



“Multisite Transcutaneous Electrical Nerve Stimulation (Exopulse Mollii Suit) in Fibromyalgia: A Randomized, Double-Blind, Sham-Controlled Crossover Trial Comparing Two Stimulation Modalities (FIBROPULSE)”

«TENS multisite (Exopulse Mollii Suit) dans la fibromyalgie : essai randomisé en double aveugle, contrôlé, comparant deux modalités de stimulation (FIBROPULSE)»

EXOPULSE Mollii Suit and Fibromyalgia

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SIGNATURE page for a research PROTOCOL

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Title: Multisite TENS (EXOPULSE MOLLII SUIT) and Fibromyalgia: A Comparative Randomized, Double-Blind Study of Two Stimulation Protocols (FIBROPULSE)”

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The study will be carried out following the protocol, with current good practices, and with statutory and regulatory requirements.

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1. SUMMARY

Full title	Multisite Transcutaneous Electrical Nerve Stimulation (Exopulse Mollii Suit) in Fibromyalgia: A Randomized, Double-Blind, Sham-Controlled Crossover Trial Comparing Two Stimulation Modalities (FIBROPULSE)
IDRCB	2026-A00768-43
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Sponsor	Institut de la Colonne Vertébrale et des Neurosciences (ICVNS FRANCE)
Scientific justification	Fibromyalgia is a chronic and multifactorial disorder characterized by widespread musculoskeletal pain, heightened pain sensitivity, fatigue, sleep disturbances, cognitive complaints, and affective symptoms such as anxiety and depression. Despite the availability of pharmacological and non-pharmacological interventions, symptom control often remains suboptimal, and currently available treatments may be associated with limited efficacy or poor tolerability. Consequently, there is a growing need for effective, safe, and personalized non-pharmacological therapeutic approaches. In a previous randomized controlled trial (EXOFIB), we investigated the effects of the Exopulse Mollii Suit, a non-invasive neuromodulation device delivering multisite transcutaneous electrical nerve stimulation (TENS), in patients with fibromyalgia. Using stimulation parameters consisting of a frequency of 20 Hz, a voltage of 20 V, and a pulse width of 55–85 μs, active stimulation was associated with clinically meaningful improvements in pain, fatigue, and quality of life compared with sham stimulation. These findings provided evidence supporting the therapeutic potential of the Exopulse Mollii Suit in the management of fibromyalgia-related symptoms. However, while EXOFIB established the efficacy of active stimulation relative to sham stimulation, it did not address whether alternative stimulation parameter configurations could yield superior clinical outcomes. To date, no randomized crossover study has directly compared different active stimulation settings of the Exopulse Mollii Suit in patients with fibromyalgia. Consequently, the optimal stimulation parameters for maximizing therapeutic benefit in this population remain unknown.

	The present study has therefore been designed to compare the effects of three stimulation modalities delivered by the Exopulse Mollii Suit, including two active stimulation configurations and one sham stimulation condition. The primary objective is to evaluate and compare their effects on functional disability associated with fibromyalgia, assessed using the Fibromyalgia Impact Questionnaire (FIQ). The inclusion of a sham condition allows assessment of non-specific effects while preserving participant blinding. The stimulation conditions evaluated in this study are: • Condition A (active stimulation): frequency 20 Hz, voltage 20 V, pulse width 55–85 μs; • Condition B (active stimulation): frequency 20 Hz, voltage 20 V, pulse width 100–125 μs; • Condition C (sham stimulation): brief initial active stimulation followed by discontinuation of stimulation after one minute, while maintaining identical device settings, session duration, and study procedures in order to preserve participant blinding. By identifying the most effective stimulation setting, this study aims to optimize the clinical use of the Exopulse Mollii Suit in fibromyalgia and to contribute to the development of more individualized neuromodulation strategies. Ultimately, the findings may improve symptom management, reduce functional disability, and enhance quality of life in patients living with fibromyalgia.
Primary and secondary objectives	Primary objective: The primary objective of this study is to evaluate and compare the effects of the three stimulation modalities delivered by the Exopulse Mollii Suit (Condition A, Condition B and sham stimulation) on functional disability in patients with fibromyalgia, assessed using the Fibromyalgia Impact Questionnaire (FIQ). Secondary objectives: The secondary objectives are to evaluate and compare the effects of the three stimulation modalities on pain intensity, pain interference, pain catastrophizing, fatigue, anxiety, depression, sleep quality, quality of life, overall clinical improvement and maintenance of blinding.
Primary and secondary endpoints	Primary endpoint: The primary endpoint is the change in functional disability assessed using the Fibromyalgia Impact Questionnaire (FIQ) across the three stimulation conditions (Condition A, Condition B and sham stimulation). FIQ scores will be collected at Visits V1, V2, V3, V4, V5 and V6. Secondary endpoints: • Pain intensity, assessed using the Visual Analogue Scale for pain (VAS pain) at Visits V1, V2, V3, V4, V5, and V6; • Pain severity and pain interference, assessed using the Brief Pain Inventory (BPI) at Visits V1, V2, V3, V4, V5, and V6; • Pain catastrophizing, assessed using the Pain Catastrophizing Scale (PCS) at Visits V1, V2, V3, V4, V5, and V6; • Daily pain evolution, assessed using a daily pain diary based on the VAS pain throughout the study period; • Fatigue, assessed using the Visual Analogue Scale for fatigue (VAS fatigue) at Visits V1, V2, V3, V4, V5, and V6;

	• Anxiety and depression symptoms, assessed using the Hospital Anxiety and Depression Scale (HADS) at Visits V1, V2, V3, V4, V5, and V6; • Global sleep quality, assessed using the Pittsburgh Sleep Quality Index (PSQI) at Visits V1, V2, V3, V4, V5, and V6; • Subjective sleep experience, assessed using the Leeds Sleep Evaluation Questionnaire (LSEQ) at Visits V1, V2, V3, V4, V5, and V6; • Health-related quality of life, assessed using the Short Form-36 Health Survey (SF-36) at Visits V1, V2, V3, V4, V5, and V6; • Overall clinical improvement, assessed using the Clinical Global Impression (CGI) scale at Visits V2, V4, and V6; • Maintenance of blinding, assessed using the blinding questionnaire at Visits V2, V4, and V6.
Design of the study	This study is a randomized, double-blind, sham-controlled crossover trial consisting of three successive four-week stimulation periods, each separated by a two-week washout period. Participants will receive the three stimulation conditions in a randomized sequence: • Condition A (active stimulation): frequency 20 Hz, voltage 20 V, pulse width 55–85 μs; • Condition B (active stimulation): frequency 20 Hz, voltage 20 V, pulse width 100–125 μs; • Condition C (sham stimulation): brief initial active stimulation followed by discontinuation of stimulation after one minute, while maintaining identical session duration and device conditions in order to preserve participant blinding. Each stimulation period will last four weeks. A two-week washout period will be implemented between consecutive stimulation periods to minimize potential carry-over effects. The study has been designed to compare three stimulation modalities delivered by the Exopulse Mollii Suit, including two active stimulation configurations and one sham stimulation condition. This crossover design allows each participant to receive all three stimulation modalities in a randomized sequence.
Population of study participants	Adult patients with fibromyalgia.
Inclusion criteria	- Patients aged between 18 and 75 years, - Patients with a definite diagnosis of fibromyalgia according to the American College of Rheumatology (ACR) 2010 criteria, set for at least one month - Patients should be French speakers, able to understand verbal instructions, and affiliated with the national health insurance.

Exclusion criteria	- Patient included in another research protocol during the study period; - Inability to comply with study procedures or follow-up requirements for geographical, social, or organizational reasons; - Any contraindication to the use of the Exopulse Mollii Suit as specified in the device user manual; - Any significant neurological, psychiatric, cardiovascular, musculoskeletal, or other medical condition that, in the opinion of the investigator, could interfere with study participation, outcome assessment, or participant safety, with the exception of anxiety and depression commonly associated with fibromyalgia; - Modification of pharmacological treatment related to fibromyalgia or initiation/modification of non-pharmacological therapies within the three months preceding inclusion; - Introduction of another therapeutic medical device during the study period; - Pregnant women; - Breastfeeding women; - Individuals subject to a legal protection measure (guardianship, curatorship, or judicial protection order).
Interventions or products under investigation	The Exopulse Mollii Suit is a CE-marked neuromodulation device with a favorable safety profile, good tolerability, and ease of use. Developed by Exoneural Network AB, the device consists of a full-body garment incorporating 58 electrodes capable of delivering transcutaneous electrical stimulation to 40 muscle groups using low-frequency (20 Hz), low-intensity electrical currents (current intensity: 2 mA; pulse width: 25–170 µs). The stimulation is not intended to induce muscle contraction but rather to modulate pain processing through activation of large-diameter afferent fibers, thereby reducing nociceptive transmission in accordance with the gate control theory of pain. The device is intended for pain reduction and is used as a daily, non-pharmacological neuromodulation intervention. The present study has been designed as a parameter-optimization study aimed at comparing two active stimulation configurations of the Exopulse Mollii Suit in patients with fibromyalgia. The objective is to determine which active stimulation setting provides the greatest improvement in functional disability and associated symptoms. A sham stimulation condition is included as a methodological control to preserve blinding and assess potential non-specific effects associated with device use and study participation.
Comparator arm	Randomized, double-blind, sham-controlled crossover study comparing three stimulation modalities (Condition A, Condition B and sham stimulation).
Other interventions added by the study	Not applicable
Expected benefits for the participants and society	This study aims to identify the optimal stimulation configuration of the Exopulse Mollii Suit for patients with fibromyalgia. By comparing three stimulation modalities, including two active stimulation settings and one sham stimulation condition, the study seeks to identify the most effective stimulation approach for improving functional disability and other fibromyalgia-related symptoms. The inclusion of a sham stimulation condition will facilitate the assessment of non-specific treatment effects while maintaining participant blinding. The findings are expected to contribute to the optimization of neuromodulation protocols and support the development of more individualized, evidence-based, non-pharmacological treatment strategies for patients with fibromyalgia.

