4 | Pemeriksaan fisik dan neurologis | |

**Paraf Dokter Pemeriksa : _____ Tanggal : _____**

## FORMULIR DOKTER PEMERIKSA

| FORMULIR PEMERIKSAAN 4 | | |
|---|---|---|
| PEMERIKSAAN INDIKATOR RASA NYERI NON- VERBAL | | |
| Nama | : | |
| Tanggal | : | |
| Waktu | : | |
| Kunjungan ke | : | |

Penilaian:

- Beri nilai 0 jika perilakunya tidak teramati.
- Beri nilai 1 jika perilaku muncul secara singkat selama beraktivitas atau sedang beristirahat.

Jumlah angka indikasi dihitung untuk perilaku yang diamati :

- saat sedang beristirahat,
- dalam pergerakan, dan
- keseluruhan.

Tidak ada batas nilai yang jelas dalam mengindikasikan tingkat keparahan suatu rasa nyeri; sebaliknya, keberadaan perilaku apa pun dapat menjadi indikasi suatu rasa sakit, menjamin investigasi pengobatan, dan pengawasan lebih lanjut dari para praktisi

| No | Perilaku | Saat beraktivitas | Saat beristirahat |
|---|---|---|---|
| 1 | Keluhan vocal: nonverbal (Menghela napas, terkesiap, erangan, menggeram, menangis) | | |
| 2 | Ekspresi Wajah/Meringis (Alis berkerut, mata menyipit, gigi terkatup rapat, bibir mengatup, mulut menganga, ekspresi terdistorsi) | | |
| 3 | Bersiap (Mencengkeram atau berpegangan pada mebel, perkakas, atau area yang terdampak selama bergerak) | | |
| 4 | Gelisah (Terus atau sesekali berganti posisi, berayun, tangan bergerak sesekali atau terus menerus, tidak bisa diam) | | |

| | | | |
|---|---|---|---|
| **5** | Menggosok (Memijat bagian yang terdampak) | | |
| **6** | Keluhan vocal: verbal (Ucapan mengekspresikan ketidaknyamanan atau rasa sakit (misalnya; “aduh”, “sakit”); mengumpat saat bergerak; berseru atau protes [misalnya, “berhenti”, “cukup”] | | |
| | **Nilai total** | | |

**Paraf Dokter Pemeriksa : _____ Tanggal : _____**

## FORMULIR DOKTER PEMERIKSA

| FORMULIR PEMERIKSAAN 5 | | |
|---|---|---|
| PEMERIKSAAN RENTANG GERAK | | |
| Nama | : | |
| Tanggal | : | |
| Waktu | : | |
| Kunjungan ke | : | |

| |
|---|
| **S** |
| **O** |
| **A** |
| **P** |

**Paraf Dokter Pemeriksa : _____ Tanggal : _____**

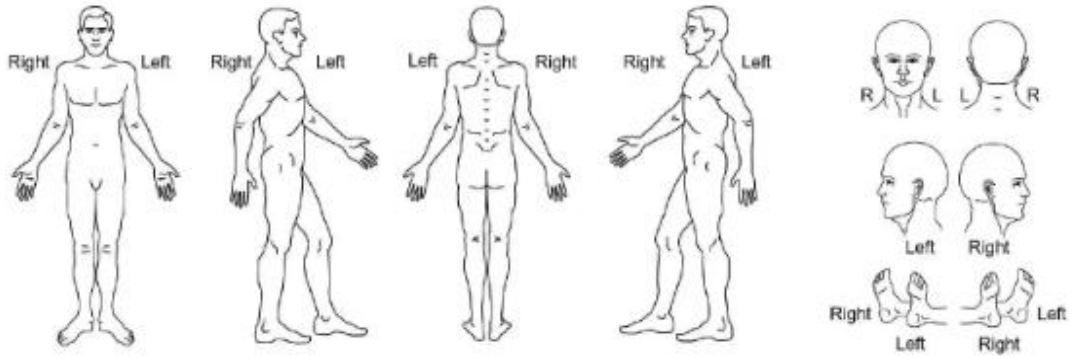
## FORMULIR DOKTER PEMERIKSA

| **FORMULIR PEMERIKSAAN 6** | | |
|---|---|---|
| PEMERIKSAAN KEKUATAN OTOT | | |
| Nama | : | |
| Tanggal | : | |
| Waktu | : | |
| Kunjungan ke | : | |

