FibrAPSpé Protocol

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"Fibromyalgia and Specific Physical Activity

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AMENDMENTS TO THE ORIGINAL PROTOCOL
Version 1.1 of 10/12/2018

Modification	Pattern	Protocol version
Amendment 1	Addition of an inclusion criterion Change in the version of the FIQ used	2.0 of 22/05/2019
Amendment 2	Change of Principal Investigator at the Centre d'Evaluation et de Traitement de la Douleur - CHD Vendée - La Roche sur Yon	2.0 of 22/05/2019
Amendment 3	Modification of an inclusion criterion Addition of the collection of analgesic and painkiller treatments Addition of 2 collaborating investigators	3.0 of 02/10/2019

LIST OF ABBREVIATIONS

ANSM	National Agency for the Safety of Medicines and Health Products
AMM	Marketing Authorisation
ARC	Clinical Research Associate (monitor)
GCP	Good Clinical Practice
CETD	Pain Assessment and Treatment Centre
CHD	Departmental Hospital Centre
CIS	Independent Monitoring Committee
PPC	Committee for the Protection of Individuals
CNIL	Commission Nationale de l'Informatique et des Libertés
CRF	Case Report Form
EAPA	Adapted Physical Activity Teacher
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EQ-5D-5L	5-level EQ 5D (EQ: EuroQuol Group)
EVA	Visual Analogue Scale
EvIG	Serious Adverse Event
ISG	Serious Adverse Effect
EIGI	Unexpected Serious Adverse Effect
FIQR	Fibromyalgia Impact Questionnaire Revised
HAD	Hospital Anxiety and Depression scale
ICH	International Conference on Harmonization
MR	CNIL Reference Methodology
CPR	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SSS	Symptom Severity Scale
TEC	Clinical Study Technician
WPI	Widespread bread Index

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INTRODUCTION

Fibromyalgia is a common, costly and controversial condition (Häuser et al., 2015; Häuser, Ablin, Perrot, & Fitzcharles, 2017)one of the origins of which is the sensitisation of the central nervous system to pain (Häuser et al., 2015).

The usual treatment consists of multimodal management including physical activity (Häuser et al., 2015). This dosage should be adapted to the patient's health needs (Eijsvogels & Thompson, 2015). The currently recommended physical exercise is aerobic work combined with muscle strengthening (Bidonde et al., 2017; Häuser, Ablin, Perrot, & Fitzcharles, 2017)with no evidence of superiority of effectiveness of one over the other (Macfarlane et al., 2017). The recommended dosage for aerobic exercise is 20 minutes (or twice 10 minutes), two to three times a week (70-80% of the Theoretical Maximum Heart Rate) (Bidonde et al., 2017; Macfarlane et al., 2017).

At the Centre Hospitalier Départemental (CHD) Vendée, an adapted physical activity is offered to fibromyalgia patients thanks to the "Siel Bleu" association group. This physical activity, carried out with patients suffering from different pathologies, is non-specific.

In parallel, a preliminary study has shown the benefit of lifestyle coaching with fibromyalgia patients, carried out by specifically trained physiotherapists, nurses and sports coaches, on quality of life (Hackshaw et al., 2016).

Another possibility seems to be to offer personalised coaching with a physical activity adapted to the patient's physical and organisational constraints, and specific to his or her pathology. This solution would make it possible to adapt to the patient's choice of physical activities, to ensure better adaptation to their physical and organisational constraints as well as better individualised follow-up.

1. RATIONALE FOR THE STUDY

1.1. POSITIONING OF THE RESEARCH

Fibromyalgia is a common, costly and controversial condition (Häuser et al., 2015; Häuser, Ablin, Perrot, & Fitzcharles, 2017). Hauser et al. report that most studies place the prevalence of this condition between 2 and 4% (Häuser et al., 2015). Two French studies estimate a prevalence of 1.4 and 1.8% (Bannwarth et al., 2017). (Bannwarth et al., 2009; Perrot, Vicaut, Servant, & Ravaud, 2011). The incidence would be 6.88‰ in men and 11.28‰ in women (Häuser et al., 2015).

Fibromyalgia is a complex syndrome, incorporating a wide range of symptoms and functional impairments (Fitzcharles et al., 2013; Häuser et al., 2015, 2017). While genetic, stress and environmental origins are mentioned, the inclusion of the central nervous system, with a "central sensitisation" to pain, seems a key element (Häuser et al., 2015). This formulation means that the central nervous system has a role in the modulation of pain (Williams & Gracely, 2006) and in the development of co-morbid symptoms (sleep disorder, fatigue, memory, depressed mood). In addition, there are two types of subjects, those with a trigger following a nociceptive input and those without a triggering history (Häuser et al., 2015). It is possible that the triggering mechanism of central sensitisation is different (i.e.: bottom-up[1] for the former and top-down for the latter).

The usual treatment consists of multimodal management: functional, psychological, pharmacological and socio-professional. The most common non-drug treatments are: pain education, cognitive-behavioural treatments, multi-component therapies (education or psychology combined with physical exercise) and aerobic exercise (Häuser et al., 2015). The dosage of this physical exercise should be adapted to the patient's health needs (Eijsvogels & Thompson, 2015). The currently recommended physical exercise is aerobic work combined with muscle strengthening (Bidonde et al., 2017; Häuser et al., 2017)with no evidence of superiority of effectiveness of one over the other (Macfarlane et al., 2017). In addition, dry and aquatic exercise appear to be equally effective (Bidonde et al., 2014; Macfarlane et al., 2017). The recommended dosage for aerobic exercise is 20 minutes (or twice 10 minutes), two to three times per week (70-80% of the Theoretical Maximum Heart Rate) and 8 repetitions per exercise 2 to 3 times per week (Bidonde et al., 2017; Macfarlane et al., 2017). At the CHD Vendée, fibromyalgia patients are offered adapted physical activity with the "Siel Bleu" association group. This group activity is non-specific since it is carried out with patients suffering from different pathologies. Moreover, this activity is limited by the material possibilities of the association group, which cannot move heavy equipment or instruments (elliptical, rowing machine, swimming pool, etc.). The choice was made to offer one endurance session per week with a ten-minute warm-up, forty minutes of *interval training* and ten minutes of rest. Participants can log on to the association's website to follow a complementary exercise programme if they wish.

