

STUDY PROTOCOL

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The FROSTBLOCK trial: Protocol for a randomized controlled trial of intra-articular corticosteroid injection with or without suprascapular nerve block in frozen shoulder

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Abstract

Background Frozen shoulder is a challenging musculoskeletal disorder, affecting between 2 and 5% of people, with a higher incidence among those with diabetes and thyroid issues. This condition can persist for years and can be very demanding for both patients and healthcare providers due to the intense pain and restricted shoulder movement. Literature shows that intra-articular corticoid injection (IACI) and suprascapular nerve block (SSNB) can improve pain and range of motion in these patients. The objective of this study is to investigate if there is any significant difference in pain reduction and functional recovery when treated with a combination of gleno-humeral IACI and SSNB compared to a gleno-humeral IACI paired with a placebo SSNB.

Methods A two-arm, single-centre, randomized, parallel-group controlled trial will be conducted. Eligible patients will be randomly assigned (1:1 allocation) to long-acting SSNB + IACI and placebo SSNB + IACI. The primary endpoint is the mean change from baseline to 3 months in the Shoulder Pain and Disability Index (SPADI) score. Secondary outcomes will evaluate quality of life, functionality, pain (measured by a Numeric Pain Rating Scale), kinesiophobia, work status, health care service, and a safety assessment. The main paper will be based on the repeated measures collected up to 12 months from baseline.

Discussion The aim of this study is to determine the additional effect on pain relief and functional improvement in frozen shoulder patients when a long-acting SSNB is administered, compared to a placebo SSNB, in combination with an intra-articular corticosteroid injection. Additionally, we will aim to determine which patients benefit most from these treatments. This study could lead to a change in the standard of care for patients in the painful phase of frozen shoulder.

Trial registration ClinicalTrials.gov NCT06229964. Registered on 9 January 2024.

Keywords Frozen shoulder, Adhesive capsulitis of the shoulder, Intra-articular corticosteroid injection, Ultra-sound guided injection, Suprascapular nerve block, Randomized controlled trial, Joint Diseases, Musculoskeletal diseases, Bursitis

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Introduction

Background and rationale {6a}

Frozen shoulder (FS) is a common disease affecting 2 to 5% of the general population, with a higher prevalence in patients suffering from diabetes and thyroid dysfunction [1–4]. This condition can persist for years and can be very demanding for both patients and healthcare providers due to the intense pain and restricted shoulder movement [5–7]. In the early stage, most patients identify night pain, pain with rapid or unguarded movements and pain aggravated by movement or lying on the affected shoulder [8]. Combined with marked pain and limitation in all directions of shoulder range of motion, it is easy to understand that suffering from frozen shoulder has a detrimental effect on quality of life and the ability to perform activities of daily living [7, 9].

The overall treatment aim for this condition is to improve pain and increase functionality, thereby incorporating individualized goalsetting in a shared decision-making process. Patient education on the clinical course of FS and different possible therapeutic interventions, including self-management strategies, should always come first [10]. Clinicians should promote activity modification to utilize pain-free, functional ROM and stretching of the shoulder capsule matching the patient's current level of irritability [7].

Intra-articular corticosteroid injections (IACI) into the gleno-humeral (GH) joint, combined with shoulder mobility and stretching exercises, have shown to be more effective in providing short-term (4–6 weeks) pain relief and improved function compared to exercises alone [7, 10–13]. The UK FROST trial concluded in 2020 that when compared to IACI, neither manipulation under anaesthesia (MUA) nor arthroscopic capsular release (ACR) were clinically superior [14]. In a more recent article, Rex et al. placed these results in the context of 8 other randomized controlled trials and compared IACI to MUA, ACR and hydrodilatation [15]. These findings confirmed that neither IACI, MUA nor ACR are clinically superior and evidence for hydrodilatation was inconclusive [15].

Common sense, in accordance with the National Institute of Health and Care Excellence (NICE) guidelines, recommends that treatments should be offered in a stepped approach from least to most invasive [16]. In their systematic review from 2020, Challoumas et al. show that in the early phase of frozen shoulder IACI is associated with better short-term outcomes, with possible benefits extending in the mid-term. These authors recommend to combine an IACI with education for home-based exercises and physiotherapy to increase the chances of resolution of symptoms by 6 months [13].

Unfortunately, not all patients show sufficient improvement in pain and function with IACI and need other complementary therapies. The suprascapular nerve (SSN) provides 60 to 70% of sensory innervation of the shoulder and suprascapular nerve block (SSNB) has shown, in meta-analysis, to significantly improve pain and ROM in patients with FS [17]. However, this systematic review has several limitations. Blinding was not always sufficient to rule out a placebo effect, different injection techniques and products (local anaesthetics with or without corticosteroids) were used and only data for pain and ROM shoulder could be aggregated as shoulder function was not evaluated in enough trials.

In a rigorous triple blinded RCT, we demonstrated that three successive SSNB with local anaesthetics did not improve shoulder pain and function more than three placebo injections in patients suffering from subacute FS [18]. On the other hand, it has been hypothesized that the SSN may be involved in the pathogenesis of FS and that therefore using optimal approach and drugs (combination of local anaesthetics and corticosteroids) in SSNB should be further evaluated in high-quality RCTs [17].

In a retrospective review of 102 patients, Jung et al. showed that the combination of an IACI with an SSNB further increased treatment efficacy compared to a single IACI in frozen shoulder patients, as pain, ROM and function scored significantly better at different time points (2 weeks, 2 months and 1 year) [19]. To our knowledge, no previous prospective randomized controlled trial (RCT) has investigated the added value of an SSNB combined with an IACI, administered under ultrasound guidance with the same total corticosteroid dosage in both treatment arms, and ensuring quadruple blinding (participant, care provider, investigator and outcomes assessor).

Objectives {7}

The aim of this study is to determine if there is any difference in pain relief and function in patients with frozen shoulder when given a gleno-humeral (GH) IACI with a SSNB compared to an GH IACI with a placebo SSNB. The primary objective is to examine whether an IACI with a SSNB significantly improves the Shoulder Pain and Disability Index (SPADI) at 3 months compared to a GH IACI with a placebo SSNB. The secondary objectives are to explore differences between IACI with SSNB versus IACI with placebo SSNB in patients with FS for obtaining pain relief, increasing functional ability, health-related quality of life, shoulder range of motion, pain self-efficacy, work ability and decreasing kinesiophobia, healthcare service use, adverse effects and use of rescue therapy. Finally, we want to identify which patients will benefit most from GH IACI or the combination of GH IACI and SSNB.

