Efficacy of Xylocaine-Impregnated Compress Application in Reducing Perprocedural Pain During Ultrasound-Guided Infiltration of a Retrigger Finger : A Randomized Double-Blind Controlled Study (SAUTYLO)

HUMAN INTERVENTION RESEARCH PROTOCOL FOR A DRUG FOR HUMAN USE

Version N°1.1 dated 15/09/2021

Project code: APHP210094 / EUDRACT No.: 2021-002052-36

Coordinating Investigator: Dr Henri GUERINI
Radiology Department B
Paris Centre-GH Cochin University Hospitals
27, Rue du Faubourg Saint-Jacques
75014 Paris, France
Phone: +33 1 58 41 25 02
Email: henri.guerini@aphp.fr

Scientific Leader: Dr Christelle NGUYEN
Rehabilitation and Rehabilitation Service Locomotor and Spine Pathologies
Device Rehabilitation
Paris Centre-GH Cochin University Hospitals
27, Rue du Faubourg Saint-Jacques
75014 Paris, France
Tel: +33 1 58 41 29 45 / Fax: +33 1 58 41 25 38
Email: christelle.nguyen2@aphp.fr

Promoter :
AP-HP
Clinical Research and Innovation Department (DRCI)
Saint-Louis Hospital
1, Avenue Claude Vellefaux, 75010 Paris
DRCI-Headquarters project referent: Karine GOUDE-ORY
Phone +33(0)1 44 84 17 22 Fax +33(0)1 44 84 17 01
Email: karine.goude@aphp.fr

Busy structure
Follow-up of research:
URC-CIC Paris Descartes Necker Cochin - Site Tarnier
89 Rue d'Assas
75006 Paris
DRCI-URC project referent: Laetitia PEAUDECERF
Tel.: 01 58 41 12 13 / Fax: 01 58 41 11 83
Email: laetitia.peaudecerf@aphp.fr

Structure in charge of the Vigilance Sector - DRCI (AP-HP),
Vigilance: Fernand Widal Hospital - 200, rue du Faubourg Saint-Denis
75475 Paris /
Sarra DALIBEY, Head of the Vigilance Sector
Tel.: +33 (0)1 40 27 57 85
Email: sarra.dalibey@aphp.fr

Clinical Research and Innovation Department (DRCI)
Saint Louis Hospital 75010 PARIS

Research Protocol SIGNATURE Page

Research Code: APHP210094

Title: Efficacy of the application of a Xylocaine-impregnated compress in the reduction of per-procedural pain during ultrasound-guided infiltration of a trigger finger: a double-blind randomized controlled study (SAUTYLO)

Version N°1.1 dated 15/09/2021

The research will be conducted in accordance with the protocol, the best practices in force and the legislative and regulatory provisions in force.

The coordinating investigator:

Dr Henri GUERINI
Radiology B
Paris Centre-GH Cochin University Hospitals
27, Rue du Faubourg Saint-Jacques
75014 Paris, France

Date:
Signature :

The Proponent

Assistance Publique-Hôpitaux de Paris
Clinical Research and Innovation Department
Saint Louis Hospital
1 Avenue Claude Vellefaux
75010 PARIS

Date:
Signature :

TABLE OF CONTENTS

1 SYNOPTIC SUMMARY

Full title	Efficacy of Xylocaine-Impregnated Compress Application in Reducing Perprocedural Pain During Ultrasound-Guided Infiltration of a Trigger Finger: A Double-Blind, Randomized Controlled Study
Acronym / Reference	SAUTYLO
Coordinating Investigator	Dr Henri GUERINI Radiology Department B Paris Centre-GH Cochin University Hospitals 27, Rue du Faubourg Saint-Jacques - 75014 Paris, France Phone : 01 58 41 25 02 Email: henri.guerini@aphp.fr
Scientific Manager	Dr Christelle NGUYEN Department of Rehabilitation and Rehabilitation of the Musculoskeletal System and Spine Pathologies Paris Centre-Cochin Hospital Group University Hospitals 27, Rue du Faubourg Saint-Jacques - 75014 Paris, FRANCE Tel: +33 1 58 41 29 45 / Fax: +33 1 58 41 25 38 Email: christelle.nguyen2@aphp.fr
Promoter	Assistance Publique-Hôpitaux de Paris / DRCI
Scientific justification	Ultrasound-guided trigger finger injections are a frequent and painful invasive procedure. However, there is no current recommendation for the management of intraprocedural pain, and in the majority of cases the infiltration is performed without prior skin anesthesia. Xylocaine patches are controversially effective in the management of acute pain and in common practice they are not prescribed in advance, are poorly adapted to the topography of the finger, and thus are not applied. On the other hand, a recent study has shown the interest of administering lidocaine 2% by J-tip, a needle-free injection technique not available in France, before an infiltration of a trigger finger. We hypothesize that a compress soaked in Xylocaine 20 mg/ml solution for injection, applied 15 minutes before the procedure, would reduce per-procedural pain.
Objective and primary endpoint	The main objective is to evaluate the effectiveness of the application of a compress impregnated with Xylocaine 20 mg/ml solution for injection, on the reduction of per-procedural pain from an ultrasound-guided infiltration of a trigger finger. The primary outcome is the mean pain intensity during the procedure on a self-administered numerical scale (EN) (0, no pain and 100, maximum pain).
Secondary objectives and endpoints	The secondary objectives are to evaluate the adverse effects and acceptability of pain during the procedure according to the patient and according to the operator. Secondary outcomes are adverse events according to a self-administered open-ended question and the level of acceptability of pain during the procedure for the patient according to the patient himself and according to the operator on a self-administered NE (0, not at all acceptable and 100, completely acceptable).
Experimental design	Single-center, randomized, controlled, double-blind study.
Population concerned	Adult patients with trigger fingers requiring ultrasound-guided infiltration of cortisonic derivatives
Inclusion criteria	- Patients aged 18 years or older - Trigger finger (clinical definition with painful difficulty or even trigger when extending a finger) with indication for ultrasound-guided infiltration of cortisonic derivatives - Preliminary medical examination

	- Written consent - Affiliation to a Social Security scheme
Non-inclusion criteria	- Neurological conditions affecting the hand other than carpal tunnel syndrome - Intra-articular infiltration of the hand or wrist ≤ 2 months - Allergy to Xylocaine - Contraindication to xylocaine or cortisonic derivatives - Cognitive or behavioural impairment that makes assessment impossible - Persons referred to in Articles L 1121-5; 6 ; 8 ; 9 of the Public Health Code (protected adults, under guardianship or curatorship, etc.) - Pregnancy and breastfeeding; Lack of contraception for women of childbearing age - Participant unable to speak, read and write French
Treatment(s) on trial	Development phase: IV Xylocaine 2% impregnated compress
Benchmark treatment	Compress impregnated with saline
Other acts or procedures related to care	Ultrasound-guided infiltration of cortisonic derivatives
Expected benefits for participants and society	This practice, if it proves to be effective, would reduce the pain during trigger finger injections in a simple, practical, inexpensive way, easily achievable on a daily basis.
Risks and constraints added by research	15-minute wait before the infiltration is carried out Risk: A
Practical procedure	Selection and inclusion at the same visit: the investigator, an experienced radiologist, confirms the clinical and ultrasound diagnosis of trigger fingers, confirms the inclusion and non-inclusion criteria, has the informed consent signed, includes and randomizes the patient. On the same day as the inclusion visit: application of a compress 15 minutes before the infiltration, impregnated with xylocaine 20 mg/ml or physiological serum, before carrying out the ultrasound-guided infiltration. Evaluation of perprocedural pain immediately after the procedure, by numerical scale.
Number of Selected Subjects	60
Number of centres	1
Research Timeline	Duration of inclusion: 12 months Duration of participation (treatment + follow-up): 1 consultation Total duration: 12 months Duration of ban from participating in other research: none
Number of planned inclusions per centre per month	5
Statistical analysis	Statistical analysis will be performed on an intention-to-treat basis (all randomized patients will be analyzed in their randomization arm) according to a predefined statistical analysis plan. There will be no intermediate analysis.
Source of funding	Foundation of the Future
Independent Oversight Committee Planned	No