[1] Bottom-up processes use information from the sensory organs and analyse the environment on the basis of this information, in contrast to top-down processes which use knowledge about the structure of the environment and influence perception.

According to Bennet et al. (2009), a 14% decrease in quality of life since baseline is considered clinically significant (Bennett, Bushmakin, Cappelleri, Zlateva, & Sadosky, 2009). Evaluated in a cohort study of 10 patients (Hackshaw et al., 2016)the interest of a 37% improvement in quality of life following lifestyle coaching by nurses, physiotherapists and adapted physical activity teachers, encourages us to propose personalised coaching with a physical activity adapted to the patient and specific to her pathology. We believe that this solution would allow for adaptation to the patient's choice of physical activities, but would also allow for better individualised follow-up and better adaptation to the patient's physical and organisational constraints, with a better medium and long-term impact on quality of life.

We hypothesize an improvement in the quality of life of fibromyalgia patients in the medium (6 months) and long term (12 months) thanks to personalized coaching (specific physical activity).

The objective of our study is to compare the impact of two physical activity management in fibromyalgia patients at 6 and 12 months:

1. **Control group: Traditional non-specific management in a common "multipathology" group, with activity trackers**
2. **Experimental group: Specific management in a "fibromyalgia patients" group, with activity trackers**

1.2. BENEFITS AND RISKS FOR RESEARCH PARTICIPANTS

Benefits

Individual benefit

Physical activity improves pain, quality of life and body mass quality of patients.
We expect this innovative health sport coaching to optimise these improvements (in quality of life, pain and body mass quality) compared to standard patient management.

Collective benefit

- This new treatment modality will improve the care available to the algologist for the treatment of his patients.

- We also wanted to evaluate a new, simple and rapid test of kinesiophobia using isochrony between an imagined movement and an executed movement to predict a patient's adherence to physical activity management. If this test is effective, it will allow better targeting of patients who can benefit from a rehabilitation programme using physical activity coaching.
- Finally, an evaluation of an innovative patient monitoring with impedancemetry should make it possible to propose new monitoring tools for evaluating patients with fibromyalgia.

Risks

No excess risk due to participation in the study is expected

In both arms of the study, the physical activity sessions are likely to cause more or less diffuse pain, aches, cramps, fatigue and discomfort. These symptoms are not specific to the study and are minimised by the supervision, which enables the absence of cardiac risk to be verified. Nevertheless, they may be felt as an increase in fibromyalgia pathology and experienced in a pejorative way by certain patients; this risk is minimised by the explanations provided within the framework of the research.

The constraints associated with attending the sessions and filling in the questionnaires were considered minimal, but could increase the anxiety of some participants.

Benefit/risk balance

The research manager qualifies the research in the first instance as **interventional research with minimal risks and constraints**, since :

- ✓ All procedures are performed in the usual way *(assessments, clinical examinations, interventions in physical activities)* and defined in the order of 12 April 2018 set by the Ministry.

The research does not focus on innovative or obsolete techniques or strategies.

Apart from the specialised physical activity offered to patients in the experimental group, the overall management of the patient will be identical to usual practice.

Consequently, the particular modalities of implementation in the research represent negligible constraints for the person who lends himself to the research. (Article R 1121-3 of the Public Health Code (CSP), decree n° 2006-477 of 26 April 2006).

The person in charge of the research will therefore, before any implementation of the research, submit the study protocol to the South-East III Committee for the Protection of Individuals (Comité de Protection des Personnes Sud-Est III) in accordance with Article L 1121-1 of the

Public Health Code (CSP) as they result from the laws n° 2004-806 of 9 August 2004 and n° 2006-450 of 18 April 2006 relating to public health policy, for a favourable opinion and confirmation of the research's qualification.

The bibliographical references are given in the annex to the document.

2. OBJECTIVES AND JUDGING CRITERIA

2.1. OBJECTIVE AND PRIMARY ENDPOINT

Main objective

To compare the benefit of a specific 6-month physical activity programme on **patients' quality of life.**

Primary endpoint

Evolution of the **Fibromyalgia Impact Questionnaire** Revised (FIQR) score (quality of life questionnaire specific to the management of fibromyalgia patients) between the beginning of the treatment (D0) and at 6 months (M6).

2.2. OBJECTIVES AND SECONDARY EVALUATION CRITERIA

Secondary objectives

Compare between the 2 randomisation arms:

1. The evolution of pain intensity between the beginning of the treatment (D0), at 6 months (M6) and at 12 months (M12),
2. The presence of neuropathic pain and its evolution,
3. The evolution of isochrony between a physically executed and mentally simulated movement (Moseley, 2004; Moseley et al., 2008)
4. The evolution of anxiety and the presence of signs of the depressive series
5. The evolution of pain on muscle compression

6. The severity of the symptoms
7. Monitoring physical activity with activity trackers
8. The evolution of lean body mass measured on an impedance scale
9. The evolution of kinesiophobia
10. Changes in quality of life between the start of treatment (D0) and 12 months (M12)
11. Continuity of physical activity after the end of coaching

