BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-069153
Article Type:	Protocol
Date Submitted by the Author:	14-Oct-2022
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Keywords:	Rheumatology < INTERNAL MEDICINE, IMMUNOLOGY, GENERAL MEDICINE (see Internal Medicine)

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Competing interests: None declared.

Word count: 2.545 (excluding title page, abstract, references, figures and tables)

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ARTICLE SUMMARY

Abstract:

Introduction: Fibromyalgia is a polysymptomatic syndrome with a prevalence between 0.2 and 13% of the population and causes work disabilities in approximately half of affected patients. Several treatments to fibromyalgia have been proposed with partial improvement. This study aims to evaluate the efficacy of hyperbaric oxygen therapy and when it should be introduced to fibromyalgia.

Methods and Analysis: This is a protocol for an open-label, crossover, randomised clinical trial comparing treatment with hyperbaric oxygen and standardized treatment to fibromyalgia. In the proposed study, 56 individuals with fibromyalgia will be randomised in a 1:1 ratio into a single, fixed, random block, in which one group will receive hyperbaric oxygen therapy and another will receive standard treatment. Subsequently, the groups will be crossed. Participants will be evaluated at baseline, eight and 16 weeks based on functional impairment assessed with the Fibromyalgia Impact Questionnaire - Brazilian Portuguese version, psychopathological symptoms questionnaire and short-form quality of life questionnaire. The improvement of symptoms concerning the moment of therapy use will be compared between groups. For sample size calculation, a moderate effect size, 80% power and 95% confidence will be estimated, in a total of 46 patients. Considering a dropout of 20%, 56 patients should be recruited.

Ethics and dissemination: The study was approved by the institutional ethics committee and assigned the number 53058421.9.0000.5133 (version 3). The results will be disseminated via publications in peer-reviewed journals and presentations in medical meetings.

Trial registration number: This study is registered in REBEC (RBR-6prps8g)/UTN U1111-1278-3224.

Strengths and limitations of the study:

- This randomised crossover clinical trial allows triple comparison between treatments in two groups, treatment in the same group and between treatment and no treatment in different groups.
- The crossover design of this study is ideal for identifying the appropriate timing of hyperbaric oxygen therapy for the treatment of fibromyalgia.
- An analysis of clinical outcomes and quality of life will allow us to assess the impact of hyperbaric oxygen therapy on fibromyalgia.
- Sample size was previously calculated.
- The protocol was previously published, minimizing publication bias.
- Due to the long-term nature of the treatment (40 sessions), participants may be lost to follow-up.

Keywords

fibromyalgia; hyperbaric oxygen therapy; chronic pain; fibromyalgia treatment; chronic fatigue; oxygenation.

INTRODUCTION

Fibromyalgia (FM) is a polysymptomatic syndrome that consists of diffuse chronic pain, fatigue, sleep disturbances and also autonomic disturbances, cognitive dysfunction, hypersensitivity to stimuli, somatic symptoms, and psychiatric disorders.[1]The prevalence of FM in the general population is lower than in the population with specific disorders,[2] but it affects between 0.2 and 13% of the population and causes work disability in approximately half of affected patients.[3,4]

Due to the absence of accurate diagnostic tools and adequate biomarkers, a diagnosis based on constantly evolving clinical criteria remains the best option.[1] Treatment and prevention constitute knowledge gaps and move towards multimodal therapies.[5–12] According to the American College of Rheumatology, generalized bilateral pain above and below the waist for at least 3 months or 11 tender points are diagnostic criteria for FM.[13,14]

Several factors are related to the results of the treatment of FM, such as genetic predisposition, personal experiences of pain, emotional-cognitive factors, mind-body relationships, and psychological capacity to deal with stress. According to the European Alliance of Rheumatology Associations (EULAR), the ideal treatment of FM must contain at least four pillars and may also utilise new adjuvant modalities.[1] It should begin with a pharmacotherapeutic modality with antidepressants, anticonvulsants, analgesics, and adjuvant nonpharmacological measures, such as patient education about the disease, regular physical activity at least three times per week, psychotherapy modalities, such as relaxation techniques, hypnosis, and cognitive-behavioural therapy. With respect to adjuvant treatment modalities, positive results have been observed with the use of medical cannabis, low laser therapy, nature activity therapies, transcutaneous electrical nerve stimulation (TENS), acupuncture and hyperbaric oxygen therapy (HOT).[6,8,9,15]

The HOT treatment modality involves patients breathing nearly 100% oxygen while inside a closed chamber in which the pressure is two to three times higher than the atmospheric pressure at sea level.[12,16] HOT has led to promising results in pre-clinical models of nociceptive, inflammatory, and neuropathic pain and clinical benefits in the treatment of chronic pain, stroke sequelae, traumatic brain injury, spinal cord trauma and autism.[15,17,18] HOT may play a role in modulating the inflammatory response after tissue injury, resulting in a decrease in the nociceptive response by 80-95% for up to 90 minutes after exposure to HOT. However, the antinociceptive effect of HOT in pre-clinical models appear to be unrelated to oxidative stress.[19] Randomized clinical trials on HOT for FM have shown reduction of pain, number of tender points, improvement of functional and neuropsychiatric questionnaires and quality of life.[15]

Several protocols for the treatment of FM with HOT have been applied with different pressure values, total number of sessions and time to begin the therapy.[15] Although the effectiveness of HOT has already been evaluated in other studies, doubts remain about the ideal time to introduce the technology and about the consistency of the results. This study aims to evaluate the efficacy of HOT and when it should be introduced for fibromyalgia.