2 SCIENTIFIC RESEARCH JUSTIFICATION

2.1 Research hypotheses

Xylocaine is a powerful anesthetic, used in particular during trigger finger injections on the infiltration pathway.
The use of compresses soaked in Xylocaine 20 mg/ml solution for injection is also a frequent and effective practice, particularly in ENT, for example after endoscopic sinus surgery (1). However, the effectiveness of applying a compress soaked in Xylocaine to the skin, prior to an infiltrative procedure, remains to be demonstrated. Its simplicity of performance and availability would make it an analgesic technique of choice.
Indeed, unlike Emla 5% © patches, whose effectiveness in the treatment of acute pain is disputed (2), which are not in practice prescribed before an infiltration, and which require an application time of around 30 to 60 minutes (see CPR), Xylocaine in injectable solution is present in all radiology practices performing invasive procedures.
We hypothesize that the application of a compress soaked in Xylocaine 20 mg/ml 15 minutes before an ultrasound-guided trigger finger infiltration would reduce per-procedural pain.

2.2 Description of knowledge relating to the pathology concerned

Trigger finger is a common pathology (2 to 3% of the general population (3)) that affects middle-aged women in particular. The most frequently affected fingers are the thumb and index finger, especially of the dominant hand. The condition is bilateral in 10 to 16% of cases (4). The trigger finger results from a mismatch between the diameter of the flexor tendons and that of the pulley.
Clinically, it is initially the cause of increased pain in the palm during extension and flexion of the fingers, with typically a protrusion when extending the affected finger. Later, extension becomes even more difficult, with the need to use the other hand to fully extend the finger. Eventually, the finger can get completely stuck in flexion.
Ultrasound can confirm the clinical diagnosis by visualizing the thickened affected flexor tendon, a diffuse thickening of the sheath, an irregular echostructure or even a laceration of the tendon (5).
Treatment can be functional, medical, or even surgical (6). Ultrasound-guided corticosteroid injections into the tendon sheath are frequently performed as a first-line treatment (7). This infiltration, which is effective, is nevertheless painful.

2.3 Summary of preclinical experiments and clinical trials concerned

Xylocaine is a powerful anesthetic. It locally interrupts the propagation of nerve impulses along the nerve fiber instead of application by blocking voltage-dependent sodium channels. Its routes of administration and galenics are varied: in solution that can be injected by infiltration, by nerve block; in gel and patch topically; oral ("viscous") gel.
To date, only one small, open-label, randomized controlled study has evaluated the effectiveness of applying percutaneous lidocaine with J-tip, a needle-free system not available in France, before trigger finger infiltration, in reducing pain (8). Per-procedural pain was significantly lower in the J-tip group.
In addition, studies concerning the application of xylocaine in solution for injection by compress applied to the skin are inconclusive (9) and mainly concern paediatric populations in post-traumatic contexts.

To date, there are no studies evaluating the effectiveness of applying xylocaine-impregnated compresses in reducing pain caused by trigger finger infiltration.

2.4 Description of the population to be studied and justification for its choice

We propose to include patients consulting in our osteoarticular radiology department in Cochin for an ultrasound-guided infiltration of a trigger finger.

2.5 Name and description of the investigational medicinal product(s)

The drug studied is Xylocaine© 20 mg/ml, solution for injection, applied to the skin for 15 minutes through an impregnated compress. We will use the generic Lidocaine Aguettant 20 mg/ml without preservatives, solution for injection, in a 10 ml polypropylene ampoule.
The placebo of the investigational drug is NaCl 0.9%, solution for injection. The SmPC states that the administration of the solution is contraindicated in severe cases of water and/or sodium retention (hypernatremia), particularly in cases of heart failure, decompensated hepatic failure (oedema and ascites failure), preeclampsia/eclampsia. It is not specified for which type of administration these contraindications apply, but it is most likely parenteral injection (IV, IM, SC) of larger volumes than that which will be applied topically (5 ml) as part of the trial.

2.6 Description and rationale of dosage, route of administration, administration schedule, and duration of treatment.

In the experimental group, we propose the application of a compress impregnated with a 10 ml ampoule of Xylocaine 20 mg/ml 15 minutes before the ultrasound-guided infiltration of the trigger finger is performed. In the comparator group, we will use a saline compress (NaCl 0.9%) as a placebo 15 minutes before the ultrasound-guided infiltration of the trigger finger.
In the 2 groups, the trigger finger infiltration will then be performed under ultrasound guidance by 4 experienced radiologists after confirmation of the ultrasound diagnosis. Infiltration corresponds to the peritendinous injection, in strict aseptic measures, of a mixture of 1 to 2 ml of Xylocaine 0.5% and cortisonic derivatives in suspension for injection (Hydrocortancyl 2.5 percent© 1 vial of 1 ml), using a subcutaneous needle and a 5 ml syringe. The correct positioning of the needle will be checked by the bubble test.

2.7 Summary of foreseeable and known benefits and risks for research participants

The immediate expected individual benefit is a reduction in per-procedural pain, thus allowing this delicate procedure to be performed in optimal conditions, and also possibly reducing the anxiety of a future infiltration (of another affected finger, or the same finger).
This practice, if it proves to be effective, would prevent pain during trigger finger injections in a simple, practical, inexpensive way, easily achievable on a daily basis.
The foreseeable risks of research are those related to the performance of a peritendinous infiltration: pain, infection, tendon rupture, vascular wound, allergy. These risks are exceptional and the risk/benefit ratio of this trial seems acceptable to us.

3 OBJECTIVES

3.1 Main objective

The main objective is to compare the effectiveness on per-procedural pain of an ultrasound-guided finger infiltration of a compress impregnated with Xylocaine 2% applied to the skin for 15 minutes before the procedure to that of a compress impregnated with physiological serum.

3.2 Secondary Objectives

The secondary objectives will be:

- Undesirable effects
- the acceptability of pain during the procedure according to the patient
- the acceptability of pain during the procedure according to the operator

4 RESEARCH DESIGN

4.1 Primary and secondary endpoints

4.1.1 Primary endpoint

The primary outcome is the mean pain intensity during the procedure on a self-administered numerical scale (EN) (0, no pain and 100, maximum pain).

4.1.2 Secondary endpoints

Secondary outcomes are adverse events according to a self-administered open-ended question and the level of acceptability of pain during the procedure for the patient according to the patient himself and according to the operator on a self-administered NE (0, not at all acceptable and 100, completely acceptable).

4.2 Description of the research methodology

4.2.1 Experimental design

- Phase IV drug trial
  - Comparative
  - Randomized
  - Controlled (comparator group)
  - Comparator group: placebo
  - In 2 parallel groups (xylocaine/placebo)
  - Distribution of subjects in groups according to a ratio (1:1)

4.2.2 Number of participating centres

The research will be monocentric, conducted in a single hospital, with 2 participating departments (Department of Rehabilitation and Rehabilitation of the Locomotor System and Spine Pathologies of Prof. François Rannou and Radiology Department B of Prof. Jean-Luc Drapé) but only one including patients (Radiology Department B of Prof. Jean-Luc Drapé). Patient recruitment will be hospital, in particular with patients referred by the Department of Rehabilitation and Rehabilitation of the Musculoskeletal System and Spine Pathologies, and outpatient, with patients referred to the osteoarticular radiology department of the Cochin

Hospital for an ultrasound-guided infiltration of a trigger finger. Announcements will also be posted in the participating departments and posted on the website of the participating departments and the intranet of the hospital group and the University.

