BMJ Open

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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2018-023742 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 03-May-2018 |
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| Keywords: | PAIN MANAGEMENT, MEDICAL EDUCATION & TRAINING, REHABILITATION MEDICINE, FIBROMYALGIA |
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# Impact of a specific training program on the neuromodulation of pain in fibromyalgia women (DouFiSport): a 24-month, controlled, randomised, double-blinded protocol.

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## *ABSTRACT*

### *INTRODUCTION*

The main symptom of fibromyalgia (FM) is diffuse pain. There is currently no etiological treatment for FM. However, all pain associations and best practice guidelines highly recommend the practice of aerobic physical activity to improve the symptoms of FM subjects. The mechanisms of dysfunctional pain are mostly central (1) and related to stress axis dysfunction (autonomic nervous system and corticotropic axis) (2). The main objective is to assess the effectiveness of a specific training program on endogenous pain control mechanisms in female fibromyalgia patients. Further aims include rebalancing the autonomic neurovegetative system, improving the quality of life and sleep quality and reintegrating patients into society and work.

### *METHODS AND ANALYSIS*

110 FM women (according to the criteria of the ACR 2010), aged 18-65 years and respecting the inclusion criteria will be recruited and randomised in two groups (active or control). The training program consists of three 45-minute sessions per week of supervised, individualised physical activity over two years. Only the intensity of the exercises is different between the two groups (moderate-intensity versus low-intensity).

All outcome measures will be conducted at baseline (T0), after 6 to 9 months of training (T6-9), then after 24 months of training (T24). The primary endpoint is the improvement of pain modulation (activation of diffuse noxious inhibitory control (DNIC)) evaluated by the stimulation test (1). The secondary endpoint will assess pain, anxiety, depression, stress, sleep disorders, pain impact on life quality, heart rate, blood pressure and salivary cortisol.

### *ETHICS AND DISSEMINATION:*

Approved by the Committee for the Protection of Persons West VI. Trial registration NCT02486965.

## Strengths and limitations of this study

► First randomised controlled double-blinded trial to assess the effects of a long-term training program (24 months) on pain control in fibromyalgia.

► To validate a training program acting on the autonomic system and to assess the neurovegetative rebalance on pain control.

► Physical activity intensity will be assessed objectively using a heart rate monitor.

► The dropout rate in patients may be important. These elements were taken into account in sample size.

► Due to the nature of the intervention, the coaching staff cannot be blinded.

*INTRODUCTION:*

Fibromyalgia affects 1.4 to 2.2% of the general population concerning predominately women (more than 80% of subjects). This syndrome is characterised by extensive and diffuse pain, mainly muscular and articular, impairing the functional abilities of the subjects. The symptoms most frequently described by fibromyalgia patients are chronic fatigue, sleep disorders, cognitive disorders and emotional disturbances (3,4). This symptomatology leads to a serious deterioration in quality of life, sometimes with a physical disability leading to social isolation and difficulties in staying in employment (recurrent work stoppages).

The diagnosis is based on the symptoms and their severity as described by the patients (5–8). Currently, there is no etiological treatment for fibromyalgia syndrome. The treatments are therefore only symptomatic.

## Physiopathology of fibromyalgia

The mechanisms of dysfunctional pain, without any identifiable organic lesions, are mostly central (1) and related to dysfunction of the stress axis (autonomic nervous system and corticotropic axis) (9–11).

At rest, fibromyalgia patients showed an increased sympathetic response and decreased parasympathetic tone (12,13). This neurovegetative dystonia is a marker of dysfunction of the stress axis (14).

Malfunctions of the corticotropic axis in fibromyalgia have been described multiple times, also marking the dysfunction of the stress axis. But the form taken by this dysfunction differs according to the different studies (15–19). The variability of salivary cortisol in response to stress reflects that of plasma free cortisol. Salivary cortisol is therefore a method of choice in experimental stress studies (20). Whatever form they take, these dysfunctions compromise the body's adaptation to daily stressful stimuli.

Studies show that this deficit of the stress axis (neurovegetative dystonia and dysfunctional corticotropic axis) is concurrent with fibromyalgia (21) and

associated with alteration of pain control (9–11). Pain control system and stress axis have close anatomical and functional links. Nociceptive, neurovegetative and corticotropic systems interact with the central nervous system. The central neuromediators implicated in the regulation of the stress axis are mostly common with those of the pain neuromodulation (endogenous opioids, norepinephrine, serotonin, etc.).

## Elite athlete's overtraining syndrome: model of stress axis dysfunction

An overtraining elite athlete may be considered as a model of dysfunction of the stress axis associated with neurovegetative dystonia. The physical and psychological effort of training is known to induce stress. High-level athletes could present an overtraining syndrome when adaptation limits of the stress axis are reached. This stress-induced phenomenon corresponds to an imbalance between training quantity and recovery. Overtrained athletes present a deconditioning syndrome close to fibromyalgia symptoms (chronic pain, sleep disorders, neurovegetative dystonia, etc.) (22–26).

## Physical activity and fibromyalgia

Most studies have shown that physical activity is more efficient compared to pharmacological treatments on fibromyalgia symptoms (27,28). Literature reviews and meta-analyses highly support the benefits of physical training in fibromyalgia patients (decreased pain and depression and improvement in overall health and physical abilities) (29)(30). Practice of aerobic exercise in fibromyalgia patients is strongly recommended by The American Pain Society (31), the Association of Medical Scientific Societies in Germany (32), the Canadian Rheumatology Association (5) and the European League Against Rheumatism (EULAR) (33). Physical exercise is the first-line treatment recommended in fibromyalgia. However there is still no consensus on the modalities of these types of training (frequency, duration, and intensity). Currently, the mechanisms underlying those specific training effects have to be defined.

The steady physical activity rebalancing autonomic system is associated with cardiovascular benefits. Fundamental endurance increases parasympathetic tone and decrease sympathetic response (34–37). Thus, strategies to rebalance the autonomic system are the most promising therapies for fibromyalgia (13,36,37).

In this study, we propose to validate a therapeutic alternative that aims to treat fibromyalgia by rebalancing the stress axis. This treatment consists of a specific supervised and individualised training program, over 2 years. This training protocol is individually adjusted in order to rebalance the neurovegetative system (parasympathetic and sympathetic). Central neuroplasticity induced by training should regulate endogenous pain control mechanisms. This specific protocol will be associated with psychotherapeutic approaches. In addition to the training program, multidisciplinary bio-psycho-social cares will be given in the pain centre of the university hospital of Brest (5).

## Objectives

The *main objective* is to assess the effectiveness of a specific training program on endogenous pain controls in fibromyalgia patients. The *secondary objectives* are to rebalance the autonomic nervous system and the corticotropic axis, to improve life and sleep quality and to reintegrate patients into society and work.

*METHODS AND ANALYSIS:*

## Design and setting

This randomised double-blind trial will compare an "active" program to a "control" program in fibromyalgia patients. Patients will be recruited at the pain center of the university hospital of Brest on the basis of general criteria. Patients should follow a re-exercise program for 24 months. The assessments will take place (i) before, (ii) between 6 to 9 months (depending the training level) and (iii) at the end of the training (24 months), in the neurological functional explorations department of the university hospital of Brest (fig.1).

## Patient and public involvement

The specific training program of this study was developed based on the results of a pilot study (39), literature data and experiences of fibromyalgia patients followed in the pain centre of the University Hospital of Brest. These patients reported benefits, constraints, difficulties, and effects on their symptoms of their training program. These information have allowed for adjust the specific training program. Patients are not involved in the recruitment and conduct of the study. During the last assessment visit, patient will be asked for assess the burden of the intervention. Upon request, a report outlining the study findings will be given to study participants.

## Study population

110 fibromyalgia patients will be included. The inclusion criteria are: female subjects; aged of 18 to 65 years; with a diagnosis of fibromyalgia clearly established according to the criteria of the American College of Rheumatology (ACR) 2010; with a body mass index (BMI) between 18.5 and 29.9kg/m$^2$; spontaneous pain intensity higher than 3/10 on a visual analog scale (VAS); pain experienced at least 3 days a week; pain caused by palpation equal to or higher than 4/10 on a VAS.

The non-inclusion criteria are: patients with a systemic disease (treated or not) generating pain of the musculoskeletal system; presenting pain other than fibromyalgia; presenting a contraindication to physical activity; having any active pathology; having modified in the last 2 months any pharmacological treatment; having a psychiatric diagnosis; taking drugs that affect cortisol secretion (decrease or increase); non-cooperating.

## Sample size

Population size is based on an expected difference of 20 points (stimulation test) (1) between the two groups, for a quantitative primary endpoint (delta VAS) of standard deviation equal to 35, and a power set at 80%. Therefore a minimum of

48 subjects per group is required for assessment. In order to take into account loss to follow-up, the sample of 110 subjects, 55 per group will be recruited.

## Randomisation

Patients will be randomised at the end of the first stimulation test, which is just before the initiation of the training. Randomisation will be conducted by the Center of Clinical Investigation (CIC) at the hospital university of Brest (electronic randomisation via Capture System). The test is stratified by age and BMI. The cut off is set at 50 years for age and 25kg/m$^2$ for BMI (two strata [18-25] and ]25-30 [).

## Intervention: Training program

The training program is planned over two years (24 months) for both groups (active/control). A minimum of 4 to 6 weeks is needed to observe a decrease in symptoms (39). This two-year duration is the minimum average training time (depending on the individual progress of each patient), necessary to regain central neuroplasticity sufficient to put back into operation diffuse noxious inhibitory controls (DNIC) and neurovegetative system (39).

The frequency, intensity, and duration of these training sessions are based upon the results of a preliminary study. Pain was significantly reduced and symptoms, such as quality of life, sleep quality, anxiety, were also highly improved in subjects undergoing this specific training after 5 years (39).

The American Pain Society recommends an intensity of 60 to 70% of the age-adjusted maximum heart rate (HRmax). At the early stage, the intensity and duration of the training sessions will be adapted to the physical condition of each subject. The intensity exercise will be 3 on the Borg CR10 scale (38). In order to promote adherence of our patients and to limit pain exacerbation, exercise intensity will start very low and then gradually increase to reach the neurovegetative goal (31)(40).

The ideal frequency is 3 training sessions per week during 45 minutes each (38,39).

**Active training group:**

*The first 6 to 9 months*: fundamental endurance training.

Subjects will perform 3 sessions per week of 45 minutes of fundamental endurance (moderate-intensity continuous training MICT: 60% HRmax), including 2 sessions supervised by a physiotherapist and 1 independent session.

*From 6-9 months (according to the rhythm, abilities, and limits) to 24 months*: Patients will begin the second stage of training: 3 sessions per week of 45 minutes each (moderate-intensity continuous training MICT (60% HRmax) and high-intensity interval training HIIT) with 1 supervised session and 2 independents sessions. When the patient reaches the initial HR goal, "fundamental endurance" will be associated with "interval training" at a high frequency intensity. HIIT will consist of 5 stages of 1 to 4 minutes at 85-90% HRmax (80-85% $V\dot{O}_2max$), interspersed by 1 to 4 minutes of active recovery at 60-75% HRmax (50-70% $V\dot{O}_2max$). Intensity will be assessed objectively using a heart rate monitor (FT2, Polar). At baseline, Tanaka's age-based prediction equation (208-0.7×age) will calculate HRmax. After *6-9 months of training, a* maximal-effort graded exercise test will determine HRmax and $V\dot{O}_2max$ for each patient.

**Control group:**

Patients will perform the same infra active training (low-intensity continuous training: LICT <50% HRmax) over two years. Supervision, monitoring, and frequency of sessions (3 x 45 minutes per week) in both groups will be equivalent.

**Training follow-up (for both groups):**

Patients will be contacted to record progress, difficulties and if necessary, to encourage them to adhere to their program. These calls will improve the compliance and will limit patients lost to follow-up.

Patients will perform a 6-minute walk test (6MWT) every 6 months (with physiotherapist). If a patient cannot achieve the specific training requested after 9 months of study, the patient will not complete the second phase of training.

Nevertheless, she will carry out all assessment visits. The main analysis will be performed on an intent-to-treat basis.

## Clinical Data, Measurements and Assessments

### Sociodemographic and clinical data

At baseline, data on age, sex, marital status, education level, and occupation will be collected. Height and weight will be recorded. Medical background and pain characteristics will be noted. All current drug and non-drug therapies (including tried and stopped) will also be collected, as well as their effectiveness on pain.

### Questionnaires and pain assessments

Measurements and questionnaires will be carried out (i) at baseline, (ii) between 6 to 9 months, and (iii) at the end of the 24 months of training.

- The **assessment of pain** will be performed by a simple verbal scale and using a visual analog scale (VAS). The Saint Antoine Pain Questionnaire (QDSA) will also assess pain. A **pain quantitative assessment** will be performed with a pressure algometer (pressure pain threshold: PPT).
- The Hospital Anxiety Depression Scale (HADS) will assess the **patient anxiodepressive state** (41).
- The Fibromyalgia Impact Questionnaire (FIQ) will assess **the impact of fibromyalgia on daily life** (42).
- The Pittsburgh Sleep Quality Index (PSQI) will assess **sleep quality and quantity** (43,44).
- The International Physical Activity Questionnaire (IPAQ) will record the **level of physical activity and the sedentary lifestyle**. The French long telephone questionnaire will be used (45).
- The Perceived Stress Scale (PSS) will assess **the antecedents of perceived stress** (46).

### Stimulation test

In order to assess endogenous pain mechanisms, such as diffuse noxious inhibitory controls (DNIC), temporal summation (TS) and perception of pain, we will use an experimental method developed by Tousignant-Laflamme and Marchand (2008). According to this well-characterised paradigm, we will induce in single session two tonic heat pain stimulations separated by a cold pressor test (1,47–49).

- Thermode test or temporal summation test **(P1):** a tonic heat pain will be administered for 2 minutes on the patient's right arm, using a thermode (CE marking n°226). The starting temperature is 32°C (skin temperature under normal conditions in temperate room (20-22°C)) (50) and will quickly reach a fixed value. The experimental temperature will be individually determined to induce 50/100 on a VAS and will remain constant during the test period (2 minutes). Throughout this entire period, the patient will evaluate their pain intensity using a Computerised Visual Analog Scale (CoVAS).

- Cold pressor test **(P2):** to elicit a prolonged pain sensation in order to trigger diffuse noxious inhibitory control (DNIC) (51), the patient's right arm will be immersed for 2 minutes in a cold water bath maintained at 12°C. The patient will continuously evaluate their pain intensity using a CoVAS.

Following this cold pressor test, the thermode test will be again performed **(P3).** Pain difference between the two (P3/P1) tonic heat pain stimulations will measure DNIC activation and represents pain modulation.

**Measurement of salivary cortisol and salivary flow**

Corticotropic axis will be assessed using measurement of salivary cortisol. Cortisol release is pulsatile (10 to 20 peaks per day) and follows a nycthemeral cycle. Maximum cortisol level is reached in the early morning. In the morning of each consultation (at baseline, in the middle and at the end of training), patients will collect salivary sample (i) for 2 minutes, when they wake up and (ii) for 2 minutes, 30 minutes later. The salivary cortisol level is measured in nmol/l. The flow rate is calculated in $ml.min^{-1}$. Samples will be frozen at -20°C. As salivary cortisol is stable, samples can be stored for many weeks in the freezer (52). After

completion of all assessment sessions, sample analysis will be completed. To avoid inter-laboratory variation, the same laboratory will assay the samples.

**Recording of Blood Pressure (BP) and Heart Rate (HR)**

After 10 minutes at rest, lying down, BP and HR will be recorded. Then, BP and HR will be measured when the patient stands up and once per minute during 4 minutes when the patient remains standing.

## Blinding strategy

Patients will not be informed of their group (active/control). The investigators will not know the patient's group. Due to the nature of the intervention (physical activity protocol), the coaching staff will not be blinded.

## Statistical analysis

*Primary endpoint analysis*: The VAS improvements (stimulation test) obtained in the both groups will be compared using the Student's test. If the required normality assumption is not sustainable, a nonparametric Wilcoxon test will be used. An alpha risk of 0.05 will be set as the limit of statistical significance. The main analysis will be performed on an intent-to-treat basis. A complementary analysis using a linear model with adjustment for age and BMI factors will be completed.

*The secondary endpoints* (quantitative: salivary cortisol, blood pressure, PPT quantified by pain threshold pressure, questionnaires assessment) will be analysed in a similar way by comparing the improvements obtained between both groups.

## Methodological limitations

The methodology of this protocol is consistent with the recommendations of the Standard Protocol Items for Randomised Trials (SPIRIT). However, because of the nature of the intervention, the coaching staff cannot be blinded. Patients and investigators will be blinded.

According to the study duration (2 years), the potential participant dropout and potential patients lost to follow-up may be important. These elements were taken into account in sample size. To limit dropout, patients will be called to encourage them and to discuss any difficulties. In second stage of training and to limit a possible long-term monotonous effect, physical activity type could be diversified in both groups. The training session will be adapted in the active group (MICT will be associated with HIIT) to reduce sympathetic hyperactivity. In order to improve compliance and long-term achievement of training, the patient may choose the physical activity type performed without supervision.

## *ETHICS AND DISSEMINATION*

### Ethics approval and consent to participate

The Committee for the Protection of Persons West VI approved this study. Patients will be informed of the objectives, constraints, risks and benefits of the study. To be included, patients will sign informed written consent. Data will be collected anonymously. The investigators will take all necessary precautions to ensure the confidentiality of the information in particular with regard to patient identity.

### Dissemination plan

The results of this study will be published in specialised scientific journals. These results will also be presented in pain and/or physical activity congresses. In addition, a doctoral thesis will be carried out on this project.

## TRIAL REGISTRATION NUMBER: NCT02486965

### Acknowledgements

The authors thank Julie Lelièvre, Marie Le Bellego, Youenn-Thor Bodéré for designing and implementing this protocol, and Phillipa Perrot for English language revision.

### Contributors

CB initiated the idea for the project. CB and ALFB developed the study design. MC, GL, BQ, AK, AW, SM, MAGM, FC, FR, LM and AD provided advice for the study design. GL and CB were responsible for supervision of project. CB will conduct

the recruitment. AK will conduct the training programme. CB, ALFB and MC will conduct the outcomes assessments and will contribute to the analysis and interpretation of the data. Both authors will contribute to the analyses and interpretation of the data. ALFB, CB and MC wrote early drafts of the manuscript. All authors approved the final version of this protocol.

**Funding Statement**
This work is supported by the French Ministry of Health (Programme Hospitalier de Recherche Clinique Interrégional 2014, project no 2014-A00743-44) PHRCi 13-100

**Competing Interests**
None declared.

**Ethics approval**
Comité de Protection des Personnes Grand Ouest VI.

**Provenance and peer review**
Not commissioned; externally peer reviewed.

## References

1. Tousignant-Laflamme Y, Pagé S, Goffaux P, Marchand S. An experimental model to measure excitatory and inhibitory pain mechanisms in humans. Brain Res. 16 sept 2008;1230:73□9.
2. Woda A, L'heveder G, Ouchchane L, Bodéré C. Effect of experimental stress in 2 different pain conditions affecting the facial muscles. J Pain Off J Am Pain Soc. mai 2013;14(5):455□66.
3. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. févr 1990;33(2):160□72.
4. Cánovas R, León I, Roldán MD, Astur R, Cimadevilla JM. Virtual reality tasks disclose spatial memory alterations in fibromyalgia. Rheumatol Oxf Engl. oct 2009;48(10):1273□8.
5. Fitzcharles M, Shir Y, Ablin JN, Buskila D, Amital H, Henningsen P, et al. Classification and clinical diagnosis of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines. Evid-Based Complement Altern Med ECAM. 2013;2013:528952.
6. Egloff N, von Känel R, Müller V, Egle UT, Kokinogenis G, Lederbogen S, et al. Implications of proposed fibromyalgia criteria across other functional pain syndromes. Scand J Rheumatol. 2015;44(5):416□24.
7. Moyano S, Kilstein JG, Alegre de Miguel C. New diagnostic criteria for fibromyalgia: Here to stay? Reumatol Clin. août 2015;11(4):210□4.
8. Wolfe F, Fitzcharles M-A, Goldenberg DL, Häuser W, Katz RL, Mease PJ, et al. Comparison of Physician-Based and Patient-Based Criteria for the Diagnosis of Fibromyalgia. Arthritis Care Res. mai 2016;68(5):652□9.
9. Bodéré C, Woda A. La douleur orofaciale idiopathique: une douleur fonctionnelle. Douleur Analgésie. 21 juin 2009;22(2):89□95.
10. Woda A, Dao T, Gremeau-Richard C. Steroid dysregulation and stomatodynia (burning mouth syndrome). J Orofac Pain. 2009;23(3):202□10.
11. Woda A, L'heveder G, Ouchchane L, Bodéré C. Effect of experimental stress in 2 different pain conditions affecting the facial muscles. J Pain Off J Am Pain Soc. mai 2013;14(5):455□66.
12. Cohen H, Neumann L, Shore M, Amir M, Cassuto Y, Buskila D. Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability. Semin Arthritis Rheum. févr 2000;29(4):217□27.
13. da Cunha Ribeiro RP, Roschel H, Artioli GG, Dassouki T, Perandini LA, Calich AL, et al. Cardiac autonomic impairment and chronotropic incompetence in fibromyalgia. Arthritis Res Ther. 2011;13(6):R190.
14. Martinez-Lavin M. Fibromyalgia as a sympathetically maintained pain syndrome. Curr Pain Headache Rep. oct 2004;8(5):385□9.
15. Kadetoff D, Kosek E. Evidence of reduced sympatho-adrenal and hypothalamic-pituitary activity during static muscular work in patients with fibromyalgia. J Rehabil Med. sept 2010;42(8):765□72.
16. Tak LM, Cleare AJ, Ormel J, Manoharan A, Kok IC, Wessely S, et al. Meta-analysis and meta-regression of hypothalamic-pituitary-adrenal axis activity in functional somatic disorders. Biol Psychol. mai 2011;87(2):183□94.
17. Riva R, Mork PJ, Westgaard RH, Lundberg U. Comparison of the cortisol

awakening response in women with shoulder and neck pain and women with fibromyalgia. Psychoneuroendocrinology. févr 2012;37(2):299□306.
18. Geiss A, Rohleder N, Anton F. Evidence for an association between an enhanced reactivity of interleukin-6 levels and reduced glucocorticoid sensitivity in patients with fibromyalgia. Psychoneuroendocrinology. mai 2012;37(5):671□84.
19. Bote ME, García JJ, Hinchado MD, Ortega E. Inflammatory/stress feedback dysregulation in women with fibromyalgia. Neuroimmunomodulation. 2012;19(6):343□51.
20. Hellhammer DH, Wüst S, Kudielka BM. Salivary cortisol as a biomarker in stress research. Psychoneuroendocrinology. févr 2009;34(2):163□71.
21. Clauw D, Ablin J. The relationship between « stress » and pain: lessons learned from fibromyalgia and related conditions. In: Current topics in pain. Castro-Lopes editor. XIIth World Congress on Pain. Seattle: IASP press; 2009. p. p.245-270.
22. McKenzie DC. Markers of excessive exercise. Can J Appl Physiol Rev Can Physiol Appl. févr 1999;24(1):66□73.
23. MacKinnon LT. Special feature for the Olympics: effects of exercise on the immune system: overtraining effects on immunity and performance in athletes. Immunol Cell Biol. oct 2000;78(5):502□9.
24. Iellamo F, Pigozzi F, Parisi A, Di Salvo V, Vago T, Norbiato G, et al. The stress of competition dissociates neural and cortisol homeostasis in elite athletes. J Sports Med Phys Fitness. déc 2003;43(4):539□45.
25. Baumert M, Brechtel L, Lock J, Hermsdorf M, Wolff R, Baier V, et al. Heart rate variability, blood pressure variability, and baroreflex sensitivity in overtrained athletes. Clin J Sport Med Off J Can Acad Sport Med. sept 2006;16(5):412□7.
26. Kajaia T, Maskhulia L, Chelidze K, Akhalkatsi V, Kakhabrishvili Z. The effects of non-functional overreaching and overtraining on autonomic nervous system function in highly trained athletes. Georgian Med News. mars 2017;(264):97□103.
27. Fontenele JB, Felix FHC. Exercise for fibromyalgia: evidence for an integrated modulation of autonomic and nociception neural regulation. Rheumatol Int. déc 2012;32(12):4075□6.
28. Rossy LA, Buckelew SP, Dorr N, Hagglund KJ, Thayer JF, McIntosh MJ, et al. A meta-analysis of fibromyalgia treatment interventions. Ann Behav Med Publ Soc Behav Med. 1999;21(2):180□91.
29. Busch AJ, Webber SC, Brachaniec M, Bidonde J, Bello-Haas VD, Danyliw AD, et al. Exercise therapy for fibromyalgia. Curr Pain Headache Rep. oct 2011;15(5):358□67.
30. Woda A, L'heveder G, Ouchchane L, Bodéré C. Effect of experimental stress in 2 different pain conditions affecting the facial muscles. J Pain Off J Am Pain Soc. mai 2013;14(5):455□66.
31. Society AP, éditeur. Guideline for the Management of Fibromyalgia Syndrome Pain in Adults and Children. American Pain Society; 2005. 109 p.
32. Häuser W, Arnold B, Eich W, Felde E, Flügge C, Henningsen P, et al. Management of fibromyalgia syndrome – an interdisciplinary evidence-based guideline. GMS Ger Med Sci. 2008;6:Doc14.
33. Macfarlane GJ, Kronisch C, Atzeni F, Häuser W, Choy EH, Amris K, et al.

EULAR recommendations for management of fibromyalgia. Ann Rheum Dis. déc 2017;76(12):e54.

34. Melanson EL, Freedson PS. The effect of endurance training on resting heart rate variability in sedentary adult males. Eur J Appl Physiol. sept 2001;85(5):442□9.

35. Reland S, Ville NS, Wong S, Gauvrit H, Kervio G, Carré F. Exercise heart rate variability of older women in relation to level of physical activity. J Gerontol A Biol Sci Med Sci. juill 2003;58(7):585□91.

36. de Abreu SB, Lenhard A, Mehanna A, de Souza HCD, Correa FM de A, Hasser EM, et al. Role of paraventricular nucleus in exercise training-induced autonomic modulation in conscious rats. Auton Neurosci Basic Clin. 15 juin 2009;148(1□2):28□35.

37. Martins-Pinge MC. Cardiovascular and autonomic modulation by the central nervous system after aerobic exercise training. Braz J Med Biol Res Rev Bras Pesqui Médicas E Biológicas Soc Bras Biofísica Al. sept 2011;44(9):848□54.

38. Häuser W, Klose P, Langhorst J, Moradi B, Steinbach M, Schiltenwolf M, et al. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials. Arthritis Res Ther. 2010;12(3):R79.

39. Bodéré C, Bodéré YT, Quinio B, Woda A, Misery L. Specific training program for the treatment of fibromyalgia: a prospective controlled study. In: 14th world congress on pain - TF505. Milan, Italy: IASP; 2012.

40. Lannersten L, Kosek E. Dysfunction of endogenous pain inhibition during exercise with painful muscles in patients with shoulder myalgia and fibromyalgia. Pain. oct 2010;151(1):77□86.

41. Krag NJ, Nørregaard J, Larsen JK, Danneskiold-Samsøe B. A blinded, controlled evaluation of anxiety and depressive symptoms in patients with fibromyalgia, as measured by standardized psychometric interview scales. Acta Psychiatr Scand. juin 1994;89(6):370□5.

42. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol. mai 1991;18(5):728□33.

43. Osorio CD, Gallinaro AL, Lorenzi-Filho G, Lage LV. Sleep quality in patients with fibromyalgia using the Pittsburgh Sleep Quality Index. J Rheumatol. sept 2006;33(9):1863□5.

44. Omachi TA. Measures of sleep in rheumatologic diseases: Epworth Sleepiness Scale (ESS), Functional Outcome of Sleep Questionnaire (FOSQ), Insomnia Severity Index (ISI), and Pittsburgh Sleep Quality Index (PSQI). Arthritis Care Res. nov 2011;63 Suppl 11:S287-296.

45. Crinière L, Lhommet C, Caille A, Giraudeau B, Lecomte P, Couet C, et al. Reproducibility and validity of the French version of the long international physical activity questionnaire in patients with type 2 diabetes. J Phys Act Health. août 2011;8(6):858□65.

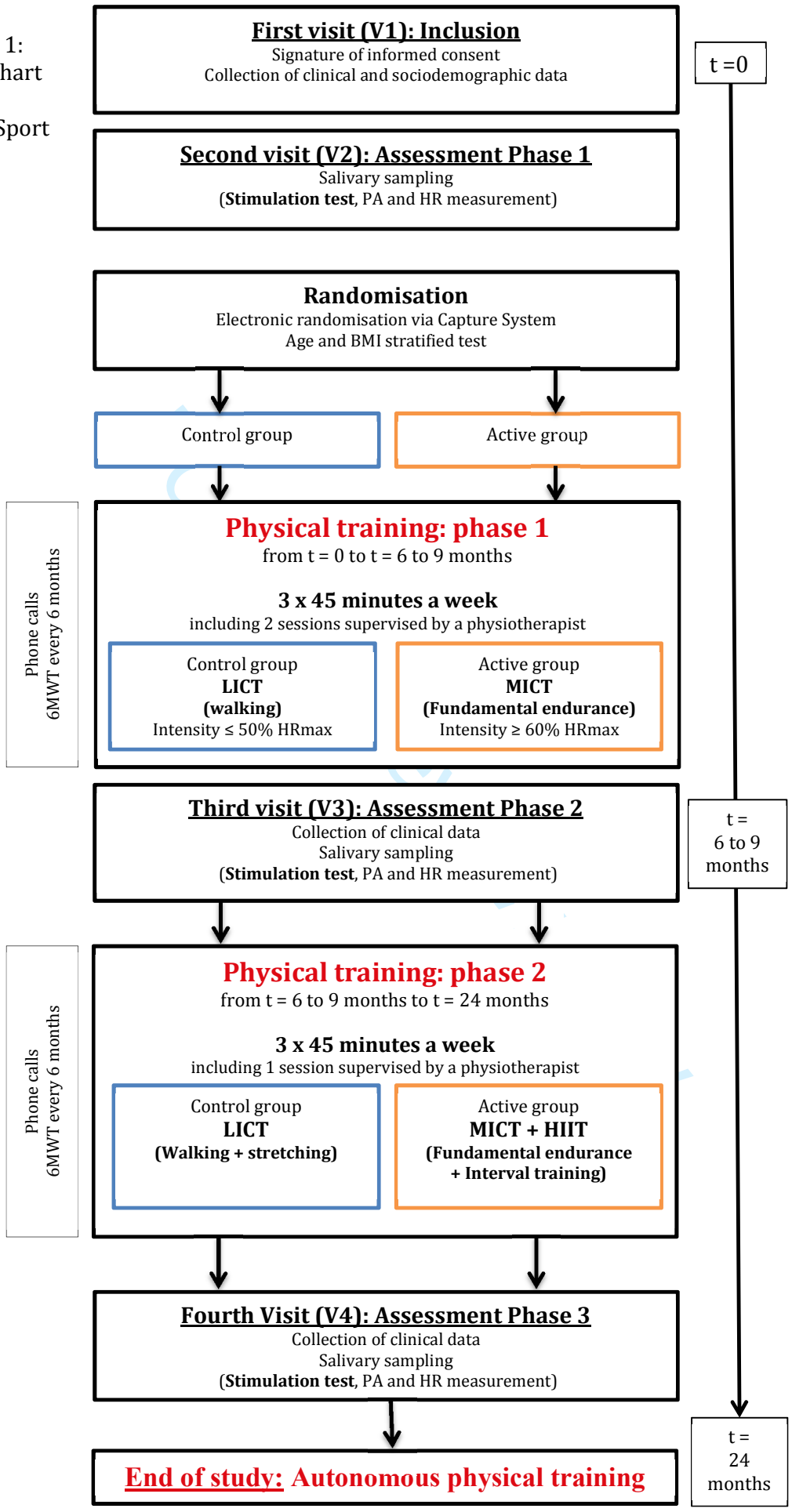
46. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. déc 1983;24(4):385□96.