MATERIALS AND METHODS

Study design and settings

This protocol was written according to the SPIRIT guidelines.[20] This work utilises a randomised, crossover primary study protocol to conduct a clinical trial comparing treatment with hyperbaric oxygen and standardized treatment at a single research centre in the rheumatology department of a tertiary university hospital.

Recruitment

All participants will be referred after primary care and will enrol in the study according to the inclusion and exclusion criteria identified in rheumatology appointments (Fig. 1). After being considered eligible as a participant, the patient will be informed verbally about the study and its objectives. Those who consent to participate will be offered the consent form (Appendix I); they will then be asked to sign the consent form, and a registration number will be incepted for the participant.

Inclusion and exclusion criteria

Patients were included if they met the following criteria: adults aged between ≥18 years and ≤70 years; diagnosis of fibromyalgia at least 2 years before inclusion based on one of two criteria – bilateral symptoms of generalized pain occurring above and below the waist for at least 3 months without another somatic disorder that warrants the symptoms and/or the presence of at least 11 of the 18 tender points.[13,14] The exclusion criteria included the following: HOT contraindications (pregnancy, use of bleomycin, cisplatin, disulfiram, and doxorubicin, middle ear surgery, untreated pneumothorax or pneumomediastinum, claustrophobia);[21] associated autoimmune rheumatologic disease (rheumatoid arthritis, systemic lupus erythematosus, scleroderma, and others) to avoid interference in the primary outcome due to the autoimune disease and inability to sign the consent form.

Withdraw from the study

The participants who wish to withdraw from the study before the completion of 32 sessions and/or interrupt the treatment for more than 5 consecutive sessions will be able to continue their assistance treatment without interruption at the rheumatology outpatient clinic and without prejudice to the usual recommended treatment, according to the orientation of the preparticipation recommendations.

Randomisation

All patients who give written consent to participate and meet the eligibility criteria, as assessed by a rheumatologist, will be randomised in a 1:1 ratio. Each participant will receive a number in sequential order. The randomisation sequence will be generated using computer software (randomizer.org). Participants will be allocated with equal probability to the intervention and will be randomised into a single, fixed, random block. The list will be prepared by an individual not belonging to the research group based in the musculoskeletal unit of the university hospital. This individual will prepare a sequence of opaque envelopes identified with the participant's registration number, containing only one intervention to be performed, according to the computer-generated sequence. In the participant researcher's allocation request, that independent individual will access the envelope and disclose its contents.

Blinding

Clinical findings will be assessed by a rheumatologist evaluator blinded to treatment allocation. Due to the nature of the intervention, evaluators, data collectors, and care providers will be blinded.

Intervention

The participants will receive daily HOT sessions 5 times per week, totalling between 32-40 procedures at the end of the protocol. Each treatment will consist of 90 minutes of oxygen therapy with an inspired fraction of medicinal oxygen (FiO2) (purity >99%) [22] at 2.3 ATA (absolute atmospheres) of pressure in individualized hyperbaric equipment registered according

to ECO BAR 800 (serial number: E4-034, manufactured in April 2015 and ECO BAR 800, serial number: E4-033, manufactured in November 2014). Each chamber will be up to date on maintenance.

The standard treatment will be offered by a rheumatologist and will consist of simultaneous patient education, fitness activity, and pharmacological treatment (antidepressants, anticonvulsants, analgesics, and myorelaxants).[1] Both groups complete the questionnaires initially after randomization. Consecutively, they will receive the same HOT protocol at different times. The early group will receive 40 HOT sessions for 8 weeks when, at the end, they will be evaluated by the same rheumatologist and applied the same baseline questionnaires and will be crossed with the standardized group, which will start treatment in the delayed group for 8 weeks according to the same protocol and will be evaluated at 16 weeks by the same rheumatologist and applied the same baseline questionnaires (Fig. 2).