4.2.3 Subject Identification

In this research, the subjects will be identified as follows:
No. Order of selection of the person in the centre (4 numerical positions) - Initial Last name - First initial. This reference is unique and will be kept for the duration of the research. A randomization number will be assigned at randomization.

4.2.4 Randomization

Patients who meet the inclusion criteria and agree to participate will be randomized at the time of the inclusion visit.

- Sequence generation: The randomization sequence will be computer-generated by a CRU statistician.
- Implementation: the randomization process will be centralized by the coordinating office (URC, Cochin Necker), which is not involved in the inclusion, follow-up or evaluation of patients. Only the independent statistician of the CRU and the IT specialist of the coordinating office who will implement the list in the secure e-CRF will have access to the randomization list.
- Allocation masking: the sequence will be masked by means of a computerized interface implemented in the e-CRF (CleanWeb).

4.2.5 Blinding procedures and measures implemented to maintain blinding

Patients, radiologists, statisticians, and investigators will be blinded from the allocation group. The pharmacy will dispense, according to the randomization list, pre-filled ampoules of either 10 ml of xylocaine (Lidocaine Aguettant 20 mg/ml without preservative, solution for injection) or 10 ml of saline (NaCl 0.9%). The 2 preparations have the same macroscopic appearance and the same echogenicity, which makes it possible to maintain the blindness of patients and radiologists.
In order to verify that placebo is considered as credible as xylocaine by patients, we will use a self-completed credibility questionnaire by patients.

4.2.6 Unblinding procedures, if applicable

Unblinding will be requested for any reason considered essential by the investigating physician on call:

- to the DRCI **outside of an emergency situation** during working days and opening hours, to the DRCI project referent tel: +33 1 44 84 17 38.
- at the poison control centre of the Fernand Widal hospital, in emergency cases (cf. emergency situations requiring unblinding), on weekends, public holidays, during the DRCI's closing hours and in the event of unavailability of work at the DRCI Telephone: **01 40 05 48 48**.

5 CONDUCT OF THE RESEARCH

Before any examination or act related to the research, the investigator obtains the *free, informed and written consent of the person who is taking part in the research or of his or her legal representative* , if applicable.
Persons likely to lend themselves to the research referred to in 1° of Article L. 1121-1 of the Public Health Code shall benefit from a prior medical examination adapted to the research.

Participants will be recruited from among patients referred to our osteoarticular radiology department at Cochin Hospital for ultrasound-guided trigger finger infiltration.

Persons whose consent is sought	Who informs and collects the consent of the person	When the person is notified	When the individual's consent is collected
The person who lends himself to the research	The Investigator	At the Selection and Inclusion Visit	At the selection and inclusion visit

5.1 Screening/Inclusion/Randomization/Intervention Visit

The investigator confirms the inclusion and non-inclusion criteria, has the informed consent signed, includes and randomizes the patient. For women of childbearing potential, the investigator will remind the patient of the need to use an effective means of contraception, pharmacological or non-pharmacological, for the duration of participation in the study. No recommendations will be made regarding contraceptive modalities after the trial.
On the same day as the selection and inclusion visit, the patient receives the compress impregnated with xylocaine or saline solution, followed by the ultrasound-guided infiltration of the trigger finger, and finally the pain felt during the infiltration is evaluated by numerical scale from 1 to 10. The operator also assesses the acceptability of the pain by the patient using a numerical scale of 1 to 10.

5.2 Research follow-up visits

There will be no follow-up search visits.

5.3 Completion visit of the research

There will be no visit at the end of the research. At the end of the research, the participant will continue his or her usual medical care. There is no exclusion period.

5.4 Expected duration of participation of individuals, description of the chronology and duration of the research

Maximum time between selection and inclusion	NA
Length of Inclusion Period	12 months
Duration of participation of subjects, including:	
• Duration of treatment:	15 minutes

• Duration of follow-up:	1 day
Total duration of the search:	12 months

5.5 Summary table or diagram of the chronology of the search

Actions	Selection, inclusion, randomization, and intervention
Information	X
Verification of inclusion and non-inclusion criteria	X
Consent	X
Medical examination	X
Randomization	X
Infiltration	X
IN PAIN	X
Adverse events	X
Acceptability of infiltration	X

5.6 Distinction between care and research

TABLE: Distinction between acts related to "care" and acts added by "research"

Acts, procedures and processing carried out in the context of research	**Care-related acts, procedures and treatments**	**Acts, procedures and treatments added by <u>research</u>**
Treatments	Trigger finger infiltration	Application of a xylocaine or saline compress

6 <u>ELIGIBILITY CRITERIA</u>

6.1 Inclusion criteria

- Patients aged 18 years or older
- Trigger finger (clinical definition with painful difficulty or even trigger when extending a finger) with indication for ultrasound-guided infiltration of cortisonic derivatives
- Preliminary medical examination
- Written consent
- Affiliation to a Social Security scheme

6.2 Non-inclusion criteria

- Neurological conditions affecting the hand other than carpal tunnel syndrome
- Intra-articular infiltration of the hand or wrist ≤ 2 months
- Xylocaine allergy
- Contraindication to xylocaine or cortisonic derivatives
- Cognitive or behavioural impairment that makes assessment impossible
- Pregnancy and breastfeeding; Lack of contraception for women of childbearing age

- Persons referred to in Articles L 1121-5; 6 ; 8 ; 9 of the Public Health Code (protected adults, under guardianship or curatorship, etc.)
- Participant unable to speak, read and write French

6.3 Recruitment procedures

Participants will be recruited from among patients referred to our osteoarticular radiology department at Cochin Hospital for ultrasound-guided trigger finger infiltration; in particular from patients referred by the Department of Rehabilitation and Rehabilitation of the Musculoskeletal System and Spine Pathologies.
The principal investigator center, Cochin Hospital, specializes in the management of spinal pathologies and musculoskeletal disorders.

	Number of Subjects
Total number of selected topics	60
Number of centres	1
Inclusion period (months)	12
Number of topics / center / month	**5**

6.4 Stop Rules

6.4.1 Criteria and modalities for premature withdrawal of research treatment

Different situations exist
- Temporary discontinuation of treatment, the investigator should document the reason for discontinuation and its resumption in the subject's source file and CRF
- Premature cessation of treatment, but the subject remains in the research until the end of his or her participation
- Premature discontinuation of treatment and discontinuation of research participation reason.

The investigator must:
- Document the reason(s)
- Collect the evaluation criteria at the time of discontinuation of participation in the research, if the subject agrees
- Provide follow-up of the subject, especially in the event of a serious adverse reaction

In the event of serious adverse events, they should be reported by the investigator to the sponsor and followed up for 6 months following the procedure. The notification of the serious adverse event will be sent by email (eig-vigilance.drc@aphp.fr) to the promoter. The serious adverse event will be followed up until it is resolved.

6.4.2 Criteria and modalities for premature termination of participation in a subject's research

- Any subject can stop participating in the research at any time and for any reason.
- The investigator may temporarily or permanently discontinue a subject's participation in research for any reason that impacts the safety of the subject or that would be in the best interests of the subject.