Secondary evaluation criteria

1. EVA at D0, M6 and M12
2. DN4 questionnaire score ≥4 at D0, M6 and M12
3. Difference between the duration of the performed movement and the imagined movement of picking up a magazine from a table at D0, M6 and M12
4. Hospital Anxiety and Depression scale (HAD) at D0, M6 and M12
5. Widespread Pain Index (WPI) (Häuser et al., 2017; Wolfe et al., 1990) at D0, M6 and M12
6. Symptom Severity Scale (SSS) (Häuser et al., 2017; Wolfe et al., 1990) at D0, M6 and M12
7. Percentage of success in achieving goals each month (M1-M12) as measured by activity tracker
   (Duration in minutes per month at least 70% of the theoretical maximum heart rate x100 / 240 minutes
   (4 weeks x 60 minutes recommended = 240 minutes)
8. Percentage and weight of lean mass measured on an impedance scale at D0, M6 and M12
9. Tampa self-questionnaire (Knapik, Saulicz, & Gnat, 2011) at D0, M6 and M12
10. FIQR at D0 and M12 and EQ5D-5L at D0, M6 and M12
11. Level of physical activity between the groups between M6 and M12
    (the duration in minutes per month between 50 and 60, between 60 and 70, between 70 and 80, between 80 and 90, and between 90 and 100% of the theoretical maximum heart rate measured with the activity tracker)

Exploratory secondary objective

Evaluating the isochrony between a physically performed and mentally simulated movement as a predictive test of improved quality of life following a physical activity programme Isochrony will be assessed by the difference between the duration of the performed movement and the imagined movement of taking a review on a table at D0. The quality of life of the patients will be assessed from the FIQR score at M6 and M12.

3. STUDY POPULATION

3.1. DESCRIPTION OF THE POPULATION

The subjects were patients suffering from fibromyalgia, recruited during their treatment by the Centre d'Evaluation et de Traitement de la Douleur de Vendée (CETD) at the sites of La Roche sur Yon, Montaigu and Luçon, as well as at the CHU in Nantes.

The study plans to include 140 patients with the aim of achieving 126 randomised patients. Inclusion will stop when the potential number of randomised patients is reached. (see paragraph 5 statistics).

3.2. INCLUSION CRITERIA

- Patient of legal age,
- Diagnosis of fibromyalgia (Häuser et al., 2017):

  4< WPI < 6 and SSS ≥9 **OR**

  WPI ≥ 6 and SSS ≥5 **AND**

  pain present in **at least** 4 of the 5 regions of the body (5 regions = 4 dials + the axis).

- Patient with FIQR ≤ 59/100
- Patient can be followed for 12 months in the CETD,
- Patient able to follow the physical activities proposed by "Siel Bleu", on a physical and organisational level,
- Patient with a smartphone and/or computer (mac/pc) with an internet connection allowing the use of a monitoring application linked to the activity tracker,
- Patient with the ability to understand the protocol and who has given consent to participate in the study,
- Patient with social security coverage.

3.3. NON-INCLUSION CRITERIA

- Patient participating in an interventional trial within 3 months of inclusion,
- Pregnant or breastfeeding women, or women with the potential to conceive without effective contraception,
- Patient who is a minor, under guardianship, curatorship or deprived of liberty,
- Patient unable to follow the protocol, as judged by the investigator, or unwilling to use the digital applications,
- Patients with contraindications to physical activity,
- Patients who have already taken part in the physical activities offered by "Siel Bleu".

3.4. FEASIBILITY

An investigation with the CETD-Vendée team, cross-checked with the files of the "Siel Bleu" association network, showed an active file of 4 new patients per week on average, i.e. 200 new patients per year.
The Nantes University Hospital estimated that it would be possible to include an active file of 24 patients per year, given their patient base and the resources required for this project.
With a 20% refusal rate, we would have 179 patients included in the year.

4. DESIGN AND STUDY PROCESS

4.1. EVALUATION METHODS

The clinical assessments will be carried out by the healthcare team (doctors and nurses) of the CETDs of the participating centres (La Roche Sur Yon, Luçon, Montaigu, CHU Nantes).
These evaluators will be different from physiotherapists or adapted physical activity teachers, regardless of the randomisation arm.

4.2. GENERAL RESEARCH METHODOLOGY

The research has the following characteristics:

- Open study,
- Multicentric (CHD Vendée, CHU Nantes),
- Controlled,
- Of superiority,
- Randomised

Duration of inclusion: 18 months

Duration of participation: 12 months *(including 6 months of adapted physical activity depending on the randomisation arm*)

Duration of the research: 30 months

Randomisation arm :

- **Control group: Classic non-specific management in a common "multipathology" group, with activity trackers:**
  - One face-to-face session per week with the "Siel Bleu" association in the different sites of the Vendée and Loire-Atlantique.
- **Experimental group: Specific telephone coaching for fibromyalgia patients, with activity trackers:**
  - A one-hour face-to-face individual session conducted by the "Siel Bleu" association - Eight telephone coaching sessions in Physical Activity - Health :
- Four 30-minute sessions by the "Siel Bleu" association
- Four 30-minute sessions by physiotherapists from participating institutions

The nine sessions will be spread over 6 months.

Concerning the continuation of physical activity after the end of the experiment (i.e. after M6), the physical activity coaching service could be provided, if the patient so wishes and on his or her initiative, by a private physiotherapist or an adapted physical activity teacher from "Siel Bleu". Similarly, standard care is based on an existing activity currently offered by "Siel Bleu" and can therefore be integrated by the patient who so requests.