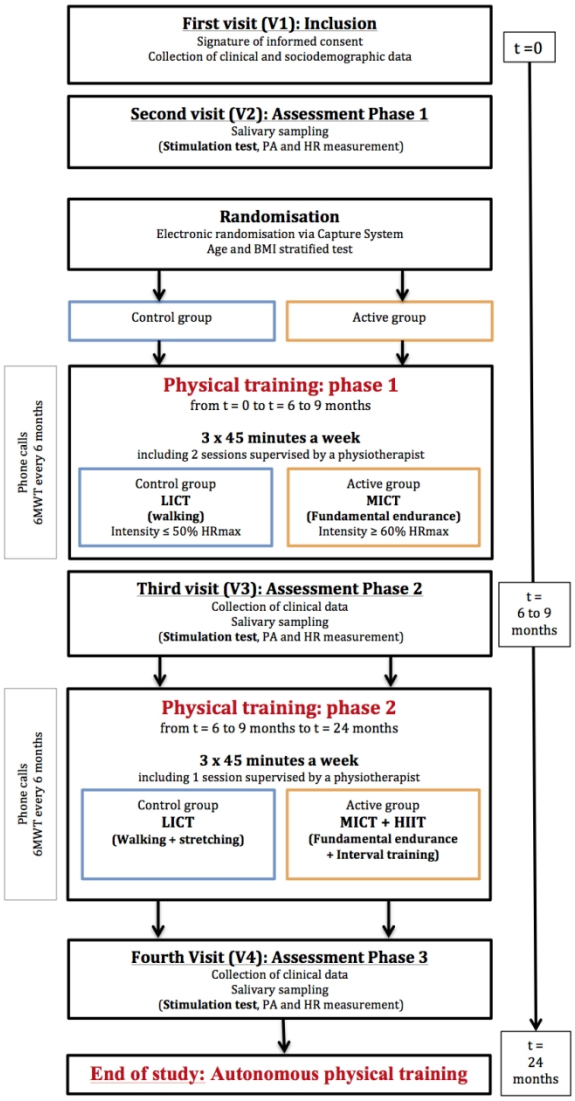
47. Marchand S, Arsenault P. Spatial summation for pain perception: interaction of inhibitory and excitatory mechanisms. Pain. févr 2002;95(3):201□6.

48. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in

fibromyalgia is related to a deficit of endogenous pain inhibition. Pain. mars 2005;114(1□2):295□302.
49. Granot M, Granovsky Y, Sprecher E, Nir R-R, Yarnitsky D. Contact heat-evoked temporal summation: tonic versus repetitive-phasic stimulation. Pain. juin 2006;122(3):295□305.
50. Barrett KE, Barman SM, Boitano S, Brooks H. Ganong's Review of Medical Physiology, 24th Edition. 24 edition. New York: McGraw-Hill Education / Medical; 2012. 768 p.
51. Potvin S, Paul-Savoie E, Morin M, Bourgault P, Marchand S. Temporal summation of pain is not amplified in a large proportion of fibromyalgia patients. Pain Res Treat. 2012;2012:938595.
52. Kirschbaum C, Hellhammer DH. Salivary cortisol in psychoneuroendocrine research: recent developments and applications. Psychoneuroendocrinology. 1994;19(4):313□33.

Figure 1: Flow chart of DouFiSport






Flow chart of DouFiSport

209x296mm (150 x 150 DPI)

# NOTICE D'INFORMATION ET FORMULAIRE DE CONSENTEMENT

## IMPACT D'UN PROGRAMME D'ENTRAINEMENT SPECIFIQUE SUR LA NEUROMODULATION DES DOULEURS CHEZ LES SUJETS FIBROMYALGIQUES

**N° IDRCB:** 2014-A00743-44

**Promoteur :** CHRU de Brest – 2 Avenue Foch, 29609 Brest cedex

**Investigateur coordonnateur**

**Docteur L'heveder Gildas,**
MD, neurologue, MSc
Chef du pôle Neurolocomoteur, Gériatrique et Infectiologique
EFN, Hôpital La Cavale Blanche, CHRU Brest
29609 Brest Cedex

Madame,

Nous vous invitons à participer à une étude clinique intitulée *Impact d'un programme d'entraînement spécifique sur la neuromodulation des douleurs chez les sujets fibromyalgiques (DouFiSport).* Le CHRU de Brest est le promoteur de cette étude, il en est responsable et en assure l'organisation.

Avant d'accepter de participer à ce projet de recherche, veuillez prendre le temps de lire, de comprendre et de considérer attentivement les renseignements qui suivent. Ce document vous explique le but de ce projet de recherche, ses procédures, avantages, risques et inconvénients. Nous vous invitons à poser toutes les questions que vous jugerez utiles au médecin qui vous présente ce document. Votre décision de participer ou non à cette étude n'affectera en rien la qualité des soins qui vous sont offerts actuellement ou à l'avenir. Si vous décidez de participer à cette recherche, vous devrez signer un formulaire de consentement en fin de ce document. Cette signature confirmera que vous êtes d'accord de participer à cette étude.

### 1- CONTEXTE CLINIQUE

La fibromyalgie touche aujourd'hui 1,4 à 2,2 % de la population générale. Le principal symptôme est la présence de douleurs diffuses souvent musculaires et articulaires. Nous savons aujourd'hui qu'il existe un dysfonctionnement des contrôles de la douleur chez le sujet fibromyalgique. Nous allons évaluer la neuromodulation de la douleur c'est-à-dire la modification de votre perception de la douleur par l'adaptation de votre système nerveux. Notre hypothèse est qu'un programme d'entrainement spécifique permettrait de rééquilibrer les contrôles de la douleur.

De plus, plusieurs études ont mis en évidence que l'activité physique avait des effets plus importants sur les symptômes de la fibromyalgie que la plupart des traitements pharmacologiques. La société américaine de la douleur (2005), l'association des sociétés médicales scientifiques en Allemagne (2008) et la société canadienne de rhumatologie (2012), recommandent, avec le plus haut grade, la pratique des exercices aérobies chez les patients souffrants de douleurs diffuses.

A ce jour, les thérapeutiques traditionnellement proposées ne permettent pas de traiter les syndromes douloureux diffus, mais permettent simplement une amélioration temporaire des symptômes.

## 2- OBJECTIF

Le but de cette étude est d'obtenir grâce à un programme d'entraînement spécifique, une réduction (voire la suppression) des douleurs chez les patients souffrants de douleurs diffuses. L'objectif, à terme, serait de proposer une politique de santé publique qui serait systématiquement proposée aux patients en sus des prises en charge globales afin de soigner la fibromyalgie. Il s'agit d'un essai randomisé en simple aveugle (vous ne connaîtrez pas le groupe auquel vous appartiendrez), comparant un programme d'entrainement actif à un programme contrôle.

Vous êtes une femme et vous souffrez de douleurs diffuses. Vous avez entre 18 et 65 ans, et possédez un certificat d'aptitude au sport, nous vous proposons de participer à l'étude.

## 3- DEROULEMENT DE L'ETUDE

Cette étude se déroule dans le centre d'étude et de traitement de la douleur (CETD) de Brest. Au total 110 femmes souffrant de douleurs diffuses y participeront.

Les participantes seront réparties au hasard dans 2 groupes :

- groupe « entraînement »
- groupe « contrôle »

Les patientes ne seront pas informées du groupe auquel elles appartiennent.

Le groupe contrôle est un programme d'entrainement encadré par des kinésithérapeutes et des professeurs en Activité Physique Adaptée, identique au programme actif dans son suivi, mais dont l'intensité des séances est plus faible.

Le programme d'entraînement est prévu sur deux ans. La fréquence, la durée, le suivi et l'encadrement des séances sont identiques pour les 2 groupes. Seule l'intensité des exercices demandés sera modifiée entre le groupe « entraînement » et le groupe « contrôle ».

Votre participation consistera à suivre un programme d'entraînement spécifique, encadré et individualisé pendant 2 ans et à vous présenter à 4 visites. Les visites sont prévues **au service des explorations fonctionnelles (adresse)** ……

**L'entraînement :**
Le programme d'entraînement consiste en **3 séances de 45 minutes d'activité physique par semaine durant 2 ans.** L'intensité des exercices est initialement très faible et sera progressivement augmentée en fonction de vos capacités et de votre tolérance à l'effort.

Durant les 6 à 9 premiers mois, il vous sera demandé de réaliser chaque semaine, deux séances d'entraînement individuelles, encadrées par un kinésithérapeute à son cabinet, et une séance en autonomie à domicile, en extérieur ou en club de sport. Le kinésithérapeute est un kinésithérapeute libéral, spécialisé en réentraînement à l'effort et spécifiquement formé à l'étude par l'équipe investigatrice. Il encadrera vos gestes sportifs, vous donnera les conseils adaptés à votre posture et lors des étirements. Les coordonnées du kinésithérapeute et les horaires de vos séances d'entraînement vous seront transmis lors des visites d'évaluation.
Une montre cardiofréquencemètre vous sera donnée afin que vous puissiez mesurer vous-même, l'intensité de votre effort.

Après cette période de 6 à 9 mois, vous réaliserez un test d'effort maximal afin d'évaluer votre capacité physique et d'adapter avec plus de précision vos séances d'entraînement. Ce test aura lieu……
……
Adresse du service (CHRU de Brest) et sera réalisé par un cardiologue.

Les mois suivants et jusqu'à la fin de l'étude (2 ans), il vous sera demandé de réaliser une séance d'entraînement en petit groupe (5 à 6 personnes), encadré par un professeur en Activité Physique Adaptée (APA) spécifiquement formé, et deux séances en autonomie à domicile, en extérieur ou en club de sport. Cet entraînement aura lieu dans une salle de sport spécialisée dans le réentraînement à l'effort. Votre professeur en APA sera spécifiquement formé

par l'équipe investigatrice. Il encadrera vos gestes sportifs, vous donnera les conseils adaptés à votre posture et lors des étirements.

Pour le suivi de votre entraînement, vous recevrez un appel téléphonique chaque semaine durant les 3 premiers mois, puis un appel téléphonique tous les 15 jours durant les mois suivants et jusqu'à la fin de l'étude. Cet appel permettra de suivre votre entraînement, et si nécessaire de vous motiver.
Pour le suivi de votre progression un test de marche de 6 minutes (TM6) sera réalisé par le kinésithérapeute puis par le professeur en APA tous les 6 mois. Il vous sera simplement demandé de marcher la distance la plus grande durant 6 minutes.

Vous recevrez en sus du programme d'entraînement, une prise en charge multidisciplinaire habituelle, biologique (traitements médicamenteux inchangés), un suivi psychologique et une prise en charge par une assistante sociale au besoin, au centre d'étude et de traitement de la douleur (CETD) dans lequel vous êtes suivi.

**Les Visites :**

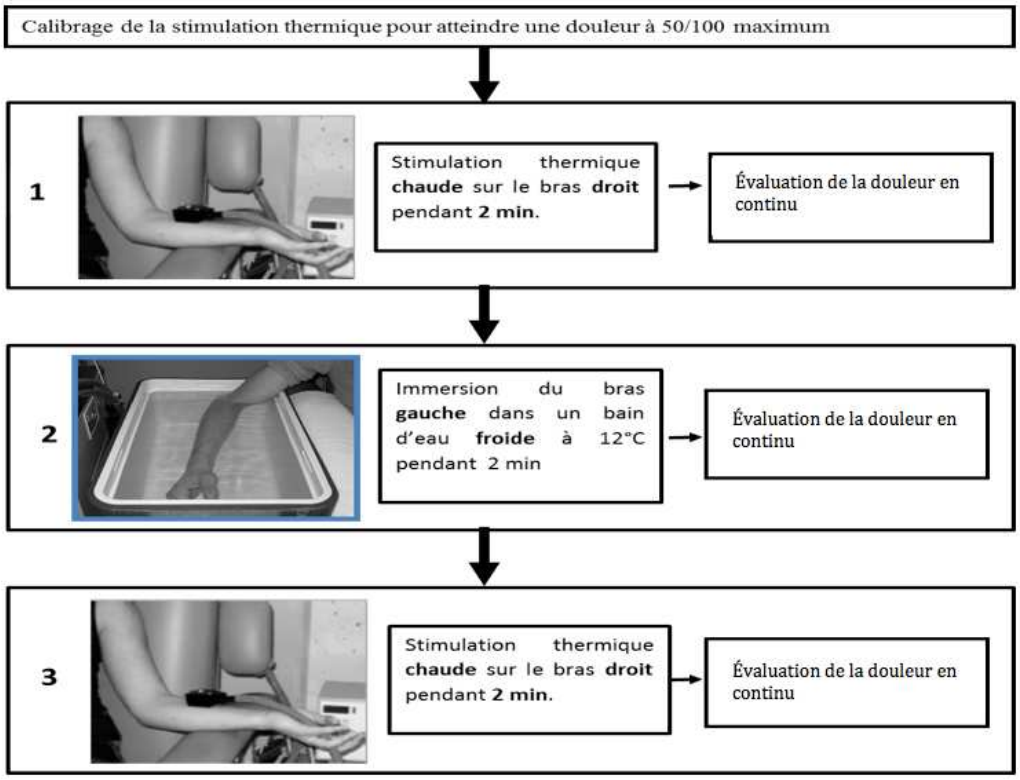
- Première visite (durée approximative 1 heure) :
Cette visite consistera en un entretien d'une heure environ au cours duquel nous recueillerons vos données démographiques (âge, niveau d'éducation, profession). Vous compléterez 5 questionnaires (QDSA, HADS, FIQ, IQSP, PSS) portant sur votre douleur et votre sensibilité, l'impact de la fibromyalgie sur vous, votre niveau d'anxiété (absent, faible, élevé), votre stress et la qualité de votre sommeil, ainsi que 2 échelles d'évaluation de la douleur (EVA et EVS). Nous compléterons ensemble un questionnaire portant sur vos activités physiques des 7 derniers jours (IPAQ) et mesurerons votre seuil douloureux à la pression (PPT) à l'aide d'un algomètre à pression. L'algomètre applique une pression croissante sur un point gâchette (Les points gâchettes - "trigger points" sont des points à partir desquels la douleur se déclenche lors du mouvement ou de la palpation). La pression est arrêtée dès l'instant où vous ressentirez une douleur.

A l'issue de cette visite, il vous sera remis un kit salivaire afin de mesurer le taux de cortisol (hormone qui joue un rôle de régulation de l'organisme face au stress) et le débit salivaire. Vous réaliserez ce test salivaire le matin de la visite suivante. Cette seconde visite sera programmée +/- 7 jours après la première visite.

- Deuxième visite (durée approximative 2 heures) :
Le matin de cette 2ème visite, vous réaliserez vous-même à votre domicile, deux prélèvements salivaires à l'aide du kit remis lors de la visite précédente. Il vous faudra cracher dans le kit à votre réveil pendant 2 minutes, puis 30 minutes après votre lever pendant 2 minutes également. Ces prélèvements salivaires vont permettre de mesurer votre taux de cortisol salivaire et le débit salivaire.
Avant de commencer l'entraînement au CHU, nous procéderons au test d'évaluation de la douleur de deux heures environ. Ce test consiste à placer sur votre avant bras droit une sonde thermique nommée thermode (cf. figure ci-dessous), qui diffusera une chaleur chaude pendant 2 minutes. Cette chaleur aura été déterminée au préalable pour qu'elle atteigne le seuil d'une douleur modérée (inférieure ou égale à 5 sur une échelle comprise entre 0 et 10). Nous évaluerons l'intensité de votre douleur en continu à l'aide d'une échelle d'évaluation électronique de la douleur EVA. Puis, nous plongerons votre avant bras gauche pendant 2 minutes dans un bain d'eau froide à 12°C. Nous évaluerons de nouveau l'intensité de votre douleur en continu. Enfin, nous évaluerons à nouveau pendant 2 minutes votre douleur à la chaleur par la sonde thermique sur votre bras droit. Avant le test de la thermode, la pression artérielle et la fréquence cardiaque seront enregistrés.

Avant votre retour à votre domicile, nous vous proposerons une dernière entrevue de 10 minutes, selon vos attentes, afin d'échanger sur l'étude, les ressentis et vos questionnements. Vous retournerez à votre domicile dès que vous le souhaiterez.
Les coordonnées de votre kinésithérapeute, ainsi que les horaires de vos séances d'entraînement vous seront transmises.

Des kits de prélèvement salivaire, ainsi que les auto-questionnaires, vous seront remis pour la visite suivante.




A l'issu de cette deuxième visite, vous serez répartie au hasard dans le groupe « entraînement » ou dans le groupe « contrôle ». Vous ne connaitrez pas le groupe dans lequel vous êtes situé.

Vous commencerez vos séances d'entraînement, encadrées par votre kinésithérapeute, dans la semaine suivant cette seconde visite.

- Troisième visite (durée approximative 2 heures 30 min) :
Cette visite aura lieu après 6 à 9 mois d'entraînement. Un membre de l'équipe investigatrice vous appellera pour fixer la date et l'horaire de cette visite. Elle consistera en un entretien d'une heure, puis à l'enregistrement des neurophysiologiques d'une durée de deux heures.

Le matin de cette 3ème visite, vous réaliserez vous-même à votre domicile, deux prélèvements salivaires à l'aide du kit remis lors de la visite précédente. Il vous faudra cracher dans le kit à votre réveil pendant 2 minutes, puis 30 minutes après votre lever pendant 2 minutes également. Ces prélèvements salivaires vont permettre de mesurer votre taux de cortisol salivaire et le débit salivaire.

Au cours de l'entretien (60 min), vous compléterez les questionnaires portant sur votre douleur et votre sensibilité, l'impact de la fibromyalgie sur vous, votre niveau d'anxiété (absent, faible, élevé), votre stress et la qualité de votre sommeil ainsi qu'une échelle d'évaluation de la douleur (EVA).
Si vous le souhaitez, vous aurez la possibilité de remplir ces auto-questionnaires chez vous lors de la semaine précédent cette visite. Si vous le préférez, ces auto-questionnaires pourront être remplis directement sur place, lors de cette troisième visite, avec l'aide d'un membre de l'équipe investigatrice. Nous compléterons ensemble le questionnaire concernant votre activité physique (IPAQ) et nous mesurerons votre seuil de douleur à la pression à l'aide d'un algomètre à pression (PPT).

Puis nous procèderons au deuxième test d'évaluation de la douleur (test de la thermode) (90 min). Cette évaluation est en tout point identique à celle de la visite précédente. Les mêmes évaluations complémentaires seront réalisées : prélèvement salivaire le matin, ressentie douloureux avant le test de la thermode et enregistrement de la pression artérielle et de la fréquence cardiaque avant le test de la thermode.

Avant votre retour à votre domicile, nous vous proposerons une dernière entrevue de 10 minutes, selon vos attentes, afin d'échanger sur l'étude, les ressentis et vos questionnements. Vous retournerez à votre domicile dès que vous le souhaiterez.

En fonction de vos capacités physiques et de la tolérance à l'effort, le kinésithérapeute assurant l'encadrement de l'entraînement décidera de votre poursuite à la deuxième partie de l'étude. Si vous ne poursuivez pas cette deuxième partie, vous continuerez votre prise en charge habituelle.

Dans quinzaine de jours suivant cette visite, les patientes des 2 groupes réaliseront un test d'effort maximal sur ergocycle dans le service de médecine du sport du CHRU de Brest, afin d'adapter l'intensité des séances d'entraînement.

Les coordonnées de votre professeur en APA, ainsi que les horaires de vos séances d'entraînement vous seront transmises. Vous commencerez vos séances d'entraînement, encadrées par votre professeur en APA, dans les 7 jours suivant cette troisième visite.

- Quatrième visite (durée approximative 2 heures) :
Cette dernière visite aura lieu après les deux ans d'entraînement. Un membre de l'équipe investigatrice vous appellera pour fixer la date et l'horaire de cette visite.
Dans le mois précèdent cette visite, vous recevrez par voie postale les kits de prélèvements salivaires, ainsi que les auto-questionnaires.

Le matin de cette 4ème visite, vous réaliserez vous-même à votre domicile, deux prélèvements salivaires à l'aide du kit remis lors de la visite précédente. Il vous faudra cracher dans le kit à votre réveil pendant 2 min, puis 30 minutes après votre lever pendant 2 min également. Ces prélèvements salivaires vont permettre de mesurer votre taux de cortisol salivaire et le débit salivaire.

Comme lors de la visite précédente, elle consistera en un entretien d'une heure au cours duquel vous compléterez les 5 questionnaires portant sur votre douleur et votre sensibilité, l'impact de la fibromyalgie sur vous, votre niveau d'anxiété (absent, faible, élevé), votre stress et la qualité de votre sommeil, ainsi que 2 échelles d'évaluation de la douleur (EVA et EVS). Si vous le souhaitez, vous aurez la possibilité de remplir ces auto-questionnaires chez vous lors de la semaine précédent cette visite. Si vous le préférez, ces auto-questionnaires pourront être remplis directement sur place, lors de cette quatrième visite, avec l'aide d'un membre de l'équipe investigatrice. Nous compléterons ensemble le questionnaire concernant votre activité physique (IPAQ) et nous mesurerons votre seuil de douleur à la pression à l'aide d'un algomètre à pression (PPT).

Puis nous procèderons au troisième et dernier test d'évaluation de la douleur (test de la thermode) d'une durée de une heure et 30 minutes. Cette évaluation est en tout point identique à celle des deux visites précédentes. Les mêmes évaluations complémentaires seront réalisées : prélèvement salivaire le matin, ressentie douloureux avant le test de la thermode et enregistrement de la pression artérielle et de la fréquence cardiaque avant le test de la thermode.

## 4- BENEFICES

Votre participation à cette recherche a pour but d'améliorer la prise en charge de la douleur des patients souffrants de douleurs diffuses, voire de proposer une option thérapeutique pour ces patients. Votre participation a également pour but de mieux comprendre les mécanismes physiopathologiques à l'origine des douleurs diffuses.

A titre individuel, les bénéfices attendus sont une réduction (voire la suppression) des douleurs, une amélioration de la qualité de vie et une amélioration du sommeil.

A cela, s'ajoute également les bénéfices reconnus de la pratique sportive sur le maintien de la santé : prévention du surpoids et de l'obésité, diminution du stress oxydant, prévention des pathologies cardiovasculaires, réduction des dysfonctions métaboliques, évacuation du stress, prévention des cancers…

## 5- RISQUES

Les risques de l'étude sont ceux liés à la pratique sportive. Un bilan cardiovasculaire sera réalisé avant de débuter l'entraînement. D'autre part, cette pratique sera encadrée tout au long de l'étude par un kinésithérapeute puis par un professeur en APA, afin de limiter les risques de blessures.

Les évaluations mises en place vont induire une douleur expérimentale qualifiée de modérée, aigue et temporaire. Elles n'entraineront aucune lésion de l'organisme. Cette intensité de douleur permet d'induire une sensation douloureuse suffisante mais non excessive et de mobiliser l'ensemble des mécanismes du système douloureux. La sensation ressentie est d'une part ponctuelle et disparait dès l'arrêt de la stimulation thermique. Différentes études ont déjà utilisées cette méthode et aucun effet secondaire n'a été relevé. Les risques sont donc mineurs et ne dépasseront pas le temps imparti au recueil des données neurophysiologiques. Par ailleurs, vous aurez la possibilité de mettre fin à la stimulation dès que vous le souhaitez. Si toutefois la douleur ressentie est persistante ou jugée trop intense, l'étude est arrêtée et le médecin qui vous suit pourra vous administrer un antalgique adapté à la douleur (palier 1 ou 2) selon son appréciation.

Le risque psychologique de ce protocole est que vous vous sentiez découragée par votre incapacité à maintenir un effort physique. Afin d'éviter cette situation, le programme d'entraînement a été conçu pour que la progression soit individuellement adaptée avec des objectifs à la séance, à moyen et à long terme, et ce programme est accompagné par un kinésithérapeute, puis par un professeur en APA.

## 6- PARTICIPATION VOLONTAIRE

Votre participation à cette étude est entièrement volontaire. Vous êtes libre de refuser d'y participer ainsi que de mettre un terme à votre participation à n'importe quel moment, sans encourir aucune responsabilité ni aucun préjudice. Dans ce cas, vous devez informer le médecin qui vous suit de votre décision.

Dans le cas où vous retiriez votre consentement, nous effectuerons un traitement informatique de vos données personnelles sauf opposition écrite de votre part.

Durant l'étude, vous serez avertie par votre médecin, si des faits nouveaux pouvaient affecter votre volonté de participer à l'étude.

Les Autorités de Santé, votre médecin investigateur ou le promoteur peuvent décider de mettre un terme à votre participation à l'étude à n'importe quel moment sans votre consentement préalable. Si cela devait se produire, vous en serez averti et les raisons vous seraient expliquées.

D'autre part, pour votre participation complète à cette étude, une indemnisation des frais de déplacements est prévue, pour les visites à J0, 1 an et à 2 ans, aux frais réels dans la limite de 50 euros par visite.

## 7- OBTENTION D'INFORMATIONS COMPLEMENTAIRES

Si vous le souhaitez, le Docteur [……..], que vous pourrez joindre au numéro de téléphone suivant [:……], pourra répondre, aux horaires ouvrés, à toutes vos questions concernant cette étude.
A l'issue de l'étude, et à votre demande, vous pourrez être informée des résultats globaux de la recherche par votre médecin investigateur.

## 8- CONFIDENTIALITE ET UTILISATION DES DONNEES MEDICALES

Dans le cadre de la recherche biomédicale à laquelle le CHRU de Brest et votre médecin vous propose de participer, un traitement de vos données personnelles va être mis en œuvre pour permettre d'analyser les résultats de la recherche au regard de l'objectif de cette dernière, qui vous a été présenté. A cette fin, les données médicales recueillies, y compris tout questionnaire et les données relatives à vos habitudes de vie vous concernant, seront transmises au Promoteur de la recherche. Ces données seront identifiées par un numéro de code et vos initiales.

Le personnel impliqué dans l'étude est soumis au secret professionnel, tout comme votre médecin traitant. Ces données pourront également, dans des conditions assurant leur confidentialité, être transmises aux autorités de santé françaises.

Conformément aux dispositions de loi relative à l'informatique aux fichiers et aux libertés (loi du 6 janvier 1978), vous disposez d'un droit d'accès et de rectification. Vous disposez également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel susceptibles d'être utilisées dans le cadre de cette recherche et d'être traitées.
Vous pouvez également accéder directement ou par l'intermédiaire d'un médecin de votre choix à l'ensemble de vos données médicales en application des dispositions de l'article L 1111-7 du Code de la Santé Publique. Ces droits s'exercent auprès du médecin qui vous suit dans le cadre de la recherche et qui connaît votre identité.

## 9- ASSURANCE

Un contrat d'assurance HDI Gerling – Tour Opus 12,77, Esplanade de la Défense – 92914 Paris la Défense, n° 0101214214002-150015-10998 a été souscrit par le promoteur de l'essai, le CHRU de Brest, pour couvrir les risques liés à cette recherche. Cette assurance couvre la responsabilité du promoteur en tant que promoteur d'une recherche biomédicale et celle de tout autre intervenant, en accord avec l'article L 1121-7 du Code de la Santé Publique.

## 10- AVIS FAVORABLE DU CPP

Conformément à la loi n°2004-806 du 9 août 2004 relative à la politique de santé publique, le Comité de Protection des Personnes Ouest VI a étudié ce projet de recherche et a émis un avis favorable à sa réalisation le 02 Décembre 2014.

## 11- AUTORISATION DE L'ANSM

Conformément à la loi n°2004-806 du 9 août 2004 relative à la politique de santé publique, l'ANSM a étudié ce projet de recherche et a émis une autorisation à sa réalisation le 25 Juin 2014.

**FORMULAIRE DE CONSENTEMENT**

**DOUFISPORT : IMPACT D'UN PROGRAMME D'ENTRAINEMENT SPECIFIQUE SUR LA NEUROMODULATION DES DOULEURS CHEZ LES SUJETS FIBROMYALGIQUES**

***Promoteur : CHRU de Brest – 2 Avenue Foch – 29609 Brest Cedex.***

**De :** Mme :……
Adresse : ……

**Le Docteur** …….. (Tél : _ _ / _ _ / _ _ / _ _ / _ _ /)
Du Centre de (adresse)…… …… **m'a proposé de participer à l'étude clinique DouFiSport. Je suis informée que la durée de l'étude est prévue sur 2 ans** Je pourrai à tout moment, lui demander des informations complémentaires. J'ai lu et compris la notice d'information, dont j'ai obtenu la copie. Le médecin investigateur a répondu à toutes mes questions concernant l'étude.

J'ai eu le temps nécessaire pour réfléchir à mon implication dans cette étude, et je suis consciente que ma participation est entièrement volontaire et que cette étude n'engendrera aucun surcoût à ma charge. Je peux à tout moment décider de quitter l'étude sans motiver ma décision et sans qu'elle n'entraîne de conséquences dans la qualité de ma prise en charge.

J'ai compris que les données collectées à l'occasion de la recherche seront protégées dans le respect de la confidentialité. Elles pourront uniquement être consultées par les personnes soumises au secret professionnel appartenant à l'équipe du médecin investigateur, mandatées par le promoteur ou les représentants des autorités de santé.

J'accepte le traitement informatisé des données à caractère personnel me concernant dans les conditions prévues par la loi Informatique et liberté. J'ai été informé de mon droit d'accès et de rectification des données me concernant.

Je certifie être affiliée au régime de la Sécurité Sociale.

J'ai été informée que, conformément à la réglementation sur les études cliniques, le CPP Ouest VI a rendu un avis favorable pour la réalisation de cette recherche et que l'ANSM l'a également autorisée.