- Subject lost to sight: we do not know what has become of the subject. The investigator should make every effort to re-establish contact with the subject (and document it in the source file) to at least know whether the subject is alive or deceased

In the event of premature termination of a subject's research, or withdrawal of consent, the data concerning him or her collected before the premature termination may be used.
- If agreed, the primary endpoint, secondary endpoints, and safety assessment will be collected according to the protocol schedule.
- Stopping a subject's participation will not change his or her usual management in relation to his or her disease.
- In the event of serious adverse events, refer to the corresponding vigilance section

The report card must list the various reasons for stopping participation in research:
- ☐ Inefficiency
- ☐ Adverse effect
- ☐ Other medical problem
- ☐ Personal reason of the subject
- ☐ Explicit withdrawal of consent
- ☐ Lost from sight

6.4.3 Follow-up of subjects following a cessation of research participation

In the event of discontinuation of research participation, if the subject agrees, the primary endpoint, secondary endpoints, and safety assessment will be collected according to the schedule set out in the protocol.

Stopping a subject's participation will not change his or her usual management in relation to his or her disease.

In the event of serious adverse events during premature discontinuation of treatment and participation in the patient's research: see section 6.4.1

6.4.4 Modalities for replacing these subjects, if applicable

Subjects that have been released will not be replaced.

6.4.5 Stopping part or all of the research

A distinction should be made between the following 3 decisions:
- Premature and temporary termination of research with suspension of inclusions
- Premature permanent termination of an arm of research
- Premature and permanent termination of the entire research

For these 3 decisions, a distinction must be made between 2 situations for processing:
- Premature and immediate discontinuation of treatment in all subjects upon decision
- Subjects are allowed to complete their treatment

The AP-HP sponsor or the Competent Authority (ANSM) may prematurely, temporarily or definitively, interrupt all or part of the research, in the following situations:
- firstly, in the event of unexpected serious adverse reactions (SUSARS) in one treatment arm or an imbalance of serious adverse reactions between the 2 treatment arms, requiring a reassessment of the benefit/risk balance of the research
- similarly, unforeseen events, new information relating to the product, in view of which the objectives of the research or the clinical program will probably not be achieved, may lead the AP-HP sponsor or the Competent Authority (ANSM) to prematurely interrupt the research
- the AP-HP promoter reserves the right to permanently suspend inclusions, at any time, if it turns out that the inclusion objectives are not achieved.

In the event of discontinuation of the research, the subjects included in the research will be followed until the end of their participation, as provided for by the protocol.

In the event of premature termination of the research for safety reasons, the decision and justification are transmitted by the sponsor AP-HP within 15 days to the Competent Authority (ANSM) and the CPP, accompanied by the recommendations of the Independent Supervisory Committee (if applicable) in the context of a substantial modification.

7 TREATMENT OF RESEARCH PARTICIPANTS

7.1 Description of the investigational drug

The investigational drug will be Xylocaine© 20 mg/ml, solution for injection, applied to the skin through an impregnated compress applied for 15 minutes. We will use the generic Lidocaine Aguettant 20 mg/ml without preservatives, solution for injection, in a 10 ml polypropylene ampoule. The product will be stored at temperature in accordance with the manufacturer's instructions. The placebo of the investigational drug will be NaCl 0.9%, solution for injection.
The experimental drugs, xylocaine or placebo, will be prepared under a laminar airflow hood by the PUI of the investigating center, which is responsible for the double-blinding of the study. The final packaging is a 10 ml propylene ampoule of xylocaine or saline labelled by the PUI pharmacists.
The experimental drug, xylocaine or placebo, is administered in a topical application, by impregnated compress, 15 minutes before the ultrasound-guided infiltration performed by an experienced operator.

7.2 Description of the traceability elements that accompany the investigational drug

The traceability of the experimental drug will be ensured according to the usual circuit of the Cochin hospital pharmacy.
The product vial or its placebo shall be stored in airtight bags bearing the date of preparation and labelled with the name of the trial and the patient number, in a separate room from the storage area, until the CRA is passed or until the end of the trial for control purposes.
Each step of the circuit is traced and the general accounting form is completed at each step.
After each monitoring or at the end of the trial, the vials of the product or its placebo will be destroyed by the PUI and a certificate of destruction will be drawn up and sent to the sponsor.
The traceability of the administration will be reported in the patient file and also in the e-CRF.

7.3 Authorized and prohibited treatments (drug, adjunctive, surgical), including rescue medications

No treatment (medicinal, auxiliary, surgical) will be prohibited. Co-interventions will be recorded in the e-CRF.

7.4 Methods for monitoring treatment adherence

Adherence to treatment will be monitored during the inclusion/intervention and assessment which takes place on the same day.

8 EFFECTIVENESS EVALUATION

8.1 Description of efficacy endpoints

The effectiveness of the treatment will be evaluated on the mean intensity of the per-procedural pain.

8.2 Methods and planned timelines for measuring, collecting, and analyzing efficacy endpoints

The mean intensity of per-procedural pain will be assessed on a self-administered NE (0, no pain and 100, maximum pain) immediately after the procedure. The participant will be blinded to the allocated treatment.

9 SPECIFIC RESEARCH COMMITTEES

9.1 Scientific committee

- Committee members: Dr Christelle NGUYEN, Prof. Jean-Luc DRAPÉ, Prof. Antoine FEYDY, Dr Henri GUERINI, Dr Raphaël CAMPAGNA, Dr Fabrice THÉVENIN, Pr François RANNOU
- Missions: define the objective, write the protocol, propose modifications to the protocol during the research.
- Modalities of operation: annual meeting

9.2 Steering Committee

- Members of the committee: Dr Christelle NGUYEN, Prof. Jean-Luc DRAPÉ, representatives of the promoter (Dr Hendy ABDOUL, DRCI-Siège and DRCI-URC project referents)
- Missions: define the general organization of the research, coordinate information, initially determine the methodology and monitor the progress of the research, propose actions to be taken during the research. The developer DRCI remains the decision-maker.
- Modalities of operation: annual meeting

10 SAFETY ASSESSMENT – RISKS AND CONSTRAINTS ADDED BY RESEARCH

10.1 Procedures for recording and reporting adverse events

10.1.1 Definitions

According to Article R.1123-46 of the Public Health Code:

- **Adverse event**

Any harmful manifestation occurring in a person who is involved in research involving the human person, whether or not this manifestation is related to the research or to the product on which the research relates.

- **Adverse effect**

An adverse event occurring in a person who is involved in research involving the human person, when this event is related to the research or the product on which the research relates.

- **Adverse Reaction to an Investigational Drug**

An adverse event occurring in a person who is engaged in research involving humans, when that event is related to the research or product to which the research relates.

- **Serious adverse event or reaction**

Any adverse event or effect that results in death, endangers the life of the person who is the subject of the research, requires hospitalization or prolongation of hospitalization, causes significant or long-term disability or disability, or results in a congenital anomaly or malformation, and in the case of the drug, regardless of the dose administered.

- **Unexpected adverse reaction to an investigational drug**

Any adverse reaction to the product whose nature, severity, frequency or course does not agree with the reference safety information mentioned in the SmPC or in the Investigator's Brochure when the product is not authorised.