The results of this trial will help to guide clinical practice treating patients with FS and improve resource allocation.

Trial design {8}

FROSTBLOCK is a prospective, two-arm, single-center, randomized, parallel-group controlled trial to compare USG-IA corticoid with USG- SSNB to USG-IA corticoid with placebo SSNB, in an intention-to-treat analysis.

Participants will be randomized (1:1) to (a) USG SSNB+USG IACI or (a) USG placebo SSNB+USG IACI, while both groups are educated to do home-based exercises and encouraged to follow physiotherapy to increase their chances of resolution of symptoms. Patients will have a follow-up period until 12 months after the intervention.

Methods: participants, interventions and outcomes

Study settings {9}

The study will be conducted in an academic hospital Universitair Ziekenhuis Brussel, located in Brussels, Belgium. Details on the study site can be found at ClinicalTrials.gov with identifier: NCT06229964 or at euclinicaltrials.eu with EUCT number 2024–513057-78–00.

Eligibility criteria {10}

This study will focus on adult patients (≥ 18 years) suffering from frozen shoulder. The diagnosis of frozen shoulder is based on published clinical practice guidelines and defined as a self-limiting disease characterized by pain and functional restriction in both active and passive shoulder motion lasting more than 1 month, for which radiographic findings of the shoulder joint are unremarkable [7, 20]. Patients need to be able to read, write and speak Dutch or French. Each patient can only participate once in the study. Written informed consent to participate in the study must be obtained from the subject prior to initiation of any study-mandated procedure.

Exclusion criteria are as follows: posttraumatic or post-surgical stiff shoulder syndrome, a history of trauma at the onset of symptoms, rheumatologic or neurologic disease involving the shoulder, cervical radiculopathy, coagulation disorder or treatments with anticoagulants, hypersensitivity to local anaesthetics or MRI contrast agent, an inability to understand the study procedures, psychiatric illness, pregnancy, systematic yeast infections, hypovolaemia, infections at the injection site, a medical history of malignant hyperthermia, major conduction disorders, acute cardiac decompensation, shock conditions, convulsions, and patients who have received prior SSNB in the ipsilateral shoulder or who have received an IACI in the ipsilateral shoulder in the 3 months before study participation.

Who will take informed consent? {26}

The treating physician (physical and rehabilitation medicine specialist, orthopaedic surgeons or diabetologist) will inform the eligible patients about the project. Thereafter, an investigator of the FROSTBLOCK study will contact the patients by telephone to further inform eligible patients about the project. In case they provide oral consent, they will be screened for inclusion/exclusion criteria during this phone call. Eligible patients (based on the telephone screening) who are willing to participate will receive further detailed oral and written information about the study and will have the opportunity to ask questions. Finally, they will be asked to sign off informed consent in their language of choice (Dutch or French) before participation.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

This study will not collect biological samples.

Interventions

Active comparator: SSNB + IACI

Patients randomized to this arm will receive an USG-SSNB (20 mg methylprednisolone acetate and 5 mL Ropivacaine 2 mg/ml) followed by an USG-IACI (40 mg methylprednisolone acetate and 1 mL Ropivacaine 2 mg/ml). Total injection volume for the IACI is 2 mL.

Placebo comparator: short-acting SSNB + IACI

Patients randomized to this arm will receive an USG-SSNB (5 mL Linisol 10 mg/ml) followed by an USG-IACI (40 mg methylprednisolone acetate and 1 mL Ropivacaine 2 mg/ml). Total injection volume for the IACI is 2 mL.

Standard of care

Rehabilitation/physiotherapy is considered standard of care and will be prescribed to all included patients. All patients will complete rehabilitation under supervision of their own physiotherapist. The investigators will provide some guidelines and criteria but is the physiotherapist's choice how to implement these guidelines in clinical practice:

- Patient education on home-exercises: monitoring of peak pain, at rest/night and after rehabilitation sessions using a Numeric-Pain-Rating-Scale (0–10) (NPRS) to evaluate tissue irritability and guide physiotherapy and rehabilitation.
- Use of passive physiotherapy (cold, heat or electric therapies) to treat pain.
- Active and passive mobilization of the shoulder under the pain threshold, Maitland mobilization,

stretch exercises such as table slides and wall climbers.

- Use of affected upper limb in pain free range of motion (ROM) is allowed and stimulated.
- Progressively increase time and frequency of Total-End-Range-Time (TERT) positions to increase ROM.

Patients are allowed to continue their usual pain medicine. Patients will keep a diary to log usage of pain medication and physiotherapy visits.

According to article 2 (2)(3) of the European Clinical Trials Regulation, this clinical trial qualifies as a low intervention clinical trial.

Explanation for choice of comparators {6b}

For both SSNB and IACI, the beneficial value has already been demonstrated. Yet, there is no prospective evidence available to support the combination of SSNB and IACI, which could potentially decrease pain and increase function even more [7, 11–13, 15, 17].

The use of a short-acting SSNB prior to USG IACI has emerged in our clinical experience through demand and feedback from patients in order increase patient experience during the USG IACI procedure.

All patients will receive 2 concomitant USG injections in their affected shoulder: first a SSNB than an IACI.

For the control arm, a short-acting SSNB is performed with a short-acting local anaesthetic (Linisol 2%) and no cortico-steroids. For the intervention group, SSNB is performed with a long-acting anaesthetic (5 mL Ropivacaine 2%) and 20 mg methylprednisolone acetate. For both groups, the injected volume (5 ml) is the same. The advantage of using a short-acting anaesthetic as a placebo injection instead of a saline, is that at the time of injection the patient may perceive the anticipated short effect of the anaesthetic similar to the intervention SSNB. Trial simulation indicates that the equivalent of 20 mg of methylprednisolone is sufficient to increase the mean duration of peripheral nerve blocks [27] and this dosage will be used for SSNB in this study.

All patients then receive an IACI consisting of 40 mg methylprednisolone acetate and 1 mL Ropivacaine 2 mg/ml in the affected shoulder. Although evidence [22–25] suggests that 20 mg of triamcinolone or methylprednisolone maybe as effective as 40 mg in treating frozen shoulder, the 40-mg dosage remains the most common choice in clinical and research practice [26] and was therefore chosen selected for this trial.

In this trial, patients will be offered rescue therapy if necessary, consisting of an USG SSNB+IACI in their affected shoulder, every 3 months after inclusion, with a maximum of 3 interventions in 12 months.