| |
|---|
| **S** |
| **O** |
| **A** |
| **P** |

**Paraf Dokter Pemeriksa : _____ Tanggal : _____**

## FORMULIR FISIOTERAPIS

| PEMBERIAN OBAT TOPIKAL | | |
|---|---|---|
| NOMOR OBAT TOPIKAL YANG DIBERIKAN : | | |
| Nama | : | |
| Tanggal | : | |
| Waktu | : | |
| Kunjungan ke | : | |
| Lokasi area pengaplikasian obat topikal   | | |
| Sebelah Kiri / Kanan | : | |

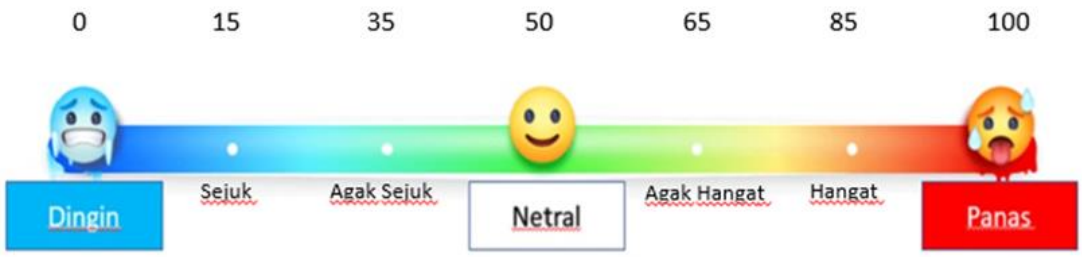
**Paraf Fisioterapis : _____ Tanggal : _____**

## FORMULIR PASIEN

| **FORMULIR PEMERIKSAAN 7** | | |
|---|---|---|
| **PEMERIKSAAN SENSASI TERMAL (ASHRAE)** | | |
| **Nama** | **:** | |
| **Tanggal** | **:** | |
| **Waktu** | **:** | |
| **Kunjungan ke** | **:** | |

**Sensasi Termal**

Mohon lingkari skala berikut yang sesuai dengan yang Anda rasakan setelah diaplikasikan obat topikal




Reference:M. Schweiker, M. André and F. Al-Atrash et al. / Energy & Buildings 211 (2020) 109761

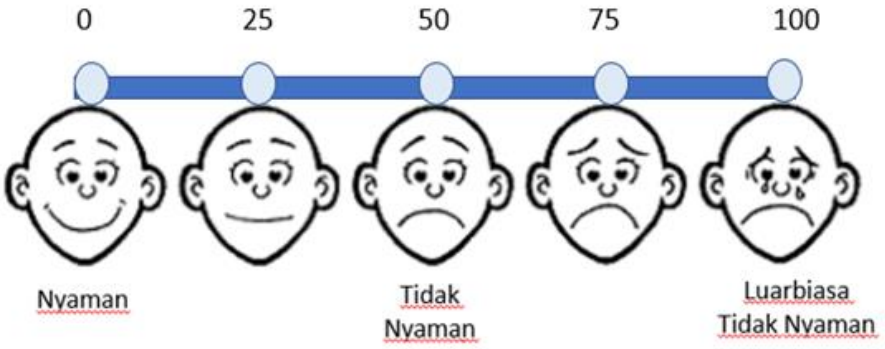
Sensasi termal tersebut dirasakan dalam waktu :

_____ Menit

_____ Detik

**Kenyamanan setelah aplikasi obat topikal**

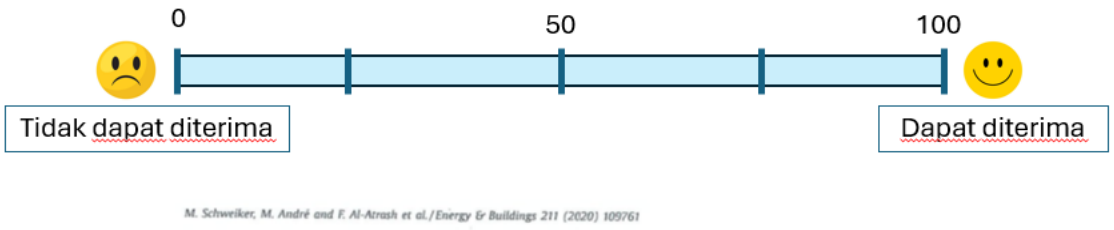
Mohon lingkari skala berikut yang sesuai dengan yang Anda rasakan setelah diaplikasikan obat topikal