Minimal risks and burden added by the study	Exopulse Mollii suit-related side effects are minimal to none. Patients will be asked not to participate in other protocols during this study.
Scope of the study	Evaluation of the effects of three stimulation modalities delivered by the Exopulse Mollii Suit (Condition A, Condition B and sham stimulation) on functional disability, pain intensity, pain interference, pain catastrophizing, fatigue, anxiety, depression, sleep quality, quality of life, overall clinical improvement and maintenance of blinding in patients with fibromyalgia.
Number of participants included	The primary outcome is FIQ total score. The sample size was calculated assuming a medium effect size (Cohen's $f = 0.25$), 5% two-sided significance level, 80% power, yielding $n=19$ participation. Taking into consideration a 20% dropout rate, the required number of participants is 24. Calculation took into consideration previous works (Mattar et al., 2025).
Number of centers	It is a national monocentric study Site: Clinical Neurophysiology Department, Henri Mondor Hospital, Creteil, France
Schedule for the study	- Inclusion period: 15 months - Participation period (treatment + follow-up): 16 weeks - Total duration: 18 months Estimated start date: May 15 ,2026 Estimated end date: October 31, 2027
Number of enrolments expected per month	Number of participants (who will sign a consent form) • In France: 24 (1 to 2 patients per month) • In other countries: not applicable
Statistical analysis	Statistical analyses will be performed using IBM SPSS Statistics software (version 31.0 or later). The primary endpoint will be analysed by comparing changes in Fibromyalgia Impact Questionnaire (FIQ) scores across the three stimulation conditions (Condition A, Condition B and sham stimulation). When assumptions of normality are met, a repeated-measures ANOVA adapted to the crossover design will be used. If a significant overall effect is observed, pairwise post-hoc comparisons will be performed with appropriate correction for multiple testing (Bonferroni correction or equivalent). If normality assumptions are not met, the Friedman test will be used, followed by Dunn's post-hoc comparisons with correction for multiple testing. Secondary outcomes will be analysed using similar approaches according to the nature and distribution of the data. Statistical significance will be assessed using two-sided tests with an alpha level of 0.05.
Funding sources	Institut de la Colonne Vertébrale et des Neurosciences

2. SCIENTIFIC JUSTIFICATION FOR THE RESEARCH

2.1. Current state of knowledge given the research

2.1.1 *Fibromyalgia: Definition, prevalence, and impact*

Fibromyalgia is a chronic pain condition that seems to be more frequent with female sex, increasing age, presence of comorbidities (i.e., rheumatic diseases), and a family history of this condition (Queiroz, 2013; Wolfe et al., 2013). Fibromyalgia is considered a 'specific pain disorder' or a 'functional somatic syndrome' by the rheumatological and the whole medical community, respectively (Wolfe et al., 2014). Although it was first perceived as a 'muscle callus' in the mid-ninth century or 'generalized fibrositis' in the 1950s, the term 'fibromyalgia' was adopted after scientific works had ruled out an underlying inflammation (Wolf & Wallit, 2003; Okifuji & Hare, 2013; Wolfe et al., 2014). The condition is nowadays characterized by the chronic occurrence of pain affecting the musculoskeletal system, a sensitivity to pressure stimuli, and a low threshold to noxious stimuli (Wolf & Wallit, 2003; Wolfe et al., 2014). The topography of pain is widespread, although it could be more pronounced in some bodily regions (i.e., neck or back) (Wolfe, 2014). The pain is usually continuous but can fluctuate and could be sharp, stabbing, burning, or aching in nature with or without hyperalgesia and allodynia (Wolfe, 2014). In addition, it could occur at rest but can also be movement-related. Fibromyalgia is a prevalent condition that could affect up to 9.3% of individuals globally, and its prevalence is expected to increase as the last updated criteria for diagnosing this condition no longer relies on the presence of tender points (Queiroz, 2013; Wolfe et al., 2013). Fibromyalgia seems to result in individual and societal burdens (Annemans et al., 2009). Besides pain, patients suffer from a wide range of symptoms, including fatigue, sleep disturbance, anxiety and depression manifestations, fear of movement, other somatic symptoms (e.g., headaches, abdominal pain, (morning) stiffness, sexual dysfunction), cognitive symptoms (known as 'fibro fog'), and altered quality of life (Wolf & Wallit, 2003; Burwinkle et al., 2005). In addition, although fibromyalgia does not receive the same attention as other chronic conditions (i.e., hypertension, diabetes), it seems to have a comparable societal burden (Ghavidel-Parsa et al., 2015). Worldwide data suggest that fibromyalgia leads to a high economic burden resulting from direct costs such as treatments and medical consultations, and indirect ones such as loss of productivity, missed working days, change in employment status, early retirement, out-of-pocket costs, and difficulty to perform unpaid informal care giving (caring for a child, house and yard work, etc.) (Schaefer et al., 2011; Winkelmann et al., 2011; Kim et al., 2013; Ghavidel-Parsa et al., 2015).

The burden seems more pronounced in patients with higher symptom severity (Schaefer et al., 2011; Winkelmann et al., 2011).

2.1.2 Potential underlying mechanisms of fibromyalgia

Despite the frequency and impact of fibromyalgia, understanding the underlying mechanisms of this condition and developing satisfactory interventions remain challenging tasks. From a pathophysiological perspective, the etiology of fibromyalgia is far from being unveiled. However, neuroimaging and neurophysiological studies support the occurrence of a hyperactive nociceptive system (involved in detecting and processing nociceptive stimuli) and/or a defective antinociceptive pain inhibitory system at the origin of this condition (for reviews see, Schmidt-Wilcke & Clauw, 2011; Schmidt-Wilcke & Diers, 2017). Moreover, insights from functional brain neuroimaging suggest functional abnormalities involving the insular cortex and/or its connections. For instance, an alteration in the crosstalk among different sensory modalities (i.e., known as cross-modal sensory hypersensitivity) in the context of fibromyalgia could manifest as an increase in the activity of the insula – a central hub within the pain perception network - in response to an aversive visual stimulus, a finding that was associated with pain intensity in patients with fibromyalgia (Schmidt-Wilcke & Diers, 2017). Also, a heightened pain perception might arise from a hyperconnectivity between the insula, on one side, and pain as well as other networks (i.e., default-mode network), on the other side (Schmidt-Wilcke & Diers, 2017). Furthermore, insight from proton magnetic resonance spectroscopy suggests a GABAergic/glutamatergic imbalance toward an excitatory state within the pain networks (i.e., insula) (Schmidt-Wilcke & Diers, 2017). The serotonergic and dopaminergic systems might also be implicated according to neuroendocrine, neuroimaging, and pharmacological studies (Okifuji & Hare, 2013; Wolfe et al., 2014).

Besides central factors, peripheral factors might also contribute to the pathophysiology of fibromyalgia, albeit the available data are still scarce and heterogeneous (Drewes et al., 1993; Okifuji & Hare, 2013). Among the reported muscular abnormalities in patients with fibromyalgia are reduced blood flow, muscle hypoxia, and metabolic defects (low energy metabolites at the muscular level) (Bengtsson & Henriksson, 1989; Park et al., 1998; Sprott et al., 2000; Elvin et al., 2006; for review see Okifuji & Hare, 2013).

Furthermore, recent evidence suggests fibromyalgia may involve immune system abnormalities, with autoantibodies increasing nerve sensitivity, potentially exacerbating pain perception and contributing to the overall symptomatology of the disorder (Ghavidel-Parsa et

al., 2015). Additionally, recent studies have provided further insights into the neuroimmune interactions involved in fibromyalgia, highlighting the role of cytokine imbalances in promoting chronic pain and the dysregulation of autonomic nervous system activity (Findeisen et al. 2025).

2.1.3 Management of fibromyalgia: Available interventions and present limitations

Several pharmacological and alternative interventions have been applied for the treatment of pain in patients with fibromyalgia. More than 40 molecules have been tested and have resulted in different benefits and side-effects profiles (Schmidt-Wilcke & Clauw, 2011). In addition to the potential side effects that arise from pharmacological agents, only 10-25% of patients exhibit a meaningful pain reduction following medications in placebo-controlled trials (Johnson et al., 2017). Current pharmacological treatments that are approved for treating fibromyalgia consist of antidepressants (i.e., milnacipran and duloxetine) and antiepileptic drugs (i.e., pregabalin), but monotherapy rarely yields satisfactory management in patients with fibromyalgia (Johnson et al., 2017). In this context, a wide range of non-pharmacological methods has also been discussed by the European League Against Rheumatism (EULAR) for the management of fibromyalgia (Macfarlane et al., 2017). EULAR endorsed a graduated management plan that focuses on alternative interventions, which include exercise, physical therapy, and psychotherapies (i.e., including meditation and mindfulness-based interventions).