Intervention description {11a}

The suprascapular nerve block is performed by injecting at the floor of the suprascapular fossa, between the suprascapular notch and the spinoglenoid notch, as described by Peng et al. and Harmon et al. [28, 29].

The patient is placed in a sitting position with the study side hand resting on the contralateral leg. To obtain an uninterrupted view of the ultrasound screen, the operator positions himself behind the patient with the ultrasound machine (Logiq P9 R3 from GE from GE Healthcare, Chicago, IL, WA, USA) in front of the patient. An initial scan is performed with the ultrasound transducer (ML6-15-RS Matrix Linear HF probe, 58 mm wideband Matrix Linear Array Ultrasound Probe) parallel to the scapular spine to identify the suprascapular fossa. The ultrasound transducer is then inserted into a sterile protection sheath, the skin is cleaned with a chlorhexidine solution. A sterile ultrasound gel (Konix® sterile contact medium for ultrasound from Turkuaz Inc, Istanbul, Turkey) is used to perform the procedure. Under aseptic conditions, a 21-Gauge, 90-mm needle is inserted (with an in-plane approach) in the longitudinal axis of the ultrasound beam to localize the tip of the needle near to the suprascapular nerve in the suprascapular notch. After an aspiration test to double-check needle positioning because of the nearby artery, 5 mL of fluid is injected with the spread being visualized.

The ultrasound guided intra-articular injection by a posterior approach with the patient in a semi-prone position. The affected shoulder is at the uppermost position, and, if necessary, the ipsilateral arm is placed over a pillow to maximize comfort and stability. The ultrasound transducer is positioned over the long axis of the myotendinous junction of the infraspinatus tendon just inferior to the scapular line to view the contours of the posterior glenoid rim, posterior glenoid labrum, and posterior portion of the humeral head. These structures must be viewed simultaneously on the ultrasound image to insure the correct injection spot. The injection needle is introduced at the skin surface just lateral to the transducer and in an oblique lateral to medial direction. The skin is cleaned with a chlorhexidine solution, and sterile ultrasound gel (Konix® sterile gel, Turkuaz Inc, Istanbul, Turkey) is used as contact medium. A 90-mm needle is aseptically introduced through an in-plane approach to continuously visualize as it passes obliquely from the skin surface to the glenohumeral joint. Passage of the needle tip into the glenohumeral joint is generally associated with a distinct feeling of transient capsular resistance followed by the sensation of a resistance-free space. The actual joint injection can then be performed [30, 31].

Criteria for discontinuing or modifying allocated interventions for a given trial participant {11b}

The participants can withdraw from the study at any time (Fig. 1). The investigator is also allowed to withdraw a patient from the study at any time. The cause of withdrawal is registered. The intervention can be discontinued in case the primary investigator and sponsor consider this appropriate with regard to patient safety. In case of any unexpected, severe, or life-threatening AEs, they will decide whether the patient should be discontinued from the intervention or not. If the patient is discontinued from the intervention, we will ask if we may continue the follow-up to record outcome measures according to the protocol. If a patient does not complete the study protocol, the following data will be collected, demographic data, data regarding AEs and the time and cause of the dropout. All available data will be included in the analysis if permission is granted by the patient. If a patient chooses to withdraw informed consent and terminates participation in the study, this will not affect the relation to the investigator or study staff nor will it in any way influence on future treatment.

Strategies to improve adherence to intervention protocols {11c}

Blinded administrative staff will schedule all appointments between patients and investigators according to study protocol and preferences of both parties. Patients will receive email notifications with an overview of their appointments and SMS-text reminders 48 h before each appointment.

Relevant concomitant care and interventions that are permitted or prohibited during the trial {11d}

Included patients will be asked not to start any new paramedical interventions between the start of the study and the 3-month follow-up, since this protocol provides current gold-standard care for their condition.

Provisions for post-trial care {30}

This study does not provide post-trial care. There is no anticipated harm for trial participation and consequently no compensation for anticipated harm.

Outcomes {12}

Primary outcomes

The “Shoulder Pain and Disability Index” (SPADI) at 3 months will be used as the primary outcome measure. The SPADI was developed to measure current shoulder pain and disability in an outpatient setting. It is a self-administered index consisting of 13 items, divided into

two subscales: 5 items for pain and 8 items for disability. It can be completed by patients in less than 5 min and has shown good reliability and construct validity in the assessment of shoulder impairments and in particular frozen shoulder [32]. Each subscale is summed and transformed to a score out of 100. A mean is taken of the two subscales to give a total score out of 100, higher score indicating greater pain and impairment or disability.

Secondary outcomes

Pain intensity The Numerical Pain Rating Scale (NPRS) will be used for the assessment of shoulder pain. It is a subjective measure in which individuals rate their pain on an 11-point numerical scale. The scale is composed of 0 (no pain at all) to 10 (worst imaginable pain). It is the simplest and most commonly used pain rating scale and offers numerous advantages, including ease of administration and scoring, multiple response options and no reported age-related difficulties in its use [33].

Physical activity and functional disability Three scores will be used to evaluate pain and disability at different time points: SPADI, Constant-Murley Score (CMS) and PROMIS29-Upper Extremity 9 items.

The CMS is a composite scale divided into four sections: pain (15 points), activities of daily living (20 points), ROM (40 points) and strength (25 points) with a total score ranging from 0 (worst possible) to 100 (best possible) [34]. Patients are asked to verbally rate each parameter while ROM and strength are evaluated by a trained investigator. The CMS is commonly used in clinical practice and research applications and has shown excellent responsiveness for different shoulder conditions [35].

The third questionnaire used to assess pain and function is the nine-item Patient-Reported Outcomes Measurement (PROM) Information System (PROMIS)-Upper Extremity short form. It has been validated against different legacy PROM and general health scores [36].

Item levels are scored numerically for an individual's response to each question. PROMIS instruments are always expressed as a score relative to the mean of a group (*T*-score). The mean score in a population is assigned the value 50. The standard deviation is equal to 10 points. Higher scores (above the mean score) mean more of the concept being measured.