Follow-up

Enrolled patients will undergo assessments by a blinded rheumatologist at baseline, 8 weeks, and 16 weeks (Fig. 2). In addition, during the baseline, 8-week, and 16-week appointments, they will be subjected to additional pain assessment with the Visual Analogue Scale (VAS), [23] functional evaluation using the FIQR-Br, [24] psychopathological evaluation using the EAS-40 [25] and the SF-12 quality of life questionnaire. [26]

Risks and modifications

The risks described in the literature in decreasing order of frequency will be considered those related to the treatment with hyperbaric oxygen therapy: hypoglycaemia in diabetic patients, barotraumas, central nervous system intoxication by oxygen (convulsive seizures), pulmonary toxicity related to a long time of exposure to oxygen, temporary changes in eye refraction, and acceleration of the lens opacification process.[27–32] Before each HOT session, medical and nursing evaluations specialized in hyperbaric medicine will be carried out as risk reduction and control measures. The patient will be asked about possible side effects and situations that could trigger them, which will be recorded in a form preestablished by qualified professionals in hyperbaric medicine who will perform the treatment.

Adherence

Daily reminders are performed by the hyperbaric medicine team for adherence purposes and with the following approach: education on the importance of following study guidelines for treatment adherence; instructions on equalization manoeuvres and their effects; guidelines in the first session on adverse effects and how to identify them; notification of exclusion from the study if there are more than 5 consecutive days of absence of treatment; importance of notifying the hyperbaric medicine team quickly about possible adverse effects reported in the informed consent; instruction on the flowchart of care in case of intercurrences in the first care of the hyperbaric medicine team.

Concomitant care

The use of antibiotic, hormonal and non-hormonal anti-inflammatory drugs for less than 10 days due to adverse effects should not be considered as a covariate, as well as the use of topical drugs in the ear, for example.

Concomitant drugs or therapies that will be considered prohibited will be strong analgesic drugs that are introduced during the research without justification or prior evaluation by the rheumatology medical team or other treatment methodology that was not introduced before randomization such as hypnotherapy.

Outcomes

The primary outcome will be the improvement in the pain visual analogue scale (VAS), the functional impairment FIQR-Br and the psychopathological symptoms EAS-40 evaluations conducted by the same rheumatologist who conducted the initial evaluation at different times.

The improvement in the quality of life of the participants after the intervention, the number of tender points and level of pain assessed by a blinded rheumatologist, and the side effects will be analysed as secondary outcomes.

Data collection and management

Participant data will be collected through the study forms (Appendices II, III, IV) and stored on the RedCap platform, which will be used as the study repository. The original study forms will be inserted and kept on file with the principal investigator. Participants' files must be stored in numerical order and in a safe and accessible place. Participant files will be kept in storage for a period of 5 years after the conclusion of the study. The principal investigator will supervise the completion of the electronic spreadsheet and will be responsible for its security and correct completion. Incorrect or missing data will be evaluated by the principal investigator and corrected where necessary. During the study, a committee consisting of the main researcher, a coresearcher, the cosupervisor, and the main supervisor will monitor the data. The verification by one of the coresearchers of the adequate completion of the questionnaires that will be used may contribute to a strategy to avoid data loss. A loss of up to 20% of the sample was estimated, and patients considered dropouts will be analysed in the groups in which they were initially allocated.

Confidentiality

Each participant will receive a number upon inclusion in the study, which will be used for their identification in the trial. All data will be stored in the RedCap repository, and only the main researchers will have access to it. The set of data for statistical analysis will not use personalized identifications, thereby protecting the patient's individuality. All the data of the participants will be protected in the dissemination of the results, both in publication and at academic conferences. All information collected will be used only for this research and will not be exchanged with other institutions.

Data access and dissemination

The study protocol will be available upon request. Study data will be collected for academic and noncommercial use, and any participant will have access to their data per their request. The researchers involved in the study will have access to the summary data of the research at the end, and they will be able to publish the study and present it at a scientific event. To ensure confidentiality, data dispersed to project team members will be masked from any information identifying the participants.

Patient and public involvement

Patients participating in the study will not be involved in the development of this protocol. The results of the study will be made available to patients upon request.

Sample size

The software G*Power 3.1[33] was used to calculate the sample size. The study by Efrati et al.[15] guided the calculation when considering the hypothesis for a clinical improvement of the somatic and neuropsychiatric symptoms of fibromyalgia, associated with a moderate effect size ($f = 0.25$); [34] the correlation between measurements ($r = 0.30$), correction for nonsphericity ($\varepsilon = 1.0$), 80% power and 95% confidence were also included in the calculation.

Ultimately, a total of 46 patients will be required. Considering a loss to follow-up ("dropout") of 20%, 56 patients should be recruited, with 28 patients in each group.