Recent developments have introduced innovative pharmacological agents like milnacipran and pregabalin, in addition to non-pharmacological interventions such as mindfulness-based stress reduction and aquatic exercise, expanding the array of options available to enhance fibromyalgia care and alleviate patient symptoms (Benjamin et al. 2025).

In addition, there is a growing interest in exploring the effects of electrotherapy in the management of fibromyalgia (Coskun Benlidayi, 2020). Non- pharmacological interventions have comparable effects relative to medications but seem to be more acceptable and have lower side effects according to patients' ratings (Taylor et al., 2019).

2.1.4 Mollii Suit as a potential tool to manage pain and other fibromyalgia symptoms

Despite the existing interventions and the ongoing efforts to optimize the management of patients with fibromyalgia, an important number of physicians and patients remain totally or partially unsatisfied with the treatment outcomes. This unmet need warrants further research

to explore the potential of other treatment options.

Transcutaneous Electrical Nerve Stimulation (TENS) has been applied in the context of fibromyalgia, and some trials have documented promising results (for reviews, see Coskun Benlidayi, 2020). However, one should note that practical difficulties could arise when using TENS at home or in clinical practice (i.e., correctly attaching electrodes). In addition, TENS could target a limited number of muscle groups which might not take into consideration the widespread pain distribution that occurs in patients with fibromyalgia.

The Exopulse Mollii method has been developed by Exoneural Network (initially Interventions AB), a Swedish med-tech company, in an attempt to overcome the previously mentioned limitations. Mollii is a full-body garment with 58 integrated electrodes that can transcutaneously stimulate 40 groups of muscles using a low-intensity electric current.

In 2021, we conducted a randomized, double-blind, placebo-controlled study (EXOFIB) under the identification number N°IDRCB: 2021-A01668-33 (NCT05361577, ClinicalTrials.gov). The aim of the study was to assess the effects of the Exopulse Mollii Suit on fibromyalgia-related symptoms. The study included two phases. In the first phase, each participant was randomly assigned to receive two stimulation blocks (active and sham) separated by a two-week washout period. Each block consisted of 14 daily sessions, each lasting 60 minutes. Following the first phase, all participants entered phase two, an open-label phase, during which they were asked to wear the active suit daily for four consecutive weeks. To minimize the risk of carryover between stimulation conditions—and consistent with our previous work (Mattar et al., 2025) as well as our team's experience in neuromodulation—we consider a two-week washout period to be an appropriate approach to ensure a full return to baseline before the next stimulation phase. A one-week interval would be too close to the 48-hour reference applicable to a single session and may insufficiently account for interindividual variability. This choice of duration has also been adopted in several clinical trials using repeated TENS sessions, including the study by Köke and colleagues, which implemented a crossover design with two two-week treatment periods separated by a two-week washout. The results of this study showed significant reductions in pain and improvements in quality of life following two weeks of active intervention compared to the sham condition. Moreover, notable reduction in fatigue, depression, and anxiety were observed during the open-label phase. These findings suggest that the Exopulse Mollii Suit could play a role in alleviating fibromyalgia-related symptoms. However, the effect sizes were small to medium (Mattar et al., 2025).

Building on the results of the EXOFIB study, the present investigation does not aim to re-establish the efficacy of the Exopulse Mollii Suit in patients with fibromyalgia. Rather, it has been designed to further evaluate the effects of different stimulation modalities delivered by the device and to determine whether variations in stimulation parameters influence clinical outcomes.

To date, no randomized controlled crossover study has directly compared different stimulation modalities of the Exopulse Mollii Suit in this population. Consequently, the relative effects of the available stimulation settings remain insufficiently documented.

The present study will compare three stimulation modalities: two active stimulation configurations differing in pulse width (55–85 μ s versus 100–125 μ s), while maintaining identical frequency and voltage settings, and a sham stimulation condition. Functional disability, assessed using the Fibromyalgia Impact Questionnaire (FIQ), constitutes the primary outcome measure. The sham condition is included to preserve participant blinding and to allow the assessment of potential non-specific effects associated with device use and study participation.

This approach is consistent with the conclusions of the EXOFIB study, which highlighted the need for further investigations aimed at optimizing Exopulse Mollii Suit stimulation protocols in fibromyalgia. The objective is to compare the clinical effects of the different stimulation modalities on functional disability and other key fibromyalgia-related symptoms, including pain, fatigue, sleep disturbances, affective symptoms, and quality of life.

The crossover design allows each participant to serve as their own control, thereby reducing inter-individual variability and improving the efficiency of treatment comparisons. In the statistical analysis, treatment condition and treatment period will be taken into account in order to appropriately assess potential period effects. As the Exopulse Mollii Suit is intended to provide symptomatic relief rather than modify the underlying disease process, the study focuses on evaluating changes in symptom severity and functional impact associated with each stimulation modality.

2.2. Description of the population to be studied and justification for the choice of participants

The primary objective of this study is to evaluate and compare the effects of three stimulation modalities delivered by the Exopulse Mollii Suit (Condition A, Condition B and sham

stimulation) on functional disability in patients with fibromyalgia, assessed using the Fibromyalgia Impact Questionnaire (FIQ).

As the study is specifically designed to investigate the effects of these stimulation modalities in individuals with fibromyalgia, only participants with a confirmed diagnosis of fibromyalgia will be eligible for inclusion. Patients with fibromyalgia represent the target population for whom the Exopulse Mollii Suit may provide symptomatic benefit and in whom the relative effects of different stimulation modalities are clinically relevant

2.3. Interventions and products which will be performed or used as standard care management

Participants enrolled in this study will continue to receive their usual standard of care for fibromyalgia throughout the study period, including routine medical evaluation, pharmacological treatment, and non-pharmacological management when applicable. Participation in the study will not replace or modify standard clinical care.

The research-specific procedures consist primarily of the administration of validated clinical questionnaires and symptom assessments, together with the use of the Exopulse Mollii Suit according to the study protocol. These procedures are designed to evaluate and compare the effects of the three stimulation modalities investigated in this study (Condition A, Condition B and sham stimulation) on functional disability and other fibromyalgia-related symptoms.

2.4. Interventions added to the research

This study will evaluate the effects of the Exopulse Mollii Suit, a CE-marked assistive medical device delivering non-invasive transcutaneous electrical stimulation. The study has been designed to compare three stimulation modalities delivered by the device: two active stimulation configurations differing in pulse width while maintaining identical frequency and voltage settings, and one sham stimulation condition. The sham condition is included to preserve participant blinding and to assess potential non-specific effects associated with device use and study participation.

The device complies with Regulation (EU) 2017/745 (Medical Device Regulation) and holds a valid CE certification (Certification number: 28620137548; valid until November 5, 2027). Its intended uses include the relaxation of spastic muscles, maintenance or improvement of range of motion, muscle activation and re-education, prevention of disuse atrophy, enhancement of local blood circulation, and symptomatic relief of chronic pain conditions.

The Exopulse Mollii Suit consists of:

- The EXOPULSE Body Garments (jacket and pants), which incorporate electrodes, conductive wires, and connectors linked to a detachable control unit. Their intended purpose is to transmit electrical stimulation from the control unit to selected nerves and muscle groups throughout the body. These components are non-invasive, non-active medical devices classified as Class I according to Rule 1 of Annex VIII of Regulation (EU) 2017/745.
- The EXOPULSE Control Unit, a battery-powered active medical device that delivers low-energy electrical pulses through the body garments to targeted nerves and muscle groups. It is classified as a Class IIa medical device according to Rule 9 of Annex VIII of Regulation (EU) 2017/745.

An illustration of the device is available in Figure 1.

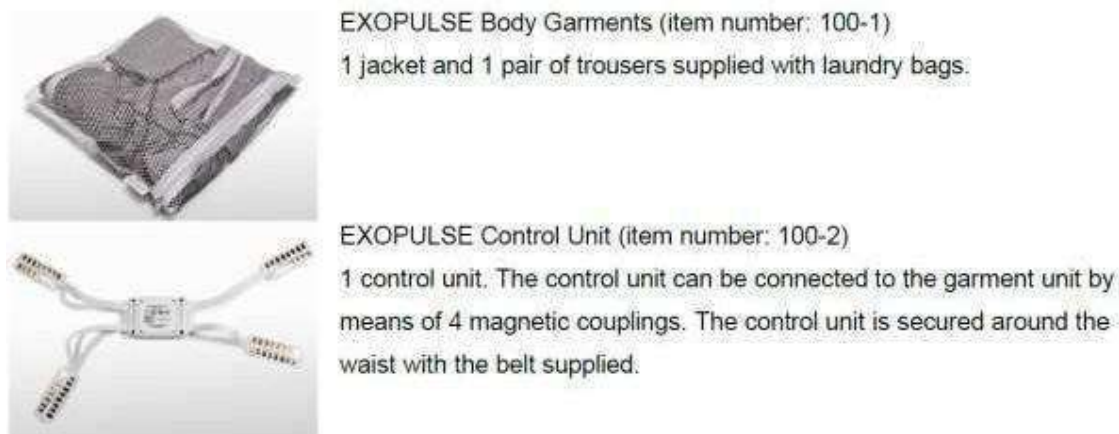


Figure 1. EXOPULSE Mollii suit composition

As previously stated, the available interventions targeting pain in patients with fibromyalgia are limited by their modest efficacy and numerous side effects. Therefore, developing novel therapies would help to overcome the current limitations. Transcutaneous Electrical Nerve Stimulation (TENS) has proven some efficacy in fibromyalgia and pain management (for reviews, see Johnson et al., 2021 & 2022). However, one should note that practical difficulties could arise when using TENS at home or in clinical practice (i.e., correctly attaching electrodes). To overcome these limitations, the Exopulse Mollii suit has been developed by Exoneural Network (initially Interventions AB), a Swedish med-tech company. It represents an innovative approach for non-invasive electro-stimulation to reduce pain.