4.3. RESEARCH AND ANALYSIS TECHNIQUES

Detailed description of the evaluation parameters

The revised Fibromyalgia Impact Questionnaire (FIQR, Appendix 5) is a self-administered questionnaire to assess the quality of life of the fibromyalgia patient (Burckhardt, Clark, & Bennett, 1991). Composed of 10 items, the first item includes eleven questions rated from 0 to 3 on a Likert scale. Items 2 and 3 ask the patient to indicate the number of days they felt well and the number of days they were unable to work (including housework) due to fibromyalgia symptoms. Items 4 to 10 are horizontal linear scales marked in 10 steps on which the patient rates work difficulties, pain, fatigue, morning fatigue, stiffness, anxiety and depression. The Minimum Clinically Important Difference is 14%. (Bennett et al., 2009). This means that a 14% difference in the FIQR score is clinically important.

The Visual Analogue Scale (VAS) of pain is used to assess the progression of pain (Scott & Huskisson, 1976). . The therapist should explain the use of the scale by presenting the ruler with the extremes: "You have to move the cursor, with no pain on the left and the maximum pain you can imagine on the right". It is marked from 0 to 100 on a ruler, the patient must move a cursor on the side without graduation. The therapist reports the intensity of the pain felt on the graduated side. The Minimum Detectable Change is 11, while the Minimum Clinically Important Difference is 13.7 points out of 100. The evaluation of the pain will be done on the different areas of pain felt by the patient (cervical, limb).

The DN4 questionnaire (Appendix 6) is used for the detection of neuropathic pain. The first part is based on the history, the second on a clinical examination. This questionnaire is administered by the therapist. If the score is greater than or equal to 4/10, the test will be considered positive (Bouhassira et al., 2005).

The isochrony between executed and imagined movement is a test inspired by the work of Moseley (2004) showing an alteration in the temporality of imagined movement in chronic pain patients. Patient positioning: initially, the patient has the upper limb and hand at the side of the body, with the feet 30cm from a table. A magazine is positioned by the operator flat, at the edge and not protruding from the table. First, the operator will ask the patient, "On my 'go' signal, you will take the magazine lying flat in front of you with your dominant hand and bring the limb back along your body at your comfort speed.
When you have brought your limb back, you will say "stop". I will stop the clock at your end stop.
This movement is to be done twice. The operator will note the 2 times in seconds and hundredths. In a second step, the operator will ask the patient: "At my starting "top", you will, without actually doing it and without moving, imagine taking with your dominant hand the magazine lying flat in front of you

and imagine bringing the limb back along your body at your comfort speed. When you have imagined bringing your limb back, you will say "stop". I will stop the clock at your end stop. This movement is to be done twice. The operator will note the 2 times in seconds and hundredths.

The Hospital Anxiety and Depression scale (HAD, Appendix 8) is a screening instrument for anxiety and depressive disorders. It consists of 14 items rated from 0 to 3. Seven questions relate to anxiety (total A) and seven others to the depressive dimension (total D), thus making it possible to obtain two scores (maximum score for each score = 21) (Zigmond & Snaith, 1983).

The Widespread Pain Index (WPI, Appendix 9) is a score given by the patient according to the number of affected areas (Häuser et al., 2017)

The Symptom Severity Scale (SSS, Appendix 10) is scored by the patient and includes headache, pain, cramp in the abdomen and depression (Häuser et al., 2017)

The percentage of target attainment will be calculated by averaging the attainment of monthly results, compared to clinical practice guidelines from the results recorded by the use of activity trackers

- ⇨ Duration in minutes per month at least 70% of the theoretical maximum heart rate x100 / 240 minutes
  (4 weeks x 60 minutes recommended = 240 minutes)

The percentage (%) and dry mass (in kg) of lean mass will be measured on an impedance scale

Analgesic and painkiller treatments: the consumption of analgesic and painkiller treatments in the week preceding the inclusion visits, M6 and M12 will be collected.

The Tampa Kinesiophobia Index **Scale (TSK-CF, Appendix 7) was** designed and validated to estimate the level of kinesiophobia present in an individual at the time of assessment, with the aim of adjusting the intervention accordingly, and subsequently assessing whether the intervention has had an effect on this common problem among people with persistent pain. The higher the score, the greater the level of kinesiophobia. A score of 40/68 is considered significant kinesiophobia (Vlaeyen et al. 1995), and the Tampa scale can also be used as a follow-up criterion.

Annex 11 consists of 2 pages: the **EQ-5D** descriptive system and the EQ visual analogue scale (EQ VAS).

The descriptive system consists of five dimensions: mobility, personal care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problem, mild problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate their health

status by ticking the box next to the most appropriate statement in each of the 5 dimensions. The VAS EQ system records the patient's self-assessed health status on a vertical visual analogue scale, where the assessment criteria are entitled "The best health you can imagine" and "The worst health you can imagine". The VAS can be used as a quantitative measure of health outcomes that reflects the patient's own judgement.
The **level of physical activity** between the groups will be measured each month. It will be measured with activity trackers based on the time in minutes per month between 50 and 60, 60 and 70, 70 and 80, 80 and 90, and 90 and 100% of the theoretical maximum heart rate.

The activity trackers are OH1 wristbands from Polar™ (User Manual - Appendix 12). They retrieve, throughout the exercise, the heart rate of the subject thanks to optical sensors. The bracelet is either connected directly to a smartphone to record this frequency, or connectable to a computer in order to retrieve the data written in memory. There is no GPS on the bracelet. Patients will be specifically asked not to activate the GPS mode of the application if they are using a smartphone, in order to comply with the General Data Protection Regulation (GDPR) and data minimisation.
The data is implemented on a private PolarFlow™ cloud account of the subject, accessible by personal private codes. The subject grants a right, retractable at any time and in real time, to transfer the data to PolarFlow for Coach™ (software allowing access to patient training statistics), which can be accessed by therapists and the person in charge of implementing the Case Report Form (CRF), again by personal private codes.