<u>According to Article R.1123-46 of the Public Health Code and the Notice to Sponsors of Clinical Trials of Medicinal Products (ANSM):</u>

- **Developments**

Any new data that may lead to a re-evaluation of the benefit-risk balance of the research or product being researched, to changes in the use of that product, in the conduct of the research, or in documents related to the research, or to the suspension or interruption or modification of the protocol of the research or similar research.
For trials involving the first administration or use of a health product in people who do not have any medical conditions: any serious adverse reactions.
Examples:
a) any clinically significant increase in the frequency of occurrence of an expected serious adverse reaction;
b) suspected unexpected serious adverse reactions in participants who have completed the trial and which are reported by the investigator to the sponsor, as well as any follow-up reports;
(c) any new fact concerning the conduct of the clinical trial or the development of the investigational medicinal product, where such new fact is likely to affect the safety of the participants.
For example:

- a serious adverse event that may be related to the investigations and diagnostic procedures of the trial and that could alter the course of the trial,
- a significant risk to the trial population, such as a lack of efficacy of the investigational drug used in the treatment of a life-threatening disease,
- significant safety findings from a recently completed animal study (such as a carcinogenicity study),

- an early or temporary termination for safety reasons of a trial conducted with the same investigational medicinal product in another country,
- an unexpected serious adverse reaction related to a non-investigational drug necessary to carry out the trial (e.g. "challenge agents", rescue treatment)

(d) the recommendations of the Independent Oversight Committee (ISC), if any, if relevant to the safety of persons,
(e) any unexpected serious adverse reaction transmitted to the sponsor by another sponsor of a clinical trial conducted in a third country on the same medicinal product.

10.1.2 Roles of the Investigator

The investigator should **assess for each adverse event its severity** and report all serious and non-serious adverse events in the e-CRF.

The investigator should **document serious adverse events as best as possible** and give the definitive medical diagnosis as far as possible.

The investigator should **assess the intensity** of adverse events using general terms:

- *Mild: tolerated by the patient, not interfering with daily activities*
- *Moderate: uncomfortable enough to impair daily activities*
- *Severe: Prevents daily activities*

The investigator should **assess the causal relationship of** serious adverse events to the investigational drug.

The method used by the investigator, based on the WHO Uppsala Monitoring Centre (WHO) method, is based on the following 4 causal terms:

- Certain
- Probable/plausible,
- Possible,
- Unlikely (not excluded).

Their definition is presented in the following table (extract from WHO-UMC causality categories, version of 17/04/2012).

Tableau : WHO-UMC causality categories (extrait)

Causality term	Assessment criteria*
Certain	· Event or laboratory test abnormality, with plausible time relationship to drug intake ** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable / Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake ** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake ** · that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

* All points should be reasonably complied with

** Or study procedures

10.1.2.1 Serious adverse events requiring prompt notification by the investigator to the sponsor

In accordance with Article R.1123-49 of the Public Health Code, the investigator shall notify the sponsor without delay from the day on which he becomes aware of them of all serious adverse events occurring during a research referred to in 1° of Article L.1121-1, with the exception of those identified in the protocol as not requiring notification without delay.

A serious adverse event has one of the following criteria:

1- event that results in death,
2- an event that endangers the life of the person who is involved in the research,
3- event that requires hospitalization or prolongation of hospitalization,
4- an event that causes a significant or lasting disability or disability,
5- an event that results in a birth defect or malformation.

10.1.2.2 Protocol specifics

10.1.2.2.1 Other events requiring prompt notification by the investigator to the sponsor

- Adverse events deemed "medically significant"

These adverse events must be notified to the sponsor by the investigator without delay from the day on which they become known, according to the same procedures and deadlines as serious adverse events (see above).

- Exposition ***in utero***

Any pregnancy that occurs during the course of the research, even if it is not associated with an adverse event, must be notified to the sponsor by the investigator without delay from the day on which it becomes known.

10.1.2.2.2 Serious adverse events not requiring prompt reporting by the investigator to the sponsor

These serious adverse events are only collected in the case report form. An extraction of these serious adverse events from the report form will be carried out every month by the CRU.

- *Natural and usual course of the pathology*

- scheduled hospitalization for the follow-up of the pathology studied,
- hospitalization for routine treatment or monitoring of the pathology under study not associated with a deterioration in the subject's condition,
- Worsening of the pathology studied

- *Special Circumstances*

- Hospitalization for a pre-existing condition
- Hospitalization for medical or surgical treatment scheduled prior to research
- Admission for social or administrative reasons

- *Adverse events likely to be related to treatments prescribed as part of the care during the follow-up of the research*

These adverse effects must be reported by the investigator to the regional pharmacovigilance centre to which he or she belongs.

Adverse events likely to be related to the treatments prescribed as part of the care during the follow-up of the research will only be collected in the case report form.

10.1.2.3 Prompt notification period of SAEs by the investigator to the sponsor

The investigator should promptly notify the sponsor of serious adverse events as defined in the relevant section:

- from the date of signing the consent
- for the entire duration of the participant's follow-up, as predicted by the research.

10.1.2.4 Procedures and deadlines for notifying the sponsor

The initial SAE report is the subject of a written report signed by the investigator using a research-specific SAE notification form provided for this purpose (in the e-CRF).

Each item in this document must be completed by the investigator to allow the sponsor to perform a relevant analysis.

The initial notification of a serious adverse event to the sponsor must be followed promptly by a detailed additional written report(s) to monitor the progress of the case under vigilance or to complete the information.

The investigator will transmit, as far as possible, any document that may be useful to the sponsor (medical reports, biological results, results of additional examinations, etc.). These documents will have to be anonymized. In addition, they must be supplemented by the following information: acronym of the research, number and initials of the participant on all pages submitted.

Any adverse events will be followed up until they are fully resolved (stabilization to a level deemed acceptable by the investigator or return to the previous state) even if the participant has left the research.

The initial notification, the SAE monitoring reports and any other document will be sent to the promoter represented by its Vigilance sector, by email (eig-vigilance.drc@aphp.fr). It should be noted that it is possible to send SAEs to the Vigilance sector by fax on 01 44 84 17 99 only in the event of an unsuccessful attempt to send SAEs by e-mail (in order to avoid duplication).

In the case of research with e-CRF:

- the investigator completes the SAE notification form in the e-CRF, validates it, prints it, signs it and then sends it by fax;
- in the event that it is impossible to connect to the e-CRF, the investigator will complete, sign and send the SAE notification form to the Vigilance sector. As soon as the connection is restored, he will regularize by completing the EIG notification form in the e-CRF.

The investigator should respond to any request for additional information from the sponsor.

For any questions relating to the notification of an adverse event, it is possible to contact the Vigilance sector by email: vigilance.drc@aphp.fr.

In the event of *in utero* exposure, the investigator completes the "notification and follow-up form for a pregnancy that appeared during a research".
The investigator must follow the pregnant woman until the term of the pregnancy or its termination and notify the sponsor of the outcome with this form.
If the outcome of the pregnancy falls within the definition of serious adverse events (spontaneous abortion, termination of pregnancy, fetal death, congenital anomaly, etc.), the investigator should follow the SAE reporting procedures.
The initial pregnancy notification, SAE follow-up reports and any other documents will be sent to the sponsor in the same manner as specified above.
If it is a paternal exposure, the investigator must obtain the consent of the pregnant woman to collect the pregnancy information.

10.1.3 Roles of the proponent

The sponsor, represented by its Vigilance sector, evaluates the safety of each investigational drug on an ongoing basis, throughout the research.

10.1.3.1 Analysis and reporting of serious adverse events

The proponent assesses:

- the **severity** of any adverse events reported to the employee,
- their **causal link** to each investigational medicinal product and to any other treatments,
  All serious adverse events for which the investigator and/or sponsor believe that a causal relationship to the investigational medicinal product can be reasonably considered are considered to be suspected serious adverse reactions.
- the **expected or unexpected nature** of the serious adverse reactions.
  Any serious adverse reaction whose nature, severity, frequency or course does not agree with the reference safety information mentioned in the SmPC or in the Investigator's Brochure when the product is not authorised is considered unexpected.
  The assessment of the expected/unexpected nature of a serious adverse reaction is carried out by the sponsor represented by its Vigilance sector on the basis of the information described below**.**

❖ For serious adverse events likely to be related to the investigational medicinal product: please refer to the SmPC of the proprietary product **"LIDOCAINE Aguettant 20 mg/ml PRESERVATIVE-FREE, solution for injection"** inserted in the appendix.