Shoulder ROM in abduction, anterior elevation, external rotation Active and passive ROM in flexion, abduction and external rotation are measured using an adapted (large, total length 50 cm) goniometer, as described by

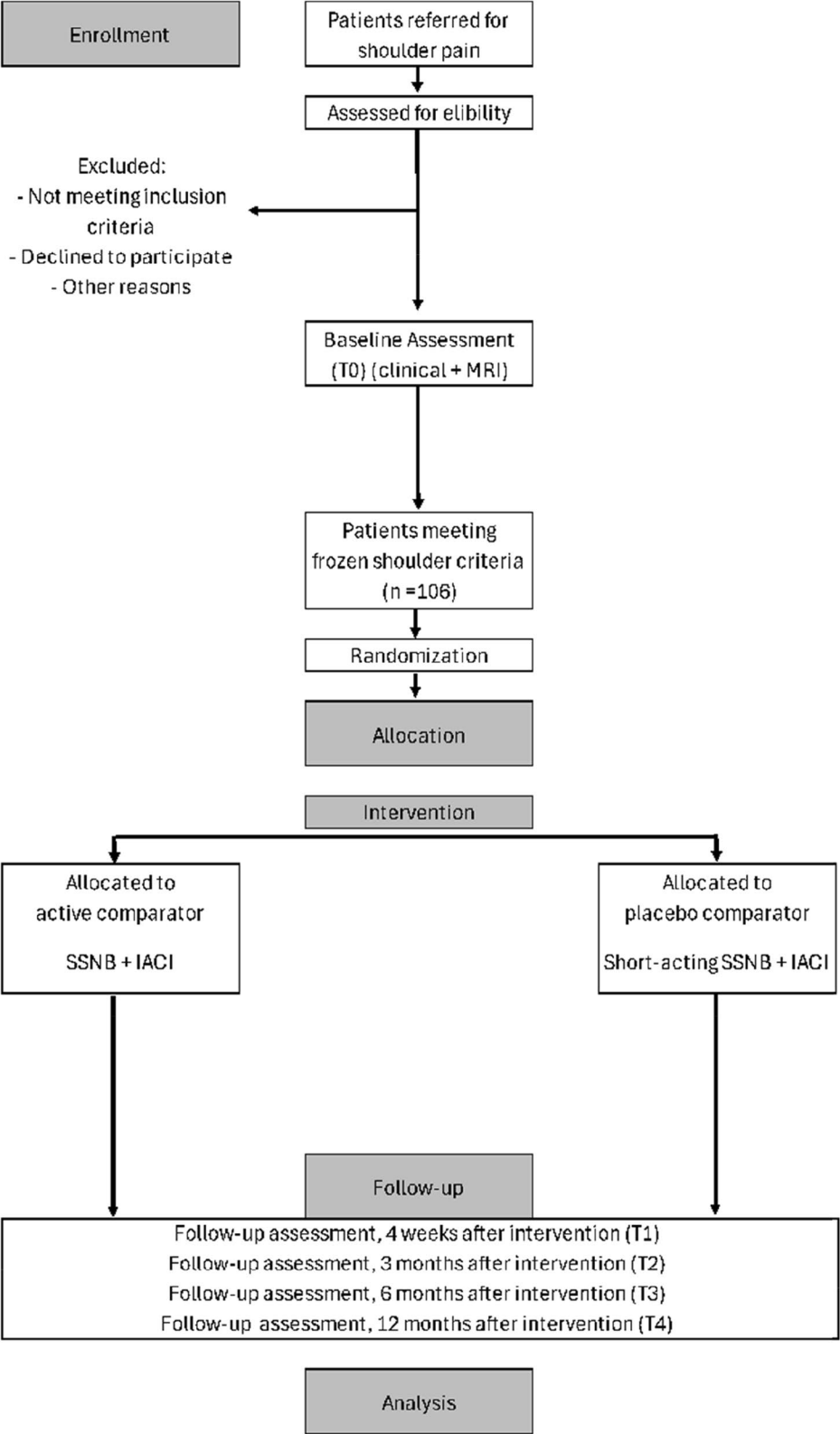


Fig. 1 Project flowchart. Participant timeline. Abbreviations: IACI intra-articular corticoid injection, *n* number, SSNB suprascapular nerve block, *T* time

Riddle et al. [37] and Sabari et al. [38], and values are expressed in degrees (°).

Clinical examination tests of the shoulder Our recent systematic review identified the Coracoid Pain Test (CPT) and the Distension Test in Passive External Rotation (DTPER) as of particular interest for the diagnosis of FS [39]. Limiting the movement of the acromion is essential for consistent scapular stabilization which is necessary to obtain reliable measurements of gleno-humeral abduction and flexion [8]. Because of our extended clinical experience, we consider that strict GH abduction could be another important variable in the early diagnosis of FS.

Coracoid Pain Test (CPT) The pain severity approach and affected-unaffected approach of the instrument-assisted CPT, as described by Mertens et al. [40], are used. The points of pressure (i.e., coracoid process, acromioclavicular (AC) joint, anterolateral subacromial area) are marked with a pencil on the seated patient. During the test, pressure on these pressure points is built up gradually to 4 kg/cm² with a digital pressure algometer (*Wagner Instruments FDX 50, Greenwich, CT, USA*). The participants score the intensity of pain for each area on the verbal VAS from 0 (no pain) to 10 points (most severe pain).

Distension Test in Passive External Rotation (DTPER) The DTPER is performed with the patient seated, the arm adducted, and the elbow bent at 90°. From this position, a smooth passive external rotation is started, the affected arm being supporting at the wrist with one hand of the examiner and the other maintaining the adducted elbow until the maximum painless point of the rotation is reached. From this point of maximum external rotation with the arm in adduction and with no pain, an abrupt distension movement is made, increasing the external rotation, causing pain in the shoulder if the test is positive. [41].

Strict passive GH abduction The patient is seated in a chair to limit trunk extension, the scapula and acromion are blocked with one hand of the examiner, while the other hand slowly brings the patient's arm in maximal abduction, while the patient's elbow is maintained in 90° flexion.

Health-related quality of life To describe the health-related quality of life (QOL), the EuroQol with 5 dimensions and 3 levels will be used [42]. The EQ-5D 3L is a generic measure of health-related quality of life developed by the EuroQol Group. It is a validated

measurement of quality of life widely used in different pathologies. The questionnaire is made up of two parts. The first part is descriptive and uses five different dimensions to score quality of life. These five dimensions are mobility, self-care, activities of the daily life, pain/discomfort and anxiety/depression. There are five different answer possibilities within each dimension, i.e. "no problem", "slight problem", "moderate problem", "severe problem" and "unable to". This renders 3125 different answer possibilities. The second part uses a visual analogue scale (VAS) to score the current health status of the patient, ranging from 0 to 100. Zero corresponds to death and 100 corresponds to a (subjective) perfect health status.