Statistical analysis

Descriptive statistics will be expressed as the mean ± standard deviation (continuous data) or numbers and percentages (categorical data). Data will be analysed with the SPSS software (version 24.0, IBM Inc.). To test differences between groups (early vs. delayed), a 2x3 ANOVA of repeated measures will be performed based on a crossover design with a sequence effect. Post hoc comparisons will be performed with unpaired t tests for intergroup comparisons and paired t tests for intragroup comparisons. The significance level adopted will be 5% ($p<0.05$).[34]

DISCUSSION

The presented protocol intends to study the adjuvant effect of hyperbaric oxygen therapy (HOT) in patients with fibromyalgia (FM). The hypotheses about the pathogenic mechanism of FM lead to the multifactorial comprehension of the disease and still has points to clarify; but data shows that genetic factors, stressful events, peripheral (inflammatory) and central (cognitive-emotional) mechanisms are associated with neuromorphological and nociplastic changes, leading to pain misperception.[1]

The multimodal treatment has been rapidly growing as the ideal option for FM.[9] In this strategy, the combination of pharmacological and nonpharmacological treatment strategies, such as education in pain neuroscience, fitness activity, psychological support, physical therapy techniques and nature exposure, offers option that may improve the adherence of the treatment. In this sense, the introduction of other adjuvant therapeutic modality as oxygen therapy improves the effectiveness .

HOT consists of a treatment methodology with a low risk of complications and few contraindications,[27,30] that can greatly reduce the pain symptoms of FM patients, due to its immunomodulatory action on several cells of the immune system and by acting on the inflammatory pathways of different tissues. Furthermore, the role of HOT in inducing neuroplasticity in FM patients was endorsed by studies showing clinical and brain functionality improvement through SPECT.[15,16,18]

The strengths of this study are the possibility of evaluating the best time to apply HOT based on functional and neuropsychiatric scores, in addition to ratifying the effectiveness of the method as a adjuvant treatment for FM. The risk of losing participants due to the long period of the intervention and the moderate power of the sample size ratio for the primary outcome should be mentioned as limitations. The study may generate new hypotheses for the application of HOT in FM and its effects on neuroplasticity and the modulation of the inflammatory process.

Ethics and dissemination

This protocol and the model of the informed consent form contained in Appendix I were reviewed and approved by the Research Ethics Committee of the university hospital according to the protocol 53058421.9.00005133 and by the Brazilian Clinical Trials Registry (ReBEC) as registered RBR-6prps8g, UTN U1111-1278-3224.

Author's Contributions: JMN was the main researcher involved in the study concept and design, data collection, and drafting of the manuscript. VAS, AFMJ, AFMM, ATL, ROF and NRBR initiated the study design. ATL, ROF, VAS, and AFMM will take part in the implementation and data collection. JMN, VAS, AFMJ, AFMM, and NRBR provided statistical insights into the clinical trial design. VAS, AFMJ, AFMM, ATL, ROF and NRBR will perform

primary statistical analysis. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Funding statement: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
Competing interests statement: None declared.
Trial status: This trial is not recruiting patients at the time of submission of this manuscript.
Word Count: 2.545
Protocol version: protocol V3, from September/2022.
Patient consent for publication will be obtained.

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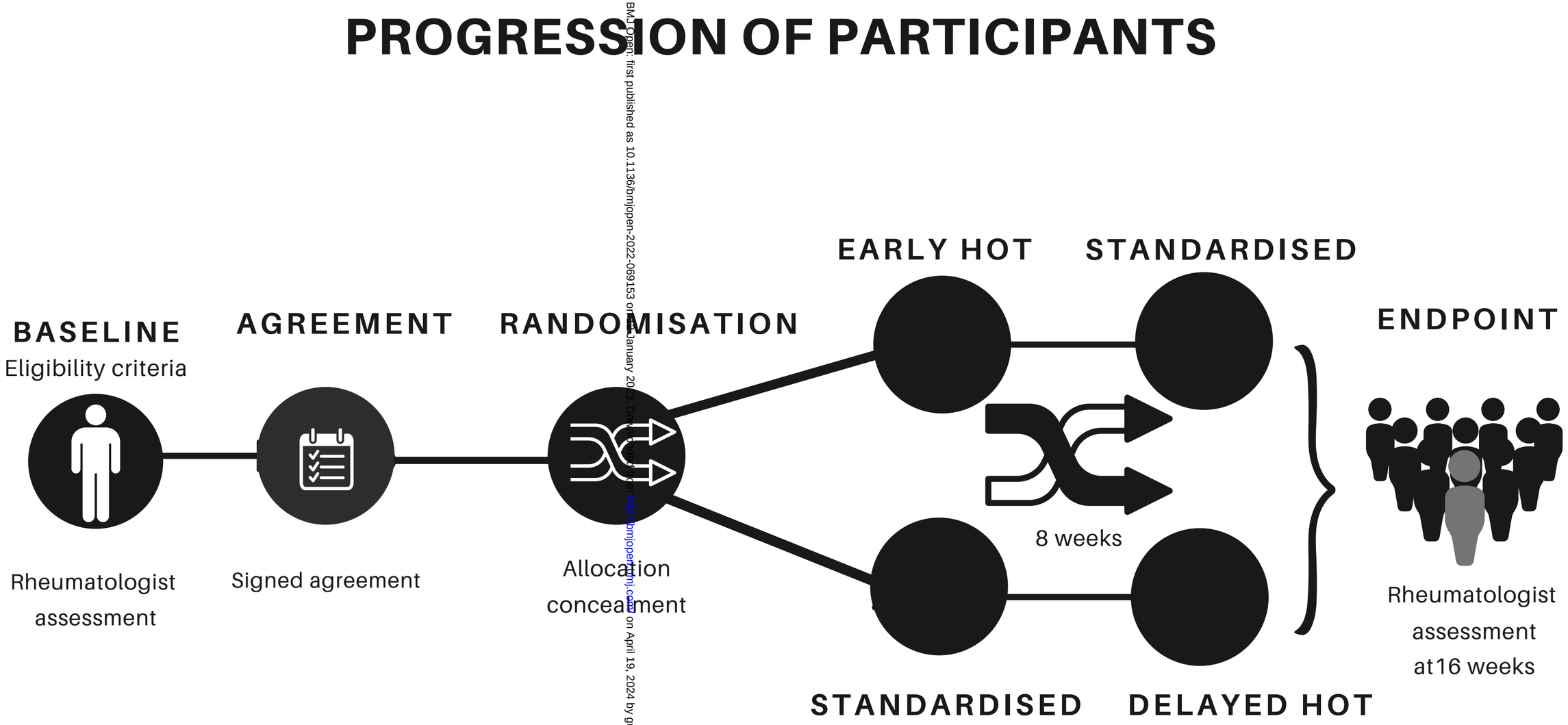
Fig. 1: Participant progression flowchart. HOT: Hyperbaric oxygen therapy.