Fait en deux exemplaires originaux

À ……, le ……

Nom, prénom de l'investigateur :

Nom, prénom du volontaire :

Signature :

Signature :

**Un exemplaire cosigné pour le volontaire, un exemplaire cosigné pour l'investigateur et une copie pour le promoteur**


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry |
| | 2b | All items from the World Health Organization Trial Registration Data Set |
| Protocol version | 3 | Date and version identifier |
| Funding | 4 | Sources and types of financial, material, and other support |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors |
| | 5b | Name and contact information for the trial sponsor |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) |
| **Introduction** | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention |
| | 6b | Explanation for choice of comparators |
| Objectives | 7 | Specific objectives or hypotheses |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) |

**Methods: Participants, interventions, and outcomes**

| | | |
|---|---|---|
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size |

**Methods: Assignment of interventions (for controlled trials)**

Allocation:

| | | |
|---|---|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions |

| | | |
|---|---|---|
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial |
| **Methods: Data collection, management, and analysis** | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) |
| **Methods: Monitoring** | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed |

| | | |
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| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor |
| **Ethics and dissemination** | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code |

## Appendices

| | | |
|---|---|---|
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Impact of a specific training program on the neuromodulation of pain in fibromyalgia women (DouFiSport): a 24-month, controlled, randomised, double-blinded protocol. |
| Trial registration | 2a | NCT02486965 |
| Protocol version | 3 | version number 5.0 of 21/06/2016 |
| Funding | 4 | This work is supported by the French Ministry of Health (Programme Hospitalier de Recherche Clinique Interrégional 2014) PHRCi 13-100 |

| | | |
|---|---|---|
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors: |

Anaïs Le Fur-Bonnabesse[1,2,3], investigator
Mathilde Cabon[1], investigator
Gildas L'Heveder[4], co-ordinating investigator
Aurélie Kermarrec[5], coaching staff (physiotherapist)
Bertrand Quinio[3], scientific associate
Alain Woda[6], scientific associate
Serge Marchand[7], scientific associate
Amandine Dubois[8,9,1], investigator
Marie-Agnès Giroux-Metges[10,11], scientific associate
Fabrice Rannou[10,11] scientific associate
Laurent Misery[1], scientific associate
Céline Bodéré[1,2,3], principal investigator, scientific responsible

1 Laboratory of Interactions Keratinocytes-Neurons, EA4685, Faculty of Medicine and Health Sciences, University of Western Brittany (UBO), Brest, France
2 Dental faculty, University of Western Brittany (UBO), Brest, France
3 Assessment and treatment center of pain, University Hospital of Brest, Brest, France
4 Neurological functional explorations, University Hospital of Brest, Brest, France.
5 Training institute of physiotherapy University Hospital of Brest, Brest, France.
6 University Clermont Auvergne, CROC and Teaching Hospital EA3847, Odontology Department, Clermont-Ferrand, France
7 Department of surgery, Faculty of medicine, University of Sherbrooke, Sherbrooke, Canada
8 Laboratory of psychology: Cognition, Behaviour, Communication (LP3C), EA1285, Rennes, France
9 Department of Psychology, University of Western Brittany (UBO), Brest, France.
10 ORPHY, Optimisation of Physiological Regulations, EA4324, Faculty of Medicine and Health Sciences , University of Western Brittany (UBO), Brest, France
11 Respiratory Functional Exploration Unit, University Hospital of Brest, Brest, France.

CB initiated the idea for the project.
CB and ALFB developed the study design.
MC, GL, BQ, AK, AW, SM, MAGM, FR, LM and AD provided advice for the study design.
GL and CB are responsible for supervision of project. CB will conduct the recruitment.
AK will conduct the training programme.
CB, ALFB and MC will conduct the outcomes assessments and will contribute to the analysis and interpretation of the data.
Both authors will contribute to the analyses and interpretation of the data.
ALFB, CB and MC wrote early drafts of the manuscript.
All authors approved the final version of this protocol.

5b Name and contact information for the trial sponsor:

Rémi BRAJEUL, directeur adjoint
Délégation à la Recherche Clinique et à l'Innovation (DRCI)
CHRU de Brest
2 Avenue Foch
29609 Brest Cedex
France

5c Role of study sponsor and funders :

- Evaluation of serious adverse events
- Transmission of annual safety reports
- Quality assurance and monitoring activities
- Approval of any amendment of the protocol

| | | |
|---|---|---|
| Background and rationale | 6a | Fibromyalgia affects 1.4 to 2.2% of the general population concerning predominately women (more than 80% of subjects). This syndrome is characterised by extensive and diffuse pain, mainly muscular and articular, impairing the functional abilities of the subjects. The symptoms most frequently described by fibromyalgia patients are chronic fatigue, sleep disorders, cognitive disorders and emotional disturbances (3,4). This symptomatology leads to a serious deterioration in quality of life, sometimes with a physical disability leading to social isolation and difficulties in staying in employment (recurrent work stoppages).<br>The diagnosis is based on the symptoms and their severity as described by the patients (5–8). Currently, there is no etiological treatment for fibromyalgia syndrome. The treatments are therefore only symptomatic.<br><br>**Physiopathology of fibromyalgia**<br>The mechanisms of dysfunctional pain, without any identifiable organic lesions, are mostly central (1) and related to dysfunction of the stress axis (autonomic nervous system and corticotropic axis) (9–11).<br>At rest, fibromyalgia patients showed an increased sympathetic response and decreased parasympathetic tone (12,13). This neurovegetative dystonia is a marker of dysfunction of the stress axis (14).<br>Malfunctions of the corticotropic axis in fibromyalgia have been described multiple times, also marking the dysfunction of the stress axis. But the form taken by this dysfunction differs according to the different studies (15–19). The variability of salivary cortisol in response to stress reflects that of plasma free cortisol. Salivary cortisol is therefore a method of choice in experimental stress studies (20).<br>Whatever form they take, these dysfunctions compromise the body's adaptation to daily stressful stimuli.<br><br>Studies show that this deficit of the stress axis (neurovegetative dystonia and dysfunctional corticotropic axis) is concurrent with fibromyalgia (21) and associated with alteration of pain control (9–11).<br>Pain control system and stress axis have close anatomical and functional links. Nociceptive, neurovegetative and corticotropic systems interact with the central nervous system. The central neuromediators implicated in the regulation of the stress axis are mostly common with those of the pain neuromodulation (endogenous opioids, norepinephrine, serotonin, etc.). |

**Elite athlete's overtraining syndrome: model of stress axis dysfunction**

An overtraining elite athlete may be considered as a model of dysfunction of the stress axis associated with neurovegetative dystonia. The physical and psychological effort of training is known to induce stress. High-level athletes could present an overtraining syndrome when adaptation limits of the stress axis are reached. This stress-induced phenomenon corresponds to an imbalance between training quantity and recovery. Overtrained athletes present a deconditioning syndrome close to fibromyalgia symptoms (chronic pain, sleep disorders, neurovegetative dystonia, etc.) (22–26).

**Physical activity and fibromyalgia**

Most studies have shown that physical activity is more efficient compared to pharmacological treatments on fibromyalgia symptoms (27,28). Literature reviews and meta-analyses highly support the benefits of physical training in fibromyalgia patients (decreased pain and depression and improvement in overall health and physical abilities) (29)(30). Practice of aerobic exercise in fibromyalgia patients is strongly recommended by The American Pain Society (31), the Association of Medical Scientific Societies in Germany (32), the Canadian Rheumatology Association (5) and the European League Against Rheumatism (EULAR) (33). Physical exercise is the first-line treatment recommended in fibromyalgia. However there is still no consensus on the modalities of these types of training (frequency, duration, and intensity). Currently, the mechanisms underlying those specific training effects have to be defined.

The steady physical activity rebalancing autonomic system is associated with cardiovascular benefits. Fundamental endurance increases parasympathetic tone and decrease sympathetic response (34–37). Thus, strategies to rebalance the autonomic system are the most promising therapies for fibromyalgia (13,36,37).

In this study, we propose to validate a therapeutic alternative that aims to treat fibromyalgia by rebalancing the stress axis. This treatment consists of a specific supervised and individualised training program, over 2 years. This training protocol is individually adjusted in order to rebalance the neurovegetative system (parasympathetic and sympathetic). Central neuroplasticity induced by training should regulate endogenous pain control mechanisms.

| | | |
|---|---|---|
| Objectives | 7 | The *main objective* is to assess the effectiveness of a specific training program on endogenous pain controls in fibromyalgia patients. The *secondary objectives* are to rebalance the autonomic nervous system and the corticotropic axis, to improve life and sleep quality and to reintegrate patients into society and work. |

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|---|---|---|
| Trial design | 8 | This randomised double-blinded trial will compare an "active" program to a "control" program in fibromyalgia patients. |

**Methods: Participants, interventions, and outcomes**

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|---|---|---|
| Study setting | 9 | Patients will be recruited at the pain center of the university hospital of Brest on the basis of general criteria. Patients should follow a re-exercise program for 24 months. The assessments will take place (i) before, (ii) between 6 to 9 months (depending the training level) and (iii) at the end of the training (24 months), in the neurological functional explorations department of the university hospital of Brest (France). |
| Eligibility criteria | 10 | The inclusion criteria are: female subjects; aged of 18 to 65 years; with a diagnosis of fibromyalgia clearly established according to the criteria of the American College of Rheumatology (ACR) 2010; with a body mass index (BMI) between 18.5 and 29.9kg/m²; spontaneous pain intensity higher than 3/10 on a visual analog scale (VAS); pain experienced at least 3 days a week; pain caused by palpation equal to or higher than 4/10 on a VAS.<br><br>The non-inclusion criteria are: patients with a systemic disease (treated or not) generating pain of the musculoskeletal system; presenting pain other than fibromyalgia; presenting a contraindication to physical activity; having any active pathology; having modified in the last 2 months any pharmacological treatment; having a psychiatric diagnosis; taking drugs that affect cortisol secretion (decrease or increase); non-cooperating. |

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| Interventions | 11a | The training program is planned over two years (24 months) for both groups (active/control). A minimum of 4 to 6 weeks is needed to observe a decrease in symptoms (38). This two-year duration is the minimum average training time (depending on the individual progress of each patient), necessary to regain central neuroplasticity sufficient to put back into operation diffuse noxious inhibitory controls (DNIC) and neurovegetative system (39).<br>The frequency, intensity, and duration of these training sessions are based upon the results of a preliminary study. Pain was significantly reduced and symptoms, such as quality of life, sleep quality, anxiety, were also highly improved in subjects undergoing this specific training after 5 years (39). The American Pain Society recommends an intensity of 60 to 70% of the age-adjusted maximum heart rate (HRmax). At the early stage, the intensity and duration of the training sessions will be adapted to the physical condition of each subject. In order to promote adherence of our patients and to limit pain exacerbation, exercise intensity will start very low and then gradually increase to reach the neurovegetative goal (31)(40).<br><br>**Active training group:**<br>*The first 6 to 9 months*: fundamental endurance training.<br>Subjects will perform 3 sessions per week of 45 minutes of fundamental endurance (moderate-intensity continuous training MICT: 60% HRmax), including 2 sessions supervised by a physiotherapist and 1 independent session.<br>*From 6-9 months (according to the rhythm, abilities, and limits) to 24 months*: Patients will begin the second stage of training: 3 sessions per week of 45 minutes each (moderate-intensity continuous training MICT (60% HRmax) and high-intensity interval training HIIT) with 1 supervised session and 2 independents sessions. When the patient reaches the initial HR goal, “fundamental endurance” will be associated with “interval training” at a high frequency intensity. HIIT will consist of 5 stages of 1 to 4 minutes at 85-90% HRmax (80-85% $V\dot{O}_2max$), interspersed by 1 to 4 minutes of active recovery at 60-75% HRmax (50-70% $V\dot{O}_2max$). Intensity will be assessed objectively using a heart rate monitor (FT2, Polar). At baseline, Tanaka’s age-based prediction equation (208-0.7×age) will calculate HRmax. After *6-9 months of training, a* maximal-effort graded exercise test will determine HRmax and $V\dot{O}_2max$ for each patient.<br><br>**Control group:**<br>Patients will perform the same infra active training (low-intensity continuous training: LICT <50% HRmax) over two years. Supervision, monitoring, and frequency of sessions (3 x 45 minutes per week) in both groups will be equivalent. |

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant: If a patient cannot achieve the specific training requested after 9 months of study, the patient will not complete the second phase of training.

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence: Patients will be contacted to record progress, difficulties and if necessary, to encourage them to adhere to their program. These calls will improve the compliance and will limit patients lost to follow-up.
Patients will perform a 6-minute walk test (6MWT) every 6 months (with physiotherapist).

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial: This specific protocol will be associated with psychotherapeutic approaches. In addition to the training program, multidisciplinary bio-psycho-social cares will be given in the pain center of the university hospital of Brest (France).

| | | |
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| Outcomes | 12 | **Primary outcomes:** In order to assess endogenous pain mechanisms, such as diffuse noxious inhibitory controls (DNIC), temporal summation (TS) and perception of pain, we will use an experimental method developed by Tousignant-Laflamme and Marchand (2008). According to this well-characterised paradigm**,** we will induce in single session two tonic heat pain stimulations separated by a cold pressor test (1,47–49). The VAS improvements (stimulation test) obtained in the both groups will be compared.<br><br>**Secondary outcomes:**<br>A simple verbal scale, a visual analog scale, and the Saint Antoine Pain Questionnaire (QDSA), will perform the **assessment of pain**. A **pain quantitative assessment** will be performed with a pressure algometer (pressure pain threshold: PPT).<br>Questionnaires will assess **patient anxiodepressive state** (Hospital Anxiety Depression Scale), **the impact of fibromyalgia on daily life** (Fibromyalgia Impact Questionnaire), **sleep quality and quantity** (Pittsburgh Sleep Quality Index), **the level of physical activity and the sedentary lifestyle** (International Physical Activity Questionnaire), **the antecedents of perceived stress** (Perceived Stress Scale).<br>**Blood Pressure** (BP) and **Heart Rate** (HR) will be recorded.<br>**Corticotropic axis** will be assessed using measurement of salivary cortisol and salivary flow.<br><br>Quantitative assessment (salivary cortisol, blood pressure, PPT quantified by pain threshold pressure, questionnaires assessment) will be analysed by comparing the improvements obtained between both groups. |

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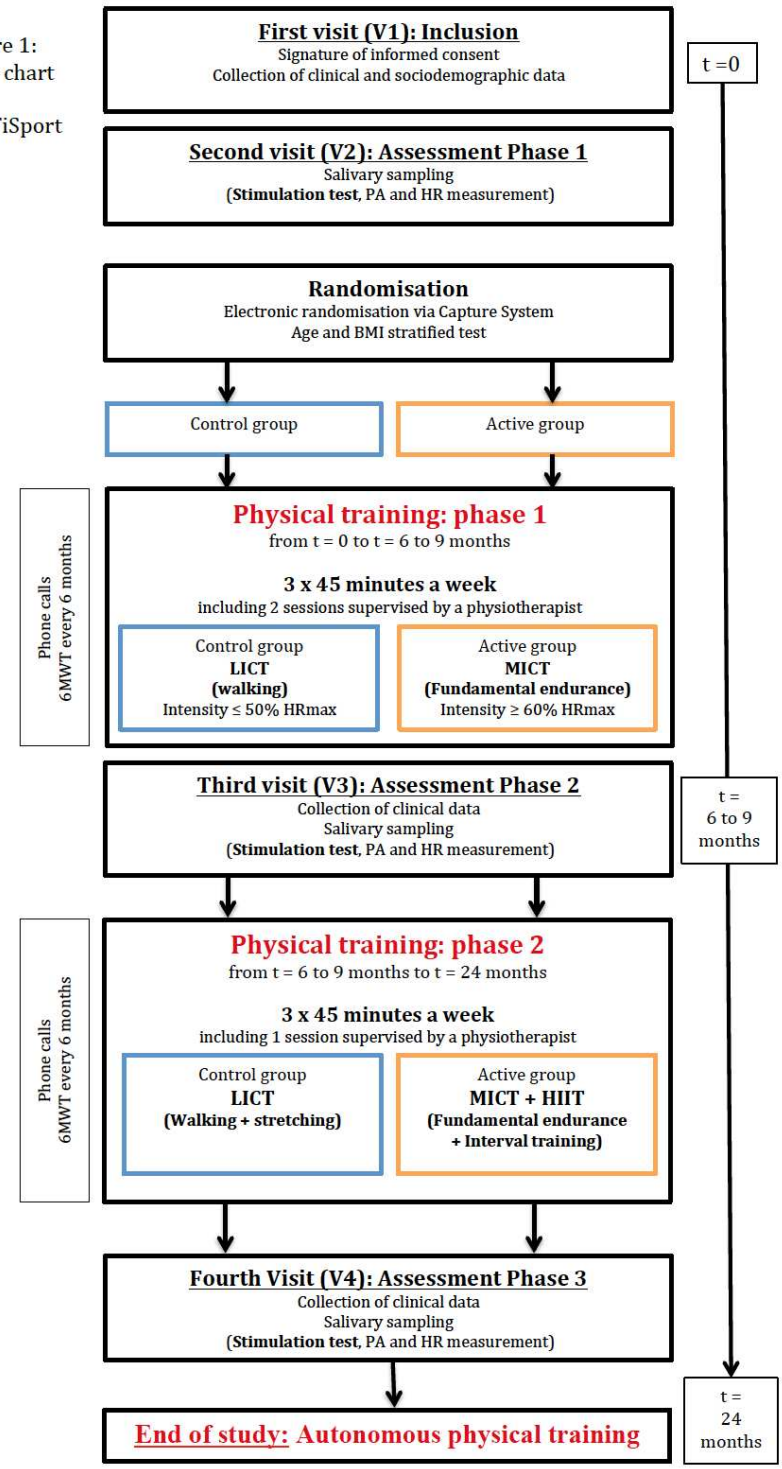
| Participant timeline | 13 | The training program is planned over two years (24 months) for both groups (active/control). Subjects will perform 3 training sessions per week of 45 minutes.<br>Patient will participate in 4 visits (1 inclusion visit and 3 assessment visits) during these two years. |

Figure 1: Flow chart of DouFiSport



| | | |
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| Sample size | 14 | Population size is based on an expected difference of 20 points (stimulation test) (1) between the two groups, for a quantitative primary endpoint (delta VAS) of standard deviation equal to 35, and a power set at 80%. Therefore a minimum of 48 subjects per group is required for assessment. In order to take into account loss to follow-up, the sample of 110 subjects, 55 per group will be recruited. |
| Recruitment | 15 | Patients will be recruited at the pain centre of the university hospital of Brest on the basis of general criteria. |

**Methods: Assignment of interventions (for controlled trials)**

Allocation:

| | | |
|---|---|---|
| Sequence generation | 16a | Patients will be randomised at the end of the first stimulation test (second visit: V2), which is just before the initiation of the training. The test is stratified by age and BMI. The cut off is set at 50 years for age and 25kg/m$^2$ for BMI (two strata [18-25] and ]25-30 []. |
| Allocation concealment mechanism | 16b | Electronic randomisation via Capture System |
| Implementation | 16c | The allocation sequence will generate by the Center of Clinical Investigation (CIC) at the hospital university of Brest (France). The principal investigator will enrol participants, and will assign participants to interventions. |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions: Patients will be blinded (they will not be informed of their group (active/control)). The investigators, outcome assessors and data analysts will be blinded. |
| | 17b | If blinded, circumstances under which unblinding is permissible: Due to the nature of the intervention (physical activity protocol), the coaching staff will not be blinded. |

**Methods: Data collection, management, and analysis**

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| Data collection methods | 18a | Measurements and questionnaires will be carried out (i) at baseline, (ii) between 6 to 9 months, and (iii) at the end of the 24 months of training.<br>**Sociodemographic and clinical data**<br>At baseline, data on age, sex, marital status, education level, and occupation will be collected. Height and weight will be recorded. Medical background and pain characteristics will be noted. All current drug and non-drug therapies (including tried and stopped) will also be collected, as well as their effectiveness on pain.<br>**Questionnaires and pain assessments**<br>• The **assessment of pain** will be performed by a simple verbal scale and using a visual analog scale (VAS). The Saint Antoine Pain Questionnaire (QDSA) will also assess pain. A **pain quantitative assessment** will be performed with a pressure algometer (pressure pain threshold: PPT).<br>• The Hospital Anxiety Depression Scale (HADS) will assess the **patient anxiodepressive state** (41).<br>• The Fibromyalgia Impact Questionnaire (FIQ) will assess **the impact of fibromyalgia on daily life** (42).<br>• The Pittsburgh Sleep Quality Index (PSQI) will assess **sleep quality and quantity** (43,44).<br>• The International Physical Activity Questionnaire (IPAQ) will record the **level of physical activity and the sedentary lifestyle**. The French long telephone questionnaire will be used (45).<br>• The Perceived Stress Scale (PSS) will assess **the antecedents of perceived stress** (46).<br><br>**Stimulation test**<br>In order to assess endogenous pain mechanisms, such as diffuse noxious inhibitory controls (DNIC), temporal summation (TS) and perception of pain, we will use an experimental method developed by Tousignant-Laflamme and Marchand (2008) (1,47–49).<br>- Thermode test or temporal summation test **(P1):** a tonic heat pain will be administered for 2 minutes on the patient's right arm, using a thermode (CE marking n°226). The starting temperature is 32°C (skin temperature under normal conditions in temperate room (20-22°C)) (50) and will quickly reach a fixed value. The experimental temperature will be individually determined to induce 50/100 on a VAS and will remain constant during the test period (2 minutes). Throughout this entire period, the patient will evaluate their pain intensity using a Computerised Visual Analog Scale (CoVAS).<br>- Cold pressor test **(P2):** to elicit a prolonged pain sensation in order to trigger diffuse noxious inhibitory control (DNIC) (51), the patient's right arm will be immersed for 2 minutes in a cold water bath maintained at 12°C. The patient will continuously evaluate their pain intensity using a CoVAS.<br>Following this cold pressor test, the thermode test will be again performed **(P3).**<br>Pain difference between the two (P3/P1) tonic heat pain stimulations will measure DNIC activation and represents pain modulation. |

**Measurement of salivary cortisol and salivary flow**

Corticotropic axis will be assessed using measurement of salivary cortisol. Cortisol release is pulsatile (10 to 20 peaks per day) and follows a nycthemeral cycle. Maximum cortisol level is reached in the early morning. In the morning of each consultation (at baseline, in the middle and at the end of training), patients will collect salivary sample (i) for 2 minutes, when they wake up and (ii) for 2 minutes, 30 minutes later. The salivary cortisol level is measured in nmol/l. The flow rate is calculated in $ml.min^{-1}$. Samples will be frozen at -20°C. As salivary cortisol is stable, samples can be stored for many weeks in the freezer (52). After completion of all assessment sessions, sample analysis will be completed. To avoid inter-laboratory variation, the same laboratory will assay the samples.

**Recording of Blood Pressure (BP) and Heart Rate (HR)**

After 10 minutes at rest, lying down, BP and HR will be recorded. Then, BP and HR will be measured when the patient stands up and once per minute during 4 minutes when the patient remains standing.

18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols: To limit dropout, patients will be called to encourage them and to discuss any difficulties. In second stage of training and to limit a possible long-term monotonous effect, physical activity type could be diversified in both groups. The training session will be adapted in the active group (MICT will be associated with HIIT) to reduce sympathetic hyperactivity. In order to improve compliance and long-term achievement of training, the patient may choose the physical activity type performed without supervision. If a patient cannot achieve the specific training requested after 9 months of study, the patient will not complete the second phase of training. Nevertheless, she will carry out all assessment visits.
The main analysis will be performed on an intent-to-treat basis.

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| Data management | 19 | **Case report forms (CRF):**<br>All data collected must be recorded in the CRF immediately after the procedure. Each missing data will have to be coded. The researcher will carry out a double data entry. In addition, Checks on the consistency of these data will be instantly carried out.<br><br>Data on individuals included in the study will be made anonymous. Only the first letter of the subject's name, and the first letter of her first name will be recorded, with a specific code number.<br><br>**Quality Assurance and Control:**<br>A researcher commissioned by the study sponsor will ensure proper achievement of the study and, of data collection, recording and, reporting.<br><br>**Storage:**<br>During the study period, documents will be stored in the neurological functional explorations department of the university hospital of Brest<br>At the end of the study period, all archived documents will be transferred to a centralized archiving site (Central Archives Service - Brest) and, will be placed under the sponsor responsibility for 15 years according to institutional practices. |
| Statistical methods | 20a | *Primary outcome analysis*: The VAS improvements (stimulation test) obtained in the both groups will be compared using the Student's test. If the required normality assumption is not sustainable, a nonparametric Wilcoxon test will be used. An alpha risk of 0.05 will be set as the limit of statistical significance. The main analysis will be performed on an intent-to-treat basis. A complementary analysis using a linear model with adjustment for age and BMI factors will be completed.<br><br>*The secondary outcomes* (quantitative: salivary cortisol, blood pressure, PPT quantified by pain threshold pressure, questionnaires assessment) will be analysed in a similar way by comparing the improvements obtained between both groups. |
| **Methods: Monitoring** | | |
| Data monitoring | 21a | Because of the nature of the study (excluding health product and, duration of the study), a monitoring committee independent from the sponsor will not be constituted.<br>A researcher commissioned by the study sponsor will ensure proper achievement of the study, and of data collection, recording and reporting. |

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| | 21b | The study may be stopped early for reasons of safety (in the event of unexpected serious adverse event occurrences), efficacy or futility. The sponsor reserves the right to stop the study at any time, if the desired sample size is not achieved. |
| Harms | 22 | **The investigator** is responsible for recording and reporting all serious adverse events (EvIG) occurring during the entire study period. Regardless of the causal relationship between EvIG and the study, any EvIG will be described on the form dedicated to this matter («EvIG initial report» or «EvIG follow-up report») and will be notified to the sponsor within a time frame of 24 hours after the event occurs.<br><br>All other adverse events (non-serious adverse events) will be reported on adverse event form of the CRF. The date of occurrence, description, intensity, duration, treatment, aetiology, accountability and the decisions taken will be specified.<br><br>**The sponsor** has to analyse EvIG (the causality of the EvIG and their expected or unexpected character). The sponsor have to report all unexpected EvIG to Eudravigilance (European pharmacovigilance database), the French Health Authorities (ANSM), the Committee for the Protection of Persons (CPP) and, to the investigators. Each year, the sponsor will draft a safety report that will include:<br>- the list of unexpected and expected EvIG,<br>- a concise and critical analysis of the safety of patients included in the study.<br><br>Each adverse events will be monitored until the it will be completely resolved even if after the study period. |
| Auditing | 23 | A researcher commissioned by the sponsor will audit trial conduct. The investigator and his team undertake to make themselves available during regular Quality Control visits by this researcher. During these visits, informed consent, adherence to study protocol and, CRF data quality, will be reviewed. The investigator undertakes to accept quality control audits carried out by the sponsor, and by the competent authorities. |
| **Ethics and dissemination** | | |
| Research ethics approval | 24 | The Committee for the Protection of Persons West VI approved this study on 02/12/2014. |

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| Protocol amendments | 25 | Important protocol modifications by the investigator (eg, changes to eligibility criteria, outcomes, analyses) have to be approved by the sponsor. The sponsor must obtain a favourable opinion of the CPP and an authorization of the «Agence nationale de sécurité du médicament et des produits de santé» (ANSM) to enable the application of these amendments. A new consent of the patient participating will be collected if necessary. |
| Consent or assent | 26a | Patients will be informed of the objectives, constraints, risks and benefits of the study. Patients will be informed of their rights to refuse to participate or to withdraw from the study at any time. All information will be on information and consent form given to the patient. To be included, patients will sign informed written consent. The investigator will collect free, informed, and written consent of the patient before definitive inclusion in the study. |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable: No collection will be formed. |
| Confidentiality | 27 | Data on individuals included in the study will be made anonymous. Only the first letter of the subject's name, and the first letter of her first name will be recorded, with a specific code number. The investigators will take all necessary precautions to ensure the confidentiality of the information in particular with regard to patient identity. |
| Declaration of interests | 28 | None declared. |
| Access to data | 29 | In accordance with good clinical practice, the sponsor is responsible for seeking the agreement of those involved in this research with a view to ensure direct access to source data, source documents and reports in all research place (particularly during quality control).<br>In accordance with the legislative provisions in force (articles L.1121-3 et R.5121-13 of the French Public Health Code), the investigators will be making documents and necessary individual data available to researcher charged with study control and monitoring. |
| Ancillary and post-trial care | 30 | Pursuant to the provisions of article L1121-10 of the French Public Health Code, the sponsor (CHRU of Brest) undertakes to take out a civil liability insurance contract. |
| Dissemination policy | 31a | The results of this study will be published in specialised scientific journals. These results will be presented to participants and the public at a free public lecture organised by the health promotion department of the city of Brest. These results will also be presented to healthcare professionals and other relevant groups in pain and/or physical activity congresses. In addition, a doctoral thesis will be carried out on this project. |

## Appendices

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| Informed consent materials | 32 | See attached documentation |
| Biological specimens | 33 | Not applicable. |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

## References


1. Tousignant-Laflamme Y, Pagé S, Goffaux P, Marchand S. An experimental model to measure excitatory and inhibitory pain mechanisms in humans. Brain Res. 16 sept 2008;1230:73•9.
2. Woda A, L'heveder G, Ouchchane L, Bodéré C. Effect of experimental stress in 2 different pain conditions affecting the facial muscles. J Pain Off J Am Pain Soc. mai 2013;14(5):455•66.
3. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. févr 1990;33(2):160•72.
4. Cánovas R, León I, Roldán MD, Astur R, Cimadevilla JM. Virtual reality tasks disclose spatial memory alterations in fibromyalgia. Rheumatol Oxf Engl. oct 2009;48(10):1273•8.
5. Fitzcharles M, Shir Y, Ablin JN, Buskila D, Amital H, Henningsen P, et al. Classification and clinical diagnosis of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines. Evid-Based Complement Altern Med ECAM. 2013;2013:528952.
6. Egloff N, von Känel R, Müller V, Egle UT, Kokinogenis G, Lederbogen S, et al. Implications of proposed fibromyalgia criteria across other functional pain syndromes. Scand J Rheumatol. 2015;44(5):416•24.
7. Moyano S, Kilstein JG, Alegre de Miguel C. New diagnostic criteria for fibromyalgia: Here to stay? Reumatol Clin. août 2015;11(4):210•4.
8. Wolfe F, Fitzcharles M-A, Goldenberg DL, Häuser W, Katz RL, Mease PJ, et al. Comparison of Physician-Based and Patient-Based Criteria for the Diagnosis of Fibromyalgia. Arthritis Care Res. mai 2016;68(5):652•9.
9. Bodéré C, Woda A. La douleur orofaciale idiopathique: une douleur fonctionnelle. Douleur Analgésie. 21 juin 2009;22(2):89•95.
10. Woda A, Dao T, Gremeau-Richard C. Steroid dysregulation and stomatodynia (burning mouth syndrome). J Orofac Pain. 2009;23(3):202•10.
11. Woda A, L'heveder G, Ouchchane L, Bodéré C. Effect of experimental stress in 2 different pain conditions affecting the facial muscles. J Pain Off J Am Pain Soc. mai 2013;14(5):455•66.