Kinesiophobia A shortened version of the original 17-item Tampa Scale for Kinesiophobia (TSK) measures the extent to which a person believes that physical activity or movement may lead to (re)-injury. Patients rate each item on a four-point Likert scale, with scoring alternatives ranging from "strongly disagree" to "strongly agree". Scores range from 11 to 44 with a higher score reflecting greater pain-related fear [43, 44].

Pain self-efficacy The Pain Self-Efficacy Questionnaire (PSEQ) is a 10-item scale which assesses a person's confidence in the ability to perform a task or activity, despite the pain. Each item is scored on a 7-point Likert scale (from "not at all confident" to "completely confident"). The total score ranges from 0 to 60 with a higher score representing greater pain self-efficacy beliefs [45].

Global Rating of Change Score The Global Rating of Change Score (GRoC) is a frequently used outcome measure that is used independently to measure improvements in a patient's condition or as an anchor for other outcomes measures. On an 11-point Likert scale participants rate the clinical course of their condition since the start of the treatment: from -5 "a great deal worse" to +5 "a great deal better" with 0 being "no change" [46].

Work status and participation As we expect subgroups of frozen shoulder to be unable to work, subjects will be questioned if they are incapacitated to work due to frozen shoulder during baseline assessments. Once the symptoms and function improve, we expect patients to be able to return to work.

The Work Ability Index (WAI) measures the work ability considering physical and mental parts of work as well as different diseases and their impact on work ability. It is a 10-item questionnaire concerning current work ability compared with the lifetime best, work ability in relation to the job demands, number of current diseases diagnosed by a physician, estimated work impairment due

to diseases, sick leave, self-prognosis of work ability and mental resources [47].

A given answer to a question earns points. The sum of all these points results in the WAI score, which ranges from 7 to 49 points. The score indicates the extent to which the individual's capabilities and the job requirements are consistent with each other, a higher score indicating a better match between capabilities and job requirements.

Healthcare expenditure The interventions are expected to have an impact on health-seeking behaviour (painkiller, physiotherapy visits, ...). This will be monitored as patients will be asked to keep a diary to log usage of pain medication and physiotherapy visits.

Participant timeline {13}

The inclusion has started February 28, 2025. Data collection is expected to last until June 31, 2028. The participant timeline for FROSTBLOCK is presented in Table 2.

Sample size {14}

Sample size calculation was performed using G*Power version 3.1.9.7 for evaluating differences in SPADI from baseline to 3 months. Calculations were based on a Minimal Clinical Important Change of 13 and with a standard deviation of 22.4 (Venturin et al.) [32], using a two-tailed testing ($\alpha=0.05$) with power 80%. Allocation ratio (N_2/N_1) was defined as 1, resulting in 96 patients (48 patients in both arms) for 80% power, 110 for 85% power, and 128 for 90% power. With a 10% attrition between baseline and 3 months, as documented in a shoulder injection study by Holt et al. in 2013 [48], a total of 106 patients (53 per arm) should be recruited. Our aim will be to recruit 110 patients.

Recruitment {15}

Patient recruitment will take place in one centre, namely Universitair Ziekenhuis Brussel and started on February 28, 2025. Recruitment is expected to last for 2 years with an estimated rate of recruitment of 4 patients per month. Nevertheless, recruitment will continue until the predetermined number of patients is included, regardless of the duration of the recruitment period. Depending on the rate of inclusion, we will contact other centres to increase recruitment rate. Treating physicians (PRM and orthopaedic surgery specialists, endocrinologists, and general physicians) will screen and inform eligible patients about the study when patients are seen for painful shoulder conditions.

A Trial Site Manual will be prepared for hospital staff which will include guidance on consenting patients into

the trial and how to answer questions that might arise during consent. In addition, a poster and index card will be provided to publicize the trial to hospital staff and patients.

Assignment of interventions: allocation

Sequence generation {16a}

Participants will be allocated to each trial arm by means of an electronic randomizer, configured in "REDCap" (Vanderbilt University, Nashville, USA). The order of randomization is predetermined using a mixed-block method, with blocks randomly created with sizes two, four, and six and treatments assigned in a 1:1 ratio. This allows to reduce the predictability of the intervention arm, while keeping the advantages of a randomized block procedure. The electronic randomizer uses as input the participant details and date of consent and allocates a unique trial ID and treatment arm to that patient, recording these automatically so that no details can be altered or deleted.

Concealment mechanism {16b}

The study coordinator is an unblinded researcher and is responsible for the scheduling of all appointments and, therefore, will have access to the randomization list (Excel file). The randomization list is inaccessible for the physician-investigator, outcome assessors and statistician. The study coordinator will not perform any interventions nor measurements.

Implementation {16c}

Assignment of interventions: blinding {17}

The assessing clinician will identify patients who have been referred for a shoulder pain. An investigator (PRM specialist) will complete a CRF to confirm whether the patient is eligible or not, and when applicable, approach the patient about the study. The investigator will then provide an information sheet and answer any questions. The patient can agree to consent at that time or take up to a week to decide. When the patient does not consent, a further CRF will be completed by the investigator to briefly record the reason for the patient not consenting and their treatment plan. When patients consent and complete their baseline forms, the recruiting clinician investigator will complete the clinical examination into the e-CRF and order the MRI scan while the patient will fill in the PROMs. Before the follow-up appointment to discuss the MRI scan, the study coordinator will generate the allocation sequence using the electronic randomizer, configured in "REDCap" (Vanderbilt University, Nashville, USA) for patients taking part in the frozen shoulder treatment part of the study. The study coordinator will be responsible for ordering the allocated concealed medication to be injected.

Neither the patients nor the hospital staff will be informed of the allocation. The physician-investigator will then perform the USG SSNB and IACI with the concealed content.

The academic hospital pharmacy has the premises, qualified staff and experience required for the proper management of medicinal products used in clinical trials: reception, storage at the required temperatures, dispensing, preparation before use, if necessary, possible returns or destruction, etc.

This clinical trial being a low-intervention clinical trial, with normal prescribing practice and documentation and recording of the used amount, it is sufficient to maintain routine pharmacy documentation on receipt, storage and handling.

Who will be blinded {17a}

The patient, care provider, investigator (who administers the injections) and outcome assessor will be unaware of the type of SSNB of the allocation group. The investigational products will be prepared by the unblinded pharmacist according to a pre-defined co-variate constrained randomization key.