Fig. 2: Enrolment flowchart. HOT: Hyperbaric oxygen therapy; FIQ-Br: Brazilian Portuguese Version-Fibromyalgia Impact Questionnaire; EAS-40: psychopathological symptoms questionnaire; SF-12: short-form quality of life questionnaire; VAS: Visual Analogue Score.



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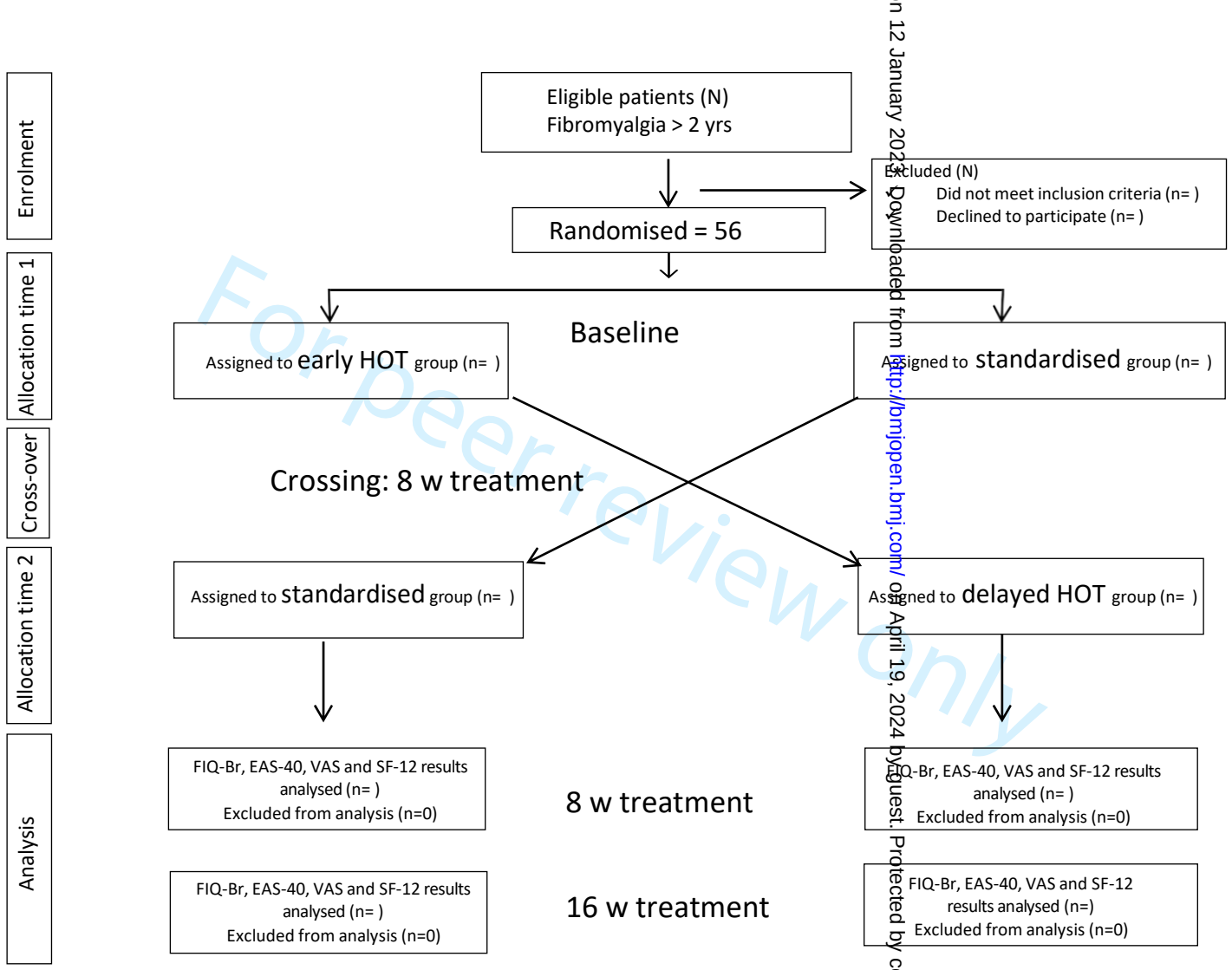