12. Cohen H, Neumann L, Shore M, Amir M, Cassuto Y, Buskila D. Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability. Semin Arthritis Rheum. févr 2000;29(4):217•27.
13. da Cunha Ribeiro RP, Roschel H, Artioli GG, Dassouki T, Perandini LA, Calich AL, et al. Cardiac autonomic impairment and chronotropic incompetence in fibromyalgia. Arthritis Res Ther. 2011;13(6):R190.
14. Martinez-Lavin M. Fibromyalgia as a sympathetically maintained pain syndrome. Curr Pain Headache Rep. oct 2004;8(5):385•9.
15. Kadetoff D, Kosek E. Evidence of reduced sympatho-adrenal and hypothalamic-pituitary activity during static muscular work in patients with fibromyalgia. J Rehabil Med. sept 2010;42(8):765•72.
16. Tak LM, Cleare AJ, Ormel J, Manoharan A, Kok IC, Wessely S, et al. Meta-analysis and meta-regression of hypothalamic-pituitary-adrenal axis activity in functional somatic disorders. Biol Psychol. mai 2011;87(2):183•94.
17. Riva R, Mork PJ, Westgaard RH, Lundberg U. Comparison of the cortisol awakening response in women with shoulder and neck pain and women with fibromyalgia. Psychoneuroendocrinology. févr 2012;37(2):299•306.
18. Geiss A, Rohleder N, Anton F. Evidence for an association between an enhanced reactivity of interleukin-6 levels and reduced glucocorticoid sensitivity in patients with fibromyalgia. Psychoneuroendocrinology. mai 2012;37(5):671•84.
19. Bote ME, García JJ, Hinchado MD, Ortega E. Inflammatory/stress feedback dysregulation in women with fibromyalgia. Neuroimmunomodulation. 2012;19(6):343•51.
20. Hellhammer DH, Wüst S, Kudielka BM. Salivary cortisol as a biomarker in stress research. Psychoneuroendocrinology. févr 2009;34(2):163•71.
21. Clauw D, Ablin J. The relationship between « stress » and pain: lessons learned from fibromyalgia and related conditions. In: Current topics in pain. Castro-Lopes editor. XIIth World Congress on Pain. Seattle: IASP press; 2009. p. p.245-270.
22. McKenzie DC. Markers of excessive exercise. Can J Appl Physiol Rev Can Physiol Appl. févr 1999;24(1):66•73.
23. MacKinnon LT. Special feature for the Olympics: effects of exercise on the immune system: overtraining effects on immunity and performance in athletes. Immunol Cell Biol. oct 2000;78(5):502•9.
24. Iellamo F, Pigozzi F, Parisi A, Di Salvo V, Vago T, Norbiato G, et al. The stress of competition dissociates neural and cortisol homeostasis in elite athletes. J Sports Med Phys Fitness. déc 2003;43(4):539•45.
25. Baumert M, Brechtel L, Lock J, Hermsdorf M, Wolff R, Baier V, et al. Heart rate variability, blood pressure variability, and baroreflex sensitivity in overtrained athletes. Clin J Sport Med Off J Can Acad Sport Med. sept 2006;16(5):412•7.
26. Kajaia T, Maskhulia L, Chelidze K, Akhalkatsi V, Kakhabrishvili Z. The effects of non-functional overreaching and overtraining on autonomic nervous system function in highly trained athletes. Georgian Med News. mars 2017;(264):97•103.
27. Fontenele JB, Felix FHC. Exercise for fibromyalgia: evidence for an integrated modulation of autonomic and nociception neural regulation. Rheumatol Int. déc 2012;32(12):4075•6.
28. Rossy LA, Buckelew SP, Dorr N, Hagglund KJ, Thayer JF, McIntosh MJ, et al. A meta-analysis of fibromyalgia treatment interventions. Ann Behav Med Publ Soc Behav Med. 1999;21(2):180•91.

29. Busch AJ, Webber SC, Brachaniec M, Bidonde J, Bello-Haas VD, Danyliw AD, et al. Exercise therapy for fibromyalgia. Curr Pain Headache Rep. oct 2011;15(5):358•67.
30. Woda A, L'heveder G, Ouchchane L, Bodéré C. Effect of experimental stress in 2 different pain conditions affecting the facial muscles. J Pain Off J Am Pain Soc. mai 2013;14(5):455•66.
31. Society AP, éditeur. Guideline for the Management of Fibromyalgia Syndrome Pain in Adults and Children. American Pain Society; 2005. 109 p.
32. Häuser W, Arnold B, Eich W, Felde E, Flügge C, Henningsen P, et al. Management of fibromyalgia syndrome – an interdisciplinary evidence-based guideline. GMS Ger Med Sci. 2008;6:Doc14.
33. Macfarlane GJ, Kronisch C, Atzeni F, Häuser W, Choy EH, Amris K, et al. EULAR recommendations for management of fibromyalgia. Ann Rheum Dis. déc 2017;76(12):e54.
34. Melanson EL, Freedson PS. The effect of endurance training on resting heart rate variability in sedentary adult males. Eur J Appl Physiol. sept 2001;85(5):442•9.
35. Reland S, Ville NS, Wong S, Gauvrit H, Kervio G, Carré F. Exercise heart rate variability of older women in relation to level of physical activity. J Gerontol A Biol Sci Med Sci. juill 2003;58(7):585•91.
36. de Abreu SB, Lenhard A, Mehanna A, de Souza HCD, Correa FM de A, Hasser EM, et al. Role of paraventricular nucleus in exercise training-induced autonomic modulation in conscious rats. Auton Neurosci Basic Clin. 15 juin 2009;148(1•2):28•35.
37. Martins-Pinge MC. Cardiovascular and autonomic modulation by the central nervous system after aerobic exercise training. Braz J Med Biol Res Rev Bras Pesqui Médicas E Biológicas Soc Bras Biofísica Al. sept 2011;44(9):848•54.
38. Häuser W, Klose P, Langhorst J, Moradi B, Steinbach M, Schiltenwolf M, et al. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials. Arthritis Res Ther. 2010;12(3):R79.
39. Bodéré C, Bodéré YT, Quinio B, Woda A, Misery L. Specific training program for the treatment of fibromyalgia: a prospective controlled study. In: 14th world congress on pain - TF505. Milan, Italy: IASP; 2012.
40. Lannersten L, Kosek E. Dysfunction of endogenous pain inhibition during exercise with painful muscles in patients with shoulder myalgia and fibromyalgia. Pain. oct 2010;151(1):77•86.
41. Krag NJ, Nørregaard J, Larsen JK, Danneskiold-Samsøe B. A blinded, controlled evaluation of anxiety and depressive symptoms in patients with fibromyalgia, as measured by standardized psychometric interview scales. Acta Psychiatr Scand. juin 1994;89(6):370•5.
42. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol. mai 1991;18(5):728•33.
43. Osorio CD, Gallinaro AL, Lorenzi-Filho G, Lage LV. Sleep quality in patients with fibromyalgia using the Pittsburgh Sleep Quality Index. J Rheumatol. sept 2006;33(9):1863•5.
44. Omachi TA. Measures of sleep in rheumatologic diseases: Epworth Sleepiness Scale (ESS), Functional Outcome of Sleep Questionnaire (FOSQ), Insomnia Severity Index (ISI), and Pittsburgh Sleep Quality Index (PSQI). Arthritis Care Res. nov 2011;63 Suppl 11:S287-296.
45. Crinière L, Lhommet C, Caille A, Giraudeau B, Lecomte P, Couet C, et al. Reproducibility and validity of the French version of the long international physical activity questionnaire in patients with type 2 diabetes. J Phys Act Health. août 2011;8(6):858•65.

46. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. déc 1983;24(4):385•96.
47. Marchand S, Arsenault P. Spatial summation for pain perception: interaction of inhibitory and excitatory mechanisms. Pain. févr 2002;95(3):201•6.
48. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain. mars 2005;114(1•2):295•302.
49. Granot M, Granovsky Y, Sprecher E, Nir R-R, Yarnitsky D. Contact heat-evoked temporal summation: tonic versus repetitive-phasic stimulation. Pain. juin 2006;122(3):295•305.
50. Barrett KE, Barman SM, Boitano S, Brooks H. Ganong's Review of Medical Physiology, 24th Edition. 24 edition. New York: McGraw-Hill Education / Medical; 2012. 768 p.
51. Potvin S, Paul-Savoie E, Morin M, Bourgault P, Marchand S. Temporal summation of pain is not amplified in a large proportion of fibromyalgia patients. Pain Res Treat. 2012;2012:938595.
52. Kirschbaum C, Hellhammer DH. Salivary cortisol in psychoneuroendocrine research: recent developments and applications. Psychoneuroendocrinology. 1994;19(4):313•33.

BMJ Open

# Impact of a specific training program on the neuromodulation of pain in fibromyalgia women (DouFiSport): a 24-month, controlled, randomised, double-blinded protocol.

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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2018-023742.R1 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 19-Jul-2018 |
| Complete List of Authors: | Le Fur Bonnabesse, Anais; Universite de Bretagne Occidentale Faculte de Medecine et des Sciences de la Sante de Brest, LIEN, EA4685; Universite de Bretagne Occidentale UFR d'Odontologie<br>Cabon, Mathilde; Universite de Bretagne Occidentale Faculte de Medecine et des Sciences de la Sante de Brest, LIEN, EA4685<br>L'Heveder, Gildas; CHRU de Brest, Explorations fonctionnelles neurologiques<br>Kermarrec, Aurélie ; CHRU de Brest, IFMK<br>Quinio, Bertrand; CHRU de Brest, Centre d'évaluation et de traitement de la douleur<br>Woda, Alain; Universite Clermont Auvergne Faculte de Chirurgie Dentaire, CROC EA3847<br>Marchand, Serge; Universite de Sherbrooke Faculte de medecine et des sciences de la sante, Department of surgery<br>Dubois, Amandine; Laboratoire de psychologie, Cognition, Behaviour, Communication (LP3C), EA1285; Universite de Bretagne Occidentale UFR Lettres et Sciences Humaines a Brest, Département de psychologie<br>Giroux-Metges, Marie-Agnes; Universite de Bretagne Occidentale Faculte de Medecine et des Sciences de la Sante de Brest, ORPHY EA4324; CHRU de Brest, Explorations fonctionnelles respiratoires<br>Rannou, Fabrice; Universite de Bretagne Occidentale Faculte de Medecine et des Sciences de la Sante de Brest, ORPHY EA4324; CHRU de Brest, Explorations fonctionnelles respiratoires<br>Misery, Laurent; Universite de Bretagne Occidentale Faculte de Medecine et des Sciences de la Sante de Brest, LIEN EA4685<br>Bodéré, Céline; Universite de Bretagne Occidentale Faculte de Medecine et des Sciences de la Sante de Brest, LIEN EA4685; CHRU de Brest, Centre d'évaluation et de traitement de la douleur |
| Primary Subject Heading: | Sports and exercise medicine |
| Secondary Subject Heading: | Medical education and training, Rehabilitation medicine, Rheumatology, Pharmacology and therapeutics |
| Keywords: | PAIN MANAGEMENT, MEDICAL EDUCATION & TRAINING, REHABILITATION MEDICINE, FIBROMYALGIA |

# Impact of a specific training program on the neuromodulation of pain in fibromyalgia women (DouFiSport): a 24-month, controlled, randomised, double-blinded protocol.

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## *ABSTRACT*

### *INTRODUCTION*

The main symptom of fibromyalgia (FM) is diffuse pain. There is currently no etiological treatment for FM. However, all pain associations and best practice guidelines highly recommend the practice of aerobic physical activity to improve the symptoms of FM subjects. The mechanisms of dysfunctional pain are mostly central (1) and related to stress axis dysfunction (autonomic nervous system and corticotropic axis) (2). The main objective is to assess the effectiveness of a specific training program on endogenous pain control mechanisms in female fibromyalgia patients. Further aims include rebalancing the autonomic neurovegetative system, improving the quality of life and sleep quality and reintegrating patients into society and work.

### *METHODS AND ANALYSIS*

110 FM women (according to the criteria of the ACR 2010), aged 18-65 years and respecting the inclusion criteria will be recruited and randomised in two groups (active or semi-active). The training program consists of three 45-minute sessions per week of supervised, individualised physical activity over two years. Only the intensity of the exercises is different between the two groups (moderate-intensity versus low-intensity).

All outcome measures will be conducted at baseline (T0), after 6 to 9 months of training (T6-9), then after 24 months of training (T24). The primary endpoint is the improvement of pain modulation (activation of diffuse noxious inhibitory control (DNIC)) evaluated by the stimulation test (1). The secondary endpoint will assess pain, anxiety, depression, stress, sleep disorders, pain impact on life quality, heart rate, blood pressure and salivary cortisol.

### *ETHICS AND DISSEMINATION:*

Approved by the Committee for the Protection of Persons West VI. Trial registration NCT02486965.

## Strengths and limitations of this study

► First randomised controlled double-blinded trial to assess the effects of a long-term training program (24 months) on pain control in fibromyalgia.

► To validate a training program acting on the autonomic system and to assess the neurovegetative rebalance on pain control.

► Physical activity intensity will be assessed objectively using a heart rate monitor.

► The dropout rate in patients may be important. These elements were taken into account in sample size.

► Due to the nature of the intervention, the coaching staff cannot be blinded.

*INTRODUCTION:*

Fibromyalgia affects 1.4 to 2.2% of the general population concerning predominately women (more than 80% of subjects). This syndrome is characterised by extensive and diffuse pain, mainly muscular and articular, impairing the functional abilities of the subjects. The symptoms most frequently described by fibromyalgia patients are chronic fatigue, sleep disorders, cognitive disorders and emotional disturbances (3,4). This symptomatology leads to a serious deterioration in quality of life, sometimes with a physical disability leading to social isolation and difficulties in staying in employment (recurrent work stoppages).

The diagnosis is based on the symptoms and their severity as described by the patients (5–8). Currently, there is no etiological treatment for fibromyalgia syndrome. The treatments are therefore only symptomatic.

## Physiopathology of fibromyalgia

The mechanisms of dysfunctional pain, without any identifiable organic lesions, are mostly central (1) and related to dysfunction of the stress axis (autonomic nervous system and corticotropic axis) (9–11).

At rest, fibromyalgia patients showed an increased sympathetic response and decreased parasympathetic tone (12,13). This neurovegetative dystonia is a marker of dysfunction of the stress axis (14).

Malfunctions of the corticotropic axis in fibromyalgia have been described multiple times, also marking the dysfunction of the stress axis. But the form taken by this dysfunction differs according to the different studies (15–19). The variability of salivary cortisol in response to stress reflects that of plasma free cortisol. Salivary cortisol is therefore a method of choice in experimental stress studies (20). Whatever form they take, these dysfunctions compromise the body's adaptation to daily stressful stimuli.

Studies show that this deficit of the stress axis (neurovegetative dystonia and dysfunctional corticotropic axis) is concurrent with fibromyalgia (21) and

associated with alteration of pain control (9–11). Pain control system and stress axis have close anatomical and functional links. Nociceptive, neurovegetative and corticotropic systems interact with the central nervous system. The central neuromediators implicated in the regulation of the stress axis are mostly common with those of the pain neuromodulation (endogenous opioids, norepinephrine, serotonin, etc.).

## Elite athlete's overtraining syndrome: model of stress axis dysfunction

An overtraining elite athlete may be considered as a model of dysfunction of the stress axis associated with neurovegetative dystonia. The physical and psychological effort of training is known to induce stress. High-level athletes could present an overtraining syndrome when adaptation limits of the stress axis are reached. This stress-induced phenomenon corresponds to an imbalance between training quantity and recovery. Overtrained athletes present a deconditioning syndrome close to fibromyalgia symptoms (chronic pain, sleep disorders, neurovegetative dystonia, etc.) (22–26).

## Physical activity and fibromyalgia

Most studies have shown that physical activity is more efficient compared to pharmacological treatments on fibromyalgia symptoms (27,28). Literature reviews and meta-analyses highly support the benefits of physical training in fibromyalgia patients (decreased pain and depression and improvement in overall health and physical abilities) (29)(30). Practice of aerobic exercise in fibromyalgia patients is strongly recommended by The American Pain Society (31), the Association of Medical Scientific Societies in Germany (32), the Canadian Rheumatology Association (5) and the European League Against Rheumatism (EULAR) (33). Physical exercise is the first-line treatment recommended in fibromyalgia. However there is still no consensus on the modalities of these types of training (frequency, duration, and intensity). Currently, the mechanisms underlying those specific training effects have to be defined.

The steady physical activity rebalancing autonomic system is associated with cardiovascular benefits. Physical activity increases parasympathetic tone and decreases sympathetic response (34–37). Mechanisms and structures involved in the activation and regulation of the neurovegetative system could interact with the central nervous system. Central relationships between the neurovegetative system and, the motor cortex, the limbic system, the hypothalamus, the pituitary gland and the basal ganglia will result in release of analgesic neurotransmitters such as adrenergic neurotransmitters (noradrenalin), serotonin and endogenous opioid (38)(39). This release of neurotransmitters due to exercise leads to increased endogenous inhibition and therefore decreases diffuse pain in FM (38). Central nervous system plasticity induced by physical training could regulate both cardiovascular adaptations (37) and endogenous pain control mechanisms (40)(41). Thus, strategies to rebalance the autonomic system are the most promising therapies for fibromyalgia (13,36,37).

In this study, we propose to validate a therapeutic alternative that aims to treat fibromyalgia by rebalancing the stress axis. This treatment consists of a specific supervised and individualised training program, over 2 years. This training protocol is individually adjusted in order to rebalance the neurovegetative system (parasympathetic and sympathetic). Central neuroplasticity induced by training should regulate endogenous pain control mechanisms. This specific protocol will be associated with psychotherapeutic approaches. In addition to the training program, multidisciplinary bio-psycho-social cares will be given in the pain centre of the university hospital of Brest (5).

## Objectives

The *main objective* is to assess the effectiveness of a specific training program on endogenous pain controls in fibromyalgia patients. The *secondary objectives* are to rebalance the autonomic nervous system and the corticotropic axis, to improve life and sleep quality and to reintegrate patients into society and work.

*METHODS AND ANALYSIS:*

## Design and setting

This randomised double-blind trial will compare an "active" program to a "semi-active" program in fibromyalgia patients. Patients will be recruited at the pain centre of the university hospital of Brest on the basis of general criteria. Patients should follow a re-exercise program for 24 months. The assessments will take place (i) before, (ii) between 6 to 9 months (depending the training level) and (iii) at the end of the training (24 months), in the neurological functional explorations department of the university hospital of Brest (fig.1).

## Patient and public involvement

The specific training program of this study was developed based on the results of a pilot study (42), data from literature and the experiences of fibromyalgia patients recorded at the pain centre of the University Hospital of Brest. These patients reported the benefits, constraints, difficulties, and effects of their training program on their symptoms. This information has allowed for adjustments to be made to the specific training program. Patients are not involved in the recruitment and conduct of the study. During the last assessment visit, patients will be asked to assess the burden of the intervention. Upon request, a report outlining the study findings will be given to study participants.

## Study population

110 fibromyalgia patients will be included. The inclusion criteria are: female subjects; aged of 18 to 65 years; with a diagnosis of fibromyalgia clearly established according to the criteria of the American College of Rheumatology (ACR) 2010; with a body mass index (BMI) between 18.5 and 29.9kg/m$^2$; spontaneous pain intensity higher than 3/10 on a visual analog scale (VAS); pain experienced at least 3 days a week; pain caused by palpation equal to or higher than 4/10 on a VAS.

The non-inclusion criteria are: patients with a systemic disease (treated or not) generating pain of the musculoskeletal system; presenting pain other than fibromyalgia; presenting a contraindication to physical activity; having any active pathology; having modified in the last 2 months any pharmacological treatment; having a psychiatric diagnosis; taking drugs that affect cortisol secretion (decrease or increase); non-cooperating.

## Sample size

Population size is based on an expected difference of 20 points (stimulation test) (1) between the two groups, for a quantitative primary endpoint (delta VAS) of standard deviation equal to 35, and a power set at 80%. Therefore a minimum of 48 subjects per group is required for assessment. In order to take into account loss to follow-up, the sample of 110 subjects, 55 per group will be recruited.

## Randomisation

Patients will be randomised at the end of the first stimulation test, which is just before the initiation of the training. Randomisation will be conducted by the Center of Clinical Investigation (CIC) at the hospital university of Brest (electronic randomisation via Capture System). The test is stratified by age and BMI. The cut off is set at 50 years for age and 25kg/m$^2$ for BMI (two strata [18-25] and ]25-30 []).

## Intervention: Training program

The training program is planned over two years (24 months) for both groups (active/semi-active). A minimum of 4 to 6 weeks is needed to observe a decrease in symptoms (42). This two-year duration is the minimum average training time (depending on the individual progress of each patient), necessary to regain central neuroplasticity sufficient to put back into operation diffuse noxious inhibitory controls (DNIC) and neurovegetative system (43).

The frequency, intensity, and duration of these training sessions are based upon both data from literature (42,44) and the results of a preliminary study. Pain was significantly reduced and symptoms, such as quality of life, sleep quality, anxiety,

were also highly improved in subjects undergoing this specific training after 5 years (43).

The American Pain Society recommends an intensity of 60 to 70% of the age-adjusted maximum heart rate (HRmax). At the early stage, the intensity and duration of the training sessions will be adapted to the physical condition of each subject. The intensity exercise will be 3 on the Borg CR10 scale (42). In order to promote adherence of our patients and to limit pain exacerbation, exercise intensity will start very low and then gradually increase to reach the neurovegetative goal (31)(45).

The ideal frequency is 3 training sessions per week during 45 minutes each (42,43).

**Active training group:**

*The first 6 to 9 months*:

Subjects will perform 3 sessions per week of 45 minutes of Moderate-Intensity Continuous Training MICT (65-75% HRmax), including 2 sessions supervised by a physiotherapist specially trained and 1 independent session.

*From 6-9 months (according to the rhythm, abilities, and limits) to 24 months*: Patients will begin the second stage of training: 3 sessions per week of at least 45 minutes each (MICT and High-Intensity Interval Training (HIIT)) with 1 supervised session and 2 independents sessions. When the patient reaches the initial HR goal, continuous training will be associated with interval training. HIIT will consist of 5 stages of 1 to 4 minutes at 85-90% HRmax, interspersed by 1 to 4 minutes of active recovery at 65-75% HRmax. Intensity will be assessed objectively using a heart rate monitor (FT2, Polar). At baseline, Tanaka's age-based prediction equation (208-0.7×age) will calculate HRmax. After *6-9 months of training, a* maximal-effort graded exercise test will determine HRmax and $V\dot{O}_2$max for each patient.

**Semi-Active group:**

Patients will perform the same infra active training (low-intensity continuous training: LICT <50% HRmax) over two years. Supervision, monitoring, and

frequency of sessions (3 x 45 minutes per week) in both groups will be equivalent.

**Training follow-up (for both groups):**

Patients will be contacted to record progress, difficulties and if necessary, to encourage them to adhere to their program. These calls will improve the compliance and will limit patients lost to follow-up (46,47). Subjects will note the characteristics (frequency, duration, intensity, type of activity, and supervision) of each training session (both supervised and independent) in a specific training logbook. The physiotherapist will frequently ask patients about their independent training session to provide advice and to motivate them. The follow-up at the pain centre will assess the compliance with the training protocol.

Patients will perform a 6-minute walk test (6MWT) every 6 months (with physiotherapist). If a patient cannot achieve the specific training requested after 9 months of study, the patient will not complete the second phase of training. Nevertheless, she will carry out all assessment visits. The main analysis will be performed on an intent-to-treat basis.

## Clinical Data, Measurements and Assessments

### Sociodemographic and clinical data

At baseline, data on age, sex, marital status, education level, and occupation will be collected. Height and weight will be recorded. Medical background and pain characteristics will be noted. All current drug and non-drug therapies (including tried and stopped) will also be collected, as well as their effectiveness on pain.

### Questionnaires and pain assessments

Measurements and questionnaires will be carried out (i) at baseline, (ii) between 6 to 9 months, and (iii) at the end of the 24 months of training.

- The **assessment of pain** will be performed by a simple verbal scale and using a visual analog scale (VAS). The Saint Antoine Pain Questionnaire

(QDSA) will also assess pain. A **pain quantitative assessment** will be performed with a pressure algometer (pressure pain threshold: PPT).

- The Hospital Anxiety Depression Scale (HADS) will assess the **patient anxiodepressive state** (48).
- The Fibromyalgia Impact Questionnaire (FIQ) will assess **the impact of fibromyalgia on daily life** (49).
- The Pittsburgh Sleep Quality Index (PSQI) will assess **sleep quality and quantity** (50,51).
- The International Physical Activity Questionnaire (IPAQ) will record the **level of physical activity and the sedentary lifestyle**. The French long telephone questionnaire will be used (52).
- The Perceived Stress Scale (PSS) will assess **the antecedents of perceived stress** (53).

**Stimulation test**

In order to assess endogenous pain mechanisms, such as diffuse noxious inhibitory controls (DNIC), temporal summation (TS) and perception of pain, we will use an experimental method developed by Tousignant-Laflamme and Marchand (2008). According to this well-characterised paradigm, we will induce in single session two tonic heat pain stimulations separated by a cold pressor test (1,54–56).

- Thermode test or temporal summation test **(P1):** a tonic heat pain will be administered for 2 minutes on the patient's right arm, using a thermode (CE marking n°226). The starting temperature is 32°C (skin temperature under normal conditions in temperate room (20-22°C)) (57) and will quickly reach a fixed value. The experimental temperature will be individually determined to induce 50/100 on a VAS and will remain constant during the test period (2 minutes). Throughout this entire period, the patient will evaluate their pain intensity using a Computerised Visual Analog Scale (CoVAS).

- Cold pressor test **(P2):** to elicit a prolonged pain sensation in order to trigger diffuse noxious inhibitory control (DNIC) (58), the patient's right arm will

be immersed for 2 minutes in a cold water bath maintained at 12°C. The patient will continuously evaluate their pain intensity using a CoVAS.

Following this cold pressor test, the thermode test will be again performed **(P3).** Pain difference between the two (P3/P1) tonic heat pain stimulations will measure DNIC activation and represents pain modulation.

**Measurement of salivary cortisol and salivary flow**

Corticotropic axis will be assessed using measurement of salivary cortisol. Cortisol release is pulsatile (10 to 20 peaks per day) and follows a nycthemeral cycle. Maximum cortisol level is reached in the early morning. In the morning of each consultation (at baseline, in the middle and at the end of training), patients will collect salivary sample (i) for 2 minutes, when they wake up and (ii) for 2 minutes, 30 minutes later. The salivary cortisol level is measured in nmol/l. The flow rate is calculated in $ml.min^{-1}$. Samples will be frozen at -20°C. As salivary cortisol is stable, samples can be stored for many weeks in the freezer (59). After completion of all assessment sessions, sample analysis will be completed. To avoid inter-laboratory variation, the same laboratory will assay the samples.

**Recording of Blood Pressure (BP) and Heart Rate (HR)**

After 10 minutes at rest, lying down, BP and HR will be recorded. Then, BP and HR will be measured when the patient stands up and once per minute during 4 minutes when the patient remains standing.

## Blinding strategy

Patients will not be informed of their group (active/semi-active). The investigators will not know the patient's group. Due to the nature of the intervention (physical activity protocol), the coaching staff will not be blinded.

## Statistical analysis

*Primary endpoint analysis*: The VAS improvements (stimulation test) obtained in the both groups will be compared using the Student's test. If the required normality assumption is not sustainable, a nonparametric Wilcoxon test will be used. An alpha risk of 0.05 will be set as the limit of statistical significance. The

main analysis will be performed on an intent-to-treat basis. A complementary analysis using a linear model with adjustment for age and BMI factors will be completed.

*The secondary endpoints* (quantitative: salivary cortisol, blood pressure, PPT quantified by pain threshold pressure, questionnaires assessment) will be analysed in a similar way by comparing the improvements obtained between both groups.

## Methodological limitations

The methodology of this protocol is consistent with the recommendations of the Standard Protocol Items for Randomised Trials (SPIRIT). However, because of the nature of the intervention, the coaching staff cannot be blinded. Patients and investigators will be blinded.

According to the study duration (2 years), the potential participant dropout and potential patients lost to follow-up may be important. These elements were taken into account in sample size. To limit dropout, patients will be called to encourage them and to discuss any difficulties. In second stage of training and to limit a possible long-term monotonous effect, physical activity type could be diversified in both groups. The training session will be adapted in the active group (MICT will be associated with HIIT) to reduce sympathetic hyperactivity. In order to improve compliance and long-term achievement of training, the patient may choose the physical activity type performed without supervision.

# *ETHICS AND DISSEMINATION*

### Ethics approval and consent to participate

The Committee for the Protection of Persons West VI approved this study. Patients will be informed of the objectives, constraints, risks and benefits of the study. To be included, patients will sign informed written consent. Data will be collected anonymously. The investigators will take all necessary precautions to ensure the confidentiality of the information in particular with regard to patient identity.

**Dissemination plan**

The results of this study will be published in specialised scientific journals. These results will also be presented in pain and/or physical activity congresses. In addition, a doctoral thesis will be carried out on this project.

## TRIAL REGISTRATION NUMBER: NCT02486965

**Acknowledgements**
The authors thank Julie Lelièvre, Marie Le Bellego, Youenn-Thor Bodéré for designing and implementing this protocol. The authors thank the translation service of the University of Western Brittany and Phillipa Perrot for English language revision.

**Contributors**
CB initiated the idea for the project. CB and ALFB developed the study design. MC, GL, BQ, AK, AW, SM, MAGM, FR, LM and AD provided advice for the study design. GL and CB were responsible for supervision of project. CB will conduct the recruitment. AK will conduct the training programme. CB, ALFB and MC will conduct the outcomes assessments and will contribute to the analysis and interpretation of the data. Both authors will contribute to the analyses and interpretation of the data. ALFB, CB and MC wrote early drafts of the manuscript. All authors approved the final version of this protocol.