Procedure for unblinding if needed {17b}

The physician-investigator will only unblind the treatment allocation of a subject in the course of a clinical trial if unblinding is relevant to the safety of the subject. The statistician and outcome assessors will not be unblinded during the trial.

Data collection and management

Plans for assessment and collection of outcome {18a}

To optimize the study feasibility and to ensure data protection, the clinical examination measures and the self-reported measures will be completed online using “REDCap”. The first assessment is before the injections, the second assessment takes place 4 weeks after the intervention, the third assessment 3 months after the

intervention, the fourth assessment 6 months after the intervention and the fifth and final 12 months after the intervention. See Tables 1 and 2 for an overview of all the assessments and timeline. All potential endpoints are reported in Table 2. All assessors will be trained to ensure correct standardized measurements of ROM and performance of clinical tests.

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

Due to the nature of this study, the main treatment is done at one point in time, its adherence is guaranteed. The follow-up time points in this study are at 4 weeks and 3–6–12 months after the patients receive the treatment. Because of the physical examination involved, all follow-up time points must be completed by the patients at the hospital’s outpatient departments. Patients receive a SMS text reminder of upcoming appointments and follow-up phone calls to promote participant retention and completion.

Data management {19}

An Electronic Data Capture system “REDCap” will be used for data collection. The system is validated and access to all levels will be granted/revoked by the Sponsor representative. Corrections/modifications will be automatically tracked by an audit trail detailing date and time of the correction and the name of person performing the correction.

To ensure the objectivity of the clinical data, all subjects in this study will be followed up and observed by the same investigator. PROMs will be collected via web-based self-reported questionnaires that are provided to the patients on a tablet in the hospital or through a link to their personal device (smartphone, tablet or PC). To avoid missing data, an error message will appear when a question is not filled in. The data management team will perform periodic and random audits to detect any outliers or discrepancies in the data.

Table 1 Intervention description

Active Comparator: SSNB + IACI	Placebo Comparator: Short-acting SSNB + IACI
Patients randomized to this arm will receive an USG-SSNB (20 mg methylprednisolone acetate and 5 mL Ropivacaine 2 mg/ml) followed by an USG-IACI (40 mg methylprednisolone acetate and 1 mL Ropivacaine 2 mg/ml) Rehabilitation/physiotherapy is considered standard of care	Patients randomized to this arm will receive an USG-SSNB (5 mL Linisol 10 mg/ml) followed by an USG-IACI (40 mg methylprednisolone acetate and 1 mL Ropivacaine 2 mg/ml) Rehabilitation/physiotherapy is considered standard of care
All patients complete rehabilitation under supervision of their own physiotherapist. The investigators will provide some guidelines and criteria but is the physiotherapist’s choice how to implement these guidelines in clinical practice	
Patient education on home-exercise monitoring of peak pain, at rest/night and after rehabilitation sessions using a Numeric-Pain-Rating-Scale (0–10) (NPRS) to evaluate tissue irritability and guide physiotherapy and rehabilitation	
Use of passive physiotherapy (cold, heat or electric therapies) to treat pain. Active and passive mobilization of the shoulder under the pain threshold, Maitland mobilization, and stretch exercises such as table slides and wall climbers. Use of affected upper limb in pain free range of motion (ROM) is tolerated and stimulated. Progressively increase time and frequency of Total-End-Range-Time (TERT) positions to increase ROM	

Table 2 Participant timeline

Outcome	Intake (T0)	4 weeks (T1)	3 months (T2)	6 months (T3)	12 months (T4)
Screening (inclusion and exclusion criteria)	x				
Informed consent	x				
Patient's demographics	x				
Medical History					
SPADI	x	x	X Primary Endpoint	x	x
NPRS	x	x	x	x	x
CMS	x	x	x	x	x
EQ-5D 3L	x	x	x	x	x
PROMIS-29 UE	x	x	x	x	x
Shoulder ROM: ABD—ANT—ExtRot	x	x	x	x	x
FS clinical tests	x	x	x	x	x
RC clinical tests	x				
TSK-11	x	x	x	x	x
PSEQ	x	x	x	x	x
GROc	x	x	x	x	x
WAI	x	x	x	x	x
Work Status	x	x	x	x	x
Health Care Service Use	x	x	x	x	x
Adverse Effects		x	x	x	x
Current or Rescue Therapy	x	x	x	x	x
MRI scan	x				

During the research, the physicians-investigators and assessors will be responsible for the data management and storage. Following the research, the PI will be fully responsible for data management and storage.

During the research, all obtained data will be stored on a dedicated page on Vrije Universiteit Brussel SharePoint (system-encrypted) with access limited to the investigators and supervisors. A back-up will be foreseen on a secure external hard drive. Following the research, all data will be relocated to the Vrije Universiteit Brussel Archive where it will be archived for 25 years. All possible personal identifiable data (vide infra) will be removed from the archived data. The Trial will be conducted in compliance with the requirements of the EU General Data Protection Regulation 2016/679 (GDPR), the relevant Belgian laws implementing the GDPR including the Belgian Privacy Act of 30 July 2018 on the protection of privacy in relation to the processing of personal data.

Confidentiality [27]

Participant identification codes will be used to link data to patients. The file containing the link between participant numbers and personal data (i.e. key) will be managed by the researchers and will be locked for access by

others. As an additional security measure, the file linking the pseudonymization to the original direct identifiers will be encrypted before it is uploaded to SharePoint.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use [33]

No biological specimens will be obtained during the conduct of the trial.

Statistical methods

The flow of participants through each stage of the trial will be presented in a Consolidated Standards of Reporting Trials (CONSORT) diagram [49]. Unadjusted SPADI will be summarized descriptively (n, mean, SD, median, minimum and maximum) at each time point by treatment group and overall.

Demographic data for each group will be presented using a frequency table, with categorical variables presented as proportions and numeric variables presented as mean with standard deviations or median with range, depending on skewness of data.

Parametric data will be presented as mean with 95% confidence intervals (95% CI), non-parametric data

as median with 25–75% interquartile range (IQR) and binary data as percentages with 95% CI. Differences between groups will be analysed using *t*-test if normally distributed data, non-parametric by rank-sum test and binary data by Fisher's exact test or chi-squared test.

Statistical methods for primary and secondary outcomes {20a}

The primary analysis will be performed on the intention-to-treat (ITT) population.