The sponsor shall declare any suspicion of an unexpected serious adverse reaction (SUSAR), within the regulatory deadlines, to the French National Agency for the Safety of Medicines and Health Products (ANSM):

- The initial report must be made without delay from the day on which the sponsor became aware of it in the case of an unexpected serious adverse reaction resulting in death or life-threatening and within 15 days from the day on which the sponsor became aware of it in the case of other unexpected serious adverse reactions;
- All relevant additional information must be reported by the sponsor in the form of monitoring reports, within 8 calendar days from the time the information is available.

Any suspected unexpected serious adverse reaction is also reported electronically in the European Eudravigilance database on adverse drug reactions set up by the European Medicines Agency (EMA).

The sponsor shall inform all relevant investigators of any data that could have an adverse impact on the safety of persons participating in the research.

Special case of double-blind research: after unblinding by the sponsor, if the product administered is the product tested: the case will therefore be reported without delay as a suspicion of unexpected serious adverse reaction(s). If the product administered is the comparator: the unexpectedness of the adverse reaction will be re-evaluated by the sponsor against the reference document of the comparator identified in the protocol.

10.1.3.2 Analysis and reporting of other safety data

This is any new data that may lead to a re-evaluation of the benefit-risk balance of the research or product being researched, to changes in the use of that product, in the conduct of the research, or in the documents relating to the research, or to the suspension or interruption or modification of the protocol of the research or similar research.
The promoter shall inform the competent authority and the Committee for the Protection of Persons of the new facts and, where appropriate, of the urgent safety measures taken, without delay from the day on which it becomes aware of them.
Following the initial declaration of a new fact, the sponsor shall send to the competent authorities in the form of a follow-up report on the new fact, any additional relevant information relating to this new fact within a maximum period of 8 days from the time when it has this information.

10.1.3.3 Annual Safety Report

The sponsor must draw up an annual Development Safety Update Report (DSUR) once a year for the duration of the research, including in particular:
- an analysis of the safety of the people who participate in the research,
- a description of the patients included in the research (demographic characteristics, etc.),
- a list of all suspected serious adverse reactions that occurred during the reporting period,
- summary tables of all serious adverse events that have occurred since the start of the research.

The report is sent to the ANSM and the CPP within 60 days after the anniversary date corresponding to the date of authorisation of the research by the ANSM.

10.1.4 Independent Oversight Committee

In the context of this research, it is not considered useful to name a CSI because it is a search for risk A.

11 DATA MANAGEMENT

11.1 Data collection methods

Clinical and paraclinical signs will be collected and entered in an electronic data collection booklet (e-CRF CleanWEB), with access restricted by a username and password, unique to

each investigating physician in charge of a patient. The data entered will be anonymised and secured, by encryption during data transfer.

11.2 Identification of data collected directly from FIUs that will be considered source data

The patients who will be included will not necessarily have all been followed in the clinical department. As a result, some clinical and socio-professional data may be collected directly in the electronic case report form and considered source data.

11.3 Right of access to source data and documents

11.3.1.1 Access to data

In accordance with GCPs:
- the sponsor is responsible for obtaining the agreement of all parties involved in the research in order to ensure direct access to all research locations, source data, source documents and reports for the purpose of quality control and audit by the sponsor,
- the investigators will make available to the persons responsible for monitoring, quality control or auditing of intervention research involving the human person, the documents and individual data strictly necessary for this control, in accordance with the legislative and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the Public Health Code).

11.3.1.2 Documents source

Source documents are defined as any original document or object that proves the existence or accuracy of a data or fact recorded during the research and will be kept in accordance with the regulations in force by the investigator or by the hospital in the case of a hospital medical record. In the context of the research, the source document will be the medical file.

11.3.1.3 Data Privacy

The persons responsible for quality control of research involving human beings (Article L.1121-3 of the Public Health Code) will take all necessary precautions to ensure the confidentiality of information relating to investigational medicinal products, research, the persons who are suitable for it, and in particular with regard to their identity and the results obtained.
These persons, in the same way as the investigators themselves, are subject to professional secrecy (under the conditions defined by Articles 226-13 and 226-14 of the Criminal Code).
During research involving humans or at the end of it, the data collected on suitable persons and transmitted to the sponsor by the investigators (or any other specialized stakeholders) will be made non-identifying.
They must not under any circumstances display the names of the persons concerned or their addresses in plain text. Only the initials of the first and last names will be recorded, accompanied by a coded number specific to the search indicating the order of inclusion of the subjects.
The sponsor will ensure that each person who participates in the research has given his or her written consent for access to the individual data concerning him or her that is strictly necessary for the quality control of the research.

11.4 Data processing and retention of documents and data

11.4.1 Identification of the person responsible and the place(s) for the management of the data processing(s)

Data entry will be carried out on an e-CRF, filled in on the Internet after each visit by the investigator-doctors. Access to the online entry form by investigator-physicians will be limited by an access code and a unique personal password system for each user. Each investigator will also have access to a specific profile that assigns or denies access to certain functions of the system (data entry or simple visualization of the data of the enrolled patient or all the data of the study, possibility of change and validation by the ARC, etc.). The data will be stored on a secure server, with encrypted data during transmission and an automatic internal backup of a copy on the server that will host the e-CRF.

The statistical analysis of the data will be carried out by the Paris Descartes Necker / Cochin Clinical Research Unit.

11.4.2 Data Entry

Data entry will be carried out electronically via an internet browser.

11.5 Data ownership

AP-HP is the owner of the data and no use or transmission to a third party may be carried out without its prior consent.

12 STATISTICAL ASPECTS

12.1 Description of the planned statistical methods

The main analysis will be performed by a randomization arm blinded CRU statistician, under the supervision of Dr. Hendy Abdoul, using R and/or SAS version 9.4 software. There will be no intermediate analysis.
A descriptive analysis of the data will first be carried out. Qualitative data will be described as numbers and percentages, and quantitative data will be described as mean, median, standard deviation and quartiles, depending on the distribution of the data.

Primary outcome analysis: the level of pain (measured by EN) will be compared between the experimental arm and the control arm. The comparison will be carried out using a Student's or Wilcoxon's test depending on the conditions of application of the tests. A linear regression model can be performed to compare the level of pain in the 2 groups in order to take into account adjustment factors such as age, BMI or sex.

Analysis of secondary outcomes:

- Undesirable effects
- The acceptability of pain during infiltration for the patient according to the patient himself and according to the operator will be compared between the experimental arm and the control arm using a Student or Wilcoxon test depending on the conditions of application of the tests. A linear regression model can be performed to compare the mean intensity of per-procedural pain in the 2 groups in order to take into account adjustment factors such as age, BMI or sex.

Participants who are lost to follow-up will not be replaced. In case of missing data on the primary outcome, an imputation method will be performed.
All the analyses carried out will be described beforehand in the statistical analysis plan that will be carried out and validated before the basic freeze and the analysis of the data.

12.2 Assumptions for calculating the number of subjects needed and result

If we consider a difference in pain on the 15 mm numerical scale with a standard deviation of 20 [2], an alpha risk of 5%, and a power of 80%, it is necessary to include 29 patients per arm. We therefore plan to include a total of 60 patients taking into account possible loss to follow-up.

12.3 Predicted statistical significance

All tests will be bilateral, taking a first-α risk of 5% and a significance threshold p=0.05.

12.4 Method of accounting for missing, unused or invalid data

Every effort will be made to minimize missing data. As all data are collected during the single study visit, it is expected that there will be little missing data on outcomes. In case of missing data on the primary outcome, a multiple imputation method will be performed.