**Funding Statement**
This work is supported by the French Ministry of Health (Programme Hospitalier de Recherche Clinique Interrégional 2014, project no 2014-A00743-44) PHRCi 13-100

**Competing Interests**
None declared.

**Ethics approval**
Committee for the Protection of Persons West VI

**Provenance and peer review**
Not commissioned; externally peer reviewed.

## References

1. Tousignant-Laflamme Y, Pagé S, Goffaux P, Marchand S. An experimental model to measure excitatory and inhibitory pain mechanisms in humans. Brain Res. 16 sept 2008;1230:73□9.
2. Woda A, L'heveder G, Ouchchane L, Bodéré C. Effect of experimental stress in 2 different pain conditions affecting the facial muscles. J Pain Off J Am Pain Soc. mai 2013;14(5):455□66.
3. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. févr 1990;33(2):160□72.
4. Cánovas R, León I, Roldán MD, Astur R, Cimadevilla JM. Virtual reality tasks disclose spatial memory alterations in fibromyalgia. Rheumatol Oxf Engl. oct 2009;48(10):1273□8.
5. Fitzcharles M, Shir Y, Ablin JN, Buskila D, Amital H, Henningsen P, et al. Classification and clinical diagnosis of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines. Evid-Based Complement Altern Med ECAM. 2013;2013:528952.
6. Egloff N, von Känel R, Müller V, Egle UT, Kokinogenis G, Lederbogen S, et al. Implications of proposed fibromyalgia criteria across other functional pain syndromes. Scand J Rheumatol. 2015;44(5):416□24.
7. Moyano S, Kilstein JG, Alegre de Miguel C. New diagnostic criteria for fibromyalgia: Here to stay? Reumatol Clin. août 2015;11(4):210□4.
8. Wolfe F, Fitzcharles M-A, Goldenberg DL, Häuser W, Katz RL, Mease PJ, et al. Comparison of Physician-Based and Patient-Based Criteria for the Diagnosis of Fibromyalgia. Arthritis Care Res. mai 2016;68(5):652□9.
9. Bodéré C, Woda A. La douleur orofaciale idiopathique: une douleur fonctionnelle. Douleur Analgésie. 21 juin 2009;22(2):89□95.
10. Woda A, Dao T, Gremeau-Richard C. Steroid dysregulation and stomatodynia (burning mouth syndrome). J Orofac Pain. 2009;23(3):202□10.
11. Woda A, L'heveder G, Ouchchane L, Bodéré C. Effect of experimental stress in 2 different pain conditions affecting the facial muscles. J Pain Off J Am Pain Soc. mai 2013;14(5):455□66.
12. Cohen H, Neumann L, Shore M, Amir M, Cassuto Y, Buskila D. Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability. Semin Arthritis Rheum. févr 2000;29(4):217□27.
13. da Cunha Ribeiro RP, Roschel H, Artioli GG, Dassouki T, Perandini LA, Calich AL, et al. Cardiac autonomic impairment and chronotropic incompetence in fibromyalgia. Arthritis Res Ther. 2011;13(6):R190.
14. Martinez-Lavin M. Fibromyalgia as a sympathetically maintained pain syndrome. Curr Pain Headache Rep. oct 2004;8(5):385□9.
15. Kadetoff D, Kosek E. Evidence of reduced sympatho-adrenal and hypothalamic-pituitary activity during static muscular work in patients with fibromyalgia. J Rehabil Med. sept 2010;42(8):765□72.
16. Tak LM, Cleare AJ, Ormel J, Manoharan A, Kok IC, Wessely S, et al. Meta-analysis and meta-regression of hypothalamic-pituitary-adrenal axis activity in functional somatic disorders. Biol Psychol. mai 2011;87(2):183□94.

17. Riva R, Mork PJ, Westgaard RH, Lundberg U. Comparison of the cortisol awakening response in women with shoulder and neck pain and women with fibromyalgia. Psychoneuroendocrinology. févr 2012;37(2):299□306.
18. Geiss A, Rohleder N, Anton F. Evidence for an association between an enhanced reactivity of interleukin-6 levels and reduced glucocorticoid sensitivity in patients with fibromyalgia. Psychoneuroendocrinology. mai 2012;37(5):671□84.
19. Bote ME, García JJ, Hinchado MD, Ortega E. Inflammatory/stress feedback dysregulation in women with fibromyalgia. Neuroimmunomodulation. 2012;19(6):343□51.
20. Hellhammer DH, Wüst S, Kudielka BM. Salivary cortisol as a biomarker in stress research. Psychoneuroendocrinology. févr 2009;34(2):163□71.
21. Clauw D, Ablin J. The relationship between « stress » and pain: lessons learned from fibromyalgia and related conditions. In: Current topics in pain. Castro-Lopes editor. XIIth World Congress on Pain. Seattle: IASP press; 2009. p. p.245-270.
22. McKenzie DC. Markers of excessive exercise. Can J Appl Physiol Rev Can Physiol Appl. févr 1999;24(1):66□73.
23. MacKinnon LT. Special feature for the Olympics: effects of exercise on the immune system: overtraining effects on immunity and performance in athletes. Immunol Cell Biol. oct 2000;78(5):502□9.
24. Iellamo F, Pigozzi F, Parisi A, Di Salvo V, Vago T, Norbiato G, et al. The stress of competition dissociates neural and cortisol homeostasis in elite athletes. J Sports Med Phys Fitness. déc 2003;43(4):539□45.
25. Baumert M, Brechtel L, Lock J, Hermsdorf M, Wolff R, Baier V, et al. Heart rate variability, blood pressure variability, and baroreflex sensitivity in overtrained athletes. Clin J Sport Med Off J Can Acad Sport Med. sept 2006;16(5):412□7.
26. Kajaia T, Maskhulia L, Chelidze K, Akhalkatsi V, Kakhabrishvili Z. The effects of non-functional overreaching and overtraining on autonomic nervous system function in highly trained athletes. Georgian Med News. mars 2017;(264):97□103.
27. Fontenele JB, Felix FHC. Exercise for fibromyalgia: evidence for an integrated modulation of autonomic and nociception neural regulation. Rheumatol Int. déc 2012;32(12):4075□6.
28. Rossy LA, Buckelew SP, Dorr N, Hagglund KJ, Thayer JF, McIntosh MJ, et al. A meta-analysis of fibromyalgia treatment interventions. Ann Behav Med Publ Soc Behav Med. 1999;21(2):180□91.
29. Busch AJ, Webber SC, Brachaniec M, Bidonde J, Bello-Haas VD, Danyliw AD, et al. Exercise therapy for fibromyalgia. Curr Pain Headache Rep. oct 2011;15(5):358□67.
30. Woda A, L'heveder G, Ouchchane L, Bodéré C. Effect of experimental stress in 2 different pain conditions affecting the facial muscles. J Pain Off J Am Pain Soc. mai 2013;14(5):455□66.
31. Society AP, éditeur. Guideline for the Management of Fibromyalgia Syndrome Pain in Adults and Children. American Pain Society; 2005. 109 p.
32. Häuser W, Arnold B, Eich W, Felde E, Flügge C, Henningsen P, et al. Management of fibromyalgia syndrome – an interdisciplinary evidence-based

guideline. GMS Ger Med Sci [Internet]. 9 déc 2008 [cité 7 févr 2018];6. Disponible sur: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2703259/

33. Macfarlane GJ, Kronisch C, Atzeni F, Häuser W, Choy EH, Amris K, et al. EULAR recommendations for management of fibromyalgia. Ann Rheum Dis. déc 2017;76(12):e54.

34. Melanson EL, Freedson PS. The effect of endurance training on resting heart rate variability in sedentary adult males. Eur J Appl Physiol. sept 2001;85(5):442□9.

35. Reland S, Ville NS, Wong S, Gauvrit H, Kervio G, Carré F. Exercise heart rate variability of older women in relation to level of physical activity. J Gerontol A Biol Sci Med Sci. juill 2003;58(7):585□91.

36. de Abreu SB, Lenhard A, Mehanna A, de Souza HCD, Correa FM de A, Hasser EM, et al. Role of paraventricular nucleus in exercise training-induced autonomic modulation in conscious rats. Auton Neurosci Basic Clin. 15 juin 2009;148(1□2):28□35.

37. Martins-Pinge MC. Cardiovascular and autonomic modulation by the central nervous system after aerobic exercise training. Braz J Med Biol Res Rev Bras Pesqui Médicas E Biológicas Soc Bras Biofísica Al. sept 2011;44(9):848□54.

38. Brito RG, Rasmussen LA, Sluka KA. Regular physical activity prevents development of chronic muscle pain through modulation of supraspinal opioid and serotonergic mechanisms. Pain Rep. sept 2017;2(5):e618.

39. Da Silva Santos R, Galdino G. Endogenous systems involved in exercise-induced analgesia. J Physiol Pharmacol Off J Pol Physiol Soc. févr 2018;69(1):3□13.

40. Naugle KM, Naugle KE, Fillingim RB, Samuels B, Riley JL. Intensity thresholds for aerobic exercise-induced hypoalgesia. Med Sci Sports Exerc. avr 2014;46(4):817□25.

41. Law LF, Sluka KA. How does physical activity modulate pain? Pain. 2017;158(3):369□70.

42. Häuser W, Klose P, Langhorst J, Moradi B, Steinbach M, Schiltenwolf M, et al. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials. Arthritis Res Ther. 2010;12(3):R79.

43. Bodéré C, Bodéré YT, Quinio B, Woda A, Misery L. Specific training program for the treatment of fibromyalgia: a prospective controlled study. In: 14th world congress on pain - TF505. Milan, Italy: IASP; 2012.

44. Bidonde J, Busch AJ, Bath B, Milosavljevic S. Exercise for adults with fibromyalgia: an umbrella systematic review with synthesis of best evidence. Curr Rheumatol Rev. 2014;10(1):45□79.

45. Lannersten L, Kosek E. Dysfunction of endogenous pain inhibition during exercise with painful muscles in patients with shoulder myalgia and fibromyalgia. Pain. oct 2010;151(1):77□86.

46. Franke K-J, Domanski U, Schroeder M, Jansen V, Artmann F, Weber U, et al. Telemonitoring of home exercise cycle training in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2016;11:2821□9.

47. Yasmin F, Banu B, Zakir SM, Sauerborn R, Ali L, Souares A. Positive influence of short message service and voice call interventions on adherence and health outcomes in case of chronic disease care: a systematic review. BMC Med

Inform Decis Mak. 22 avr 2016;16:46.
48. Krag NJ, Nørregaard J, Larsen JK, Danneskiold-Samsøe B. A blinded, controlled evaluation of anxiety and depressive symptoms in patients with fibromyalgia, as measured by standardized psychometric interview scales. Acta Psychiatr Scand. juin 1994;89(6):370□5.
49. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol. mai 1991;18(5):728□33.
50. Osorio CD, Gallinaro AL, Lorenzi-Filho G, Lage LV. Sleep quality in patients with fibromyalgia using the Pittsburgh Sleep Quality Index. J Rheumatol. sept 2006;33(9):1863□5.
51. Omachi TA. Measures of sleep in rheumatologic diseases: Epworth Sleepiness Scale (ESS), Functional Outcome of Sleep Questionnaire (FOSQ), Insomnia Severity Index (ISI), and Pittsburgh Sleep Quality Index (PSQI). Arthritis Care Res. nov 2011;63 Suppl 11:S287-296.
52. Crinière L, Lhommet C, Caille A, Giraudeau B, Lecomte P, Couet C, et al. Reproducibility and validity of the French version of the long international physical activity questionnaire in patients with type 2 diabetes. J Phys Act Health. août 2011;8(6):858□65.
53. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. déc 1983;24(4):385□96.
54. Marchand S, Arsenault P. Spatial summation for pain perception: interaction of inhibitory and excitatory mechanisms. Pain. févr 2002;95(3):201□6.
55. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain. mars 2005;114(1□2):295□302.
56. Granot M, Granovsky Y, Sprecher E, Nir R-R, Yarnitsky D. Contact heat-evoked temporal summation: tonic versus repetitive-phasic stimulation. Pain. juin 2006;122(3):295□305.
57. Barrett KE, Barman SM, Boitano S, Brooks H. Ganong's Review of Medical Physiology, 24th Edition. 24 edition. New York: McGraw-Hill Education / Medical; 2012. 768 p.
58. Potvin S, Paul-Savoie E, Morin M, Bourgault P, Marchand S. Temporal summation of pain is not amplified in a large proportion of fibromyalgia patients. Pain Res Treat. 2012;2012:938595.
59. Kirschbaum C, Hellhammer DH. Salivary cortisol in psychoneuroendocrine research: recent developments and applications. Psychoneuroendocrinology. 1994;19(4):313□33.

**Figure legends:**

Figure 1: Flow Chart of DouFiSport

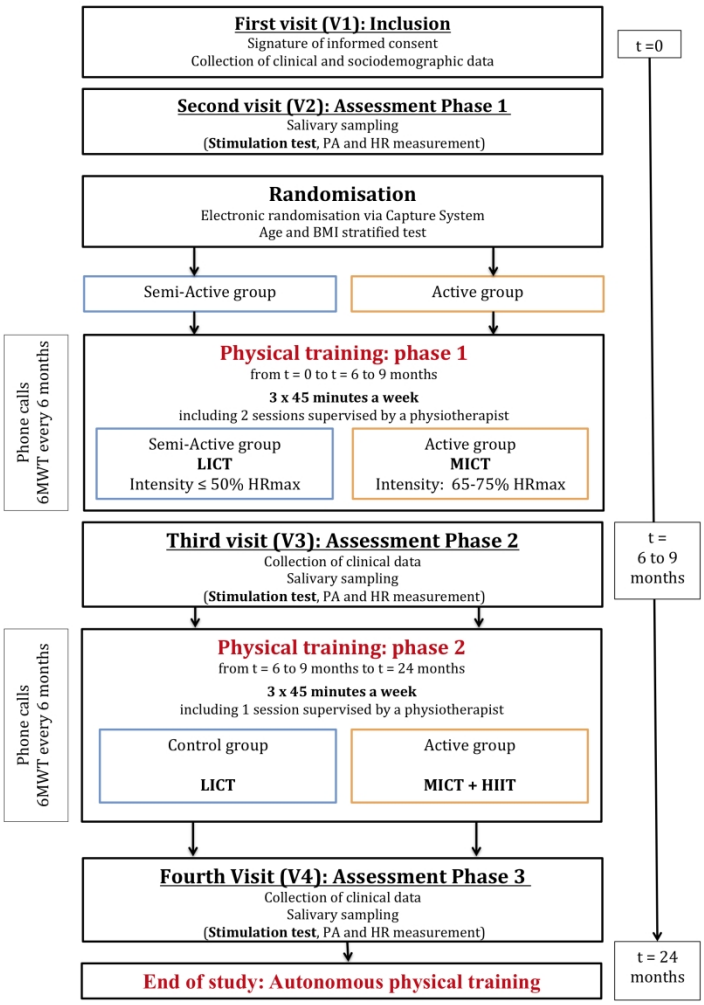


Figure 1: Flow Chart of DouFiSPort

209x297mm (300 x 300 DPI)


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Impact of a specific training program on the neuromodulation of pain in fibromyalgia women (DouFiSport): a 24-month, controlled, randomised, double-blinded protocol. |
| Trial registration | 2a | NCT02486965 |
| Protocol version | 3 | version number 5.0 of 21/06/2016 |
| Funding | 4 | This work is supported by the French Ministry of Health (Programme Hospitalier de Recherche Clinique Interrégional 2014) PHRCi 13-100 |

| | | |
|---|---|---|
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors: |

Anaïs Le Fur-Bonnabesse[1,2,3], investigator
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CB initiated the idea for the project.
CB and ALFB developed the study design.
MC, GL, BQ, AK, AW, SM, MAGM, FR, LM and AD provided advice for the study design.
GL and CB are responsible for supervision of project. CB will conduct the recruitment.
AK will conduct the training programme.
CB, ALFB and MC will conduct the outcomes assessments and will contribute to the analysis and interpretation of the data.
Both authors will contribute to the analyses and interpretation of the data.
ALFB, CB and MC wrote early drafts of the manuscript.
All authors approved the final version of this protocol.

5b Name and contact information for the trial sponsor:

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5c Role of study sponsor and funders :

- Evaluation of serious adverse events
- Transmission of annual safety reports
- Quality assurance and monitoring activities
- Approval of any amendment of the protocol

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| Background and rationale | 6a | Fibromyalgia affects 1.4 to 2.2% of the general population concerning predominately women (more than 80% of subjects). This syndrome is characterised by extensive and diffuse pain, mainly muscular and articular, impairing the functional abilities of the subjects. The symptoms most frequently described by fibromyalgia patients are chronic fatigue, sleep disorders, cognitive disorders and emotional disturbances (3,4). This symptomatology leads to a serious deterioration in quality of life, sometimes with a physical disability leading to social isolation and difficulties in staying in employment (recurrent work stoppages).<br>The diagnosis is based on the symptoms and their severity as described by the patients (5–8). Currently, there is no etiological treatment for fibromyalgia syndrome. The treatments are therefore only symptomatic.<br><br>**Physiopathology of fibromyalgia**<br>The mechanisms of dysfunctional pain, without any identifiable organic lesions, are mostly central (1) and related to dysfunction of the stress axis (autonomic nervous system and corticotropic axis) (9–11).<br>At rest, fibromyalgia patients showed an increased sympathetic response and decreased parasympathetic tone (12,13). This neurovegetative dystonia is a marker of dysfunction of the stress axis (14).<br>Malfunctions of the corticotropic axis in fibromyalgia have been described multiple times, also marking the dysfunction of the stress axis. But the form taken by this dysfunction differs according to the different studies (15–19). The variability of salivary cortisol in response to stress reflects that of plasma free cortisol. Salivary cortisol is therefore a method of choice in experimental stress studies (20).<br>Whatever form they take, these dysfunctions compromise the body's adaptation to daily stressful stimuli.<br><br>Studies show that this deficit of the stress axis (neurovegetative dystonia and dysfunctional corticotropic axis) is concurrent with fibromyalgia (21) and associated with alteration of pain control (9–11).<br>Pain control system and stress axis have close anatomical and functional links. Nociceptive, neurovegetative and corticotropic systems interact with the central nervous system. The central neuromediators implicated in the regulation of the stress axis are mostly common with those of the pain neuromodulation (endogenous opioids, norepinephrine, serotonin, etc.). |

**Elite athlete's overtraining syndrome: model of stress axis dysfunction**

An overtraining elite athlete may be considered as a model of dysfunction of the stress axis associated with neurovegetative dystonia. The physical and psychological effort of training is known to induce stress. High-level athletes could present an overtraining syndrome when adaptation limits of the stress axis are reached. This stress-induced phenomenon corresponds to an imbalance between training quantity and recovery. Overtrained athletes present a deconditioning syndrome close to fibromyalgia symptoms (chronic pain, sleep disorders, neurovegetative dystonia, etc.) (22–26).

**Physical activity and fibromyalgia**

Most studies have shown that physical activity is more efficient compared to pharmacological treatments on fibromyalgia symptoms (27,28). Literature reviews and meta-analyses highly support the benefits of physical training in fibromyalgia patients (decreased pain and depression and improvement in overall health and physical abilities) (29)(30). Practice of aerobic exercise in fibromyalgia patients is strongly recommended by The American Pain Society (31), the Association of Medical Scientific Societies in Germany (32), the Canadian Rheumatology Association (5) and the European League Against Rheumatism (EULAR) (33). Physical exercise is the first-line treatment recommended in fibromyalgia. However there is still no consensus on the modalities of these types of training (frequency, duration, and intensity). Currently, the mechanisms underlying those specific training effects have to be defined.

The steady physical activity rebalancing autonomic system is associated with cardiovascular benefits. Fundamental endurance increases parasympathetic tone and decrease sympathetic response (34–37). Thus, strategies to rebalance the autonomic system are the most promising therapies for fibromyalgia (13,36,37).

In this study, we propose to validate a therapeutic alternative that aims to treat fibromyalgia by rebalancing the stress axis. This treatment consists of a specific supervised and individualised training program, over 2 years. This training protocol is individually adjusted in order to rebalance the neurovegetative system (parasympathetic and sympathetic). Central neuroplasticity induced by training should regulate endogenous pain control mechanisms.

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| Objectives | 7 | The *main objective* is to assess the effectiveness of a specific training program on endogenous pain controls in fibromyalgia patients. The *secondary objectives* are to rebalance the autonomic nervous system and the corticotropic axis, to improve life and sleep quality and to reintegrate patients into society and work. |

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| Trial design | 8 | This randomised double-blinded trial will compare an "active" program to a "control" program in fibromyalgia patients. |

**Methods: Participants, interventions, and outcomes**

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| Study setting | 9 | Patients will be recruited at the pain center of the university hospital of Brest on the basis of general criteria. Patients should follow a re-exercise program for 24 months. The assessments will take place (i) before, (ii) between 6 to 9 months (depending the training level) and (iii) at the end of the training (24 months), in the neurological functional explorations department of the university hospital of Brest (France). |
| Eligibility criteria | 10 | The inclusion criteria are: female subjects; aged of 18 to 65 years; with a diagnosis of fibromyalgia clearly established according to the criteria of the American College of Rheumatology (ACR) 2010; with a body mass index (BMI) between 18.5 and 29.9kg/m²; spontaneous pain intensity higher than 3/10 on a visual analog scale (VAS); pain experienced at least 3 days a week; pain caused by palpation equal to or higher than 4/10 on a VAS.<br><br>The non-inclusion criteria are: patients with a systemic disease (treated or not) generating pain of the musculoskeletal system; presenting pain other than fibromyalgia; presenting a contraindication to physical activity; having any active pathology; having modified in the last 2 months any pharmacological treatment; having a psychiatric diagnosis; taking drugs that affect cortisol secretion (decrease or increase); non-cooperating. |

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| Interventions | 11a | The training program is planned over two years (24 months) for both groups (active/control). A minimum of 4 to 6 weeks is needed to observe a decrease in symptoms (38). This two-year duration is the minimum average training time (depending on the individual progress of each patient), necessary to regain central neuroplasticity sufficient to put back into operation diffuse noxious inhibitory controls (DNIC) and neurovegetative system (39).<br>The frequency, intensity, and duration of these training sessions are based upon the results of a preliminary study. Pain was significantly reduced and symptoms, such as quality of life, sleep quality, anxiety, were also highly improved in subjects undergoing this specific training after 5 years (39). The American Pain Society recommends an intensity of 60 to 70% of the age-adjusted maximum heart rate (HRmax). At the early stage, the intensity and duration of the training sessions will be adapted to the physical condition of each subject. In order to promote adherence of our patients and to limit pain exacerbation, exercise intensity will start very low and then gradually increase to reach the neurovegetative goal (31)(40).<br><br>**Active training group:**<br>*The first 6 to 9 months*: fundamental endurance training.<br>Subjects will perform 3 sessions per week of 45 minutes of fundamental endurance (moderate-intensity continuous training MICT: 60% HRmax), including 2 sessions supervised by a physiotherapist and 1 independent session.<br>*From 6-9 months (according to the rhythm, abilities, and limits) to 24 months*: Patients will begin the second stage of training: 3 sessions per week of 45 minutes each (moderate-intensity continuous training MICT (60% HRmax) and high-intensity interval training HIIT) with 1 supervised session and 2 independents sessions. When the patient reaches the initial HR goal, “fundamental endurance” will be associated with “interval training” at a high frequency intensity. HIIT will consist of 5 stages of 1 to 4 minutes at 85-90% HRmax (80-85% $V\dot{O}_2$max), interspersed by 1 to 4 minutes of active recovery at 60-75% HRmax (50-70% $V\dot{O}_2$max). Intensity will be assessed objectively using a heart rate monitor (FT2, Polar). At baseline, Tanaka’s age-based prediction equation (208-0.7×age) will calculate HRmax. After *6-9 months of training, a* maximal-effort graded exercise test will determine HRmax and $V\dot{O}_2$max for each patient.<br><br>**Control group:**<br>Patients will perform the same infra active training (low-intensity continuous training: LICT <50% HRmax) over two years. Supervision, monitoring, and frequency of sessions (3 x 45 minutes per week) in both groups will be equivalent. |

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant: If a patient cannot achieve the specific training requested after 9 months of study, the patient will not complete the second phase of training.

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence: Patients will be contacted to record progress, difficulties and if necessary, to encourage them to adhere to their program. These calls will improve the compliance and will limit patients lost to follow-up.
Patients will perform a 6-minute walk test (6MWT) every 6 months (with physiotherapist).

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial: This specific protocol will be associated with psychotherapeutic approaches. In addition to the training program, multidisciplinary bio-psycho-social cares will be given in the pain center of the university hospital of Brest (France).

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| Outcomes | 12 | **Primary outcomes:** In order to assess endogenous pain mechanisms, such as diffuse noxious inhibitory controls (DNIC), temporal summation (TS) and perception of pain, we will use an experimental method developed by Tousignant-Laflamme and Marchand (2008). According to this well-characterised paradigm**,** we will induce in single session two tonic heat pain stimulations separated by a cold pressor test (1,47–49). The VAS improvements (stimulation test) obtained in the both groups will be compared.<br><br>**Secondary outcomes:**<br>A simple verbal scale, a visual analog scale, and the Saint Antoine Pain Questionnaire (QDSA), will perform the **assessment of pain**. A **pain quantitative assessment** will be performed with a pressure algometer (pressure pain threshold: PPT).<br>Questionnaires will assess **patient anxiodepressive state** (Hospital Anxiety Depression Scale), **the impact of fibromyalgia on daily life** (Fibromyalgia Impact Questionnaire), **sleep quality and quantity** (Pittsburgh Sleep Quality Index), **the level of physical activity and the sedentary lifestyle** (International Physical Activity Questionnaire), **the antecedents of perceived stress** (Perceived Stress Scale).<br>**Blood Pressure** (BP) and **Heart Rate** (HR) will be recorded.<br>**Corticotropic axis** will be assessed using measurement of salivary cortisol and salivary flow.<br><br>Quantitative assessment (salivary cortisol, blood pressure, PPT quantified by pain threshold pressure, questionnaires assessment) will be analysed by comparing the improvements obtained between both groups. |

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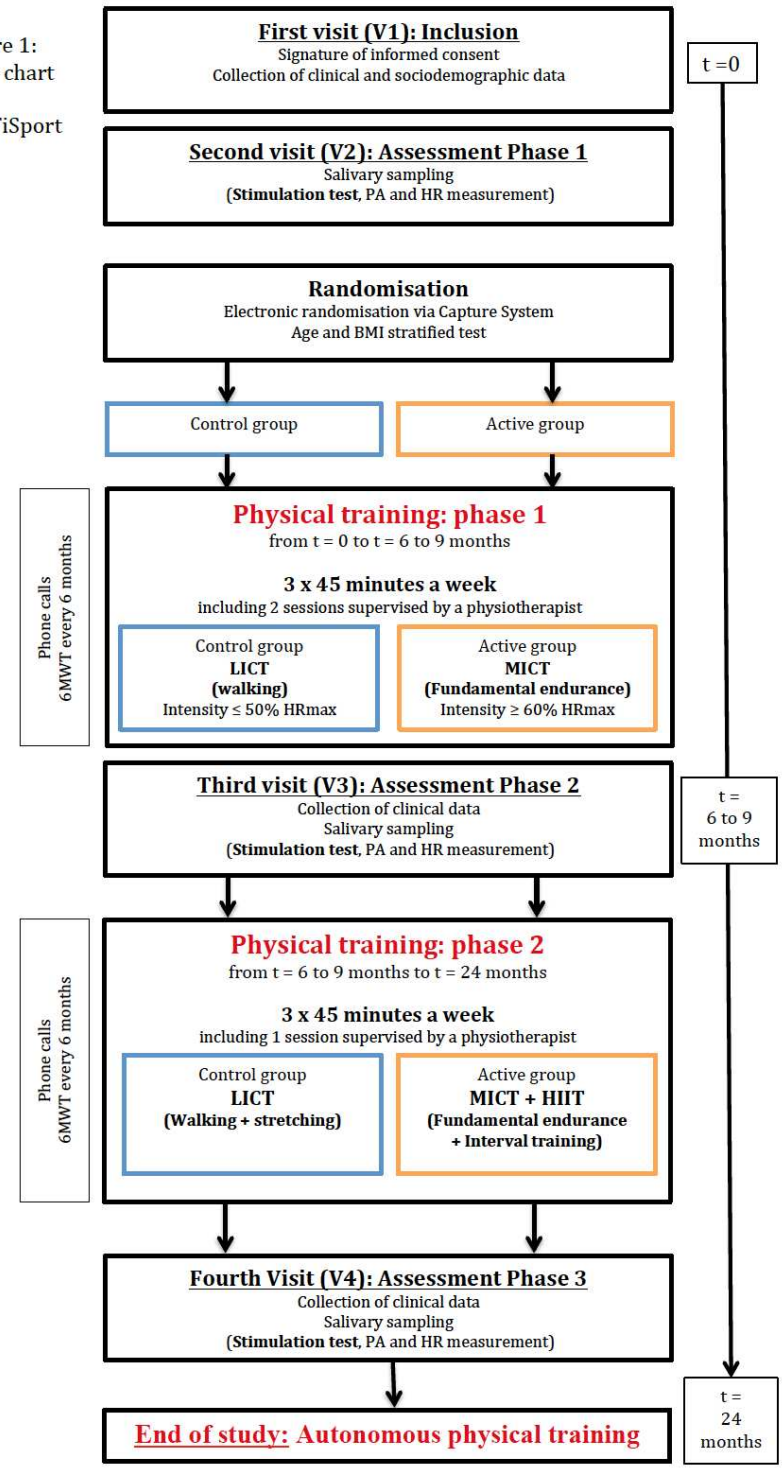
| Participant timeline | 13 | The training program is planned over two years (24 months) for both groups (active/control). Subjects will perform 3 training sessions per week of 45 minutes.<br>Patient will participate in 4 visits (1 inclusion visit and 3 assessment visits) during these two years. |

Figure 1: Flow chart of DouFiSport



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| Sample size | 14 | Population size is based on an expected difference of 20 points (stimulation test) (1) between the two groups, for a quantitative primary endpoint (delta VAS) of standard deviation equal to 35, and a power set at 80%. Therefore a minimum of 48 subjects per group is required for assessment. In order to take into account loss to follow-up, the sample of 110 subjects, 55 per group will be recruited. |
| Recruitment | 15 | Patients will be recruited at the pain centre of the university hospital of Brest on the basis of general criteria. |

**Methods: Assignment of interventions (for controlled trials)**

Allocation:

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| Sequence generation | 16a | Patients will be randomised at the end of the first stimulation test (second visit: V2), which is just before the initiation of the training. The test is stratified by age and BMI. The cut off is set at 50 years for age and 25kg/m$^2$ for BMI (two strata [18-25] and ]25-30 []. |
| Allocation concealment mechanism | 16b | Electronic randomisation via Capture System |
| Implementation | 16c | The allocation sequence will generate by the Center of Clinical Investigation (CIC) at the hospital university of Brest (France). The principal investigator will enrol participants, and will assign participants to interventions. |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions: Patients will be blinded (they will not be informed of their group (active/control)). The investigators, outcome assessors and data analysts will be blinded. |
| | 17b | If blinded, circumstances under which unblinding is permissible: Due to the nature of the intervention (physical activity protocol), the coaching staff will not be blinded. |

**Methods: Data collection, management, and analysis**

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| Data collection methods | 18a | Measurements and questionnaires will be carried out (i) at baseline, (ii) between 6 to 9 months, and (iii) at the end of the 24 months of training.<br>**Sociodemographic and clinical data**<br>At baseline, data on age, sex, marital status, education level, and occupation will be collected. Height and weight will be recorded. Medical background and pain characteristics will be noted. All current drug and non-drug therapies (including tried and stopped) will also be collected, as well as their effectiveness on pain.<br>**Questionnaires and pain assessments**<br>• The **assessment of pain** will be performed by a simple verbal scale and using a visual analog scale (VAS). The Saint Antoine Pain Questionnaire (QDSA) will also assess pain. A **pain quantitative assessment** will be performed with a pressure algometer (pressure pain threshold: PPT).<br>• The Hospital Anxiety Depression Scale (HADS) will assess the **patient anxiodepressive state** (41).<br>• The Fibromyalgia Impact Questionnaire (FIQ) will assess **the impact of fibromyalgia on daily life** (42).<br>• The Pittsburgh Sleep Quality Index (PSQI) will assess **sleep quality and quantity** (43,44).<br>• The International Physical Activity Questionnaire (IPAQ) will record the **level of physical activity and the sedentary lifestyle**. The French long telephone questionnaire will be used (45).<br>• The Perceived Stress Scale (PSS) will assess **the antecedents of perceived stress** (46).<br><br>**Stimulation test**<br>In order to assess endogenous pain mechanisms, such as diffuse noxious inhibitory controls (DNIC), temporal summation (TS) and perception of pain, we will use an experimental method developed by Tousignant-Laflamme and Marchand (2008) (1,47–49).<br>- Thermode test or temporal summation test **(P1):** a tonic heat pain will be administered for 2 minutes on the patient's right arm, using a thermode (CE marking n°226). The starting temperature is 32°C (skin temperature under normal conditions in temperate room (20-22°C)) (50) and will quickly reach a fixed value. The experimental temperature will be individually determined to induce 50/100 on a VAS and will remain constant during the test period (2 minutes). Throughout this entire period, the patient will evaluate their pain intensity using a Computerised Visual Analog Scale (CoVAS).<br>- Cold pressor test **(P2):** to elicit a prolonged pain sensation in order to trigger diffuse noxious inhibitory control (DNIC) (51), the patient's right arm will be immersed for 2 minutes in a cold water bath maintained at 12°C. The patient will continuously evaluate their pain intensity using a CoVAS.<br>Following this cold pressor test, the thermode test will be again performed **(P3).**<br>Pain difference between the two (P3/P1) tonic heat pain stimulations will measure DNIC activation and represents pain modulation. |

**Measurement of salivary cortisol and salivary flow**

Corticotropic axis will be assessed using measurement of salivary cortisol. Cortisol release is pulsatile (10 to 20 peaks per day) and follows a nycthemeral cycle. Maximum cortisol level is reached in the early morning. In the morning of each consultation (at baseline, in the middle and at the end of training), patients will collect salivary sample (i) for 2 minutes, when they wake up and (ii) for 2 minutes, 30 minutes later. The salivary cortisol level is measured in nmol/l. The flow rate is calculated in $ml.min^{-1}$. Samples will be frozen at -20°C. As salivary cortisol is stable, samples can be stored for many weeks in the freezer (52). After completion of all assessment sessions, sample analysis will be completed. To avoid inter-laboratory variation, the same laboratory will assay the samples.