Our primary analysis will compare SPADI of both treatment groups at 3 months. For both treatment comparisons, the primary outcome SPADI will be analysed using a longitudinal mixed model, including assessments at all available time points with reference to the date of randomization (4 weeks, 3, 6 and 12 months, thereby increasing power) and treating patients as a random effect. Baseline variables will be used as covariates.

The same approach will be adopted for secondary outcomes and performed according to the intention-to-treat principle. The threshold for statistical significance will be set at $p < 0.05$. A superiority margin of 13 points is chosen based on the study of Roy et al. who found in their systematic review that the minimal clinically important difference change in SPADI is between 13 [50]. Superiority will be concluded when the lower limit of the confidence interval will be above the superiority margin of 13. To address multiplicity issues, all repeated continuous outcome measures will be analyzed using linear mixed models for repeated measures (MMRM). Estimates will be generated for each time point based on the Group $\times$ Week interaction, with least squares means used to compare groups at prespecified key time points (e.g. 3 months and 12 months [Table 2]). Confirmatory testing will be restricted to the primary endpoint and a small number of key secondary endpoints (defined a priori). A hierarchical testing approach may be applied to control type I error. Remaining secondary and exploratory endpoints will be considered supportive. They will be analyzed using the same longitudinal models and presented with effect estimates and 95% confidence intervals. If more than one secondary endpoint is formally tested, a multiple comparison procedure (e.g. Holm or Hochberg adjustment) will be applied. This framework ensures that statistical inference is transparent, reproducible, and aligned with the trial registration. The main time points of interest will be 3 months (primary) and 12 months (longer-term follow-up), with results at 4 and 6 months serving to model trajectories over time.

Interim analysis {21b}

An intermediary statistical analysis will be performed at 6 months timepoint, i.e. when half of the predetermined

sample size has been reached (patients $n = 53$). In case all 3 outcomes (disability, pain, shoulder stiffness) show non-superiority at 6 months, the study will not be extended to the 12-month time point. In case of significant (and ethically disputable) inferiority of one of the treatment arms at 6 months timepoint ($p < 0.001$), we will terminate that treatment arm and all patients will be proposed to switch to the superior treatment arm and we will stop the recruitment given that the study has reached statistical significance with a lower sample size (which makes further recruitment unnecessary).

Methods for any additional analyses {e.g. subgroup analyses} {20b}

Multiple linear regression analysis will be performed to determine which clinical examination tests and/or MRI criteria, or which combination of, will have the best diagnostic accuracy in early phase frozen shoulder [21]. Correlations between MRI diagnostic criteria, physical examination tests, and clinical variables will be conducted also. Additionally, factors that predict (I) SPADI at 3–6–12 months follow-up, (II) pain NPR level at 3–6–12 months, (III) shoulder ROM at 3–6–12 months and (IV) return to work and WAI at 3–6–12 months will be determined.

Finally, patients that benefit the most from the combined SSNB + IACI will be identified through a predictive analysis. As predictor variables, SPADI-score, presence of joint capsule enhancement on MRI, shoulder ROM, age, sex, duration of symptoms and presence of diabetes will be used.

Blinded safety analysis for the total number of clinical events and safety will be performed each month. In case of a major AE (death, major nerve damage, other major medical complication), the ethics committee will be notified, and early termination of the study will be discussed.

Health economics analysis

This protocol has been designed that a later economic analysis is possible. The economic analysis is not a part of the trial and the decision to conduct such economic analysis will depend on the effectiveness results of the trial. The variables that will be collected for this purpose are EQ-5D-3L, WAI, work status, health care service use, and use of rescue medicine.

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

The primary analysis is based on longitudinal data including all timepoints and hence includes all patients with at least one outcome measure apart from baseline. All randomized participants will be followed up whenever possible, even if they discontinue treatment;

the primary analysis should include all observed data under a plausible assumption about missingness; sensitivity analyses will be performed to test the robustness of findings under alternative assumptions; and all randomized participants will be accounted for, at minimum within the sensitivity analyses (reference White I, et al. {BMJ 2011; PMID: 21300711}). This approach has been shown to provide consistent estimates under missingness-at-random (MAR). MAR occurs when the missingness is not random, but where missingness can be accounted for by model variables or previous outcome measures. Hence, if missingness is group-related, the proposed analysis method corrects for possible resulting bias. MMRM models for continuous outcome measures will probably provide valid estimates (assuming 'MAR') even if some outcome data is missing (reference PMID: 37170796; Christensen R, et al. *Acta Orthop* . 2023 May 10;94:243-249. <https://doi.org/10.2340/17453674.2023.11656>.) Patients with no outcome measures apart from baseline, hence, patients that dropped out before 4 weeks, are excluded from the primary analysis. A multiple imputation approach will be applied as a secondary and sensitivity analysis, to study the impact of these cases. The imputation model will include group, time, the baseline outcome measurement, and patient characteristics.

An investigator will track patients and ensure in-time contact with the patient for scheduling the follow-up visits to prevent missing data. Reasons for missing data will be recorded in the eCRF.

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

After the project is finalized, access restrictions will be applied to the pseudonymized data and will be specified in a data use agreement containing the following elements: evaluation of the re-use request by ethical committee (EC), non-disclosure agreement and warranties for safe storage of data.

Oversight and monitoring

Composition of the trial steering committee (TSC) {5d}

The Steering Board is the main decision-making and steering body of the project. The Steering Board consists of M.S., L.G., M.M., J.C., L.V.B, J.N. and S.H. The Steering Board organized a kick-off meeting at the start of the project to establish common working procedures. The main tasks of the Steering Board are (1) agree on common working procedures and management policies, (2) monitor overall progress and follow-up of deliverables, (3) decisions on major changes to the work programme, (4) conflict handling and (5) budget decisions. One of the most important tasks of the Steering Board is also to (re)direct all participants in the implementation of the

work programme and the timely achievement of all deliverables. Additional meetings can be organized ad hoc in case of urgent issues.

The valorization board consists of relevant stakeholders (physicians, radiologists, physiotherapists, medical statisticians) who will be asked to actively contribute to the implementation of the study findings, and any difficulties experienced during the implementation process will be discussed. The investigators are available to support the stakeholders with the implementation process. In addition, the valorization board will prepare and guide the full utilization process in the period following the completion of the research project (after-trajectory).

Composition of data monitoring committee {DMC}; its role and reporting structure {21a}

The study coordinator at Universitair Ziekenhuis Brussel will regularly monitor data that are entered in "REDCap" and in the Excel file for the functional capacity evaluation. The study coordinator is independent from the funder of this study and has no competing interests.