Exopulse Mollii suits consist of body Garments (Jacket and Pants) and a control unit. The body Garments (Jacket and Pants) contain 58 embedded electrodes that can stimulate 40 groups of

muscles, conductive wires, and connectors to a detachable control unit, whose intended purpose is to transmit electric pulses from the control unit to key nerves and corresponding muscle groups throughout the body. The control unit is a battery-powered electrical device that sends low-intensity electric pulses through connectors to the Body Garments, which in turn transmit the pulses from the connectors to key muscle groups throughout the body.

Exopulse Mollii suit is a transcutaneous electric device that uses low intensity alternating current (i.e., low frequency ~20 Hz) aiming to reduce pain. This treatment method's theoretical background primarily refers to the theory of gate control i.e., stimulation of large proprioceptive fibers would inhibit the nociceptive information transmitted by small fibers.

2.5 Summary of the known and foreseeable benefits and risks for the research participants

Benefit: The EXOFIB study demonstrated that active stimulation delivered by the Exopulse Mollii Suit was associated with improvements in pain, fatigue, affective symptoms, and quality of life in adults with fibromyalgia. These findings supported the potential therapeutic value of this non-invasive neuromodulation device for the management of fibromyalgia-related symptoms.

Building on these results, the present study has been designed to further evaluate the effects of different stimulation modalities delivered by the Exopulse Mollii Suit. Rather than re-establishing the efficacy of the device, the objective is to compare the clinical effects of three stimulation modalities, including two active stimulation configurations and one sham stimulation condition.

The study will assess and compare the effects of these stimulation modalities on functional disability, pain, fatigue, sleep quality, psychological symptoms, and quality of life. Functional disability, assessed using the Fibromyalgia Impact Questionnaire (FIQ), constitutes the primary outcome measure.

A sham stimulation condition is included as a methodological control to preserve participant blinding and to assess potential non-specific effects associated with device use and study participation. The results of this study may contribute to improving the understanding of Exopulse Mollii Suit stimulation modalities and support the development of more individualized, evidence-based, non-pharmacological treatment strategies for patients with

fibromyalgia.

Risk: The risks associated with the use of the Exopulse Mollii Suit are considered low. In previous clinical studies, including EXOFIB, no serious device-related adverse events were reported. Some participants experienced mild and transient sensations such as tingling, paresthesia, or temporary discomfort during stimulation, which resolved spontaneously at the end of the session.

More broadly, transcutaneous electrical nerve stimulation (TENS) is recognized as a safe and well-tolerated therapeutic approach when used within validated operating parameters. Available clinical data relating to the Exopulse Mollii Suit have not identified any major safety concerns.

In the present study, participants will use the device according to the manufacturer's instructions and the procedures specified in the protocol. The stimulation parameters evaluated in this study fall within the range validated for the device and covered by its CE certification. The study compares three stimulation modalities: two active stimulation configurations differing in pulse width (55–85 μ s and 100–125 μ s), while maintaining identical frequency, voltage, and session duration, and one sham stimulation condition. The sham condition consists of a brief initial stimulation followed by interruption of stimulation while maintaining identical study procedures in order to preserve participant blinding.

Based on currently available data and previous clinical experience, participation in this study is considered to present minimal and foreseeable risks.

3 OBJECTIVES AND ENDPOINTS OF THE RESEARCH

3.1 Objectives

3.1.1 Main objective

The primary objective of this study is to evaluate and compare the effects of three stimulation modalities delivered by the Exopulse Mollii Suit (Condition A, Condition B and sham stimulation) on functional disability in patients with fibromyalgia.

Functional disability will be assessed using the Fibromyalgia Impact Questionnaire (FIQ). The primary analysis will compare changes in FIQ scores across the three stimulation modalities. Assessments will be performed at Visit V1 (baseline), Visit V2 (after the first intervention

period), Visit V3 (before the second intervention period), Visit V4 (after the second intervention period), Visit V5 (before the third intervention period), and Visit V6 (after the third intervention period).

We hypothesize that the different stimulation modalities may produce different effects on functional disability in patients with fibromyalgia and that active stimulation may be associated with greater improvement than sham stimulation.

3.1.2 Secondary objectives

The secondary objectives of this study are:

- To evaluate and compare the effects of the different stimulation conditions on pain intensity, assessed using the Visual Analogue Scale (VAS);
- To evaluate and compare the effects of the different stimulation conditions on pain severity and pain interference, assessed using the Brief Pain Inventory (BPI);
- To evaluate and compare the effects of the different stimulation conditions on pain catastrophizing, assessed using the Pain Catastrophizing Scale (PCS);
- To evaluate and compare the effects of the different stimulation conditions on daily pain evolution, assessed using the pain diary;
- To evaluate and compare the effects of the different stimulation conditions on fatigue, assessed using the Visual Analogue Scale for fatigue (VAS fatigue);
- To evaluate and compare the effects of the different stimulation conditions on anxiety and depression, assessed using the Hospital Anxiety and Depression Scale (HADS);
- To evaluate and compare the effects of the different stimulation conditions on global sleep quality, assessed using the Pittsburgh Sleep Quality Index (PSQI);
- To evaluate and compare the effects of the different stimulation conditions on subjective sleep experience, assessed using the Leeds Sleep Evaluation Questionnaire (LSEQ);
- To evaluate and compare the effects of the different stimulation conditions on quality of life, assessed using the SF-36 questionnaire;
- To evaluate participants' overall perception of clinical improvement using the Clinical Global Impression (CGI) scale;
- To assess the effectiveness of participant blinding throughout the study.

3.2 Description of the research

3.2.1 Primary endpoint

The primary endpoint is the change in total Fibromyalgia Impact Questionnaire (FIQ) score associated with each stimulation modality (Condition A, Condition B and sham stimulation). The primary analysis will evaluate differences in FIQ score changes across the three stimulation modalities within the crossover design.

3.2.2 Secondary endpoints

Pain measures:

1. VAS which consists of rating the symptom on a 10 cm horizontal line going from “no pain” to “worst pain imaginable” (**Appendix B**). VAS has good psychometric properties for assessing pain (Campbell & Lewis, 1990; Kahl & Cleland, 2005) and has a high sensibility and sensitivity and a good discriminative power in patients with fibromyalgia (Marques et al., 2008).
2. The validated French version of the Brief Pain Inventory (BPI) will be used to assess pain severity (4 items) and pain interference (7 items) (Cronbach's alpha ranging from 0.86 to 0.90, Brasseur, 1997). BPI items are rated on a 10-point scale running from 0 (no pain/does not interfere) to 10 (pain as bad as you can/interferes completely) (Cleland & Ryan, 1994; Sullivan et al., 1995) (**Appendix C**).
3. The Pain Catastrophizing Scale (PCS) will also be employed, it is a valid and reliable scale that includes 13 items assessing the presence and severity of feelings or thoughts that emerge when experiencing pain. Each item is rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (all the time). It is possible to calculate a total and three subscale scores (i.e., helplessness, magnification, and rumination) (French et al., 2005). The total PCS has good psychometric properties: internal consistency (Cronbach's alpha = 0.91) and test-retest reliability ($r=0.85$ at two weeks and $r=0.77$ at six weeks) (**Appendix D**).
4. Moreover, patients will be asked to fill in a pain diary (average daily pain reporting using a VAS filled in at the end of the day) that will be used to track pain starting one week before the first stimulation period and continuing until the end of the protocol at V6

(Appendix E).

VAS scale for fatigue: Like pain, fatigue will be assessed using VAS (Dailey et al., 2020) **(Appendix F).**

Hospital Anxiety and Depression Scale (HADS): It is a 14-item generic scale with good psychometric properties (Bocéréan & Dupret, 2014). It consists of seven items assessing anxiety and seven others assessing depression. Scores can range from 0 to 21 on each subscale, with higher scores indicating worse symptomatology **(Appendix G).**

Short Form 36 Health Survey (SF-36): It is a generic survey that contains 36 items that assess the quality of life and yield eight dimensions: physical functioning, physical role, emotional role, bodily pain, general health, vitality, social functioning, and mental health (Ware et al., 1993) **(Appendix H).** The score of each dimension ranges from 0 to 100, with higher scales implying better health status. The French version has excellent convergent and discriminant validity (100% and 97.9%, respectively) and good to excellent internal consistency (Cronbach's alpha: 0.76-0.92) (Perneger et al., 1995). Given the complexity of fibromyalgia and its multidimensional impact, we chose the SF-36 rather than the SF-12 to capture a more global and detailed picture of the different quality-of-life domains and to better detect any subtle yet clinically meaningful changes.