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TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

O Senhor (a) está sendo convidado (a) como voluntário (a) a participar da pesquisa **"HOTFy: ensaio clínico randomizado para oxigenoterapia hiperbárica na fibromialgia"**. Neste estudo pretendemos "avaliar o efeito agudo e residual da oxigenoterapia hiperbárica (OHB) sobre sintomas físicos e mentais, bem como o impacto da tecnologia na qualidade de vida de pacientes portadores de fibromialgia." O motivo que nos leva a estudar "consiste na dificuldade de tratamento da fibromialgia, necessitando de novas tecnologias ou metodologias que reduzam sintomas e melhorem a qualidade de vida dos pacientes".

Para este estudo adotaremos os seguintes procedimentos: **"os pacientes serão distribuídos por sorteio em dois grupos: grupo 1 - receberá oxigenoterapia hiperbárica inicialmente e grupo 2 - receberá oxigenoterapia hiperbárica após período inicial de 2 meses. Esses grupos serão avaliados pelos critérios estabelecidos, nos seguintes momentos: inicio da pesquisa e no final dos 4 meses da inclusão."**. Os riscos envolvidos na pesquisa consistem nos " riscos relacionados com a oxigenoterapia hiperbárica: hipoglicemia (queda de glicemia) em pacientes diabéticos; dor no ouvido; crises convulsivas devido ao excesso de oxigênio; problemas pulmonares relacionados com longo tempo de exposição ao oxigênio (>120 sessões); agravamento transitório da função cardíaca em pacientes com insuficiência cardíaca grave antes de 20 sessões; alterações temporárias de refração do olho, podendo melhorar ou piorar, transitoriamente

por exemplo, miopia prévia; aceleração do processo de opacificação do cristalino (catarata). Como medidas de minimização e controle dos riscos, a avaliação médica e de enfermagem, criteriosa, pré-tratamento, questionando o paciente sobre os riscos mencionados acima, será realizada por formulário pré-estabelecido e pelos profissionais qualificados das clinicas de oxigenoterapia hiperbárica. No caso de intercorrências, será seguido fluxograma de atendimento de intercorrências aprovado por entidades certificadoras de qualidade de atendimento como Instituto de Certificação Qualidade Brasil (ICQ), respeitando padrão de certificação Organização Nacional de Acreditação (ONA) e realizado de imediato e gratuitamente."

A pesquisa poderá contribuir para **"melhoria dos sintomas físicos e mentais relacionados com a fibromialgia, além de melhorar a qualidade de vida desses pacientes".**

Para participar deste estudo você não terá nenhum custo, nem receberá qualquer vantagem financeira. Apesar disso, caso sejam identificados e comprovados danos provenientes desta pesquisa, o Senhor (a) tem assegurado o direito a indenização. O Sr. (a) será esclarecido (a) sobre o estudo em qualquer aspecto que desejar e estará livre para participar ou recusar-se a participar. Poderá retirar seu consentimento ou interromper a participação a qualquer momento. A sua participação é voluntária e a recusa em participar não acarretará qualquer penalidade ou modificação na forma em que o Sr. (a) é atendido (a) é atendido pelo pesquisador, que tratará a sua identidade com padrões profissionais de sigilo, atendendo a legislação brasileira (Resolução Nº 466/12 do Conselho Nacional de Saúde), utilizando as informações somente para os fins acadêmicos e científicos.

Os resultados da pesquisa estarão à sua disposição quando finalizada. Seu nome ou o material que indique sua participação não será liberado sem a sua permissão. O (A) Senhor (a) não será identificado (a) em nenhuma publicação que possa resultar deste estudo, mantendo a confidencialidade e a anonimização do participante. Os dados e instrumentos utilizados na pesquisa ficarão arquivados com o pesquisador responsável por um período de 5 (cinco) anos, e após esse tempo serão destruídos. Este termo de consentimento encontra-se impresso em duas vias originais, sendo que uma via será

arquivada pelo pesquisador responsável, na Unidade Músculo-esquelética do Hospital Universitário da Universidade Federal de Juiz de Fora (HU-UFJF) e a outra será fornecida ao Senhor (a).