**Recording of Blood Pressure (BP) and Heart Rate (HR)**

After 10 minutes at rest, lying down, BP and HR will be recorded. Then, BP and HR will be measured when the patient stands up and once per minute during 4 minutes when the patient remains standing.

18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols: To limit dropout, patients will be called to encourage them and to discuss any difficulties. In second stage of training and to limit a possible long-term monotonous effect, physical activity type could be diversified in both groups. The training session will be adapted in the active group (MICT will be associated with HIIT) to reduce sympathetic hyperactivity. In order to improve compliance and long-term achievement of training, the patient may choose the physical activity type performed without supervision. If a patient cannot achieve the specific training requested after 9 months of study, the patient will not complete the second phase of training. Nevertheless, she will carry out all assessment visits.
The main analysis will be performed on an intent-to-treat basis.

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| Data management | 19 | **Case report forms (CRF):**<br>All data collected must be recorded in the CRF immediately after the procedure. Each missing data will have to be coded. The researcher will carry out a double data entry. In addition, Checks on the consistency of these data will be instantly carried out.<br><br>Data on individuals included in the study will be made anonymous. Only the first letter of the subject's name, and the first letter of her first name will be recorded, with a specific code number.<br><br>**Quality Assurance and Control:**<br>A researcher commissioned by the study sponsor will ensure proper achievement of the study and, of data collection, recording and, reporting.<br><br>**Storage:**<br>During the study period, documents will be stored in the neurological functional explorations department of the university hospital of Brest<br>At the end of the study period, all archived documents will be transferred to a centralized archiving site (Central Archives Service - Brest) and, will be placed under the sponsor responsibility for 15 years according to institutional practices. |
| Statistical methods | 20a | *Primary outcome analysis*: The VAS improvements (stimulation test) obtained in the both groups will be compared using the Student's test. If the required normality assumption is not sustainable, a nonparametric Wilcoxon test will be used. An alpha risk of 0.05 will be set as the limit of statistical significance. The main analysis will be performed on an intent-to-treat basis. A complementary analysis using a linear model with adjustment for age and BMI factors will be completed.<br><br>*The secondary outcomes* (quantitative: salivary cortisol, blood pressure, PPT quantified by pain threshold pressure, questionnaires assessment) will be analysed in a similar way by comparing the improvements obtained between both groups. |
| **Methods: Monitoring** | | |
| Data monitoring | 21a | Because of the nature of the study (excluding health product and, duration of the study), a monitoring committee independent from the sponsor will not be constituted.<br>A researcher commissioned by the study sponsor will ensure proper achievement of the study, and of data collection, recording and reporting. |

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| | 21b | The study may be stopped early for reasons of safety (in the event of unexpected serious adverse event occurrences), efficacy or futility. The sponsor reserves the right to stop the study at any time, if the desired sample size is not achieved. |
| Harms | 22 | **The investigator** is responsible for recording and reporting all serious adverse events (EvIG) occurring during the entire study period. Regardless of the causal relationship between EvIG and the study, any EvIG will be described on the form dedicated to this matter («EvIG initial report» or «EvIG follow-up report») and will be notified to the sponsor within a time frame of 24 hours after the event occurs.<br><br>All other adverse events (non-serious adverse events) will be reported on adverse event form of the CRF. The date of occurrence, description, intensity, duration, treatment, aetiology, accountability and the decisions taken will be specified.<br><br>**The sponsor** has to analyse EvIG (the causality of the EvIG and their expected or unexpected character). The sponsor have to report all unexpected EvIG to Eudravigilance (European pharmacovigilance database), the French Health Authorities (ANSM), the Committee for the Protection of Persons (CPP) and, to the investigators. Each year, the sponsor will draft a safety report that will include:<br>- the list of unexpected and expected EvIG,<br>- a concise and critical analysis of the safety of patients included in the study.<br><br>Each adverse events will be monitored until the it will be completely resolved even if after the study period. |
| Auditing | 23 | A researcher commissioned by the sponsor will audit trial conduct. The investigator and his team undertake to make themselves available during regular Quality Control visits by this researcher. During these visits, informed consent, adherence to study protocol and, CRF data quality, will be reviewed. The investigator undertakes to accept quality control audits carried out by the sponsor, and by the competent authorities. |
| **Ethics and dissemination** | | |
| Research ethics approval | 24 | The Committee for the Protection of Persons West VI approved this study on 02/12/2014. |

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| Protocol amendments | 25 | Important protocol modifications by the investigator (eg, changes to eligibility criteria, outcomes, analyses) have to be approved by the sponsor. The sponsor must obtain a favourable opinion of the CPP and an authorization of the «Agence nationale de sécurité du médicament et des produits de santé» (ANSM) to enable the application of these amendments. A new consent of the patient participating will be collected if necessary. |
| Consent or assent | 26a | Patients will be informed of the objectives, constraints, risks and benefits of the study. Patients will be informed of their rights to refuse to participate or to withdraw from the study at any time. All information will be on information and consent form given to the patient. To be included, patients will sign informed written consent. The investigator will collect free, informed, and written consent of the patient before definitive inclusion in the study. |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable: No collection will be formed. |
| Confidentiality | 27 | Data on individuals included in the study will be made anonymous. Only the first letter of the subject's name, and the first letter of her first name will be recorded, with a specific code number. The investigators will take all necessary precautions to ensure the confidentiality of the information in particular with regard to patient identity. |
| Declaration of interests | 28 | None declared. |
| Access to data | 29 | In accordance with good clinical practice, the sponsor is responsible for seeking the agreement of those involved in this research with a view to ensure direct access to source data, source documents and reports in all research place (particularly during quality control).<br>In accordance with the legislative provisions in force (articles L.1121-3 et R.5121-13 of the French Public Health Code), the investigators will be making documents and necessary individual data available to researcher charged with study control and monitoring. |
| Ancillary and post-trial care | 30 | Pursuant to the provisions of article L1121-10 of the French Public Health Code, the sponsor (CHRU of Brest) undertakes to take out a civil liability insurance contract. |
| Dissemination policy | 31a | The results of this study will be published in specialised scientific journals. These results will be presented to participants and the public at a free public lecture organised by the health promotion department of the city of Brest. These results will also be presented to healthcare professionals and other relevant groups in pain and/or physical activity congresses. In addition, a doctoral thesis will be carried out on this project. |

## Appendices

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| Informed consent materials | 32 | See attached documentation |
| Biological specimens | 33 | Not applicable. |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

## References


1. Tousignant-Laflamme Y, Pagé S, Goffaux P, Marchand S. An experimental model to measure excitatory and inhibitory pain mechanisms in humans. Brain Res. 16 sept 2008;1230:73•9.
2. Woda A, L'heveder G, Ouchchane L, Bodéré C. Effect of experimental stress in 2 different pain conditions affecting the facial muscles. J Pain Off J Am Pain Soc. mai 2013;14(5):455•66.
3. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. févr 1990;33(2):160•72.
4. Cánovas R, León I, Roldán MD, Astur R, Cimadevilla JM. Virtual reality tasks disclose spatial memory alterations in fibromyalgia. Rheumatol Oxf Engl. oct 2009;48(10):1273•8.
5. Fitzcharles M, Shir Y, Ablin JN, Buskila D, Amital H, Henningsen P, et al. Classification and clinical diagnosis of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines. Evid-Based Complement Altern Med ECAM. 2013;2013:528952.
6. Egloff N, von Känel R, Müller V, Egle UT, Kokinogenis G, Lederbogen S, et al. Implications of proposed fibromyalgia criteria across other functional pain syndromes. Scand J Rheumatol. 2015;44(5):416•24.
7. Moyano S, Kilstein JG, Alegre de Miguel C. New diagnostic criteria for fibromyalgia: Here to stay? Reumatol Clin. août 2015;11(4):210•4.
8. Wolfe F, Fitzcharles M-A, Goldenberg DL, Häuser W, Katz RL, Mease PJ, et al. Comparison of Physician-Based and Patient-Based Criteria for the Diagnosis of Fibromyalgia. Arthritis Care Res. mai 2016;68(5):652•9.
9. Bodéré C, Woda A. La douleur orofaciale idiopathique: une douleur fonctionnelle. Douleur Analgésie. 21 juin 2009;22(2):89•95.
10. Woda A, Dao T, Gremeau-Richard C. Steroid dysregulation and stomatodynia (burning mouth syndrome). J Orofac Pain. 2009;23(3):202•10.
11. Woda A, L'heveder G, Ouchchane L, Bodéré C. Effect of experimental stress in 2 different pain conditions affecting the facial muscles. J Pain Off J Am Pain Soc. mai 2013;14(5):455•66.

12. Cohen H, Neumann L, Shore M, Amir M, Cassuto Y, Buskila D. Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability. Semin Arthritis Rheum. févr 2000;29(4):217•27.
13. da Cunha Ribeiro RP, Roschel H, Artioli GG, Dassouki T, Perandini LA, Calich AL, et al. Cardiac autonomic impairment and chronotropic incompetence in fibromyalgia. Arthritis Res Ther. 2011;13(6):R190.
14. Martinez-Lavin M. Fibromyalgia as a sympathetically maintained pain syndrome. Curr Pain Headache Rep. oct 2004;8(5):385•9.
15. Kadetoff D, Kosek E. Evidence of reduced sympatho-adrenal and hypothalamic-pituitary activity during static muscular work in patients with fibromyalgia. J Rehabil Med. sept 2010;42(8):765•72.
16. Tak LM, Cleare AJ, Ormel J, Manoharan A, Kok IC, Wessely S, et al. Meta-analysis and meta-regression of hypothalamic-pituitary-adrenal axis activity in functional somatic disorders. Biol Psychol. mai 2011;87(2):183•94.
17. Riva R, Mork PJ, Westgaard RH, Lundberg U. Comparison of the cortisol awakening response in women with shoulder and neck pain and women with fibromyalgia. Psychoneuroendocrinology. févr 2012;37(2):299•306.
18. Geiss A, Rohleder N, Anton F. Evidence for an association between an enhanced reactivity of interleukin-6 levels and reduced glucocorticoid sensitivity in patients with fibromyalgia. Psychoneuroendocrinology. mai 2012;37(5):671•84.
19. Bote ME, García JJ, Hinchado MD, Ortega E. Inflammatory/stress feedback dysregulation in women with fibromyalgia. Neuroimmunomodulation. 2012;19(6):343•51.
20. Hellhammer DH, Wüst S, Kudielka BM. Salivary cortisol as a biomarker in stress research. Psychoneuroendocrinology. févr 2009;34(2):163•71.
21. Clauw D, Ablin J. The relationship between « stress » and pain: lessons learned from fibromyalgia and related conditions. In: Current topics in pain. Castro-Lopes editor. XIIth World Congress on Pain. Seattle: IASP press; 2009. p. p.245-270.
22. McKenzie DC. Markers of excessive exercise. Can J Appl Physiol Rev Can Physiol Appl. févr 1999;24(1):66•73.
23. MacKinnon LT. Special feature for the Olympics: effects of exercise on the immune system: overtraining effects on immunity and performance in athletes. Immunol Cell Biol. oct 2000;78(5):502•9.
24. Iellamo F, Pigozzi F, Parisi A, Di Salvo V, Vago T, Norbiato G, et al. The stress of competition dissociates neural and cortisol homeostasis in elite athletes. J Sports Med Phys Fitness. déc 2003;43(4):539•45.
25. Baumert M, Brechtel L, Lock J, Hermsdorf M, Wolff R, Baier V, et al. Heart rate variability, blood pressure variability, and baroreflex sensitivity in overtrained athletes. Clin J Sport Med Off J Can Acad Sport Med. sept 2006;16(5):412•7.
26. Kajaia T, Maskhulia L, Chelidze K, Akhalkatsi V, Kakhabrishvili Z. The effects of non-functional overreaching and overtraining on autonomic nervous system function in highly trained athletes. Georgian Med News. mars 2017;(264):97•103.
27. Fontenele JB, Felix FHC. Exercise for fibromyalgia: evidence for an integrated modulation of autonomic and nociception neural regulation. Rheumatol Int. déc 2012;32(12):4075•6.
28. Rossy LA, Buckelew SP, Dorr N, Hagglund KJ, Thayer JF, McIntosh MJ, et al. A meta-analysis of fibromyalgia treatment interventions. Ann Behav Med Publ Soc Behav Med. 1999;21(2):180•91.

29. Busch AJ, Webber SC, Brachaniec M, Bidonde J, Bello-Haas VD, Danyliw AD, et al. Exercise therapy for fibromyalgia. Curr Pain Headache Rep. oct 2011;15(5):358•67.
30. Woda A, L'heveder G, Ouchchane L, Bodéré C. Effect of experimental stress in 2 different pain conditions affecting the facial muscles. J Pain Off J Am Pain Soc. mai 2013;14(5):455•66.
31. Society AP, éditeur. Guideline for the Management of Fibromyalgia Syndrome Pain in Adults and Children. American Pain Society; 2005. 109 p.
32. Häuser W, Arnold B, Eich W, Felde E, Flügge C, Henningsen P, et al. Management of fibromyalgia syndrome – an interdisciplinary evidence-based guideline. GMS Ger Med Sci. 2008;6:Doc14.
33. Macfarlane GJ, Kronisch C, Atzeni F, Häuser W, Choy EH, Amris K, et al. EULAR recommendations for management of fibromyalgia. Ann Rheum Dis. déc 2017;76(12):e54.
34. Melanson EL, Freedson PS. The effect of endurance training on resting heart rate variability in sedentary adult males. Eur J Appl Physiol. sept 2001;85(5):442•9.
35. Reland S, Ville NS, Wong S, Gauvrit H, Kervio G, Carré F. Exercise heart rate variability of older women in relation to level of physical activity. J Gerontol A Biol Sci Med Sci. juill 2003;58(7):585•91.
36. de Abreu SB, Lenhard A, Mehanna A, de Souza HCD, Correa FM de A, Hasser EM, et al. Role of paraventricular nucleus in exercise training-induced autonomic modulation in conscious rats. Auton Neurosci Basic Clin. 15 juin 2009;148(1•2):28•35.
37. Martins-Pinge MC. Cardiovascular and autonomic modulation by the central nervous system after aerobic exercise training. Braz J Med Biol Res Rev Bras Pesqui Médicas E Biológicas Soc Bras Biofísica Al. sept 2011;44(9):848•54.
38. Häuser W, Klose P, Langhorst J, Moradi B, Steinbach M, Schiltenwolf M, et al. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials. Arthritis Res Ther. 2010;12(3):R79.
39. Bodéré C, Bodéré YT, Quinio B, Woda A, Misery L. Specific training program for the treatment of fibromyalgia: a prospective controlled study. In: 14th world congress on pain - TF505. Milan, Italy: IASP; 2012.
40. Lannersten L, Kosek E. Dysfunction of endogenous pain inhibition during exercise with painful muscles in patients with shoulder myalgia and fibromyalgia. Pain. oct 2010;151(1):77•86.
41. Krag NJ, Nørregaard J, Larsen JK, Danneskiold-Samsøe B. A blinded, controlled evaluation of anxiety and depressive symptoms in patients with fibromyalgia, as measured by standardized psychometric interview scales. Acta Psychiatr Scand. juin 1994;89(6):370•5.
42. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol. mai 1991;18(5):728•33.
43. Osorio CD, Gallinaro AL, Lorenzi-Filho G, Lage LV. Sleep quality in patients with fibromyalgia using the Pittsburgh Sleep Quality Index. J Rheumatol. sept 2006;33(9):1863•5.
44. Omachi TA. Measures of sleep in rheumatologic diseases: Epworth Sleepiness Scale (ESS), Functional Outcome of Sleep Questionnaire (FOSQ), Insomnia Severity Index (ISI), and Pittsburgh Sleep Quality Index (PSQI). Arthritis Care Res. nov 2011;63 Suppl 11:S287-296.
45. Crinière L, Lhommet C, Caille A, Giraudeau B, Lecomte P, Couet C, et al. Reproducibility and validity of the French version of the long international physical activity questionnaire in patients with type 2 diabetes. J Phys Act Health. août 2011;8(6):858•65.

46. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. déc 1983;24(4):385•96.
47. Marchand S, Arsenault P. Spatial summation for pain perception: interaction of inhibitory and excitatory mechanisms. Pain. févr 2002;95(3):201•6.
48. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain. mars 2005;114(1•2):295•302.
49. Granot M, Granovsky Y, Sprecher E, Nir R-R, Yarnitsky D. Contact heat-evoked temporal summation: tonic versus repetitive-phasic stimulation. Pain. juin 2006;122(3):295•305.
50. Barrett KE, Barman SM, Boitano S, Brooks H. Ganong's Review of Medical Physiology, 24th Edition. 24 edition. New York: McGraw-Hill Education / Medical; 2012. 768 p.
51. Potvin S, Paul-Savoie E, Morin M, Bourgault P, Marchand S. Temporal summation of pain is not amplified in a large proportion of fibromyalgia patients. Pain Res Treat. 2012;2012:938595.
52. Kirschbaum C, Hellhammer DH. Salivary cortisol in psychoneuroendocrine research: recent developments and applications. Psychoneuroendocrinology. 1994;19(4):313•33.


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry |
| | 2b | All items from the World Health Organization Trial Registration Data Set |
| Protocol version | 3 | Date and version identifier |
| Funding | 4 | Sources and types of financial, material, and other support |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors |
| | 5b | Name and contact information for the trial sponsor |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) |
| **Introduction** | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention |
| | 6b | Explanation for choice of comparators |
| Objectives | 7 | Specific objectives or hypotheses |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) |

**Methods: Participants, interventions, and outcomes**

| | | |
|---|---|---|
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size |

**Methods: Assignment of interventions (for controlled trials)**

Allocation:

| | | |
|---|---|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions |

| | | |
|---|---|---|
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial |
| **Methods: Data collection, management, and analysis** | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) |
| **Methods: Monitoring** | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed |

| | | |
|---|---|---|
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor |
| **Ethics and dissemination** | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code |

## Appendices

| | | |
|---|---|---|
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

# Impact of a specific training program on the neuromodulation of pain in female fibromyalgia patients (DouFiSport): A 24-month, controlled, randomised, double-blind protocol

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|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2018-023742.R2 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 14-Nov-2018 |
| Complete List of Authors: | Le Fur Bonnabesse, Anais; Universite de Bretagne Occidentale Faculte de Medecine et des Sciences de la Sante de Brest, LIEN, EA4685; Universite de Bretagne Occidentale UFR d'Odontologie<br>Cabon, Mathilde; Universite de Bretagne Occidentale Faculte de Medecine et des Sciences de la Sante de Brest, LIEN, EA4685<br>L'Heveder, Gildas; CHRU de Brest, Explorations fonctionnelles neurologiques<br>Kermarrec, Aurélie ; CHRU de Brest, IFMK<br>Quinio, Bertrand; CHRU de Brest, Centre d'évaluation et de traitement de la douleur<br>Woda, Alain; Universite Clermont Auvergne Faculte de Chirurgie Dentaire, CROC EA3847<br>Marchand, Serge; Universite de Sherbrooke Faculte de medecine et des sciences de la sante, Department of surgery<br>Dubois, Amandine; Laboratoire de psychologie, Cognition, Behaviour, Communication (LP3C), EA1285; Universite de Bretagne Occidentale UFR Lettres et Sciences Humaines a Brest, Département de psychologie<br>Giroux-Metges, Marie-Agnes; Universite de Bretagne Occidentale Faculte de Medecine et des Sciences de la Sante de Brest, ORPHY EA4324; CHRU de Brest, Explorations fonctionnelles respiratoires<br>Rannou, Fabrice; Universite de Bretagne Occidentale Faculte de Medecine et des Sciences de la Sante de Brest, ORPHY EA4324; CHRU de Brest, Explorations fonctionnelles respiratoires<br>Misery, Laurent; Universite de Bretagne Occidentale Faculte de Medecine et des Sciences de la Sante de Brest, LIEN EA4685<br>Bodéré, Céline; Universite de Bretagne Occidentale Faculte de Medecine et des Sciences de la Sante de Brest, LIEN EA4685; CHRU de Brest, Centre d'évaluation et de traitement de la douleur |
| Primary Subject Heading: | Sports and exercise medicine |
| Secondary Subject Heading: | Medical education and training, Rehabilitation medicine, Rheumatology, Pharmacology and therapeutics |
| Keywords: | PAIN MANAGEMENT, MEDICAL EDUCATION & TRAINING, REHABILITATION MEDICINE, FIBROMYALGIA |

# Impact of a specific training program on the neuromodulation of pain in female fibromyalgia patients (DouFiSport): A 24-month, controlled, randomised, double-blind protocol

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## *ABSTRACT*

### *INTRODUCTION*

The main symptom of fibromyalgia (FM) is diffuse pain. There is currently no etiological treatment for FM. However, all pain associations and best practice guidelines strongly advocate the practice of aerobic physical activity to improve the symptoms of FM subjects. The mechanisms of dysfunctional pain are mostly central and related to stress axis dysfunction (autonomic nervous system and corticotropic axis). Our main objective is to assess the efficacy of a specific training program on endogenous pain control mechanisms in female fibromyalgia patients. Further aims include rebalancing the autonomic neurovegetative system, improving quality of life and sleep quality, and reintegrating patients into society and work.

### *METHODS AND ANALYSIS*

110 female FM patients diagnosed on ACR 2010 criteria, aged 18–65 years and meeting inclusion conditions will be recruited and randomised into two groups (active and semi-active). The training program will consist of three 45-minute sessions per week of supervised, individualised physical activity over two years. Only the intensity of the exercises will differ between the two groups (moderate-intensity versus low-intensity).

All outcome measures will be conducted at baseline (T0), after 6–9 months of training (T6-9), and after 24 months of training (T24). The primary endpoint will be improvement of pain modulation (activation of diffuse noxious inhibitory control (DNIC)) evaluated by the stimulation test. The secondary endpoint will be relief of pain, anxiety, depression, stress, sleep disorders, pain impact on life quality, and improved heart rate, blood pressure and salivary cortisol.

### *ETHICS AND DISSEMINATION*

This study is approved by the Committee for the Protection of Persons West VI. The results will be published in specialised scientific journals and will be presented at scientific meetings on pain and/or physical activity. Trial registration: NCT02486965.

## Strengths and limitations of this study

- First randomised controlled double-blind trial to assess the effects of a long-term training program (24 months) on pain control in fibromyalgia.
- The protocol of the training program is designed to rebalance the neurovegetative system and thereby treat fibromyalgia.
- Physical activity intensity will be assessed objectively using a heart rate monitor.
- The dropout rate in patients may be high.
- Due to the nature of the intervention, the coaching staff cannot be blinded.

*INTRODUCTION*

Fibromyalgia affects 1.4–2.2% of the general population, predominately women (more than 80% of subjects). This syndrome is characterised by extensive diffuse pain, mainly muscular and articular, impairing the functional abilities of the subjects. The symptoms most frequently described by fibromyalgia patients are chronic fatigue, sleep disorders, cognitive disorders and emotional disturbances (1,2). They lead to a severe deterioration in quality of life, sometimes with physical disability leading to social isolation and difficulties staying in employment (recurrent sick leave).

Diagnosis is based on the symptoms and their severity as described by the patients (3–6). There is currently no etiological treatment for fibromyalgia syndrome. Treatments are therefore only symptomatic.

## Physiopathology of fibromyalgia

The mechanisms of dysfunctional pain, with no identifiable organic lesions, are mostly central (7) and related to dysfunction of the stress axis (autonomic nervous system and corticotropic axis) (8,9).

At rest, fibromyalgia patients show an increased sympathetic response and decreased parasympathetic tone (10,11). This neurovegetative dystonia is a marker of dysfunction of the stress axis (12).

Malfunctions of the corticotropic axis in fibromyalgia have often been described, also marking the dysfunction of the stress axis. However, the form taken by this dysfunction differs according to the study (13–17). The variability of salivary cortisol in response to stress reflects that of plasma free cortisol. Salivary cortisol is therefore a method of choice in experimental stress studies (18). Whatever their form, these dysfunctions all compromise the body's adaptation to daily stressful stimuli.

Studies show that this deficit of the stress axis (neurovegetative dystonia and dysfunctional corticotropic axis) is concurrent with fibromyalgia (19) and associated with altered pain control (8,9). The pain control system and the stress

axis have close anatomical and functional links. Nociceptive, neurovegetative and corticotropic systems interact with the central nervous system. The central neuromediators involved in the regulation of the stress axis are mostly common with those of pain neuromodulation (endogenous opioids, norepinephrine, serotonin, etc.).

## Elite athlete's overtraining syndrome: a model of stress axis dysfunction

An overtraining elite athlete may be considered as a model of dysfunction of the stress axis associated with neurovegetative dystonia. The physical and psychological effort of training is known to induce stress. High-level athletes can present an overtraining syndrome when the adaptation limits of the stress axis are reached. This stress-induced phenomenon corresponds to an imbalance between training quantity and recovery. Overtrained athletes present a deconditioning syndrome close to fibromyalgia symptoms (chronic pain, sleep disorders, neurovegetative dystonia, intense fatigue, etc.) (20–24).

## Physical activity and fibromyalgia

Most studies have shown that physical activity is more efficacious on fibromyalgia symptoms than pharmacological treatments (25,26). Literature reviews and meta-analyses strongly support the benefits of physical training in fibromyalgia patients (decreased pain and depression and improvement in overall health and physical abilities) (27). Practice of aerobic exercise in fibromyalgia patients is strongly recommended by The American Pain Society (28), the Association of Medical Scientific Societies in Germany (29), the Canadian Rheumatology Association (3) and the European League Against Rheumatism (EULAR) (30). Physical exercise is the first-line treatment recommended in fibromyalgia, but there is still no consensus on the modalities of such training (frequency, duration, and intensity). The mechanisms underlying these specific training effects remain to be determined.

Steady physical activity rebalancing the autonomic system is associated with cardiovascular benefits. Physical activity increases parasympathetic tone and decreases sympathetic response (31–34). Mechanisms and structures involved in the activation and regulation of the neurovegetative system may interact with the central nervous system. Central relationships between the neurovegetative system and the motor cortex, the limbic system, the hypothalamus, the pituitary gland and the basal ganglia result in the release of analgesic neurotransmitters such as noradrenalin, serotonin and endogenous opioids (35)(36). This release of neurotransmitters due to exercise leads to increased endogenous inhibition and so decreases diffuse pain in FM (35). Central nervous system plasticity induced by physical training can regulate both cardiovascular adaptations (34) and endogenous pain control mechanisms (37)(38). Thus strategies to rebalance the autonomic system are the most promising therapies for fibromyalgia (11,33,34).

In this study, we set out to validate a therapeutic alternative that aims to treat fibromyalgia by rebalancing the stress axis. This treatment consists of a specific, supervised, individualised training program lasting 2 years. This training protocol is individually adjusted to rebalance the neurovegetative system (parasympathetic and sympathetic). Central neuroplasticity induced by training should regulate endogenous pain control mechanisms. This specific protocol will be associated with psychotherapeutic approaches. In addition to the training program, multidisciplinary bio-psycho-social care will be given at the pain centre of the University Hospital of Brest (3).

## Objectives

Our *main objective* is to assess the efficacy of a specific training program on endogenous pain control in fibromyalgia patients. Our *secondary objectives* are to rebalance the autonomic nervous system and the corticotropic axis, improve life and sleep quality and reintegrate patients into society and work.

*METHODS AND ANALYSIS*

## Design and setting

This randomised, double-blind trial will compare an "active" program to a "semi-active" program in fibromyalgia patients. Patients will be recruited at the pain centre of the University Hospital of Brest on the basis of general criteria. Patients are to follow a re-exercise program for 24 months. The assessments will take place (i) before, (ii) between 6 and 9 months (depending the training level) and (iii) at the end of training (24 months), in the neurological functional explorations department of the University Hospital of Brest (Fig.1).

## Patient involvement

The specific training program of this study was developed based on the results of a pilot study (39), data from literature and the experiences of fibromyalgia patients recorded at the pain centre of the University Hospital of Brest. These patients reported the benefits, constraints, difficulties, and effects of their training program on their symptoms. This information has allowed adjustments to be made to the specific training program. Patients are not involved in the recruitment and conduct of the study. At the last assessment visit, patients will be asked to assess the burden of the program. On request, a report outlining the study findings will be given to study participants.

## Study population

110 fibromyalgia patients will be included. The inclusion criteria are: female; aged 18–65 years; diagnosis of fibromyalgia clearly established according to the criteria of the American College of Rheumatology (ACR) 2010; body mass index (BMI) 18.5–29.9 kg/m$^2$; spontaneous pain intensity higher than 3/10 on a visual analogue scale (VAS); pain experienced at least 3 days a week; pain caused by palpation greater than or equal to 4/10 on a VAS.

The non-inclusion criteria are: systemic disease (treated or not) generating pain of the musculoskeletal system; pain other than fibromyalgia; contraindication to physical activity; any active health disorder; change in the last 2 months in any

pharmacological treatment; psychiatric diagnosis; taking drugs that affect cortisol secretion (decrease or increase); non-cooperating.