Sleep measures

1. The Pittsburgh Sleep Quality Index (PSQI): it is a self-rated questionnaire that evaluates sleep quality. Its 19 questions aim to assess the sleep pattern during the previous month. This scale has good psychometric properties and its utility in clinical practice and research activities has been proven **(Appendix I)** (Buysse et al., 1989).
2. Leeds Sleep Evaluation Questionnaire (LSEQ): it consists of 10 items that evaluate four domains: ease of initiating sleep, quality of sleep, ease of waking, and behavior following wakefulness. It is an easy to implement questionnaire that has been widely used to evaluate the subjective aspect of sleep. It has been employed in a huge amount of psychological and psychopharmacological studies. A relatively recent review of 2003 concluded that LSEQ is a sound measure of sleep latency and quality; its psychometric properties support its use in several clinical settings **(Appendix J)** (Zisapel & Lunden, 2003).

Pain intensity (VAS), pain severity and interference (BPI), pain catastrophizing (PCS), fatigue (VAS fatigue), anxiety and depression (HADS), sleep quality (PSQI and LSEQ), quality of life (SF-

36), and the Fibromyalgia Impact Questionnaire (FIQ) will be assessed at Visits V1, V2, V3, V4, V5, and V6. Daily pain evolution will be monitored using the pain diary throughout the study period.

At the end of each stimulation period (Visits V2, V4, and V6), participants will complete the Clinical Global Impression (CGI) scale, a 7-point measure ranging from “very much improved” to “very much worse” since the initiation of the treatment period (**Appendix K**; Busner & Targum, 2007).

At the same visits, participants will also complete a blinding questionnaire designed to assess the effectiveness of participant blinding and their perception of the stimulation condition received.

4. RESEARCH METHODOLOGY

4.1 Design of the study

The trial is designed as a randomized, double-blind, sham-controlled crossover study. It consists of three successive 4-week stimulation periods, each separated by a 2-week washout phase.

Participants will be randomly assigned to one of six possible treatment sequences and will receive the three study conditions in a randomized order: two active stimulation configurations (Conditions A and B) and one sham stimulation condition (Condition C). The study has been designed as a randomized, double-blind, sham-controlled crossover trial comparing the effects of the three stimulation modalities on functional disability and other fibromyalgia-related outcomes. The sham condition is included to preserve participant blinding and to assess potential non-specific effects associated with device use and study participation. The stimulation condition administered during each period will remain unknown to both participants and outcome assessors throughout the study.

Stimulation periods: Each participant will undergo three 4-week stimulation periods, during which daily sessions (7 sessions per week, approximately 60 minutes per session) will be performed at home.

- **Condition A:** active stimulation (20 Hz, 20 V, pulse width 55–85 μ s)
- **Condition B:** active stimulation (20 Hz, 20 V, pulse width 100–125 μ s)

- **Condition C:** sham stimulation (brief initial stimulation for 1 min, followed by a switch-off for the remainder of the session)

Each stimulation period will be separated by a 2-week washout phase to minimize potential carry-over effects between conditions.

The total duration of participation for each subject will be approximately 16 weeks [three blocks of 28 daily stimulation sessions, separated by a 2-week wash-out interval]. The inclusion period is expected to last approximately 15 months and the overall study duration is estimated at 18 months.

4.2 Number of participating sites

This is a monocentric study that will be conducted at Henri Mondor Hospital, Creteil, France.

Recruitment center: Patients will be recruited among outpatients presenting to the neurology consultation or the chronic pain consultation at Henri Mondor Hospital, Creteil, France. Dr Benjamin Bardel and Dr Samar Ayache will be in charge of the recruitment. Patients who agree to participate will sign the consent in the Clinical Neurophysiology Department of Henri Mondor Hospital, Creteil, France.

Stimulation and evaluation center: Exopulse Mollii suit stimulation sessions and assessments will be carried out in the Clinical Neurophysiology Department of Henri Mondor Hospital, Creteil, France. Dr Samar Ayache will supervise the stimulation procedures. Evaluations and data entry will be performed by Dr Benjamin Bardel. Statistical analyses will be supervised by Pr Jean-Pascal Lefaucheur.

4.3 Intervention: Exopulse Mollii suit application

Active intervention: Each session of active stimulation will last for one hour. The electrical stimulation parameters will be as follows:

- **Condition A:** Frequency of 20 Hz, electrical voltage of 20 V, and pulse width of 55–85 μ s.
- **Condition B:** Frequency of 20 Hz, electrical voltage of 20 V, and pulse width of 100–125 μ s.

Control intervention: The control condition will consist of a sham stimulation. The same Exopulse Mollii Suit will be used; however, the control unit will be programmed to deliver a

brief initial stimulation (1 minute) then the current will be switched off for the remainder of the session. This approach is intended to reproduce cutaneous sensations similar to those of the active conditions, thereby maintaining the integrity of blinding.

Depending on the randomized treatment sequence, the sham condition will mimic one of the two active stimulation configurations to ensure comparable sensory experiences across conditions. The sham condition will consist of a brief initial stimulation followed by interruption of stimulation for the remainder of the session while maintaining identical study procedures and session duration. This approach is intended to preserve participant blinding while minimizing physiological effects attributable to active stimulation. The risks associated with the sham intervention are considered minimal, as it involves only a brief exposure to stimulation parameters that fall within the validated operating range of the device.

4.4 Description of measures taken to reduce and prevent biases

4.4.1 Identification of participants

Participants will be identified using a unique study identification number assigned at inclusion. We will consecutively select eligible patients to minimize selection bias. Patients who are non-eligible or who refuse to participate will be mentioned in a centralized registry and the reasons for non-inclusion will be specified.

4.4.2 Randomization

A randomization software (<https://www.randomizer.org/>) will be used to centralize randomization and will be managed by a research technician who is not involved in protocol implementation, data collection, or data analysis. Participants will be allocated according to a balanced crossover randomization scheme across the six possible treatment sequences (ABC, ACB, BAC, BCA, CAB, and CBA), ensuring balanced representation of each sequence throughout the study.

4.4.3 Programming of control units

A research technician who is trained to use Exopulse Mollii suit and not involved in any step of the study protocol (patients' evaluation, performance of stimulation session, data collection or analysis) will program the control units for both active stimulation configurations according to the instructions provided by the investigators (**Appendix N**). Treatment allocation codes, which correspond to the different stimulation conditions, will be placed in sealed envelopes and kept unopened until study closure. Both outcome assessors and participants will remain

blinded to the specific stimulation condition they receive.

5. STUDY IMPLEMENTATION

Whose consent must be obtained	Who informs the individual and collects his/her Consent	At what point the individual is informed	At what point the consent of the individual is obtained
The participant	One of the study investigators	Screening visit	Baseline visit (at least one a week after the screening visit)

5.1 Schedule for the study

5.1.1 Screening and baseline visits

If a patient with fibromyalgia meets the inclusion criteria during a routine clinical visit, and if (s)he appears eligible and interested in this study protocol, one of the investigators provides him/her with the information form (screening visit). This visit will also help obtain the patients' weight and height to select the right Exopulse Mollii suit size. After a period of reflection of at least one week after this screening visit, the patient will be called by one of the study investigators to inquire about her/his willingness to participate in the study. In case of agreement, the patient will be invited for a baseline visit (inclusion) in the Department of Clinical Neurophysiology of Henri Mondor Hospital. During this baseline visit, the inclusion and exclusion criteria will be rechecked by the study investigator, who will explain in detail the trial procedure to the patient. If the patient is eligible and willing to participate, (s)he will receive the consent form that (s)he will sign and an ID study number will be attributed to him/her.

5.1.2 Study visits

During the baseline visit and following signature of the informed consent form, current treatments will be recorded and baseline assessments (Visit V1) will be performed. The participant's study identification number will then be transmitted to the research technician responsible for randomization. Using the predefined randomization schedule, the research technician will assign the participant to one of the six possible treatment sequences. This sequence will determine the order in which the participant receives the three stimulation modalities investigated in the study: Condition A, Condition B and Condition C (sham stimulation).

All participants will use the same Exopulse Mollii Suit throughout the study. Identical control units will be provided and programmed according to the randomized treatment sequence in order to deliver the corresponding stimulation modality during each study period. This procedure is designed to ensure allocation concealment and maintain blinding of both participants and outcome assessors throughout the study.

The suit and the control unit will be provided to the participant at the initial visit. After each 4-week stimulation period, the control unit will be returned and replaced following the 2-week washout period. The same suit will be used throughout the study, while different control units will be provided for each stimulation period according to the randomized sequence.

Participants will be provided with all batteries required for the entire duration of each stimulation period. For each 4-week period, a sufficient number of batteries will be supplied to ensure uninterrupted daily use (7 sessions per week). Prior to each stimulation period, each participant will receive all necessary batteries for the upcoming period.