Description of techniques and analyses

In the control group, the adapted physical activity intervention (in a "multipathology" group) consists of one face-to-face session per week. The face-to-face session consists of a ten-minute warmup, followed by forty minutes of *interval training*, and then ten minutes of rest with a flash nap. The *interval training is* interspersed with two minutes of gentle, positive stimulation such as self-massage and targeted infra-painful stretching.
In addition, participants are offered the opportunity to log on to the association's website to do a complementary adapted movement activity.

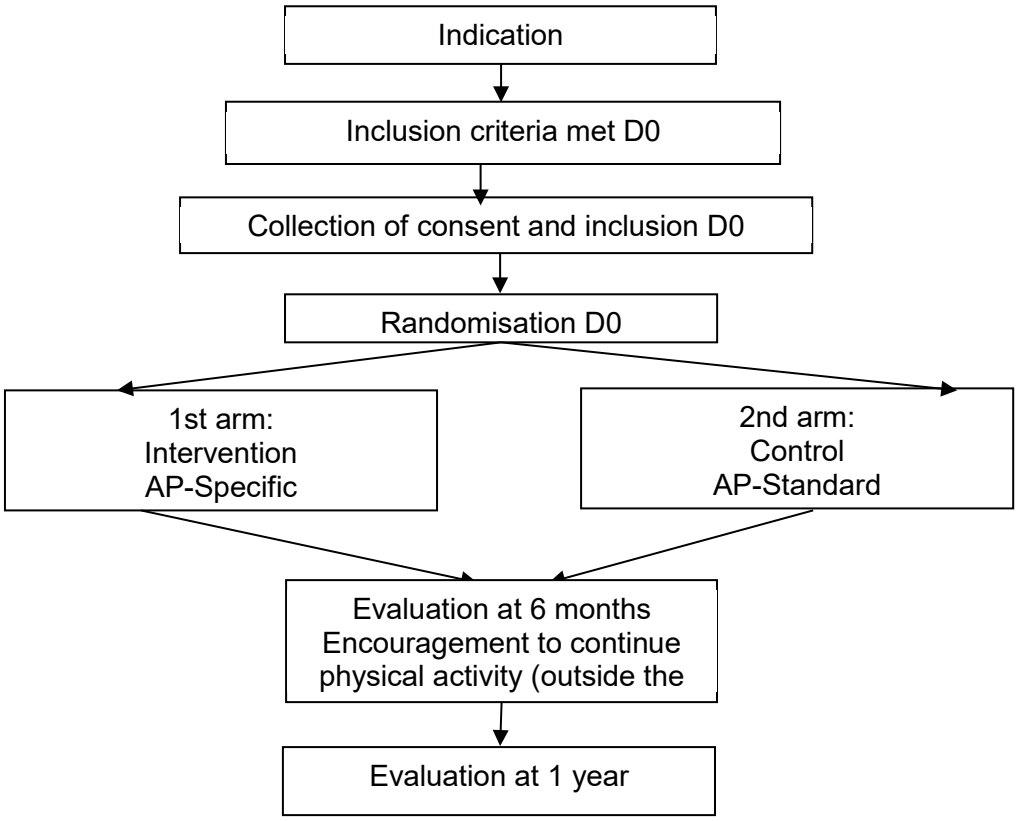
In the experimental group, the specific physical activity intervention consists of an individual face-to-face coaching session carried out by an adapted physical activity teacher (EAPA). The session will consist of therapeutic education in order to teach the basics of physical activity, its interest in the context of fibromyalgia and the rules for its implementation.

Then, the participants will be contacted by telephone eight times over the 6 months of the intervention, four times by the "Siel bleu" EAPAs and four times by the physiotherapists of the participating establishments, in order to collect their motivations, their physical and personal constraints in carrying out a physical activity in line with the recommendations.

The objective is to propose the implementation of specific physical activity(ies) according to the participants' constraints. Physiotherapists and adapted physical activity teachers will have received prior information in order to coordinate the treatment. No paid physical activities will be offered to patients.

Thanks to the activity trackers, the physical coaching will be based on the analysis of the participants' activity levels on the dedicated website.

4.4. SCHEME OF THE STUDY



4.5. STUDY SCHEDULE

TIMETABLE OF THE STUDY

Actions	J0 Inclusion visit	Between D0 and M6	M6	Between M6 and M12	M12
Patient information	X				
Collection of written consent	X				
Background	X				
Randomisation	X				
Clinical examination and questionnaires[1]	X		X		X
Encouragement to continue physical activity			X		
Physical activity with activity trackers		X	X	X[2]	X[2]
Analgesic treatments	X		X		X
Adverse events		X	X	X	X

[1] *EVA, DN4, HAD, WPI, SSS, impedance measurement, Tampa, FIQR, EQ-5D-5L*
[2] Depending on the patient's choice

4.6. IDENTIFICATION OF ALL SOURCE DATA NOT IN THE MEDICAL RECORD

- Physical activity: practice at inclusion and type of activity
- Questionnaires: FIQR, DN4, Tampa, HAD, WPI, SSS, EQ-5D-5L
- EVA
- Physical activity during the study according to the randomisation arm (% success)
- Impedance measurement

4.7. RULES FOR STOPPING A PERSON'S PARTICIPATION

Criteria for premature termination of a person's participation in research

Any patient included in the protocol who no longer wishes to participate will be prematurely withdrawn from the study as soon as the request is made.
For the modalities and duration of the follow-up of the early leavers, see the statistical section.

-Withdrawal of patient consent at any time during the study, before publication of results.
Right to object to the use of the data at any time during the study, before publication of the results
.