Reference:M. Schweiker, M. André and F. Al-Atrash et al. / Energy & Buildings 211 (2020) 109761

**Penerimaan sensasi termal yang diaplikasikan secara topikal**

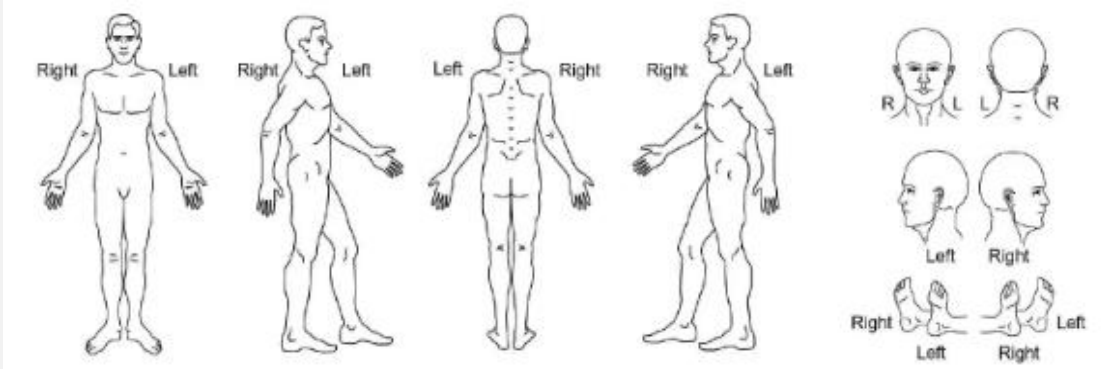
Mohon lingkari skala berikut yang sesuai dengan yang Anda rasakan setelah diaplikasikan obat topikal




M. Schweiker, M. André and F. Al-Atrash et al./Energy & Buildings 211 (2020) 109761

**Paraf Pasien : _____ Tanggal : _____**

## FORMULIR FISIOTERAPIS

| PROGRAM FISIOTERAPI DAN LATIHAN | | |
|---|---|---|
| **Nama** | **:** | |
| **Tanggal** | **:** | |
| **Waktu** | **:** | |
| **Kunjungan ke** | **:** | |
| **Lokasi area nyeri**   | | |
| **Sebelah Kiri / Kanan** | **:** | |
| **Program fisioterapi yang dilakukan** | **:** | |
| **Program latihan yang dilakukan** | **:** | |

**Paraf Fisioterapis : Tanggal :**

Appendix 2

**PROGRAM FISIOTERAPI STANDAR UNTUK PARTISIPAN**

| **Diagnosis** | **OSTEOARTRITIS** |
|---|---|
| **Program Terapi & Latihan** | **Waktu Pengerjaan (menit)** |
| **Latihan Peregangan:**<br>Peregangan otot paha belakang, Peregangan otot betis, Peregangan otot paha depan<br><br>**Latihan Isometrik:**<br>Quadriceps isometris | Tahan selama 15 detik, dilakukan sebanyak 3 set<br><br>Tahan selama 15 detik, dilakukan sebanyak 3 set |
| **Terapi Manual:**<br>Pemijatan pada area otot yang kaku dan tegang | Dilakukan oleh Fisioterapi selama 10-15 menit |
| **Terapi modalitas:**<br>TENS (*Transcutaneous Electrical Nerve Stimulation*)<br><br>Penggunaan Ultrasound | Dilakukan selama 15 menit<br><br>Dilakukan selama 10 menit |
| **Terapi tambahan jika pasien datang dalam keadaan bengkak:**<br><br>Terapi Es, kompres | Dilakukan selama 15 menit |

| **Diagnosis** | **ANKLE SPRAIN** |
|---|---|
| **Program Terapi & Latihan** | **Waktu Pengerjaan (menit)** |
| **Latihan Rentang Gerak:**<br>Mobilisasi anteroposterior sendi talokrural<br><br>**Latihan isometris:**<br>Dorsofleksi, plantarfleksi, inversi dan eversi menggunakan tahanan | 10 repetisi, 3set<br><br>Tahan 10 detik, 3set |