Participants will receive standardized training on the use of the **Exopulse Mollii Suit**. This face-to-face session (30–60 minutes) will ensure that participants are able to correctly don and operate the device, initiate and terminate stimulation, and appropriately handle the control unit. Written instructions, including visual aids, will be provided in both printed and electronic formats to support adherence.

Following training, participants will undergo three 4-week stimulation periods, during which the device will be used once daily for approximately 60 minutes (7 sessions per week). Each stimulation period will be separated by a 2-week washout phase. Participants will receive the three study conditions (Condition A, Condition B, and Condition C [sham]) according to a randomized crossover sequence.

Treatment allocation codes corresponding to the three stimulation conditions will be securely maintained and concealed until study completion. Both participants and outcome assessors will remain blinded to treatment allocation throughout the study.

Participants will complete a daily pain diary and record concomitant medication use starting one week before the first stimulation period and continuing until the final study visit (V6). Pain and fatigue will also be assessed using a Visual Analog Scale (VAS) before and after the first

and last sessions of each stimulation period. Validated outcome measures—including the Fibromyalgia Impact Questionnaire (FIQ), Brief Pain Inventory (BPI), Pain Catastrophizing Scale (PCS), Hospital Anxiety and Depression Scale (HADS), Pittsburgh Sleep Quality Index (PSQI), Leeds Sleep Evaluation Questionnaire (LSEQ), and Short Form-36 Health Survey (SF-36)—will be administered at baseline (Visit V1) and at each study visit (Visits V2, V3, V4, V5, and V6).

At the end of each stimulation period (Visits V2, V4, and V6), participants will complete the Clinical Global Impression (CGI) scale. A blinding assessment questionnaire will also be administered at these visits to evaluate the integrity of treatment concealment.

The details of the first phase of this study are displayed in **Table 1**.

	Visit 1 (Baseline) 1st condition (A, B or sham) (W1–W4)	Evaluation after the last session of the 1st condition (A, B or sham) 2-week washout period (W5–W6)	Evaluation before the 2nd condition (A, B or sham) (W7–W10)	Evaluation after the last session of the 2nd condition (A, B or sham) 2-week washout period (W11–W12)	Evaluation before the 3rd condition (A, B or sham) (W13–W16)	Evaluation after the last session of the 3rd condition (A, B or sham)
Visit	V1	V2	V3	V4	V5	V6
Information	✓					
Eligibility Criteria	✓					
Written Consent	✓					
Randomization	✓					
FIQ	✓	✓	✓	✓	✓	✓
BPI	✓	✓	✓	✓	✓	✓
VAS pain, fatigue*	✓	✓	✓	✓	✓	✓
HADS	✓	✓	✓	✓	✓	✓
PCS	✓	✓	✓	✓	✓	✓
SF-36	✓	✓	✓	✓	✓	✓
PSQI	✓	✓	✓	✓	✓	✓
LSEQ	✓	✓	✓	✓	✓	✓
Pain Diary#	✓	✓	✓	✓	✓	✓

CGI		✓		✓		✓
Blinding Questionnaire		✓		✓		✓

*BPI: Brief Pain Inventory; CGI: Clinical Global Impression; FIQ: Fibromyalgia Impact Questionnaire; HADS: Hospital Anxiety and Depression Scale; PCS: Pain Catastrophizing Scale; SF-36: Short Form 36 Health Survey (SF-36); VAS: Visual Analog Scale. PSQI: The Pittsburgh Sleep Quality Index ; LSEQ : Leeds Sleep Evaluation Questionnaire ; *The scales will be completed before and after the first session. #Evaluation will take place over starting one week before the first stimulation period and continuing until V6*

To sum up, for the whole protocol, each participant will attend six main study visits (excluding the initial screening visit, which is part of routine care):

- **Visit 1 (Baseline – V1):** Inclusion visit during which the participant will be trained to use the Exopulse Mollii Suit, undergo baseline assessments, and receive the suit along with the control unit programmed for the first stimulation condition (A, B, or sham, according to randomization).
- **Visit 2 (End of Period 1 – V2):** After four weeks of daily stimulation with the first condition, the participant will return the control unit and undergo post-treatment assessments. A 2-week washout period will then begin.
- **Visit 3 (Pre-Period 2 – V3):** Following the washout period, the participant will undergo pre-treatment assessments and receive a control unit corresponding to the second stimulation condition.
- **Visit 4 (End of Period 2 – V4):** After four weeks of daily stimulation with the second condition, the participant will return the control unit and undergo post-treatment assessments. A second 2-week washout period will then begin.
- **Visit 5 (Pre-Period 3 – V5):** Following the second washout period, the participant will undergo pre-treatment assessments and receive a control unit corresponding to the third stimulation condition.
- **Visit 6 (End of Period 3 – V6):** After four weeks of daily stimulation with the third condition, the participant will return the control unit and undergo final assessments.

Throughout the study, participants will maintain a daily pain diary and record concomitant medication use, starting one week prior to the first stimulation period and continuing until the end of the study (V6).

The Exopulse Mollii Suit does not include a built-in feature to monitor session frequency or duration. To address this limitation, participant adherence will be supported through regular remote follow-up. Short, structured contacts (e.g., via videoconference or telephone) may be scheduled to verify session completion, monitor adherence, and provide support when needed. The frequency and organization of these contacts will be adapted to ensure feasibility and acceptability, with flexibility offered to participants.

This crossover design allows a controlled within-subject comparison of the three stimulation modalities investigated in the study (Condition A, Condition B and sham stimulation), while reducing inter-individual variability and improving the efficiency of treatment comparisons.

6. ELIGIBILITY CRITERIA

6.1. Inclusion criteria

As stated above, Patients will be recruited among outpatients presenting to Neurology and chronic pain consultations at Henri Mondor Hospital, France. We will include adult patients (1) aged between 18 and 75 years and (2) with a definite diagnosis of fibromyalgia according to The American College of Rheumatology (ACR) 2010 criteria, set for at least one month (Wolfe et al., 2010) (**Appendix L**), (3) French speakers, able to understand verbal instructions, and (4) affiliated to the national health insurance (*sécurité sociale*).

6.2. Exclusion criteria

Patients will not be eligible for inclusion if they are participating in another interventional clinical study during the study period, are unable to comply with study procedures or follow-up requirements for geographical, social, or organizational reasons, or present any contraindication to the use of the Exopulse Mollii Suit as specified in the manufacturer's user manual. These contraindications include, but are not limited to, concomitant use with a cardiac stimulator, ventriculoperitoneal shunt, or intrathecal baclofen pump, as well as the presence of edema, erythema, inflammation, thrombophlebitis, or significant varicose veins in areas where stimulation is applied.

Pregnant or breastfeeding women will not be eligible for participation. Patients who have modified their pharmacological treatment related to fibromyalgia, or initiated or modified a non-pharmacological therapy within the three months preceding inclusion, will also be excluded.

In addition, patients presenting any significant neurological, psychiatric, cardiovascular, musculoskeletal, or other medical condition that, in the opinion of the investigator, could interfere with study participation, outcome assessment, or participant safety will not be eligible for inclusion, with the exception of anxiety and depression commonly associated with fibromyalgia. Individuals subject to a legal protection measure (guardianship, curatorship, or judicial protection order) will also be excluded.

Participants will be asked to maintain stable pharmacological and non-pharmacological treatments related to fibromyalgia throughout the study period. Furthermore, participants who initiate treatment with another therapeutic medical device during the study period will be withdrawn from the study on the date of treatment initiation.

6.3. Recruitment procedure

As previously mentioned, patients will be recruited among outpatients presenting to the neurology consultation or the chronic pain consultation at Henri Mondor Hospital, Creteil, France. Based on the number of patients with fibromyalgia routinely followed at Henri Mondor Hospital and on previous recruitment experience within this population, recruitment of approximately one to two participants per month is considered realistic.

Hence, we are convinced that announcements and advertisements are not needed for this study.

7. TERMINATION AND EXIT RULES

It is possible to exit from the study in some situations. The investigator must document the reason for the arrest and its recovery in the source file of the subject and the case report form (CRF) in case of temporary discontinuation. In addition, the investigator must document the reason for a premature discontinuation, but the participant remains enrolled in the study until the end of his/her participation. Patients who discontinue the study prematurely will not be replaced. Data collected prior to withdrawal may be retained and included in the statistical analyses in accordance with the participant's consent, applicable regulations, and the predefined statistical analysis plan.

7.1 Criteria and procedure for premature withdrawal from the study

- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests (e.g., serious adverse event [SAEs]). Participants may exit the study because of an intercurrent disease requiring specific medical management or change in health condition (e.g., pregnancy).
- Participants may exit the study because of any clinical worsening and requiring specific therapeutic management according to standard care.
- Participants may exit the study at any time and for any reason. Any patient can withdraw consent, at any point during the study, without any consequence.
- Participant may be lost to follow-up, without any possibility to locate the participant, although the investigator must make every effort to reconnect with the participant (and document his/her attempts in the source file), at least to determine whether the participant is alive or dead.
- The CRF must list the various reasons why the participant has discontinued the study: SAEs, another medical issue, personal reasons, explicit withdrawal of consent, lost to follow-up.