Eu, _____, portador do documento de Identidade _____ fui informado (a) dos objetivos do estudo **"HOTFy: ensaio clínico randomizado para oxigenoterapia hiperbárica na fibromialgia**", de maneira clara e detalhada e esclareci minhas dúvidas. Sei que a qualquer momento poderei solicitar novas informações e modificar minha decisão de participar se assim o desejar.

Declaro que concordo em participar desse estudo. Recebi uma via deste termo de consentimento livre e esclarecido e me foi dada à oportunidade de ler e esclarecer as minhas dúvidas.

Juiz de Fora, _____ de _____ de _____.

_____ _____

Nome e assinatura do (a) participante (a) Data

ou responsável legal

_____ _____

Pesquisador Data

_____ _____

Nome e assinatura da testemunha Data

Em caso de dúvidas com respeito aos aspectos éticos deste estudo, você poderá consultar o Comitê de Ética em Pesquisa HU-UFJF:

Rua Catulo Breviglieri, s/nº - Bairro Santa Catarina
CEP.: 36036-110 - Juiz de Fora – MG

Telefone: 4009-5167

E-mail: cep.hu@ufjf.edu.br

Revised Fibromyalgia Impact Questionnaire (FIQR-Br)

Questionário do Impacto de Fibromialgia Revisado

Sobrenome: Primeiro nome: Idade:

Instruções: Para cada questão, marque um "X" no quadrado que melhor indica o quanto a fibromialgia dificultou a realização das seguintes atividades nos últimos 7 dias.

Escovar ou pentear seus cabelos	Sem dificuldade □□□□□□□□□□ Muita dificuldade
Caminhar continuamente por 20 minutos	Sem dificuldade □□□□□□□□□□ Muita dificuldade
Preparar uma refeição em casa	Sem dificuldade □□□□□□□□□□ Muita dificuldade
Passar o aspirador, esfregar com a mão ou varrer o chão	Sem dificuldade □□□□□□□□□□ Muita dificuldade
Erguer e carregar uma sacola cheia de compras	Sem dificuldade □□□□□□□□□□ Muita dificuldade
Subir um lance de escadas	Sem dificuldade □□□□□□□□□□ Muita dificuldade
Trocar a roupa de cama	Sem dificuldade □□□□□□□□□□ Muita dificuldade
Ficar sentado por 45 minutos	Sem dificuldade □□□□□□□□□□ Muita dificuldade
Fazer compras no supermecado	Sem dificuldade □□□□□□□□□□ Muita dificuldade

Sub-total do domínio função (somente para uso interno) ☐

Lupi JB, Carvalho de Abreu DC, Ferreira MC, Oliveira RDR, Chaves TC. Brazilian Portuguese version of the Revised Fibromyalgia Impact Questionnaire (FIQR-Br): cross-cultural validation, reliability, and construct and structural validation. Disabil Rehabil. 2017 Aug;39(16):1650-1663. doi:10.1080/09638288.2016.1207106

Instruções: Para cada questão, marque um "X" no quadrado que melhor descreve o impacto global da sua fibromialgia em sua vida, nos últimos 7 dias:

A fibromialgia me impediu de realizar as atividades da semana	Nunca □□□□□□□□□□ Sempre
Eu fiquei completamente esgotado pelos meus sintomas de fibromialgia	Nunca □□□□□□□□□□ Sempre

Sub-total do domínio impacto global
(somente para uso interno) ☐

Instruções: Para cara uma das 10 questões seguintes, marque um "X" no quadrado que melhor indica a intensidade dos seus sintomas de fibromialgia nos últimos 7 dias:

Por favor, indique o seu nível de dor	Sem dor □□□□□□□□□□ Dor insuportável
Por favor,indique o seu nível de energia	Muita energia □□□□□□□□□□ Sem energia
Por favor,indique o seu nível de rigidez	Sem rigidez □□□□□□□□□□ Muitarigidez
Por favor,indique a qualidade do seu sono	Acordo bem descansado □□□□□□□□□□ Acordo muito cansado
Por favor,indique o seu nível de depressão	Sem depressão □□□□□□□□□□ Muito deprimido
Por favor, indique a qualidade de sua memória	Boa memória □□□□□□□□□□ Memória muito ruim
Por favor,indique o seu nível de ansiedade	Sem ansiedade □□□□□□□□□□ Muito ansioso