Procedures for premature termination of a person's participation in research

For details of how to use the data of people who stopped the study prematurely, see the statistics section.

Criteria for stopping part or all of the research (excluding biostatistical considerations)

Part or all of the study may be stopped permanently or temporarily by decision of the ANSM, the CPP or the study sponsor.

A written confirmation will be sent to the coordinating investigator of the study (specifying the reasons for premature termination) and to the principal investigator of each centre if applicable.

5. DATA MANAGEMENT AND STATISTICS

5.1. COLLECTION AND PROCESSING OF STUDY DATA

Data collection

One observation book (eCRF) will be created per patient. All information required by the protocol should be provided in the eCRF. It should include the data needed to confirm compliance with the protocol and all data needed for statistical analysis; it should identify major deviations from the protocol.

The persons responsible for filling in the eCRFs (investigator, CRA, etc.) must be defined and are identified in the table of delegation of responsibilities for each centre (kept in the investigator's folder).

Data coding

By signing this protocol, the principal investigator and all co-investigators agree to keep confidential the identities of the patients who participated in the study.

The transmission of a person's data for research purposes will therefore only be possible if a coding system is applied; the presentation of the research results must exclude any direct or indirect identification.

The identification of patients will be done according to the order of inclusion of patients by a number automatically assigned by the Clinsight software (eCRF) and then completed by the patients' initials.

This code will be the only information that will appear on the eCRF and will allow the eCRF to be linked to the patient afterwards.
The Research Manager is also required to code patient data on any documents he/she may have in his/her possession that are attached to the CRF.

A mapping table will be set up in each centre. This table will be kept in a secure location by the centre's principal investigator and will contain the patient code and patient data in order to be able to trace back to the patient file in case of missing or erroneous data. No clinical data will be collected in these correspondence tables.

Data processing

The collection of clinical data will be based on the setting up of a database and the creation of data entry masks similar to the observation book in accordance with the protocol and regulations currently in force.

The structure of the database and input screens will be approved by the Research Manager.

5.2. STATISTICS

Description of the planned statistical methods, including the timing of planned interim analyses

All variables will be described globally and by group. The description will include the numbers and percentages of modalities for qualitative variables and the minimum, maximum, mean, standard deviation and median for quantitative variables.

Main criterion

The patients' quality of life will be measured using the FIQR questionnaire at D0, M6 and M12. The evolution of the score at 6 and 12 months will be characterised by a graph and compared between the 2 groups using a linear regression model taking into account the baseline score at D0, the time effect, the "time*group" interaction and the repeated nature of the data.
The comparison of the evolution of the score at M6 will be tested from the M6 contrast.

Secondary criteria

The evolution of pain will be graphically characterised and compared using a mixed linear regression model taking into account the baseline data of the D0 score and the repeated nature of the data.

Neuropathic pain will be assessed using the DN4 questionnaire score. It will be compared between the two groups using a mixed generalized linear regression model taking into account the repeated nature of the data.

The evolution of the isochrony will be characterised graphically and compared using a mixed linear regression model taking into account the baseline data J0 and the repeated nature of the data.

The evolution of anxiety will be assessed from the total HAD score and compared between the two groups using a mixed linear regression model taking into account the baseline D0 score and the repeated nature of the data.

The evolution of pain on muscle compression will be assessed from the total WPI score and compared between the two groups using a mixed linear regression model taking into account the baseline score on D0 and the repeated nature of the data.

The severity of symptoms will be measured from the SSS score and compared using a mixed linear regression model taking into account the baseline data of the D0 score and the repeated nature of the data.

Physical activity monitoring will be collected every month until M12. Each month, the percentage of goal achievement will be calculated. The average percentage of success will be plotted and compared between the 2 groups using a mixed linear regression model taking into account the repeated nature of the data.

The evolution of lean body mass will be collected at D0 M6 and M12 and compared using a mixed linear regression model taking into account the repeated nature of the data.

The evolution of kinesiophobia will be assessed using the TAMPA self questionnaire at D0, M6 and M12. The total score will be compared between the groups using a mixed linear regression model taking into account the baseline score on D0 and the repeated nature of the data.

The evolution of the quality of life will be measured using the EQ5D-5L questionnaire at D0, M6 and M12. The evolution of the score will be characterised by a graph and compared between the 2 groups using a mixed linear regression model taking into account the baseline score on D0 and the repeated nature of the data.

Exploratory criterion

The evolution of the FIQR score will be evaluated using a linear mixed model taking into account the group and repeated nature of the data as well as the isochrony data at D0 in order to evaluate its predictive character.

Statistical justification of the number of inclusions

The study is a superiority trial on the decrease of the FIQR score (improvement of the quality of life) at 6 months between a control group (classic non-specific management in a common "multipathology" group) and an experimental group (specific management in a "fibromyalgia patients" group).
According to Hackshaw et al. (2016), the mean baseline QoL of the ten patients included was 49.4 (13.8) on the FIQR scale. After 6 months of intervention (life coaching including physical activity), the mean level of quality of life was 31.0 (13.2), i.e. a decrease in score of 18.4 points (37% decrease).
Evidence of a 7-point difference between the two intervention groups at M6 will be considered clinically significant.
With a power of 80%, and an alpha risk of 5%, 114 patients will be needed to show this difference. To ensure the necessary power, an additional 10% of patients will be included, for a total of 126 patients.

Expected level of statistical significance

The alpha risk is set at 5%.

Statistical criteria for stopping the research

NA

Method of accounting for missing, unused or invalid data

All missing data and the reason for it will be described in each group.

The FIQR score will be estimated and compared between the 2 groups using a linear model taking into account the repeated nature of the data, so no imputation method will be applied.