7.2 Full or partial discontinuation of the study

If inclusion objectives are not met, the sponsor ICVNS FRANCE reserves the right to permanently suspend enrolment at any time.

8. STUDY STEERING COMMITTEE

This study is conducted in accordance with Regulation (EU) 2017/745 on medical devices (MDR). It is a clinical investigation involving a CE-marked medical device.

Although the Exopulse Mollii Suit is used within its intended purpose, certain stimulation conditions evaluated in this protocol differ from those previously investigated in clinical studies. The study has been designed to assess the potential impact of parameter optimization on clinical outcomes in patients with fibromyalgia.

The study is not intended to support regulatory approval of the device but to generate clinical data on its effectiveness and safety under controlled conditions.

Participant safety will be ensured by the investigators in accordance with the study protocol and applicable regulatory requirements, including systematic monitoring and reporting of adverse events, predefined stopping criteria, and appropriate risk mitigation measures.

Given the low-risk profile of the device and the non-invasive nature of the intervention, no independent data monitoring committee is planned.

9. DATA MANAGEMENT

9.1 Data collection procedures

The investigating doctor will inform the patient about the study and obtain his/her written consent before performing any specific research act. (S)He will be in charge of patient management and the collection of study data. The investigator or a person from the investigativeteam will record data directly in a paper CRF. Later, pseudonymized data taken from the paper CRF will be entered into spreadsheets of standard software (Excel file) in order to perform statistical analyses.

9.2 Identification of data recorded directly in the CRF

The CRF will contain the following data: treatment sequence, demographic data (age and sex), and clinical data related to fibromyalgia, including the date of diagnosis, disease duration, and current treatments. It will also include assessments of pain and fatigue using the Visual Analog Scale (VAS), as well as standardized questionnaires such as the Hospital Anxiety and Depression Scale (HADS), Brief Pain Inventory (BPI), Fibromyalgia Impact Questionnaire (FIQ), Pain Catastrophizing Scale (PCS), Short Form-36 Health Survey (SF-36), Leeds Sleep Evaluation Questionnaire (LSEQ), and Pittsburgh Sleep Quality Index (PSQI). Additionally, patients will be required to complete a daily pain diary and a pain medication log to track the use of opioid and non-opioid medications throughout the study. The CRF will also include the Clinical Global Impression (CGI) and Blinding questionnaire to assess treatment perception.

9.3 Right to access data and source document

9.3.1 Data access

In accordance with good clinical practices, ICVNS FRANCE as the sponsor is responsible for ensuring all parties involved in the study, agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures. In addition, the investigators will ensure the persons in charge of monitoring, quality control and auditing the research, have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force.

9.3.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept by the investigator, or by the hospital in the case of a hospital medical file, for 15 years.

9.3.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the *Code de la Santé Publique* (French Public Health Code)) will take all necessary precautions to ensure the confidentiality of information relating to the study, the study participants and in particular their identity and the results obtained. These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the *Code Pénal* [French Criminal Code]).

During and after the research, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialized collaborators) will be rendered non-identifying.

Under no circumstances shall the names and addresses of the participants involved be shown. Only the participant's unique study identification number will be recorded, accompanied by an encoded numberspecific to the study indicating the order of enrolment.

The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

In summary, the study records will be kept as confidential as possible. The information about the patients will be carefully protected. To protect the patients' privacy, samples will be linked to a secret code. Names will only be recorded on the informed consent form. The secret code will be kept in a locked and carefully protected file, with access only granted to the study principal investigatorand authorized personnel.

The records will be monitored and may be audited without violating confidentiality.

9.4 Data processing and storage of research documents and data

Identification of the data processing manager and location(s):

The data-management work and data monitoring will be conducted by investigative team. Paper Case Report Forms (CRFs) will be used to collect demographic, clinical, and therapeutic

information, as well as clinical questionnaires filled by the patient and/or the investigator. CRFs are designed to minimize errors during transfer from source documents.

9.4.1 Data entry

Non-identifying or pseudonymized qualitative and numerical data from the CRFs will be entered into a secure, password-protected spreadsheet (Excel file) for tabular storage and further statistical analysis. Access to the electronic data will be restricted to authorized study personnel only.

In accordance with Regulation (EU) 2016/679 (General Data Protection Regulation, GDPR), the processing of personal data implemented in the context of this study is based on the performance of a task carried out in the public interest in the field of scientific research. Personal data collected during the study will be pseudonymized and processed only by authorized personnel. Study data and associated documents will be retained for 15 years after study completion in accordance with applicable regulatory requirements.

9.5 Data Ownership

ICVNS FRANCE is the sponsor of the study and the data controller for the research data collected within the framework of this study. Access to study data will be restricted to authorized persons involved in the conduct, monitoring, auditing, analysis, or regulatory oversight of the research, in accordance with applicable laws and regulations. Any disclosure of study data to third parties will be subject to applicable regulatory requirements and appropriate data protection safeguards.

All source documents, Case Report Forms (CRFs), and electronic datasets will be archived in accordance with French regulatory requirements for a period of 15 years following study completion or early termination.

10. STATISTICAL ANALYSES

Statistical analyses will be performed using IBM SPSS Statistics software (version 31.0 or later). The sample size calculation was based on the primary objective of the study, namely the comparison of the effects of the three stimulation modalities (Condition A, Condition B and sham stimulation) on functional disability measured by the Fibromyalgia Impact Questionnaire (FIQ). The estimation took into consideration the EXOFIB study (Mattar et al., 2025). Calculation was confirmed using G*Power 3.1.9.7 (Faul et al., 2007). The analysis was based on an F test for

repeated-measures ANOVA within factors. Assuming a medium effect size ($f = 0.25$), a two-sided significance level of $\alpha = 0.05$, a statistical power of 80%, and one group with six repeated measurements, a correlation of 0.50 between repeated measurements and a nonsphericity correction of $\epsilon = 1$, the required total sample size was estimated at 19 participants. Each participant will undergo three stimulation conditions and will be assessed before and after each condition. To account for an anticipated dropout rate of 20%, the required recruitment target was increased to 24 participants.

Participants will be allocated according to a balanced crossover randomization scheme across the three study conditions (Condition A, Condition B and sham stimulation), resulting in six possible treatment sequences.

Descriptive statistics will be presented as mean $\pm$ standard deviation (SD) for normally distributed continuous variables, median [interquartile range] for non-normally distributed variables, and frequencies and percentages for categorical variables.

Normality of data distribution will be assessed using the Shapiro–Wilk test and the assumption of sphericity for the intervention factor will be assessed using Mauchly's test.

The primary endpoint, defined as the change in Fibromyalgia Impact Questionnaire (FIQ) score, will be analysed by comparing the three stimulation modalities. When the assumptions of normality are met, a two-way repeated-measures analysis of variance (3×2 within-subjects ANOVA) adapted to the crossover design will be used to assess the main effect of intervention, the main effect of time, and the interaction. When a significant main effect of intervention is observed, Bonferroni-adjusted pairwise comparisons will be conducted to identify differences between interventions. If a significant intervention $\times$ time interaction is found, simple effects analyses will be performed using Bonferroni-adjusted pairwise comparisons to examine differences between interventions at each time point and/or pre–post changes within each intervention, as appropriate. If normality assumptions are not met, the Friedman test will be used, followed by Dunn's posthoc comparisons with Bonferroni correction for multiple testing. Secondary continuous outcomes, including pain intensity (VAS pain), fatigue (VAS fatigue), pain interference and severity (BPI), pain catastrophizing (PCS), anxiety and depression (HADS), sleep quality (PSQI and LSEQ), quality of life (SF-36), and daily pain diary scores, will be analysed using similar methods according to the nature and distribution of the data.

Clinical Global Impression (CGI) scores, responses to the blinding questionnaire, medication use and other categorical variables will be analysed using Chi-square tests or Fisher's exact tests when appropriate. Effect sizes will be reported when relevant and interpreted according to

conventional thresholds. Exploratory analyses may be performed to assess potential period effects or residual carry-over effects if clinically relevant patterns are observed.

All statistical tests will be two-sided and statistical significance will be defined as $p < 0.05$.

11. QUALITY CONTROL AND ASSURANCE

11.1 General organization

The sponsor must ensure the safety and respect of patients who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation center. For this purpose, the sponsor will define a strategy for opening the center and may, if necessary, set up a quality control of the data.

11.1.1 Strategy for opening the centers

Not applicable.

11.1.2 Data quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, in accordance with the Standard Operating Procedures applied within the Clinical Research and Innovation Department. The principal investigator and the members of the investigators team agree to make themselves available during visits carried out by the CRA.

11.2 Case Report forms

All information required by the protocol must be entered in the CRF and an explanation must be given for all missing data. The data must be collected as and when they are obtained and must be clearly and legibly transcribed.

Any errors identified in the CRF must be crossed out and the correct information entered next to the crossed-out data, together with the initials of the Investigator or authorized person who made the correction, the date, and if necessary, the reason for the correction.

11.3 Management of non-compliances

Any event that occurs as a result of non-compliance – by investigators or any other individual involved in the study – with the protocol, standard operating procedures, good clinical practices, or statutory and regulatory requirements must be recorded in a declaration of non-

compliance and sent to the sponsor. Non-compliance will be managed according to the sponsor's procedures.