12.5 Managing changes to the initial strategy analysis plan

A statistical analysis plan will be drafted and validated by the principal investigator and the biostatistics team prior to the baseline freeze. Any modification of the initial analysis plan will be validated by the steering committee and will be carried out before the basic freeze.

12.6 Population Selection

We propose to include patients presenting to the radiology department B for an ultrasound-guided infiltration of a trigger finger.
The main analysis will be performed on the intention-to-treat population, i.e. on all patients included in the study as they were randomized, regardless of the strategy actually received. Secondary analyses will be performed on patients with data available for the analyzed endpoint.

13 QUALITY CONTROL AND ASSURANCE

Each research project involving the human person supported by the AP-HP is classified according to the projected risk incurred by the people participating in the research thanks to the classification of interventional research involving the human person with AP-HP promotion

13.1 Organisation générale

The sponsor must ensure the safety and respect of the individuals who have agreed to participate in the research. It must set up a quality assurance system to monitor the progress of research in the investigator centres as well as possible.

To this end, the sponsor mandates Clinical Research Associates (CRAs) whose main mission is to carry out regular follow-up visits to the research sites after having carried out the opening visits.
The objectives of research monitoring, as defined in Good Clinical Practice, (GCP § 5.18.1) are to verify that:

- the right, safety and protection of persons who are suitable for research are met,
- the data reported is accurate, complete and consistent with the source documents,
- the research is conducted in accordance with the protocol in force, GCPs and the legislative and regulatory provisions in force.

13.1.1 Strategy for opening up centres

Not applicable for this single-center research.

13.1.2 Scope of center monitoring

In the case of this A-risk research, the choice of an appropriate level of monitoring was weighted according to the complexity, impact and budget of the research. To this end, the sponsor, in agreement with the coordinating investigator, determined the logistical and impact score that made it possible to obtain the level of monitoring to be set up on the research: minimum level.

13.2 Quality Control

A Clinical Research Associate (CRA) mandated by the sponsor will ensure that the research is carried out, that the data generated in writing is collected, documented, recorded and reported, in accordance with the Standard Operating Procedures implemented within the DRCI and in accordance with Good Clinical Practices as well as the legislative and regulatory provisions in force.

The investigator and the members of his team agree to make themselves available during the Quality Control visits carried out at regular intervals by the Clinical Research Associate. During these visits, the following elements will be reviewed:

- written consent;
- compliance with the research protocol and the procedures defined therein;
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical records, appointment books, originals of laboratory results, etc.);
- management of the processing used.

13.3 Case Report Book

All information required by the protocol should be recorded in the case report forms. Data will need to be collected as they are obtained, and recorded in these notebooks explicitly. Each missing data will have to be coded.
This electronic observation notebook will be set up in each of the centres using an Internet data collection medium. A guidance document for the use of this tool will be provided to investigators.
The completion of the case report form via the internet by the investigator allows the ARC to view the data quickly and remotely. The investigator is responsible for the accuracy, quality, and relevance of all data entered. In addition, when they are entered, this data is immediately checked for consistency. As such, it must validate any change in value in the CRF. These

changes are subject to an audit trail. A justification may be included in the commentary. A paper printout will be requested at the end of the study, authenticated (dated and signed) by the investigator. A copy of the authenticated document for the sponsor must be archived by the investigator.

13.4 Non-conformance management

Any event occurring as a result of non-compliance with the protocol, standard operating procedures, good clinical practices or applicable laws and regulations by an investigator or any other person involved in the conduct of the research must be declared non-compliant to the sponsor.

These non-conformities will be managed in accordance with the sponsor's procedures.

13.5 Audit / inspections

The investigators undertake to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports can be subject to regulatory audits and inspections without medical confidentiality being invoked.
An audit may be carried out at any time by persons mandated by the sponsor and independent of the research managers. Its objective is to ensure the quality of the research, the validity of its results and compliance with the law and regulations in force.
Individuals who conduct and monitor the research agree to comply with the requirements of the sponsor and the competent authority with respect to an audit or inspection of the research.

The audit may apply to all stages of research, from the development of the protocol to the publication of the results and the classification of the data used or produced in the research.

13.6 Commitment of responsibilities of the Principal Investigator

Prior to commencing research, each investigator will provide the research sponsor's representative with their dated and signed personal curriculum vitae, including their RPPS number.
Each investigator will undertake to comply with the obligations of the law and to conduct the research according to the GCP, in accordance with the terms of the Declaration of Helsinki in force.
The principal investigator of each participating centre will sign a commitment of responsibilities (DRCI type document) which will be given to the sponsor's representative.
Investigators and their collaborators will sign a delegation of functions form specifying the role of each.

14 ETHICAL AND LEGAL ASPECTS

14.1 Procedures for informing and obtaining the consent of persons participating in the research

In accordance with Article L. 1122-1-1 of the Public Health Code, no research involving the human person may be carried out on a person without his or her free and informed consent, obtained in writing after the information provided for in Article L. 1122-1 of the same Code has been provided.

A reflection period of at least 30 minutes is given to the person between the time he or she is informed and the time he or she signs the consent form.

The individual's free, informed, written consent is obtained by the investigator, or by a physician representing the investigator prior to the person's inclusion in the research at the time of the inclusion visit.

A copy of the information document and consent form dated and signed by the person participating in the research and by the principal investigator or the physician representing him or her is given to the person prior to his or her participation in the research. The principal investigator or the physician representing him will keep a copy.

A copy will be placed at the end of the study in a sealed tamper-proof envelope containing all the consent forms, which will be archived by the sponsor.

In addition, the investigator will specify in the person's medical record the person's participation in the research, the procedures for obtaining his or her consent and the procedures for providing the information for the purpose of obtaining it. The employer must keep the original copy of the form of the collection of consent of the person, dated and signed.

14.2 Prohibition on participation in other research or exclusion period provided for at the end of the research

At the end of the subject's participation, there will be no exclusion period.
During the period of participation, the subject may participate in any other intervention research protocol involving the human person, after having discussed it with the physician who is following him or her in the context of the research.

14.3 Indemnification of subjects

There is no provision for compensation for patients to compensate for the constraints related to research.

14.4 Registration in the national file of persons willing to carry out research involving human beings on the products mentioned in Article L. 5311-1 of the Public Health Code

Not applicable.

14.5 Authorisation of the premises

The research takes place in care services on people with a clinical condition for which the services are competent and requires acts usually performed in the course of their activities. Therefore, it is not necessary to have a specific location permit for research.

14.6 Legal obligations

14.6.1 Role of the proponent

The Assistance publique hôpitaux de Paris (AP-HP) is the promoter of this research and by delegation, the Clinical Research and Innovation Department (DRCI) carries out its missions, in accordance with Article L.1121-1 of the Public Health Code. Assistance Publique - Hôpitaux de Paris reserves the right to interrupt the research at any time for medical or administrative reasons; in this case, a notification will be provided to the investigator.

14.6.2 Request for an opinion from the Committee for the Protection of Persons CPP

The AP-HP, as a sponsor, obtains the favourable opinion of the CPP concerned for research involving human persons on a medicinal product for human use, prior to its implementation, within the framework of its competences and in accordance with the legislative and regulatory provisions in force.

14.6.3 Application for authorization from the ANSM

The AP-HP, as a sponsor, obtains authorisation from the ANSM for research involving human persons on a medicinal product for human use, prior to its implementation, within the framework of its competences and in accordance with the legislative and regulatory provisions in force.

14.6.4 Procedures relating to the Data Protection Regulations

The computer file used for this research is implemented in accordance with French regulations (amended Data Protection Act) and European regulations (General Data Protection Regulation – GDPR).