## Sample size

Population size is calculated on an expected difference of 20 points (stimulation test) (7) between the two groups, for a quantitative primary endpoint (delta VAS) of standard deviation equal to 35, and a power set at 80%. At least 48 subjects per group are therefore required. To take into account loss to follow-up, a sample of 110 subjects, i.e. 55 per group, will be recruited.

## Randomisation

Patients will be randomised at the end of the first stimulation test, just before initiation of the training. Randomisation will be conducted by the Centre for Clinical Investigation (CIC) at the University Hospital of Brest (electronic randomisation via Capture System). The test will be stratified by age and BMI. The cut-off will be set at 50 years for age and 25 kg/m$^2$ for BMI (two strata [18-25] and ]25-30 []).

## Training program

The training program is planned over two years (24 months) for both groups (active/semi-active). A minimum of 4–6 weeks is needed to observe a decrease in symptoms (39). This two-year duration is the minimum average training time (depending on the individual progress of each patient) necessary to regain a central neuroplasticity sufficient to restore diffuse noxious inhibitory controls (DNIC) and the neurovegetative system (40).

The frequency, intensity, and duration of these training sessions are based on both data from the literature (39,41) and the results of a preliminary study. Pain was significantly reduced and symptoms such as quality of life, sleep quality and anxiety, were also strongly improved in subjects who had undergone this specific training after 5 years (40).

The American Pain Society recommends an intensity of 60–70% of the age-adjusted maximum heart rate (HRmax). At the early stage, the intensity and duration of the training sessions will be adapted to the physical condition of each subject. The intensity exercise will be 3 on the Borg CR10 scale (39). To promote adherence of our patients and to limit pain exacerbation, exercise intensity will start very low and then increase very gradually to reach the neurovegetative goal (28)(42).

The ideal frequency is three training sessions per week each lasting 45 minutes (39,40).

**Active training group**

*First 6–9 months*

Subjects will perform three sessions per week of 45 minutes of moderate-intensity continuous training (MICT) (65-75% HRmax), including two sessions supervised by a physiotherapist specially trained and one independent session.

*From 6–9 months (according to pace, abilities, and limits) to 24 months*

Patients will begin the second stage of training: three sessions per week of at least 45 minutes each (MICT and high-intensity interval training (HIIT)) with one supervised session and two independent sessions. When the patient reaches the initial HR goal, continuous training will be associated with interval training. HIIT will consist of 5 stages of 1–4 minutes at 85–90% HRmax, interspersed by 1–4 minutes of active recovery at 65–75% HRmax. Intensity will be assessed objectively using a heart rate monitor (FT2, Polar). At baseline, Tanaka's age-based prediction equation (208 – 0.7×age) will calculate HRmax. After 6–9 months of training, a maximal-effort graded exercise test will determine HRmax and $V\dot{O}_2$max for each patient.

**Semi-active training group**

Patients will perform the same infra-active training (low-intensity continuous training: LICT < 50% HRmax) for two years. Supervision, monitoring, and frequency of sessions (3 × 45 minutes per week) in both groups will be equivalent.

### Training follow-up (for both groups)

Patients will be contacted to record progress, difficulties and if necessary to encourage them to adhere to their program. These calls will improve compliance and limit patients lost to follow-up (43,44). Subjects will note the characteristics (frequency, duration, intensity, type of activity, and supervision) of each training session (both supervised and independent) in a specific training logbook. The physiotherapist will frequently ask patients about their independent training session to provide advice and motivate them. The follow-up at the pain centre will assess compliance with the training protocol.

Patients will perform a 6-minute walk test (6MWT) every 6 months (with a physiotherapist). If a patient cannot achieve the specific training requested after 9 months of study, then she will not complete the second phase of training, but will nevertheless attend all assessment visits. The main analysis will be performed on an intent-to-treat basis.

## Clinical data, measurements and assessments

### Sociodemographic and clinical data

At baseline, data on age, sex, marital status, education level, and occupation will be collected. Height and weight will be recorded. Medical background and pain characteristics will be noted. All current drug and non-drug therapies (including tried and stopped) will also be collected, together with their effectiveness on pain.

### Questionnaires and pain assessments

Measurements and questionnaires will be carried out (i) at baseline, (ii) between 6 and 9 months, and (iii) at the end of the 24 months of training.

– The **assessment of pain** will be performed by a simple verbal scale and using a visual analogue scale (VAS). The Saint Antoine Pain Questionnaire (QDSA) will also assess pain. A **pain quantitative assessment** will be performed with a pressure algometer (pressure pain threshold: PPT).

- The Hospital Anxiety Depression Scale (HADS) will assess the **patient's anxiodepressive state** (45).
- The Fibromyalgia Impact Questionnaire (FIQ) will assess **the impact of fibromyalgia on daily life** (46).
- The Pittsburgh Sleep Quality Index (PSQI) will assess **sleep quality and quantity** (47,48).
- The International Physical Activity Questionnaire (IPAQ) will record the **level of physical activity and sedentary lifestyle**. The French long telephone questionnaire will be used (49).
- The Perceived Stress Scale (PSS) will assess **the antecedents of perceived stress** (50).

**Stimulation test**

To assess endogenous pain mechanisms, such as diffuse noxious inhibitory controls (DNIC), temporal summation (TS) and perception of pain, we will use an experimental method developed by Tousignant-Laflamme and Marchand (2008). According to this well-characterised paradigm, we will induce in single session two tonic heat pain stimulations separated by a cold pressor test (7,51–53).

**Thermode test or temporal summation test (P1):** a tonic heat pain will be administered for 2 minutes on the patient's right arm, using a thermode (CE marking No. 226). The starting temperature is 32°C (skin temperature under normal conditions in a temperate room (20–22°C)) (54) and will quickly reach a fixed value. The experimental temperature will be individually determined to induce 50/100 on a VAS and will remain constant during the test period (2 minutes). Throughout this period, the patient will evaluate her pain intensity using a Computerised Visual Analog Scale (CoVAS).

**Cold pressor test (P2):** to elicit a prolonged pain sensation to trigger diffuse noxious inhibitory control (DNIC) (55), the patient's right arm will be immersed for 2 minutes in a cold water bath maintained at 12°C. The patient will continuously evaluate her pain intensity using a CoVAS.

Following this cold pressor test, the thermode test will be performed again **(P3).**

Pain difference between the two (P3/P1) tonic heat pain stimulations will measure DNIC activation, and represents pain modulation.

### Measurement of salivary cortisol and salivary flow

Corticotropic axis will be assessed using measurement of salivary cortisol. Cortisol release is pulsatile (10–20 peaks per day) and follows a nychthemeral cycle. Cortisol level peaks in the early morning. In the morning of each consultation (at baseline, in the middle and at the end of training), patients will collect a salivary sample (i) for 2 minutes, when they wake up and (ii) for 2 minutes, 30 minutes later. The salivary cortisol level is measured in nmol/l. The flow rate is calculated in $ml.min^{-1}$. Samples will be frozen at −20°C. As salivary cortisol is stable, samples can be stored for many weeks in a freezer (56). After completion of all assessment sessions, sample analysis will be completed. To avoid inter-laboratory variation, the same laboratory will assay the samples.

### Recording of blood pressure and heart rate

After 10 minutes at rest, lying down, blood pressure (BP) and heart rate (HR) will be recorded. BP and HR will then be measured when the patient stands up and once per minute for 4 minutes while standing.

## Blinding strategy

Patients will not be informed of their group (active/semi-active). The investigators will not know the patient's group. Due to the nature of the intervention (physical activity protocol), the coaching staff will not be blinded.

## Statistical analysis

*Primary endpoint analysis*: The VAS improvements (stimulation test) obtained in the two groups will be compared using Student's *t*-test. If the required normality assumption is not sustainable, a nonparametric Wilcoxon test will be used. An alpha risk of 0.05 will be set as the limit of statistical significance. The main analysis will be performed on an intent-to-treat basis. A complementary analysis using a linear model with adjustment for age and BMI factors will be completed.

*The secondary endpoints* (quantitative data: salivary cortisol, blood pressure, PPT quantified by pain threshold pressure, questionnaire assessment) will be analysed in a similar way by comparing the improvements obtained between the two groups.

## Methodological limitations

The methodology of this protocol is consistent with the recommendations of the Standard Protocol Items for Randomised Trials (SPIRIT). However, because of the nature of the intervention, the coaching staff cannot be blinded. Patients and investigators will be blinded.

Given the study duration (2 years), potential participant dropout and loss to follow-up may be high. These risks were taken into account in setting sample size. To limit dropout, patients will be called to encourage them and to discuss any difficulties. In the second stage of training and to limit any long-term monotony effect, physical activity type can be diversified in both groups. The training session will be adapted in the active group (MICT will be associated with HIIT) to reduce sympathetic hyperactivity. To improve compliance and long-term achievement of training, the patient may choose the physical activity type performed without supervision.

# *ETHICS AND DISSEMINATION*

### Ethics approval and consent to participate

The Committee for the Protection of Persons West VI approved this study. Patients will be informed of the objectives, constraints, risks and benefits of the study. To be included, patients must sign informed written consent. Data will be collected anonymously. The investigators will take all necessary precautions to ensure the confidentiality of the information, in particular with regard to patient identity.

### Dissemination plan

The results of this study will be published in specialised scientific journals. These results will also be presented in scientific meetings on pain and/or physical activity. In addition, a doctoral thesis will be written on this project.

## TRIAL REGISTRATION NUMBER: NCT02486965

**Acknowledgements**
The authors thank Julie Lelièvre, Marie Le Bellego and Youenn-Thor Bodéré for designing and implementing this protocol. The authors thank Richard Ryan for English language editing.

**Contributors**
CB initiated the idea for the project. CB and ALFB developed the study design. MC, GL, BQ, AK, AW, SM, MAGM, FR, LM and AD provided advice for the study design. GL and CB were responsible for supervision of the project. CB will conduct the recruitment. AK will conduct the training programme. CB, ALFB and MC will conduct the outcomes assessments and will contribute to the analysis and interpretation of the data. Both authors will contribute to the analyses and interpretation of the data. ALFB, CB and MC wrote early drafts of the manuscript. All authors approved the final version of this protocol.

**Funding Statement**
This work is supported by the French Ministry of Health (Programme Hospitalier de Recherche Clinique Interrégional 2014, project No. 2014-A00743-44) PHRCi 13-100

**Competing Interests**
None declared

**Ethics approval**
Committee for the Protection of Persons West VI

**Provenance and peer review**
Not commissioned; externally peer-reviewed

## References

1. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. févr 1990;33(2):160-72.

2. Cánovas R, León I, Roldán MD, Astur R, Cimadevilla JM. Virtual reality tasks disclose spatial memory alterations in fibromyalgia. Rheumatol Oxf Engl. oct 2009;48(10):1273-8.

3. Fitzcharles M, Shir Y, Ablin JN, Buskila D, Amital H, Henningsen P, et al. Classification and clinical diagnosis of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines. Evid-Based Complement Altern Med ECAM. 2013;2013:528952.

4. Egloff N, von Känel R, Müller V, Egle UT, Kokinogenis G, Lederbogen S, et al. Implications of proposed fibromyalgia criteria across other functional pain syndromes. Scand J Rheumatol. 2015;44(5):416-24.

5. Moyano S, Kilstein JG, Alegre de Miguel C. New diagnostic criteria for fibromyalgia: Here to stay? Reumatol Clin. août 2015;11(4):210-4.

6. Wolfe F, Fitzcharles M-A, Goldenberg DL, Häuser W, Katz RL, Mease PJ, et al. Comparison of Physician-Based and Patient-Based Criteria for the Diagnosis of Fibromyalgia. Arthritis Care Res. mai 2016;68(5):652-9.

7. Tousignant-Laflamme Y, Pagé S, Goffaux P, Marchand S. An experimental model to measure excitatory and inhibitory pain mechanisms in humans. Brain Res. 16 sept 2008;1230:73-9.

8. Woda A, Dao T, Gremeau-Richard C. Steroid dysregulation and stomatodynia (burning mouth syndrome). J Orofac Pain. 2009;23(3):202-10.

9. Woda A, L'heveder G, Ouchchane L, Bodéré C. Effect of experimental stress in 2 different pain conditions affecting the facial muscles. J Pain Off J Am Pain Soc. mai 2013;14(5):455-66.

10. Cohen H, Neumann L, Shore M, Amir M, Cassuto Y, Buskila D. Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability. Semin Arthritis Rheum. févr 2000;29(4):217-27.

11. da Cunha Ribeiro RP, Roschel H, Artioli GG, Dassouki T, Perandini LA, Calich AL, et al. Cardiac autonomic impairment and chronotropic incompetence in fibromyalgia. Arthritis Res Ther. 2011;13(6):R190.

12. Martinez-Lavin M. Fibromyalgia as a sympathetically maintained pain syndrome. Curr Pain Headache Rep. oct 2004;8(5):385-9.

13. Kadetoff D, Kosek E. Evidence of reduced sympatho-adrenal and hypothalamic-pituitary activity during static muscular work in patients with fibromyalgia. J Rehabil Med. sept 2010;42(8):765-72.

14. Tak LM, Cleare AJ, Ormel J, Manoharan A, Kok IC, Wessely S, et al. Meta-analysis and meta-regression of hypothalamic-pituitary-adrenal axis activity in functional somatic disorders. Biol Psychol. mai 2011;87(2):183-94.

15. Riva R, Mork PJ, Westgaard RH, Lundberg U. Comparison of the cortisol awakening response in women with shoulder and neck pain and women with fibromyalgia. Psychoneuroendocrinology. févr 2012;37(2):299-306.

16. Geiss A, Rohleder N, Anton F. Evidence for an association between an enhanced reactivity of interleukin-6 levels and reduced glucocorticoid sensitivity in patients with fibromyalgia. Psychoneuroendocrinology. mai 2012;37(5):671-84.

17. Bote ME, García JJ, Hinchado MD, Ortega E. Inflammatory/stress feedback dysregulation in women with fibromyalgia. Neuroimmunomodulation. 2012;19(6):343-51.

18. Hellhammer DH, Wüst S, Kudielka BM. Salivary cortisol as a biomarker in stress research. Psychoneuroendocrinology. févr 2009;34(2):163-71.

19. Clauw D, Ablin J. The relationship between « stress » and pain: lessons learned from fibromyalgia and related conditions. In: Current topics in pain. Castro-Lopes editor. XIIth World Congress on Pain. Seattle: IASP press; 2009. p. p.245-270.

20. McKenzie DC. Markers of excessive exercise. Can J Appl Physiol Rev Can Physiol Appl. févr 1999;24(1):66-73.

21. MacKinnon LT. Special feature for the Olympics: effects of exercise on the immune system: overtraining effects on immunity and performance in athletes. Immunol Cell Biol. oct 2000;78(5):502-9.

22. Iellamo F, Pigozzi F, Parisi A, Di Salvo V, Vago T, Norbiato G, et al. The stress of competition dissociates neural and cortisol homeostasis in elite athletes. J Sports Med Phys Fitness. déc 2003;43(4):539-45.

23. Baumert M, Brechtel L, Lock J, Hermsdorf M, Wolff R, Baier V, et al. Heart rate variability, blood pressure variability, and baroreflex sensitivity in overtrained athletes. Clin J Sport Med Off J Can Acad Sport Med. sept 2006;16(5):412-7.

24. Kajaia T, Maskhulia L, Chelidze K, Akhalkatsi V, Kakhabrishvili Z. The effects of non-functional overreaching and overtraining on autonomic nervous system function in highly trained athletes. Georgian Med News. mars 2017;(264):97-103.

25. Fontenele JB, Felix FHC. Exercise for fibromyalgia: evidence for an integrated modulation of autonomic and nociception neural regulation. Rheumatol Int. déc 2012;32(12):4075-6.

26. Rossy LA, Buckelew SP, Dorr N, Hagglund KJ, Thayer JF, McIntosh MJ, et al. A meta-analysis of fibromyalgia treatment interventions. Ann Behav Med Publ Soc Behav Med. 1999;21(2):180-91.

27. Busch AJ, Webber SC, Brachaniec M, Bidonde J, Bello-Haas VD, Danyliw AD, et al. Exercise therapy for fibromyalgia. Curr Pain Headache Rep. oct 2011;15(5):358-67.

28. Society AP, éditeur. Guideline for the Management of Fibromyalgia Syndrome Pain in Adults and Children. American Pain Society; 2005. 109 p.

29. Häuser W, Arnold B, Eich W, Felde E, Flügge C, Henningsen P, et al. Management of fibromyalgia syndrome – an interdisciplinary evidence-based guideline. GMS Ger Med Sci [Internet]. 9 déc 2008 [cité 7 févr 2018];6. Disponible sur: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2703259/

30. Macfarlane GJ, Kronisch C, Atzeni F, Häuser W, Choy EH, Amris K, et al. EULAR recommendations for management of fibromyalgia. Ann Rheum Dis. déc 2017;76(12):e54.

31. Melanson EL, Freedson PS. The effect of endurance training on resting heart rate variability in sedentary adult males. Eur J Appl Physiol. sept 2001;85(5):442-9.

32. Reland S, Ville NS, Wong S, Gauvrit H, Kervio G, Carré F. Exercise heart rate variability of older women in relation to level of physical activity. J Gerontol A Biol Sci Med Sci. juill 2003;58(7):585-91.

33. de Abreu SB, Lenhard A, Mehanna A, de Souza HCD, Correa FM de A, Hasser EM, et al. Role of paraventricular nucleus in exercise training-induced autonomic modulation in conscious rats. Auton Neurosci Basic Clin. 15 juin 2009;148(1-2):28-35.

34. Martins-Pinge MC. Cardiovascular and autonomic modulation by the central nervous system after aerobic exercise training. Braz J Med Biol Res Rev Bras Pesqui Médicas E Biológicas Soc Bras Biofísica Al. sept 2011;44(9):848-54.

35. Brito RG, Rasmussen LA, Sluka KA. Regular physical activity prevents development of chronic muscle pain through modulation of supraspinal opioid and serotonergic mechanisms. Pain Rep. sept 2017;2(5):e618.

36. Da Silva Santos R, Galdino G. Endogenous systems involved in exercise-induced analgesia. J Physiol Pharmacol Off J Pol Physiol Soc. févr 2018;69(1):3-13.

37. Naugle KM, Naugle KE, Fillingim RB, Samuels B, Riley JL. Intensity thresholds for aerobic exercise-induced hypoalgesia. Med Sci Sports Exerc. avr 2014;46(4):817-25.

38. Law LF, Sluka KA. How does physical activity modulate pain? Pain. 2017;158(3):369-70.

39. Häuser W, Klose P, Langhorst J, Moradi B, Steinbach M, Schiltenwolf M, et al. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials. Arthritis Res Ther. 2010;12(3):R79.

40. Bodéré C, Bodéré YT, Quinio B, Woda A, Misery L. Specific training program for the treatment of fibromyalgia: a prospective controlled study. In: 14th world congress on pain - TF505. Milan, Italy: IASP; 2012.

41. Bidonde J, Busch AJ, Bath B, Milosavljevic S. Exercise for adults with fibromyalgia: an umbrella systematic review with synthesis of best evidence. Curr Rheumatol Rev. 2014;10(1):45-79.

42. Lannersten L, Kosek E. Dysfunction of endogenous pain inhibition during exercise with painful muscles in patients with shoulder myalgia and fibromyalgia. Pain. oct 2010;151(1):77-86.

43. Franke K-J, Domanski U, Schroeder M, Jansen V, Artmann F, Weber U, et al.

Telemonitoring of home exercise cycle training in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2016;11:2821-9.

44. Yasmin F, Banu B, Zakir SM, Sauerborn R, Ali L, Souares A. Positive influence of short message service and voice call interventions on adherence and health outcomes in case of chronic disease care: a systematic review. BMC Med Inform Decis Mak. 22 avr 2016;16:46.

45. Krag NJ, Nørregaard J, Larsen JK, Danneskiold-Samsøe B. A blinded, controlled evaluation of anxiety and depressive symptoms in patients with fibromyalgia, as measured by standardized psychometric interview scales. Acta Psychiatr Scand. juin 1994;89(6):370-5.

46. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol. mai 1991;18(5):728-33.

47. Osorio CD, Gallinaro AL, Lorenzi-Filho G, Lage LV. Sleep quality in patients with fibromyalgia using the Pittsburgh Sleep Quality Index. J Rheumatol. sept 2006;33(9):1863-5.

48. Omachi TA. Measures of sleep in rheumatologic diseases: Epworth Sleepiness Scale (ESS), Functional Outcome of Sleep Questionnaire (FOSQ), Insomnia Severity Index (ISI), and Pittsburgh Sleep Quality Index (PSQI). Arthritis Care Res. nov 2011;63 Suppl 11:S287-296.

49. Crinière L, Lhommet C, Caille A, Giraudeau B, Lecomte P, Couet C, et al. Reproducibility and validity of the French version of the long international physical activity questionnaire in patients with type 2 diabetes. J Phys Act Health. août 2011;8(6):858-65.

50. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. déc 1983;24(4):385-96.

51. Marchand S, Arsenault P. Spatial summation for pain perception: interaction of inhibitory and excitatory mechanisms. Pain. févr 2002;95(3):201-6.

52. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain. mars 2005;114(1-2):295-302.

53. Granot M, Granovsky Y, Sprecher E, Nir R-R, Yarnitsky D. Contact heat-evoked temporal summation: tonic versus repetitive-phasic stimulation. Pain. juin 2006;122(3):295-305.

54. Barrett KE, Barman SM, Boitano S, Brooks H. Ganong's Review of Medical Physiology, 24th Edition. 24 edition. New York: McGraw-Hill Education / Medical; 2012. 768 p.

55. Potvin S, Paul-Savoie E, Morin M, Bourgault P, Marchand S. Temporal summation of pain is not amplified in a large proportion of fibromyalgia patients. Pain Res Treat. 2012;2012:938595.

56. Kirschbaum C, Hellhammer DH. Salivary cortisol in psychoneuroendocrine research: recent developments and applications. Psychoneuroendocrinology. 1994;19(4):313-33.

## Figure legends

Figure 1. Flow Chart of DouFiSport

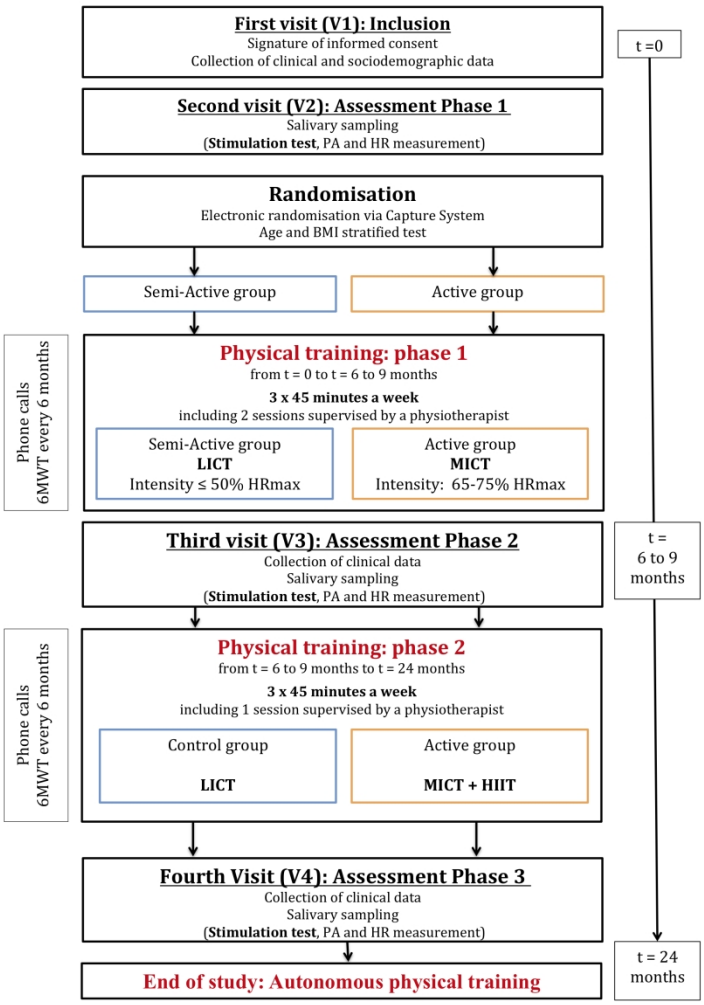


Figure 1: Flow Chart of DouFiSPort

209x297mm (300 x 300 DPI)


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Impact of a specific training program on the neuromodulation of pain in fibromyalgia women (DouFiSport): a 24-month, controlled, randomised, double-blinded protocol. |
| Trial registration | 2a | NCT02486965 |
| Protocol version | 3 | version number 5.0 of 21/06/2016 |
| Funding | 4 | This work is supported by the French Ministry of Health (Programme Hospitalier de Recherche Clinique Interrégional 2014) PHRCi 13-100 |

| | | |
|---|---|---|
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors: |

Anaïs Le Fur-Bonnabesse[1,2,3], investigator
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Gildas L'Heveder[4], co-ordinating investigator
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CB initiated the idea for the project.
CB and ALFB developed the study design.
MC, GL, BQ, AK, AW, SM, MAGM, FR, LM and AD provided advice for the study design.
GL and CB are responsible for supervision of project. CB will conduct the recruitment.
AK will conduct the training programme.
CB, ALFB and MC will conduct the outcomes assessments and will contribute to the analysis and interpretation of the data.
Both authors will contribute to the analyses and interpretation of the data.
ALFB, CB and MC wrote early drafts of the manuscript.
All authors approved the final version of this protocol.

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5c Role of study sponsor and funders :

- Evaluation of serious adverse events
- Transmission of annual safety reports
- Quality assurance and monitoring activities
- Approval of any amendment of the protocol

| | | |
|---|---|---|
| Background and rationale | 6a | Fibromyalgia affects 1.4 to 2.2% of the general population concerning predominately women (more than 80% of subjects). This syndrome is characterised by extensive and diffuse pain, mainly muscular and articular, impairing the functional abilities of the subjects. The symptoms most frequently described by fibromyalgia patients are chronic fatigue, sleep disorders, cognitive disorders and emotional disturbances (3,4). This symptomatology leads to a serious deterioration in quality of life, sometimes with a physical disability leading to social isolation and difficulties in staying in employment (recurrent work stoppages).<br>The diagnosis is based on the symptoms and their severity as described by the patients (5–8). Currently, there is no etiological treatment for fibromyalgia syndrome. The treatments are therefore only symptomatic.<br><br>**Physiopathology of fibromyalgia**<br>The mechanisms of dysfunctional pain, without any identifiable organic lesions, are mostly central (1) and related to dysfunction of the stress axis (autonomic nervous system and corticotropic axis) (9–11).<br>At rest, fibromyalgia patients showed an increased sympathetic response and decreased parasympathetic tone (12,13). This neurovegetative dystonia is a marker of dysfunction of the stress axis (14).<br>Malfunctions of the corticotropic axis in fibromyalgia have been described multiple times, also marking the dysfunction of the stress axis. But the form taken by this dysfunction differs according to the different studies (15–19). The variability of salivary cortisol in response to stress reflects that of plasma free cortisol. Salivary cortisol is therefore a method of choice in experimental stress studies (20).<br>Whatever form they take, these dysfunctions compromise the body's adaptation to daily stressful stimuli.<br><br>Studies show that this deficit of the stress axis (neurovegetative dystonia and dysfunctional corticotropic axis) is concurrent with fibromyalgia (21) and associated with alteration of pain control (9–11).<br>Pain control system and stress axis have close anatomical and functional links. Nociceptive, neurovegetative and corticotropic systems interact with the central nervous system. The central neuromediators implicated in the regulation of the stress axis are mostly common with those of the pain neuromodulation (endogenous opioids, norepinephrine, serotonin, etc.). |

**Elite athlete's overtraining syndrome: model of stress axis dysfunction**

An overtraining elite athlete may be considered as a model of dysfunction of the stress axis associated with neurovegetative dystonia. The physical and psychological effort of training is known to induce stress. High-level athletes could present an overtraining syndrome when adaptation limits of the stress axis are reached. This stress-induced phenomenon corresponds to an imbalance between training quantity and recovery. Overtrained athletes present a deconditioning syndrome close to fibromyalgia symptoms (chronic pain, sleep disorders, neurovegetative dystonia, etc.) (22–26).

**Physical activity and fibromyalgia**

Most studies have shown that physical activity is more efficient compared to pharmacological treatments on fibromyalgia symptoms (27,28). Literature reviews and meta-analyses highly support the benefits of physical training in fibromyalgia patients (decreased pain and depression and improvement in overall health and physical abilities) (29)(30). Practice of aerobic exercise in fibromyalgia patients is strongly recommended by The American Pain Society (31), the Association of Medical Scientific Societies in Germany (32), the Canadian Rheumatology Association (5) and the European League Against Rheumatism (EULAR) (33). Physical exercise is the first-line treatment recommended in fibromyalgia. However there is still no consensus on the modalities of these types of training (frequency, duration, and intensity). Currently, the mechanisms underlying those specific training effects have to be defined.

The steady physical activity rebalancing autonomic system is associated with cardiovascular benefits. Fundamental endurance increases parasympathetic tone and decrease sympathetic response (34–37). Thus, strategies to rebalance the autonomic system are the most promising therapies for fibromyalgia (13,36,37).

In this study, we propose to validate a therapeutic alternative that aims to treat fibromyalgia by rebalancing the stress axis. This treatment consists of a specific supervised and individualised training program, over 2 years. This training protocol is individually adjusted in order to rebalance the neurovegetative system (parasympathetic and sympathetic). Central neuroplasticity induced by training should regulate endogenous pain control mechanisms.