11.4 Audit

The investigators agree to consent to 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 may be subject to regulatory audits. These audits and inspections cannot be refused on the grounds of medical secrecy. An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research. The audit aims to ensure the quality of the study, the validity of the results, and compliance with the legislation and regulations in force. The persons who manage and monitor the study agree to comply with the sponsor's audit requirements. The audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

11.5 Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (*Répertoire Partagé des Professionnels de Santé*, Collective Database of Health Professionals). The CV must include any previous involvement in clinical research and related training. Each investigator will commit to comply with legislation and to conduct the study in line with regulations, by the Declaration of Helsinki.

The Principal Investigator will sign a commitment of responsibility which will be sent to the sponsor's representative.

The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

11.6 Adverse Events Recording

Recording and reporting of adverse events that occur during clinical investigations will be according to article 80 of EU REGULATION 2017/745 and the notice to Sponsor of the French Health Authority (*Avis au promoteur*; Agence nationale de sécurité du médicament et des produits de santé [ANSM]). Recording and reporting of serious adverse events that occur

during clinical investigations will be according to articles 87-90 of EU REGULATION 2017/745.

The documents are fully available on the following links:

<https://eur-lex.europa.eu/legal-content/FR/TXT/PDF/?uri=CELEX:32017R0745&from=EN>

<https://ansm.sante.fr/vos-demarches/industriel/dispositifs-medicaux-vigilance-des-investigations-cliniques> (Avis aux promoteurs (IC déposées après le 26 mai 2021) –Partie IV)

The sponsor will fully record all of the following:

- (a) any adverse event of a type identified in the clinical investigation plan as being critical to the evaluation of the results of that clinical investigation;
- (b) any serious adverse event;
- (c) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
- (d) any new findings in relation to any event referred to in points (a) to (c).

The period for reporting shall take account of the severity of the event. Where necessary to ensure timely reporting, the sponsor may submit an initial report that is incomplete followed up by a complete report. Upon request by any Member State in which the clinical investigation is being conducted, the sponsor shall provide all the required information.

Below are the definitions of adverse event, serious adverse event, device deficiency, incident, and serious incident:

‘Adverse event’ means any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users, or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

‘Serious adverse event’ means any adverse event that led to any of the following: (a) death, (b) serious deterioration in the health of the subject, that resulted in any of the following: (i) life-threatening illness or injury, (ii) permanent impairment of a body structure or a body function, (iii) hospitalization or prolongation of patient hospitalization, (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, (v) chronic disease, (c) fetal distress, fetal death or a congenital physical or mental impairment or birth defect.

‘Device deficiency’ means any inadequacy in the identity, quality, durability, reliability, safety, or performance of an investigational device, including malfunction, use errors, or inadequacy in information supplied by the manufacturer.

‘Incident’ means any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect.

‘Serious incident’ means any incident that directly or indirectly led, might have led, or might lead to any of the following: (a) the death of a patient, user, or other person, (b) the temporary or permanent serious deterioration of a patient's, user's or other person's state of health, (c) a serious public health threat.

The current study does not bear any serious medical risk. Electrical stimulation is used daily in neurological rehabilitation, especially in Transcutaneous Electrical Nerve Stimulation, to treat pain. The reported adverse effects consist of a mild skin sensation (e.g., tingling) under the stimulation electrode, which may occur during the stimulation session and resolve afterward. Inappropriate application may cause irritation, hypersensitivity and skin burns beneath the stimulation electrodes. Serious adverse events are rare and should not occur with proper use. TENS may interfere with monitoring equipment and should not be placed close to transdermal drug delivery systems (Johnsson 2008). In the current study, any implanted electrical device is an exclusion criterion. No serious side effects have been reported with the Exopulse Mollii suit. Mild adverse events (such as pain) will be assessed in a study-specific diary designed for the participants and this information will be collected weekly and acted upon when found to be necessary. If the adverse events were to persist after the stimulation is over, the subject would contact the primary investigator to assess the problem and treat it as needed as per the usual standard of care. If the patients experience irritation, hypersensitivity or skin burns, they will be instructed to stop the stimulation sessions and contact the investigator using the contact details provided in this document.

Given that anxiety and depressive symptoms will be assessed throughout the study using the Hospital Anxiety and Depression Scale (HADS), any participant presenting clinically significant psychological distress, severe depressive symptoms, or any indication of suicidal ideation identified during study assessments will be promptly referred to the appropriate healthcare professional for further evaluation and management according to standard clinical practice. The investigator will document any such event and determine whether continued participation in the study remains appropriate.

12. ETHICAL AND LEGAL CONSIDERATIONS

This research will be performed in conformity with “Clinical Investigation of medical devices for Human Subjects –Good Clinical Practice (ISO 14155:2020); MDR ((EU) 2017/745 Regulation on Medical Devices” which concerns good clinical practice for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the clinical performance or effectiveness and safety of medical devices.

12.1 Methods for informing research participants and obtaining their consent

A reflection period of 1 week is given to the individual between the time when he or she is informed and when he or she signs the consent form.

The person’s freely given written informed consent will be obtained by the principal investigator, a physician representing the investigator, or a qualified person, before the person is enrolled in the study (baseline visit).

A copy of the information note and consent form, signed and dated by the research participant and by the principal investigator, the physician representing the investigator, or a qualified person, will be given to the individual before they participate in the study. The principal investigator or the physician representing him/her will keep a copy.

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

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her consent as well as the methods used for providing information to collect it. The investigator will retain one copy of the signed and dated consent form.

12.2 Prohibition from participating in another clinical study or exclusion period after the study, if applicable

No exclusion period of participation after the participant has been finished this study is defined in the context of this research.

The participant may not be enrolled in another interventional study protocol involving human participants for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study.

The participants can however participate in other non-interventional studies.

12.3 Compensation for Participants

Subjects receive no compensation for their participation. Participants will be reimbursed for their travel expenses (i.e., transport costs) (during all the visits) on actual amounts upon presentation of receipts.

12.4 Legal obligations

Institut de la Colonne Vertébrale et des Neurosciences (ICVNS FRANCE) is the sponsor of this study and carries out the study's missions per Article L.1121-1 of the *Code de la Santé Publique* (French Public Health Code). ICVNS FRANCE reserves the right to halt the study at any time for medical or administrative reasons. In this case, a notification will be sent to the investigator.

12.5 Request for approval from the CPP (Research Ethics Committee)

Before initiation of the study, ICVNS FRANCE, as sponsor, will obtain approval from the competent Comité de Protection des Personnes (CPP) in accordance with applicable regulatory requirements.

12.6 Informing the ANSM

ICVNS FRANCE will send the approval from the CPP (Research Ethics Committee) and the summary of the protocol to the ANSM for information.

12.7 Procedures relating to data protection regulations

The computer file used for this research is implemented by French (amended “*Informatique et Libertés*” law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

This research is governed by the CNIL (French Data Protection Agency) “Reference Methodology for processing personal data used within the scope of health research” (amended MR-001).

ICVNS FRANCE, as sponsor of the research, has signed a declaration of compliance with this “Reference Methodology” based on the internal procedures of the entity managing the data. The data will not be sent to another country at any time, including after the end of the study. The processing of personal data implemented in the context of this research is based on the performance of a task carried out in the public interest in the field of scientific research, in accordance with the General Data Protection Regulation (GDPR) and applicable French data protection legislation. Personal data collected during the study will be pseudonymized and processed only by authorized personnel. Research data and associated documents will be

retained for 15 years after study completion in accordance with applicable regulatory requirements.

12.8 Amendments to the research

Any substantial modification to the protocol by the principal investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain approval from the CPP (Research Ethics Committee) before the amendment can be implemented.

The information note and the consent form can be revised, if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

12.9 Final study report

The final report for the research involving human participants referred to in Article R1123-67 of the *Code de la Santé Publique* (French Public Health Code) is written and signed by the sponsor and the investigator.

A report summary drafted according to the reference plan of the competent authority must be sent to the competent authority within one year following the end of the study, i.e., the end of the participation of the last participant in the study.

12.10 Archiving

Specific documents for research involving human participants with Minimal Risks and Burden are to be archived by the investigator and the sponsor for 15 years following the end of the research.

This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the center who participated in the study;
- A sealed envelope for the sponsor containing a copy of all the information notes and consent forms signed by all individuals at the center who participated in the study;
- Study binders for the investigator and the sponsor, including (non-exhaustive list):
 - the successive versions of the protocol (identified by the version number and its date), and any appendices
 - decisions of the CPP (Research Ethics Committee)
 - any correspondence
 - the enrolment list or register
 - the appendices specific to the research

- final study report

13. FUNDING

The 'Institut de la Colonne Vertébrale et des Neurosciences ' will fund this study.

14. PUBLICATION RULES

This study will be registered on ClinicalTrials.gov prior to participant enrolment.

Published data resulting from the study will not mention the names of the people who participated in this study. The data will be published in peer-reviewed journals. Following the study, the data will be safely stored.

14.1 Mention of the sponsor ICVNS FRANCE in the acknowledgments of the text

The sponsor is l'Institut de la Colonne Vertébrale et des Neurosciences (ICVNS FRANCE).

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