Managing changes to the original strategy analysis plan

NA

Selection of persons to be included in the analyses

The main analysis will be performed on the Intent-to-Treat (ITT) population, i.e. on all randomised patients.
A sensitivity analysis will be performed on the Per Protocol (PP) population including randomised patients for whom no major protocol deviations were identified.
A data review meeting will be held to review and define the major criterion or not for each of the deviations.

Randomisation

Randomisation will be carried out in a 1:1 ratio and will be done in blocks.

Randomisation will be carried out in Ennov Clinical by connecting to the website: https://www.dirc-hugo-online.org/csonline/. The connection will be made through a login, a password and a study number, delivered by the data manager of the Research Unit of the La Roche sur Yon Hospital. The following information must be filled in:

-First initial of the name,
-First initial of the first name,
-Month and Year of birth,
Compliance with inclusion and non-inclusion criteria (yes/no),

Randomisation will be carried out by the investigator after confirmation of the possibility of inclusion in the study. The inclusion number will be assigned automatically during randomisation.

An email confirmation will be sent to the person who performed the randomisation and to all persons involved.

The randomisation list will be carried out by the statistician of the Research Unit of the CHD of La Roche sur Yon. An explanatory guide to randomisation will be available online in Ennov Clinical

6. VIGILANCE AND MANAGEMENT OF ADVERSE EVENTS

6.1. DEFINITIONS

Vigilance	It is the monitoring of medicines, medical devices and other health products. It also consists of the prevention of the risk of adverse effects resulting from their use, whether this risk is potential or proven,
Adverse events (AEs)	Any harmful event occurring in a person who is a subject of research involving the human person, whether or not the event is related to the research or the product to which the research relates.
Intensity of Adverse Events (AEs)	It will be scored according to the criteria chosen when the protocol was drafted For any event not noted in the chosen classification, the rating will be as follows: 1 = benign 2 = moderate 3 = severe 4 = life-threatening 5 = death
Adverse effects (AEs)	An adverse event occurring in a person who is a subject of research involving the human subject, where that event is related to the research or the product to which the research relates.
Serious adverse events (SAEs)/Events (SAEs)	Any adverse effect/event that : * results in death, * is life-threatening, * results in temporary or permanent incapacity or disability, * requires or prolongs the patient's hospitalization, * causes a congenital or neonatal anomaly, * is medically important (the list of medically important effects/events is defined by the EMA).

Unexpected adverse events (AEs)	Any adverse reaction whose nature, severity or course is not consistent with the information about the products, procedures and methods used in the research.
New fact	Any new information that may lead to a reassessment of the riskbenefit balance of the research or the investigational product, to changes in the use of the investigational product, in the conduct of the research, or in the documentation of the research, or to the suspension or discontinuation or modification of the research protocol or similar research. For trials involving the first administration or use of a health product in persons without medical conditions: any serious adverse reaction.
Abuse	Intentional, persistent or sporadic excessive use of a drug that is accompanied by harmful physical or psychological reactions.
Overdose	Administration of an amount of drug, given at one time or cumulatively, that is above the maximum recommended dose according to the rules of compliance or use of the product. Clinical judgement should always be applied.
	(actual overdose: due to too much raw material / relative overdose: due to predisposing factors of the patient such as renal insufficiency, hypoalbuminemia...)
Misuse or off-label use	Situation where the product is intentionally used in a way that does not comply with the specifications for use of the product (e.g. different route of administration/posology or indication than listed in the reference document).
Medication error (ME)	Corresponds to any omission or unintentional, proven (or potential) performance of an act during the care process, *in the circuit (from manufacture to administration)* involving a product that may be the cause of a risk or an adverse event for the patient. The risk of error or potential error concerns situations where the error has not occurred, has been intercepted but could have occurred

6.2. LIST OF EXPECTED ARS

Within the framework of this protocol, the expected ARs are :

Concerning physical activity :

ARs related to physical activity are of the following types:

- musculoskeletal problems with more or less diffuse pain (limbs, neck, back, abdomen...), aches, contractures, cramps, musculoskeletal trauma including tendonitis...
- general/metabolic: hunger, malaise, shortness of breath, weight loss, weight gain.

Regarding the usual drug treatments for the disease:

The prescription of treatments is not modified by participation in the study. Given their diversity, it is not possible to propose an exhaustive list of expected effects.

The medicinal management of fibromyalgia and associated symptoms involves various pharmacological classes. The drugs are used within the framework of their MA and the expected AEs are listed in the current SPCs of the specialities concerned.

Medical devices can also be used (TENS, etc.) within the framework of their indications, their AEs are mentioned in the instructions for use.

6.3. MANAGING ADVERSE EVENTS

Collection of EvI/EI

In this minimal risk, minimal burden research, the protocol does not involve any changes to the usual management of patients.

The AEs related to the pathology studied (fibromyalgia), its treatment, the co-pathologies and their respective treatments, are neither to be entered in the vigilance part of the CRF, nor to be notified.

Under the responsibility of the investigator, as in the case of care, the notification of complications and AEs is part of the regulated systems: AEs related to drugs and DMs transmitted to the pharmacovigilance systems, materialovigilance, complications of procedures and examinations integrated into the risk management system of the institutions, etc...
The data concerning fibromyalgia and its evolution are traced in the dedicated part of the CRF.

In the framework of this study, which aims at the interest of a specific 6-month physical activity programme on the quality of life of the patients, only **the complications and AEs of the techniques having a potential impact on the protocol objective** will be collected and notified if a severity criterion exists:
- functional problems following the sessions that prevent the performance/continuation of physical activity
-malfunction of the activity tracking system

All developments and pregnancies that occur during the study will be traced and reported to the sponsor.

Notification of SAEs / EvIG

EvIGs and EIGs are notified to the appropriate vigilance circuits (a copy will be kept in the patient's clinical file).