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| Objectives | 7 | The *main objective* is to assess the effectiveness of a specific training program on endogenous pain controls in fibromyalgia patients. The *secondary objectives* are to rebalance the autonomic nervous system and the corticotropic axis, to improve life and sleep quality and to reintegrate patients into society and work. |

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|---|---|---|
| Trial design | 8 | This randomised double-blinded trial will compare an "active" program to a "control" program in fibromyalgia patients. |

**Methods: Participants, interventions, and outcomes**

| | | |
|---|---|---|
| Study setting | 9 | Patients will be recruited at the pain center of the university hospital of Brest on the basis of general criteria. Patients should follow a re-exercise program for 24 months. The assessments will take place (i) before, (ii) between 6 to 9 months (depending the training level) and (iii) at the end of the training (24 months), in the neurological functional explorations department of the university hospital of Brest (France). |
| Eligibility criteria | 10 | The inclusion criteria are: female subjects; aged of 18 to 65 years; with a diagnosis of fibromyalgia clearly established according to the criteria of the American College of Rheumatology (ACR) 2010; with a body mass index (BMI) between 18.5 and 29.9kg/m²; spontaneous pain intensity higher than 3/10 on a visual analog scale (VAS); pain experienced at least 3 days a week; pain caused by palpation equal to or higher than 4/10 on a VAS.<br><br>The non-inclusion criteria are: patients with a systemic disease (treated or not) generating pain of the musculoskeletal system; presenting pain other than fibromyalgia; presenting a contraindication to physical activity; having any active pathology; having modified in the last 2 months any pharmacological treatment; having a psychiatric diagnosis; taking drugs that affect cortisol secretion (decrease or increase); non-cooperating. |

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| Interventions | 11a | The training program is planned over two years (24 months) for both groups (active/control). A minimum of 4 to 6 weeks is needed to observe a decrease in symptoms (38). This two-year duration is the minimum average training time (depending on the individual progress of each patient), necessary to regain central neuroplasticity sufficient to put back into operation diffuse noxious inhibitory controls (DNIC) and neurovegetative system (39).<br>The frequency, intensity, and duration of these training sessions are based upon the results of a preliminary study. Pain was significantly reduced and symptoms, such as quality of life, sleep quality, anxiety, were also highly improved in subjects undergoing this specific training after 5 years (39). The American Pain Society recommends an intensity of 60 to 70% of the age-adjusted maximum heart rate (HRmax). At the early stage, the intensity and duration of the training sessions will be adapted to the physical condition of each subject. In order to promote adherence of our patients and to limit pain exacerbation, exercise intensity will start very low and then gradually increase to reach the neurovegetative goal (31)(40).<br><br>**Active training group:**<br>*The first 6 to 9 months*: fundamental endurance training.<br>Subjects will perform 3 sessions per week of 45 minutes of fundamental endurance (moderate-intensity continuous training MICT: 60% HRmax), including 2 sessions supervised by a physiotherapist and 1 independent session.<br>*From 6-9 months (according to the rhythm, abilities, and limits) to 24 months*: Patients will begin the second stage of training: 3 sessions per week of 45 minutes each (moderate-intensity continuous training MICT (60% HRmax) and high-intensity interval training HIIT) with 1 supervised session and 2 independents sessions. When the patient reaches the initial HR goal, “fundamental endurance” will be associated with “interval training” at a high frequency intensity. HIIT will consist of 5 stages of 1 to 4 minutes at 85-90% HRmax (80-85% $V\dot{O}_2max$), interspersed by 1 to 4 minutes of active recovery at 60-75% HRmax (50-70% $V\dot{O}_2max$). Intensity will be assessed objectively using a heart rate monitor (FT2, Polar). At baseline, Tanaka’s age-based prediction equation (208-0.7×age) will calculate HRmax. After *6-9 months of training, a* maximal-effort graded exercise test will determine HRmax and $V\dot{O}_2max$ for each patient.<br><br>**Control group:**<br>Patients will perform the same infra active training (low-intensity continuous training: LICT <50% HRmax) over two years. Supervision, monitoring, and frequency of sessions (3 x 45 minutes per week) in both groups will be equivalent. |

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant: If a patient cannot achieve the specific training requested after 9 months of study, the patient will not complete the second phase of training.

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence: Patients will be contacted to record progress, difficulties and if necessary, to encourage them to adhere to their program. These calls will improve the compliance and will limit patients lost to follow-up.
Patients will perform a 6-minute walk test (6MWT) every 6 months (with physiotherapist).

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial: This specific protocol will be associated with psychotherapeutic approaches. In addition to the training program, multidisciplinary bio-psycho-social cares will be given in the pain center of the university hospital of Brest (France).

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| Outcomes | 12 | **Primary outcomes:** In order to assess endogenous pain mechanisms, such as diffuse noxious inhibitory controls (DNIC), temporal summation (TS) and perception of pain, we will use an experimental method developed by Tousignant-Laflamme and Marchand (2008). According to this well-characterised paradigm**,** we will induce in single session two tonic heat pain stimulations separated by a cold pressor test (1,47–49). The VAS improvements (stimulation test) obtained in the both groups will be compared.<br><br>**Secondary outcomes:**<br>A simple verbal scale, a visual analog scale, and the Saint Antoine Pain Questionnaire (QDSA), will perform the **assessment of pain**. A **pain quantitative assessment** will be performed with a pressure algometer (pressure pain threshold: PPT).<br>Questionnaires will assess **patient anxiodepressive state** (Hospital Anxiety Depression Scale), **the impact of fibromyalgia on daily life** (Fibromyalgia Impact Questionnaire), **sleep quality and quantity** (Pittsburgh Sleep Quality Index), **the level of physical activity and the sedentary lifestyle** (International Physical Activity Questionnaire), **the antecedents of perceived stress** (Perceived Stress Scale).<br>**Blood Pressure** (BP) and **Heart Rate** (HR) will be recorded.<br>**Corticotropic axis** will be assessed using measurement of salivary cortisol and salivary flow.<br><br>Quantitative assessment (salivary cortisol, blood pressure, PPT quantified by pain threshold pressure, questionnaires assessment) will be analysed by comparing the improvements obtained between both groups. |

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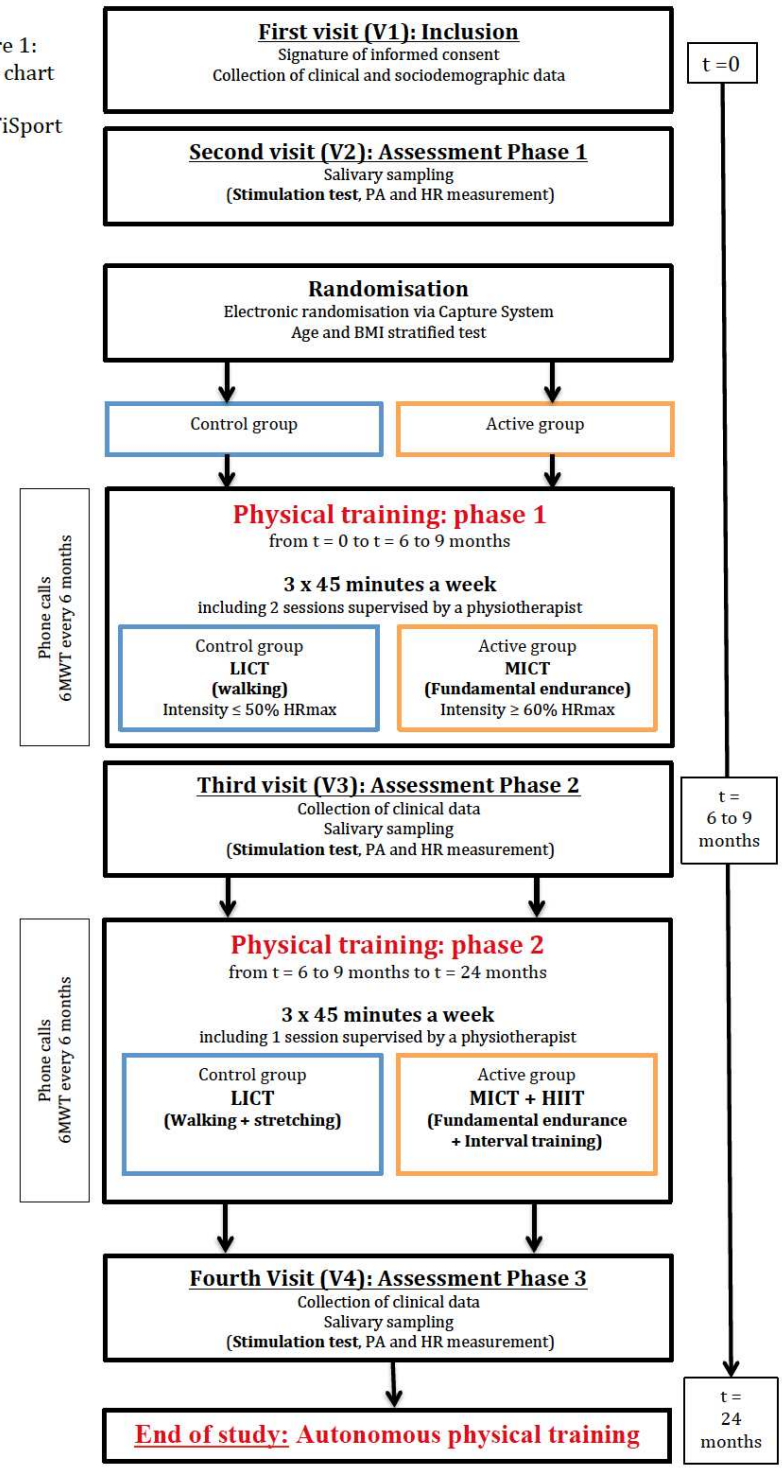
| Participant timeline | 13 | The training program is planned over two years (24 months) for both groups (active/control). Subjects will perform 3 training sessions per week of 45 minutes.<br>Patient will participate in 4 visits (1 inclusion visit and 3 assessment visits) during these two years. |

Figure 1: Flow chart of DouFiSport



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| Sample size | 14 | Population size is based on an expected difference of 20 points (stimulation test) (1) between the two groups, for a quantitative primary endpoint (delta VAS) of standard deviation equal to 35, and a power set at 80%. Therefore a minimum of 48 subjects per group is required for assessment. In order to take into account loss to follow-up, the sample of 110 subjects, 55 per group will be recruited. |
| Recruitment | 15 | Patients will be recruited at the pain centre of the university hospital of Brest on the basis of general criteria. |

**Methods: Assignment of interventions (for controlled trials)**

Allocation:

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| Sequence generation | 16a | Patients will be randomised at the end of the first stimulation test (second visit: V2), which is just before the initiation of the training. The test is stratified by age and BMI. The cut off is set at 50 years for age and 25kg/m$^2$ for BMI (two strata [18-25] and ]25-30 []). |
| Allocation concealment mechanism | 16b | Electronic randomisation via Capture System |
| Implementation | 16c | The allocation sequence will generate by the Center of Clinical Investigation (CIC) at the hospital university of Brest (France). The principal investigator will enrol participants, and will assign participants to interventions. |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions: Patients will be blinded (they will not be informed of their group (active/control)). The investigators, outcome assessors and data analysts will be blinded. |
| | 17b | If blinded, circumstances under which unblinding is permissible: Due to the nature of the intervention (physical activity protocol), the coaching staff will not be blinded. |

**Methods: Data collection, management, and analysis**

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| Data collection methods | 18a | Measurements and questionnaires will be carried out (i) at baseline, (ii) between 6 to 9 months, and (iii) at the end of the 24 months of training.<br>**Sociodemographic and clinical data**<br>At baseline, data on age, sex, marital status, education level, and occupation will be collected. Height and weight will be recorded. Medical background and pain characteristics will be noted. All current drug and non-drug therapies (including tried and stopped) will also be collected, as well as their effectiveness on pain.<br>**Questionnaires and pain assessments**<br>• The **assessment of pain** will be performed by a simple verbal scale and using a visual analog scale (VAS). The Saint Antoine Pain Questionnaire (QDSA) will also assess pain. A **pain quantitative assessment** will be performed with a pressure algometer (pressure pain threshold: PPT).<br>• The Hospital Anxiety Depression Scale (HADS) will assess the **patient anxiodepressive state** (41).<br>• The Fibromyalgia Impact Questionnaire (FIQ) will assess **the impact of fibromyalgia on daily life** (42).<br>• The Pittsburgh Sleep Quality Index (PSQI) will assess **sleep quality and quantity** (43,44).<br>• The International Physical Activity Questionnaire (IPAQ) will record the **level of physical activity and the sedentary lifestyle**. The French long telephone questionnaire will be used (45).<br>• The Perceived Stress Scale (PSS) will assess **the antecedents of perceived stress** (46).<br><br>**Stimulation test**<br>In order to assess endogenous pain mechanisms, such as diffuse noxious inhibitory controls (DNIC), temporal summation (TS) and perception of pain, we will use an experimental method developed by Tousignant-Laflamme and Marchand (2008) (1,47–49).<br>- Thermode test or temporal summation test **(P1):** a tonic heat pain will be administered for 2 minutes on the patient's right arm, using a thermode (CE marking n°226). The starting temperature is 32°C (skin temperature under normal conditions in temperate room (20-22°C)) (50) and will quickly reach a fixed value. The experimental temperature will be individually determined to induce 50/100 on a VAS and will remain constant during the test period (2 minutes). Throughout this entire period, the patient will evaluate their pain intensity using a Computerised Visual Analog Scale (CoVAS).<br>- Cold pressor test **(P2):** to elicit a prolonged pain sensation in order to trigger diffuse noxious inhibitory control (DNIC) (51), the patient's right arm will be immersed for 2 minutes in a cold water bath maintained at 12°C. The patient will continuously evaluate their pain intensity using a CoVAS.<br>Following this cold pressor test, the thermode test will be again performed **(P3).**<br>Pain difference between the two (P3/P1) tonic heat pain stimulations will measure DNIC activation and represents pain modulation. |

**Measurement of salivary cortisol and salivary flow**

Corticotropic axis will be assessed using measurement of salivary cortisol. Cortisol release is pulsatile (10 to 20 peaks per day) and follows a nycthemeral cycle. Maximum cortisol level is reached in the early morning. In the morning of each consultation (at baseline, in the middle and at the end of training), patients will collect salivary sample (i) for 2 minutes, when they wake up and (ii) for 2 minutes, 30 minutes later. The salivary cortisol level is measured in nmol/l. The flow rate is calculated in $ml.min^{-1}$. Samples will be frozen at -20°C. As salivary cortisol is stable, samples can be stored for many weeks in the freezer (52). After completion of all assessment sessions, sample analysis will be completed. To avoid inter-laboratory variation, the same laboratory will assay the samples.

**Recording of Blood Pressure (BP) and Heart Rate (HR)**

After 10 minutes at rest, lying down, BP and HR will be recorded. Then, BP and HR will be measured when the patient stands up and once per minute during 4 minutes when the patient remains standing.

18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols: To limit dropout, patients will be called to encourage them and to discuss any difficulties. In second stage of training and to limit a possible long-term monotonous effect, physical activity type could be diversified in both groups. The training session will be adapted in the active group (MICT will be associated with HIIT) to reduce sympathetic hyperactivity. In order to improve compliance and long-term achievement of training, the patient may choose the physical activity type performed without supervision. If a patient cannot achieve the specific training requested after 9 months of study, the patient will not complete the second phase of training. Nevertheless, she will carry out all assessment visits.
The main analysis will be performed on an intent-to-treat basis.

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| Data management | 19 | **Case report forms (CRF):**<br>All data collected must be recorded in the CRF immediately after the procedure. Each missing data will have to be coded. The researcher will carry out a double data entry. In addition, Checks on the consistency of these data will be instantly carried out.<br><br>Data on individuals included in the study will be made anonymous. Only the first letter of the subject's name, and the first letter of her first name will be recorded, with a specific code number.<br><br>**Quality Assurance and Control:**<br>A researcher commissioned by the study sponsor will ensure proper achievement of the study and, of data collection, recording and, reporting.<br><br>**Storage:**<br>During the study period, documents will be stored in the neurological functional explorations department of the university hospital of Brest<br>At the end of the study period, all archived documents will be transferred to a centralized archiving site (Central Archives Service - Brest) and, will be placed under the sponsor responsibility for 15 years according to institutional practices. |
| Statistical methods | 20a | *Primary outcome analysis*: The VAS improvements (stimulation test) obtained in the both groups will be compared using the Student's test. If the required normality assumption is not sustainable, a nonparametric Wilcoxon test will be used. An alpha risk of 0.05 will be set as the limit of statistical significance. The main analysis will be performed on an intent-to-treat basis. A complementary analysis using a linear model with adjustment for age and BMI factors will be completed.<br><br>*The secondary outcomes* (quantitative: salivary cortisol, blood pressure, PPT quantified by pain threshold pressure, questionnaires assessment) will be analysed in a similar way by comparing the improvements obtained between both groups. |
| **Methods: Monitoring** | | |
| Data monitoring | 21a | Because of the nature of the study (excluding health product and, duration of the study), a monitoring committee independent from the sponsor will not be constituted.<br>A researcher commissioned by the study sponsor will ensure proper achievement of the study, and of data collection, recording and reporting. |

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| | 21b | The study may be stopped early for reasons of safety (in the event of unexpected serious adverse event occurrences), efficacy or futility. The sponsor reserves the right to stop the study at any time, if the desired sample size is not achieved. |
| Harms | 22 | **The investigator** is responsible for recording and reporting all serious adverse events (EvIG) occurring during the entire study period. Regardless of the causal relationship between EvIG and the study, any EvIG will be described on the form dedicated to this matter («EvIG initial report» or «EvIG follow-up report») and will be notified to the sponsor within a time frame of 24 hours after the event occurs.<br><br>All other adverse events (non-serious adverse events) will be reported on adverse event form of the CRF. The date of occurrence, description, intensity, duration, treatment, aetiology, accountability and the decisions taken will be specified.<br><br>**The sponsor** has to analyse EvIG (the causality of the EvIG and their expected or unexpected character). The sponsor have to report all unexpected EvIG to Eudravigilance (European pharmacovigilance database), the French Health Authorities (ANSM), the Committee for the Protection of Persons (CPP) and, to the investigators. Each year, the sponsor will draft a safety report that will include:<br>- the list of unexpected and expected EvIG,<br>- a concise and critical analysis of the safety of patients included in the study.<br><br>Each adverse events will be monitored until the it will be completely resolved even if after the study period. |
| Auditing | 23 | A researcher commissioned by the sponsor will audit trial conduct. The investigator and his team undertake to make themselves available during regular Quality Control visits by this researcher. During these visits, informed consent, adherence to study protocol and, CRF data quality, will be reviewed. The investigator undertakes to accept quality control audits carried out by the sponsor, and by the competent authorities. |
| **Ethics and dissemination** | | |
| Research ethics approval | 24 | The Committee for the Protection of Persons West VI approved this study on 02/12/2014. |

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| Protocol amendments | 25 | Important protocol modifications by the investigator (eg, changes to eligibility criteria, outcomes, analyses) have to be approved by the sponsor. The sponsor must obtain a favourable opinion of the CPP and an authorization of the «Agence nationale de sécurité du médicament et des produits de santé» (ANSM) to enable the application of these amendments. A new consent of the patient participating will be collected if necessary. |
| Consent or assent | 26a | Patients will be informed of the objectives, constraints, risks and benefits of the study. Patients will be informed of their rights to refuse to participate or to withdraw from the study at any time. All information will be on information and consent form given to the patient. To be included, patients will sign informed written consent. The investigator will collect free, informed, and written consent of the patient before definitive inclusion in the study. |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable: No collection will be formed. |
| Confidentiality | 27 | Data on individuals included in the study will be made anonymous. Only the first letter of the subject's name, and the first letter of her first name will be recorded, with a specific code number. The investigators will take all necessary precautions to ensure the confidentiality of the information in particular with regard to patient identity. |
| Declaration of interests | 28 | None declared. |
| Access to data | 29 | In accordance with good clinical practice, the sponsor is responsible for seeking the agreement of those involved in this research with a view to ensure direct access to source data, source documents and reports in all research place (particularly during quality control).<br>In accordance with the legislative provisions in force (articles L.1121-3 et R.5121-13 of the French Public Health Code), the investigators will be making documents and necessary individual data available to researcher charged with study control and monitoring. |
| Ancillary and post-trial care | 30 | Pursuant to the provisions of article L1121-10 of the French Public Health Code, the sponsor (CHRU of Brest) undertakes to take out a civil liability insurance contract. |
| Dissemination policy | 31a | The results of this study will be published in specialised scientific journals. These results will be presented to participants and the public at a free public lecture organised by the health promotion department of the city of Brest. These results will also be presented to healthcare professionals and other relevant groups in pain and/or physical activity congresses. In addition, a doctoral thesis will be carried out on this project. |

## Appendices

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| Informed consent materials | 32 | See attached documentation |
| Biological specimens | 33 | Not applicable. |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

## References


1. Tousignant-Laflamme Y, Pagé S, Goffaux P, Marchand S. An experimental model to measure excitatory and inhibitory pain mechanisms in humans. Brain Res. 16 sept 2008;1230:73•9.
2. Woda A, L'heveder G, Ouchchane L, Bodéré C. Effect of experimental stress in 2 different pain conditions affecting the facial muscles. J Pain Off J Am Pain Soc. mai 2013;14(5):455•66.
3. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. févr 1990;33(2):160•72.
4. Cánovas R, León I, Roldán MD, Astur R, Cimadevilla JM. Virtual reality tasks disclose spatial memory alterations in fibromyalgia. Rheumatol Oxf Engl. oct 2009;48(10):1273•8.
5. Fitzcharles M, Shir Y, Ablin JN, Buskila D, Amital H, Henningsen P, et al. Classification and clinical diagnosis of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines. Evid-Based Complement Altern Med ECAM. 2013;2013:528952.
6. Egloff N, von Känel R, Müller V, Egle UT, Kokinogenis G, Lederbogen S, et al. Implications of proposed fibromyalgia criteria across other functional pain syndromes. Scand J Rheumatol. 2015;44(5):416•24.
7. Moyano S, Kilstein JG, Alegre de Miguel C. New diagnostic criteria for fibromyalgia: Here to stay? Reumatol Clin. août 2015;11(4):210•4.
8. Wolfe F, Fitzcharles M-A, Goldenberg DL, Häuser W, Katz RL, Mease PJ, et al. Comparison of Physician-Based and Patient-Based Criteria for the Diagnosis of Fibromyalgia. Arthritis Care Res. mai 2016;68(5):652•9.
9. Bodéré C, Woda A. La douleur orofaciale idiopathique: une douleur fonctionnelle. Douleur Analgésie. 21 juin 2009;22(2):89•95.
10. Woda A, Dao T, Gremeau-Richard C. Steroid dysregulation and stomatodynia (burning mouth syndrome). J Orofac Pain. 2009;23(3):202•10.
11. Woda A, L'heveder G, Ouchchane L, Bodéré C. Effect of experimental stress in 2 different pain conditions affecting the facial muscles. J Pain Off J Am Pain Soc. mai 2013;14(5):455•66.

12. Cohen H, Neumann L, Shore M, Amir M, Cassuto Y, Buskila D. Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability. Semin Arthritis Rheum. févr 2000;29(4):217‑27.
13. da Cunha Ribeiro RP, Roschel H, Artioli GG, Dassouki T, Perandini LA, Calich AL, et al. Cardiac autonomic impairment and chronotropic incompetence in fibromyalgia. Arthritis Res Ther. 2011;13(6):R190.
14. Martinez-Lavin M. Fibromyalgia as a sympathetically maintained pain syndrome. Curr Pain Headache Rep. oct 2004;8(5):385‑9.
15. Kadetoff D, Kosek E. Evidence of reduced sympatho-adrenal and hypothalamic-pituitary activity during static muscular work in patients with fibromyalgia. J Rehabil Med. sept 2010;42(8):765‑72.
16. Tak LM, Cleare AJ, Ormel J, Manoharan A, Kok IC, Wessely S, et al. Meta-analysis and meta-regression of hypothalamic-pituitary-adrenal axis activity in functional somatic disorders. Biol Psychol. mai 2011;87(2):183‑94.
17. Riva R, Mork PJ, Westgaard RH, Lundberg U. Comparison of the cortisol awakening response in women with shoulder and neck pain and women with fibromyalgia. Psychoneuroendocrinology. févr 2012;37(2):299‑306.
18. Geiss A, Rohleder N, Anton F. Evidence for an association between an enhanced reactivity of interleukin-6 levels and reduced glucocorticoid sensitivity in patients with fibromyalgia. Psychoneuroendocrinology. mai 2012;37(5):671‑84.
19. Bote ME, García JJ, Hinchado MD, Ortega E. Inflammatory/stress feedback dysregulation in women with fibromyalgia. Neuroimmunomodulation. 2012;19(6):343‑51.
20. Hellhammer DH, Wüst S, Kudielka BM. Salivary cortisol as a biomarker in stress research. Psychoneuroendocrinology. févr 2009;34(2):163‑71.
21. Clauw D, Ablin J. The relationship between « stress » and pain: lessons learned from fibromyalgia and related conditions. In: Current topics in pain. Castro-Lopes editor. XIIth World Congress on Pain. Seattle: IASP press; 2009. p. p.245-270.
22. McKenzie DC. Markers of excessive exercise. Can J Appl Physiol Rev Can Physiol Appl. févr 1999;24(1):66‑73.
23. MacKinnon LT. Special feature for the Olympics: effects of exercise on the immune system: overtraining effects on immunity and performance in athletes. Immunol Cell Biol. oct 2000;78(5):502‑9.
24. Iellamo F, Pigozzi F, Parisi A, Di Salvo V, Vago T, Norbiato G, et al. The stress of competition dissociates neural and cortisol homeostasis in elite athletes. J Sports Med Phys Fitness. déc 2003;43(4):539‑45.
25. Baumert M, Brechtel L, Lock J, Hermsdorf M, Wolff R, Baier V, et al. Heart rate variability, blood pressure variability, and baroreflex sensitivity in overtrained athletes. Clin J Sport Med Off J Can Acad Sport Med. sept 2006;16(5):412‑7.
26. Kajaia T, Maskhulia L, Chelidze K, Akhalkatsi V, Kakhabrishvili Z. The effects of non-functional overreaching and overtraining on autonomic nervous system function in highly trained athletes. Georgian Med News. mars 2017;(264):97‑103.
27. Fontenele JB, Felix FHC. Exercise for fibromyalgia: evidence for an integrated modulation of autonomic and nociception neural regulation. Rheumatol Int. déc 2012;32(12):4075‑6.
28. Rossy LA, Buckelew SP, Dorr N, Hagglund KJ, Thayer JF, McIntosh MJ, et al. A meta-analysis of fibromyalgia treatment interventions. Ann Behav Med Publ Soc Behav Med. 1999;21(2):180‑91.

29. Busch AJ, Webber SC, Brachaniec M, Bidonde J, Bello-Haas VD, Danyliw AD, et al. Exercise therapy for fibromyalgia. Curr Pain Headache Rep. oct 2011;15(5):358•67.
30. Woda A, L'heveder G, Ouchchane L, Bodéré C. Effect of experimental stress in 2 different pain conditions affecting the facial muscles. J Pain Off J Am Pain Soc. mai 2013;14(5):455•66.
31. Society AP, éditeur. Guideline for the Management of Fibromyalgia Syndrome Pain in Adults and Children. American Pain Society; 2005. 109 p.
32. Häuser W, Arnold B, Eich W, Felde E, Flügge C, Henningsen P, et al. Management of fibromyalgia syndrome – an interdisciplinary evidence-based guideline. GMS Ger Med Sci. 2008;6:Doc14.
33. Macfarlane GJ, Kronisch C, Atzeni F, Häuser W, Choy EH, Amris K, et al. EULAR recommendations for management of fibromyalgia. Ann Rheum Dis. déc 2017;76(12):e54.
34. Melanson EL, Freedson PS. The effect of endurance training on resting heart rate variability in sedentary adult males. Eur J Appl Physiol. sept 2001;85(5):442•9.
35. Reland S, Ville NS, Wong S, Gauvrit H, Kervio G, Carré F. Exercise heart rate variability of older women in relation to level of physical activity. J Gerontol A Biol Sci Med Sci. juill 2003;58(7):585•91.
36. de Abreu SB, Lenhard A, Mehanna A, de Souza HCD, Correa FM de A, Hasser EM, et al. Role of paraventricular nucleus in exercise training-induced autonomic modulation in conscious rats. Auton Neurosci Basic Clin. 15 juin 2009;148(1•2):28•35.
37. Martins-Pinge MC. Cardiovascular and autonomic modulation by the central nervous system after aerobic exercise training. Braz J Med Biol Res Rev Bras Pesqui Médicas E Biológicas Soc Bras Biofísica Al. sept 2011;44(9):848•54.
38. Häuser W, Klose P, Langhorst J, Moradi B, Steinbach M, Schiltenwolf M, et al. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials. Arthritis Res Ther. 2010;12(3):R79.
39. Bodéré C, Bodéré YT, Quinio B, Woda A, Misery L. Specific training program for the treatment of fibromyalgia: a prospective controlled study. In: 14th world congress on pain - TF505. Milan, Italy: IASP; 2012.
40. Lannersten L, Kosek E. Dysfunction of endogenous pain inhibition during exercise with painful muscles in patients with shoulder myalgia and fibromyalgia. Pain. oct 2010;151(1):77•86.
41. Krag NJ, Nørregaard J, Larsen JK, Danneskiold-Samsøe B. A blinded, controlled evaluation of anxiety and depressive symptoms in patients with fibromyalgia, as measured by standardized psychometric interview scales. Acta Psychiatr Scand. juin 1994;89(6):370•5.
42. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol. mai 1991;18(5):728•33.
43. Osorio CD, Gallinaro AL, Lorenzi-Filho G, Lage LV. Sleep quality in patients with fibromyalgia using the Pittsburgh Sleep Quality Index. J Rheumatol. sept 2006;33(9):1863•5.
44. Omachi TA. Measures of sleep in rheumatologic diseases: Epworth Sleepiness Scale (ESS), Functional Outcome of Sleep Questionnaire (FOSQ), Insomnia Severity Index (ISI), and Pittsburgh Sleep Quality Index (PSQI). Arthritis Care Res. nov 2011;63 Suppl 11:S287-296.
45. Crinière L, Lhommet C, Caille A, Giraudeau B, Lecomte P, Couet C, et al. Reproducibility and validity of the French version of the long international physical activity questionnaire in patients with type 2 diabetes. J Phys Act Health. août 2011;8(6):858•65.

46. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. déc 1983;24(4):385•96.
47. Marchand S, Arsenault P. Spatial summation for pain perception: interaction of inhibitory and excitatory mechanisms. Pain. févr 2002;95(3):201•6.
48. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain. mars 2005;114(1•2):295•302.
49. Granot M, Granovsky Y, Sprecher E, Nir R-R, Yarnitsky D. Contact heat-evoked temporal summation: tonic versus repetitive-phasic stimulation. Pain. juin 2006;122(3):295•305.
50. Barrett KE, Barman SM, Boitano S, Brooks H. Ganong's Review of Medical Physiology, 24th Edition. 24 edition. New York: McGraw-Hill Education / Medical; 2012. 768 p.
51. Potvin S, Paul-Savoie E, Morin M, Bourgault P, Marchand S. Temporal summation of pain is not amplified in a large proportion of fibromyalgia patients. Pain Res Treat. 2012;2012:938595.
52. Kirschbaum C, Hellhammer DH. Salivary cortisol in psychoneuroendocrine research: recent developments and applications. Psychoneuroendocrinology. 1994;19(4):313•33.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry |
| | 2b | All items from the World Health Organization Trial Registration Data Set |
| Protocol version | 3 | Date and version identifier |
| Funding | 4 | Sources and types of financial, material, and other support |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors |
| | 5b | Name and contact information for the trial sponsor |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) |
| **Introduction** | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention |
| | 6b | Explanation for choice of comparators |
| Objectives | 7 | Specific objectives or hypotheses |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) |

**Methods: Participants, interventions, and outcomes**

| | | |
|---|---|---|
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size |

**Methods: Assignment of interventions (for controlled trials)**

Allocation:

| | | |
|---|---|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions |

| | | |
|---|---|---|
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial |
| **Methods: Data collection, management, and analysis** | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) |
| **Methods: Monitoring** | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed |

| | | |
|---|---|---|
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor |
| **Ethics and dissemination** | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code |

## Appendices

| | | |
|---|---|---|
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.