Adverse event reporting and harms {22}

Investigators will seek information on AEs during each patient contact. All events, whether reported by the patient or noted by trial staff, will be recorded in the patient's medical record and in the e-CRF within a reasonable time after becoming aware. If available, the diagnosis should be reported on the AE page, rather than the individual signs or symptoms. If no diagnosis is available, the Investigator should record each sign and symptom as individual AEs.

The following minimum information should be recorded for each AE: AE description, start and stop date of the AE, severity, seriousness, causality assessment to the study interventions, outcome. All AEs must be evaluated by an Investigator as to seriousness, severity and causality.

The Investigator is responsible for ensuring that all safety events are recorded in the (e)CRF and reported to the Sponsor in accordance with instructions provided below.

The Sponsor will promptly evaluate all serious adverse effects (SAEs) and AEs against medical experience to identify and expeditiously communicate possible new safety findings to Investigators and based on applicable legislation.

If the investigator becomes aware of a serious adverse event with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical trial in a subject treated by him or her, the investigator shall, without undue delay, report the serious adverse event to the sponsor.

The sponsor has the obligation to, once a year throughout the clinical trial (or on request), submit a progress

report to the EC's containing an overview of all SARs that occurred during the reporting period and taking into account all new available safety information received during the reporting period.

Frequency and plans for auditing trial conduct {23}

The study staff will submit a summary of the progress of the trial to the central ethics committee once a year. The following information will be provided: date of inclusion of the first subject, number of included subjects, number of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems and amendments. There is no planned on-site auditing of the trial. However, to ensure compliance with relevant regulations, an independent quality assurance representative may review this trial. This implies that auditors will have the right to audit the site(s) at any time during and/or after the completion of the trial and will have access to the data generated during the clinical investigation, source documents and patient's files.

Plans for communicating important protocol modifications to relevant parties (e.g. trial participants, ethical committee) {25}

All protocol amendments will be approved by the ethics committee prior to implementation. If relevant, patients will be informed of protocol modifications.

Dissemination plans {31a}

Within 1 year from the end of a clinical trial in all Member States concerned, the sponsor will submit to the EU database CTIS a summary of the results of the clinical trial. The content of the summary of the results is set out in CTR Annex IV. It shall be accompanied by a summary written in a manner that is understandable to laypersons. Furthermore, we will communicate findings of this trial via the publication of scientific manuscripts and presentations on national and international symposia, as well as through social media. The main paper will be based on the repeated measures collected up to 12 months from baseline.

Declaration of interests {28}

The independent members of the DMC and TSC will sign a form to confirm that they have no competing interests to declare. Competing interests of the authors are presented at the end of the protocol.

Discussion

The FROSTBLOCK study will evaluate whether the combination of long-acting SSNB with an IACI will improve pain and function more than an IACI with a placebo SSNB in patients with frozen shoulder. We expect that the SSNB+IACI group will have a superior outcome

compared to the placebo SSNB+IACI group in terms of the primary outcome measure. A recent qualitative study concluded that patients convey a strong desire in seeking a corticosteroid injection while seemingly dismissing the associated risks [51]. If our hypothesis is confirmed, this study could lead to a change in the standard of care for patients in the painful phase of frozen shoulder. Our final objective is on identifying which patients will experience the most significant benefits from GH IACI, whether used on its own or alongside SSNB.

Like all studies, our study has several limitations. First, this study does not include a group of patients with placebo SSNB and placebo IACI to assess natural history of frozen shoulder. Second, the study is limited to patients with frozen shoulder without a history of trauma, surgery or neurologic disease involving the shoulder and may not be generalizable to all patients.

Conclusions

This study could offer valuable insights into the treatment and clinical diagnosis of this common condition and potentially lead to enhanced patient care.

Trial status

Recruitment started on February 28, 2025. The current protocol is version 3, published on September 3, 2024. Recruitment is expected to last for 2 years with an estimated rate of recruitment of 4 patients per month.

Abbreviations:

AE	Adverse event
DMC	Data Monitoring Committee
EC	Ethical Committee
e-CRF	Electronic Case Report Form
GDPR	General Data Protection Regulation
PI	Principal Investigator
TSC	Trial Steering Committee
CMS	Constant-Murley Score
CPT	Coracoid Pain Test
DTPER	Distension Test in Passive External Rotation
EQ-5D 3L	EuroQol with five dimensions and 3 levels
GH	Gleno-humeral
IA	Intra-articular
NPRS	Numeric Pain Rating Scale
PROMIS-29 UE-SF	Patient-Reported Outcomes Measurement Information System (PROMIS)—Upper Extremity short form
RC	Rotator cuff
ROM	Range of motion
RTW	Return to work
SAE	Serious adverse event
SPADI	Shoulder Pain and Disability Index
SSNB	Suprascapular nerve block
TERT	Total End Range Time
TSK-11	Tampa Scale for Kinesiophobia
USG	Ultrasound-Guided
WAI	Work Ability Index

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Authors' contributions (31b)

M.S. is the principal investigator; he conceived the study and responsible for writing the draft manuscript, supported by M.M., L.G., M.M., J.C., L.V.B., J.N. and S.H. M.M., L.G., J.C., L.V.B., J.N. and S.H. participated in the design of the study and contributed intellectual content. The authors read and approved the final manuscript.

Funding (4)

This study is funded by the Department of Physical Medicine and Rehabilitation of Universitair Ziekenhuis Brussel. The funder does not have a role in the design of the study; the collection, analysis and interpretation of the data; or the writing of the manuscript.

Data availability (29)

The Steering Board has access to the pseudonymised final trial dataset. Any materials to support the protocol can be supplied on motivated request, under the condition that the current study is not compromised.

Declarations

Ethics approval and consent to participate (24)

The study protocol was approved by the Federal Agency for Medicines and Health Products of Belgium (EU CT number: 2024-513057-78-00).

Consent for publication (32)

This manuscript does not contain personal identifiers or any other personal data from patients. All non-identifiable data are available, on request, from the corresponding author.

Competing interests (28)

Marc Schiltz has received speaker fees from Heel and Ipsen. Lisa Goudman is a postdoctoral research fellow funded by the Research Foundation Flanders (FWO), Belgium (project number 12ZF622N). Maarten Moens has received speaker fees from Medtronic. STIMULUS received independent research grants from Medtronic. The authors declare no competing interests.

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