In the context of this protocol, new developments, special situations, and complications that may impact the study objective are listed in the CRF and will be taken into account in the analyses planned according to the study schedule.

Only new developments and malfunctions in the tracking system should be reported to the promoter without delay after becoming aware of them so that corrective measures can be put in place.

Notification period to the promoter

The investigator is responsible for collecting and reporting to the appropriate monitoring system the various complications presented by patients.
It is the investigator's responsibility to record and report all AEs/SGEs, special situations or developments, as described above, whether expected or not, occurring during the entire study:

- from the date of signature of the randomisation -
  and until the end of the study (i.e. M12)

6.4. MODALITIES AND DURATION OF FOLLOW-UP OF INDIVIDUALS FOLLOWING THE OCCURRENCE OF ADVERSE EVENTS

Any event, especially a serious one, must be followed up until recovery, consolidation or death (closed event).
Every pregnancy should be monitored at least until the birth of the child.

7. ADMINISTRATIVE AND REGULATORY ASPECTS

7.1. RIGHT OF ACCESS TO SOURCE DATA AND DOCUMENTS

The medical data of each patient will be transmitted only to the sponsor or any person duly authorised by the sponsor, and, where appropriate, to the authorised health authorities, under conditions that guarantee their confidentiality.
The sponsor and the regulatory authorities may request direct access to the medical record for verification of the clinical trial procedures and/or data, and within the limits permitted by the laws and regulations.

7.2. DATA PRIVACY

Persons with direct access shall take all necessary precautions to ensure the confidentiality of information relating to the persons who have access, in particular as regards their identity and the results obtained. These

persons, as well as the investigators themselves, are subject to professional secrecy (according to the conditions defined by articles 226-13 and 226-14 of the penal code).
During or after the research, the data collected on the subjects and transmitted by the participants will be made anonymous.
Under no circumstances should the names of the persons concerned or their addresses appear in clear text. Only the first two letters of the subject's name and the first letter of the subject's first name will be recorded, along with a study-specific code number indicating the order of inclusion of subjects.

7.3. COMPUTERISED DATA AND SUBMISSION TO THE CNIL

This study falls within the scope of the "Reference Methodology" (MR-001) in application of the provisions of Article 54 paragraph 5 of Law No. 78-17 of 6 January 1978, as amended, relating to information technology, files and freedoms. This change was approved by decision of 14 August 2016. The CHD Vendée in La Roche sur Yon, the study's promoter, signed a commitment to comply with this "Reference Methodology".
In view of the risk to the rights and freedoms of research participants (use of a new technology), an impact assessment will be carried out.

7.4. MONITORING OF THE TRIAL

Monitoring will be carried out by the Promotion Department of the Research Directorate. A Clinical Research Associate (CRA) will regularly visit each site (investigator and pharmacy) in order to carry out quality control of the data reported in the observation books.

The protocol has been classified according to the estimated level of risk to the patient undergoing the research. It will be monitored as follows:

Risk A: low or negligible foreseeable risk

On-site monitoring visits will be organised after an appointment with the investigator. During these visits, the following will be reviewed

- informed consent
- compliance with the study protocol and the procedures defined therein
- quality of the data collected in the observation book: accuracy, missing data, consistency of data with "source" documents (medical records, appointment books, original laboratory results, etc.) - management of any products.

7.5. INSPECTION / AUDIT

In the context of this study, an inspection or audit may take place. The sponsor and/or the participating centres must be able to give access to the data to the inspectors or auditors.

7.6. ETHICAL CONSIDERATIONS

Patient information

Patients will be fully and fairly informed, in understandable terms, of the objectives and constraints of the study, of their rights to refuse to participate in the study or of the possibility to withdraw at any time.

All of this information is contained in an information and consent form given to the patient. The patient's free, informed and written consent will be obtained by the investigator, or a physician representing the investigator, before final inclusion in the study. A copy of the information and consent form signed by both parties will be given to the patient, and the investigator will retain the original. A copy will be placed at the end of the study in a sealed tamper-proof envelope containing all the consent forms, which will be archived by the sponsor.

Committee for the Protection of Individuals

The sponsor undertakes to submit the study project for prior authorisation by a Personal Protection Committee (CPP). The information communicated concerns, on the one hand, the modalities and nature of the research and, on the other hand, the guarantees provided for the patients participating in this trial.

7.7. INFORMATION TO THE COMPETENT AUTHORITIES

This protocol will be reported to the ANSM.

7.8. AMENDMENTS TO THE PROTOCOL

Requests for substantial changes will be sent by the promoter to the relevant CPP for its opinion in accordance with the law in force and its implementing decrees.

An updated dated version of the amended protocol will be required.
The information and consent form will need to be amended if necessary.

7.9. FINANCING AND INSURANCE

The promoter finances the study and takes out an insurance policy to cover the financial consequences of its civil liability, in accordance with the regulations.

7.10. RULES ON PUBLICATION

Authorship will be in accordance with the International Committee of Medical Journal Editors' rules for publication of research papers submitted to medical journals. The project leader, Thomas Rulleau, will be listed as first author. Yves-Marie Pluchon, or in the case of a change of institution, his replacement at the CETD of the CHD, will appear as the last author. The other authors will appear in the following order: François Etcheverrigaray, second author, Lucie Planche, third author, Margot Miot, fourth author, Aline Liaigre, fifth author, and the principal investigator of the secondary centre, penultimate author.

7.11. ARCHIVING OF SOURCE DATA

The investigator must keep all information about the study for at least 15 years after the end of the study. At the end of the study, the investigator will also receive a copy of the data of each patient in his centre via a CD-ROM sent by the institution responsible for the Research.

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