- Commitment to comply with the "Reference Methodology" MR 001

This research falls within the framework of the "Reference Methodology for the processing of personal data implemented in the context of research in the field of health " (MR-001 as amended). AP-HP, the promoter of the research, has signed a commitment to comply with this "Reference Methodology".

14.6.5 Research Changes

Any substantial changes made to the protocol by the coordinating investigator should be forwarded to the sponsor for approval. After this agreement, the promoter must obtain a favourable opinion from the CPP and an authorisation from the ANSM within the framework of their respective competences prior to its implementation.

The information note and the consent form may be revised if necessary, in particular in the event of a substantial change in the search or the occurrence of adverse effects.

14.6.6 Final Research Report

The final report of research involving humans referred to in Article R1123-67 of the CSP is drawn up and signed by the sponsor and the investigator. A summary of the report drawn up in accordance with the reference plan of the competent authority shall be submitted to the competent authority within one year after the end of the research, corresponding to the end of the participation of the last person who participates in the research.

14.6.7 Archiving

The specific documents of an intervention research involving humans on a medicinal product for human use will be archived by the investigator and the sponsor for a period of 15 years after the end of the research.

This indexed archiving includes:

- A sealed investigator's envelope containing a copy of all signed briefing notes and consent forms for all individuals at the centre who participated in the research;
- A sealed envelope for the sponsor containing a copy of all briefing notes and signed consent forms for all individuals at the site who participated in the research;
- The "research" binders for the Investigator and the sponsor including (non-exhaustive list):
  - the successive versions of the protocol (identified by the number and date of version), its annexes
  - the ANSM's authorisations and the CPP's opinions
  - correspondence letters,
  - the list or register of inclusion,
  - research-specific annexes
  - the final report of the research.
- Data collection documents

15 FINANCING AND INSURANCE

15.1 Source of funding

The Fondation de l'Avenir has agreed to finance the study to the tune of 29,448 euros, i.e. the entire budget estimated by the URC of Cochin, as part of their 2020 call for projects "Diseases of the large number".

15.2 Insurance

The Sponsor takes out insurance for the entire duration of the research guaranteeing its own civil liability as well as that of any doctor involved in the conduct of the research. It also ensures full compensation for the harmful consequences of the research for the person who participates in it and his or her beneficiaries, unless he or she can prove that the damage is not attributable to his or her fault or that of any participant, without it being possible to oppose the act of a third party or the voluntary withdrawal of the person who had initially consented to the research.

The Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with the company HDI-GLOBAL SE through BIOMEDIC-INSURE for the entire duration of the

research, guaranteeing its civil liability as well as that of any participant (doctor or staff involved in the conduct of the research), in accordance with Article L.1121-10 of the CSP.

16 PUBLICATION RULES

The AP-HP must be mentioned in the affiliations of the author(s) of the publications resulting from this research and mention the AP-HP sponsor (DRCI) and the source of funding, and send us a copy (see below the terms of affiliation and mention of the sponsor and the funder).

16.1 Mention of the AP-HP's affiliation for projects promoted or managed by the AP-HP

- If an author has several affiliations (AP-HP, University, INSERM, etc.), as the RBM is funded through an internal call for tenders from the AP-HP, the first affiliation should be "AP-HP"
- Each of these affiliations must be identified by an address separated by a semicolon (;)
- The AP-HP institution must appear under the acronym "**AP-HP**" first in the address followed precisely by: **AP-HP**, hospital, department, city, postal code, France

16.2 Mention of the AP-HP promoter (DRCI) in the manuscript's acknowledgments

"The sponsor was Assistance Publique-Hôpitaux de Paris (Clinical Research and Innovation Department)"

16.3 Mention of the funder in the manuscript's acknowledgments

« The study was funded by a grant from Assistance Publique-Hôpitaux de Paris »

This search will be recorded on the http://clinicaltrials.gov website

17 BIBLIOGRAPHY

(1) Mo, Ji-Hun, Young-Min Park, and Young-Jun Chung. “Effect of Lidocaine-Soaked Nasal Packing on Pain Relief after Endoscopic Sinus Surgery.” *American Journal of Rhinology & Allergy* 27, no. 6 (November 2013): e174–77. https://doi.org/10.2500/ajra.2013.27.3942.

(2) Bai, Yaowu, Timothy Miller, Mingjuan Tan, Lawrence Siu-Chun Law, and Tong Joo Gan. “Lidocaine Patch for Acute Pain Management: A Meta-Analysis of Prospective Controlled Trials.” *Current Medical Research and Opinion* 31, no. 3 (March 4, 2015): 575–81. https://doi.org/10.1185/03007995.2014.973484.

(3) Moore, J. S. “Flexor Tendon Entrapment of the Digits (Trigger Finger and Trigger Thumb).” *Journal of Occupational and Environmental Medicine* 42, no. 5 (May 2000): 526–45. https://doi.org/10.1097/00043764-200005000-00012.

(4) Vasiliadis, Angelo V., and Iraklis Itsiopoulos. “Trigger Finger: An Atraumatic Medical Phenomenon.” *The Journal of Hand Surgery (Asian-Pacific Volume)* 22, no. 02 (June 2017): 188–93. https://doi.org/10.1142/S021881041750023X.

(5) Mifune, Yutaka, Atsuyuki Inui, Ryosuke Sakata, Yoshifumi Harada, Fumiaki Takase, Masahiro Kurosaka, and Takeshi Kokubu. “High-Resolution Ultrasound in the Diagnosis of Trigger Finger and

Evaluation of Response to Steroid Injection." *Skeletal Radiology* 45, no. 12 (December 2016): 1661–67. https://doi.org/10.1007/s00256-016-2485-5.

(6) Ryzewicz, Mark, and Jennifer Moriatis Wolf. "Trigger Digits: Principles, Management, and Complications." *The Journal of Hand Surgery* 31, no. 1 (January 2006): 135–46. https://doi.org/10.1016/j.jhsa.2005.10.013.

(7) Anderson, B., and S. Kaye. "Treatment of Flexor Tenosynovitis of the Hand ('trigger Finger') with Corticosteroids. A Prospective Study of the Response to Local Injection." *Archives of Internal Medicine* 151, no. 1 (January 1991): 153–56.

(8) Earp, Brandon E., Spencer J. Stanbury, Ariana N. Mora, and Philip E. Blazar. "Needle-Free Jet Lidocaine Administration for Preinjection Anesthesia in Trigger Finger Injection: A Randomized Controlled Trial." *The Journal of Hand Surgery* 42, no. 8 (August 2017): 618–22. https://doi.org/10.1016/j.jhsa.2017.05.001.

(9) Stewart, Gail M., Pippa Simpson, and Norman M. Rosenberg. "Use of Topical Lidocaine in Pediatric Laceration Repair: A Review of Topical Anesthetics:" *Pediatric Emergency Care* 14, no. 6 (December 1998): 419–23. https://doi.org/10.1097/00006565-199812000-00012.

18 LIST OF ADDENDA

18.1 List of Investigators

18.2 Serious Adverse Event Reporting Form

18.3 Pregnancy Notification and Follow-up Form

18.4 Summary of Product Characteristics (SmPC)

RCP LIDOCAINE AGUETTANT 20 mg/ml PRESERVATIVE-FREE, solution for injection

http://agence-prd.ansm.sante.fr/php/ecodex/rcp/R0302137.htm

CPR 0.9 PERCENT SODIUM CHLORIDE, SOLUTION FOR INJECTION IN AMPOULE

http://agence-prd.ansm.sante.fr/php/ecodex/frames.php?specid=63060256&typedoc=R&ref=R0249852.htm

18.5 Questionnaires and scales

18.6 Patient card