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| **Terapi Manual:**<br>Pemijatan pada area otot yang kaku dan tegang | Dilakukan oleh Fisioterapi selama 10-15 menit |
| **Terapi modalitas:**<br>TENS (*Transcutaneous Electrical Nerve Stimulation*)<br>Penggunaan Ultrasound | Dilakukan selama 15 menit<br>Dilakukan selama 10 menit |
| **Terapi tambahan jika pasien datang dalam keadaan bengkak:**<br>Terapi Es, kompres<br>Ankle Pumping | Dilakukan selama 15 menit<br>Dilakukan 10 repetisi, dilakukan sebanyak 3set |

| **Diagnosis** | **TENDINITIS PATELLA** |
|---|---|
| **Program Terapi & Latihan** | **Waktu Pengerjaan (menit)** |
| **Latihan Fleksibilitas:**<br>Fleksibilitas fleksor pinggul dan paha depan<br>Mobilitas lumbosacral<br>**Latihan Isometrik:**<br>Quadriceps isometric<br>**Latihan Penguatan:**<br>Side Lying abduction, clam shell, hipe hike satu kaki | Dilakukan 3 set 15 repetisi<br>Tahan 10 detik, dilakukan 3set<br>Dilakukan 3 set 15 repetisi |
| **Terapi Manual:**<br>Pemijatan pada area otot yang kaku dan tegang | Dilakukan oleh Fisioterapi selama 10-15 menit |
| **Terapi modalitas:**<br>TENS (*Transcutaneous Electrical Nerve Stimulation*)<br>Penggunaan Ultrasound | Dilakukan selama 15 menit<br>Dilakukan selama 10 menit |

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| **Terapi tambahan jika pasien datang dalam keadaan bengkak:**<br><br>Terapi Es, kompres | <br><br>Dilakukan selama 15 menit |

| **Diagnosis** | **TENNIS ELBOW** |
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| **Program Terapi & Latihan** | **Waktu Pengerjaan (menit)** |
| **Latihan Rentang Gerak:**<br><br>Rentang gerak sendi siku pasif dan aktif<br><br>**Latihan Isometris:**<br><br>Fleksor/ekstensor pergelangan tangan | Dilakukan 10-12 repetisi, 3set<br><br>Tahan 10 detik, dilakukan 3 set |
| **Terapi manual:**<br><br>Pemijatan pada area otot yang kaku dan tegang | Dilakukan oleh Fisioterapi selama 10-15 menit |
| **Terapi modalitas:**<br><br>TENS (*Transcutaneous Electrical Nerve Stimulation*)<br><br>Penggunaan Ultrasound | <br><br>Dilakukan selama 15 menit<br><br>Dilakukan selama 10 menit |
| **Terapi tambahan jika pasien datang dalam keadaan bengkak:**<br><br>Terapi Es, kompres | <br><br>Dilakukan selama 15 menit |

| **Diagnosis** | **BACK PAIN** |
|---|---|
| **Program Terapi & Latihan** | **Waktu Pengerjaan (menit)** |
| **Latihan Isometris:**<br><br>Abdominal Isometrik<br><br>**Latihan Peregangan:**<br><br>Knee to Chest (single & double), Pelvic Twist, Hamstring Bridge, Cat & Camel, Cobra & Childpose | Tahan selama 10 detik, Dilakukan sebanyak 3 set<br><br>Tahan selama 15 detik, dilakukan sebanyak 3 set |

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| **Terapi manual:**<br>Pemijatan pada area otot yang kaku dan tegang | Dilakukan oleh Fisioterapi selama 10-15 menit |
| **Terapi modalitas:**<br>TENS (*Transcutaneous Electrical Nerve Stimulation*)<br>Penggunaan Ultrasound | Dilakukan selama 15 menit<br>Dilakukan selama 10 menit |