Lupi JB, Carvalho de Abreu DC, Ferreira MC, Oliveira RDR, Chaves TC. Brazilian Portuguese version of the Revised Fibromyalgia Impact Questionnaire (FIQR-Br): cross-cultural validation, reliability, and construct and structural validation. Disabil Rehabil. 2017 Aug;39(16):1650-1663. doi:10.1080/09638288.2016.1207106

Por favor,indique o seu nível de sensibilidade ao toque	Sem sensibilidade □□□□□□□□□□ Muita sensibilidade
Por favor, indique o nível de equilíbrio do seu corpo	Sem desequilíbrio □□□□□□□□□□ Muito desequilíbrio
Por favor, indique o seu nível de sensibilidade a barulhos altos, luzes fortes, odores e frio	Sem sensibilidade □□□□□□□□□□ Muita sensibilidade

Sub-total do domínio sintomas (somente para uso interno) ☐

PONTUAÇÃO TOTAL – FIQR (somente para uso interno) ☐

Pontuação do FIQR

O Questionário do Impacto da Fibromialgia Revisado, é composto por 21 itens que investigam 3 domínios.

Domínios e Conjuntos

Domínios	Número de itens	Conjuntos de itens	Item invertido	Orientação para os Domínios
Função	9	1-9	Não	Pontuação mais baixa = Melhor qualidade de vida
Impacto global	2	10, 11	Não	
Sintomas	10	12-21	Não	

Lupi JB, Carvalho de Abreu DC, Ferreira MC, Oliveira RDR, Chaves TC. Brazilian Portuguese version of the Revised Fibromyalgia Impact Questionnaire (FIQR-Br): cross-cultural validation, reliability, and construct and structural validation. Disabil Rehabil. 2017 Aug;39(16):1650-1663. doi:10.1080/09638288.2016.1207106

Pontuação dos Domínios

Itens da escala	Cada item é graduado em uma escala numérica de 0 a 10
Ponderação/ coeficiente dos itens	Não
Faixa de pontuação	- A pontuação para o domínio da função varia de 0 a 90 - A pontuação para a gama do domínio impacto global varia de 0 a 20 - A pontuação para a faixa do domínio sintomas varia de 0 a 100 e - O alcance total FIQR de 0 a 100
Pontuação dos domínios	O FIQR é pontuado em três etapas: - Para cada item, a escala numérica é pontuada entre 0 e 10 - A pontuação para cada um dos três domínios é obtido somando-se a pontuação de cada item neste domínio - Um fator de normalização é aplicado a cada uma das três pontuações dos domínios: a pontuação do domínio função deve ser dividida por 3, o conjunto de pontuação do domínio impacto global é dividido por 1 (ou seja, ele é deixado inalterado), e o escore do domínio sintoma é dividido por 2 - O FIQR pontuação total é a soma das três pontuações dos domínios normalizados
Interpretação e análise de questões não respondidas	No caso do paciente deixar de responder alguma questão, o seguinte sistema de ponderação precisa ser utilizado para minimizar esse problema: se apenas X questões do primeiro domínio (função) forem respondidas o escore final das X questões deve ser multiplicado por 9/x (uma vez que existem 9 itens para o domínio função). De modo semelhante deve ser realizado para o segundo domínio (Impacto Global) que contém apenas 2 itens. Assim, o escore final deve ser multiplicado por 2/x e o terceiro domínio (Sintomas) com 10 itens deve ter uma ponderação de 10/x. O questionário deve

Lupi JB, Carvalho de Abreu DC, Ferreira MC, Oliveira RDR, Chaves TC. Brazilian Portuguese version of the Revised Fibromyalgia Impact Questionnaire (FIQR-Br): cross-cultural validation, reliability, and construct and structural validation. Disabil Rehabil. 2017 Aug;39(16):1650-1663. doi:10.1080/09638288.2016.1207106

	ser considerado inválido se três ou mais questões individuais não forem respondidas.
Interpretação de múltiplas respostas para um item	Se o sujeito faz várias respostas para um item, o item não pode ser pontuado. O questionário deve ser considerado inválido se o sujeito faz várias respostas para três ou mais itens individuais
Interpretação e análise das respostas de itens não representativos	No caso de alguns itens do primeiro domínio (ou seja, o domínio função) não puderem ser respondidos, porque não realizou essa atividade nos últimos 7 dias ou é fisicamente incapaz de realizar essa atividade, a seguinte alteração deve ser usada para a questão sentinela deste domínio *"Marque o quadrado que melhor indica o quanto a fibromialgia dificultou na realização de cada um dos 9 itens e atividades durante os últimos 7 dias. Se você não executou uma atividade particular nos últimos 7 dias, marque a taxa de dificuldade para a última vez que realizou esta atividade. Se você não pode realizar essa atividade, marque a última caixa de opções"* O domínio pode ser marcado como descrito no procedimento de pontuação

Lupi JB, Carvalho de Abreu DC, Ferreira MC, Oliveira RDR, Chaves TC. Brazilian Portuguese version of the Revised Fibromyalgia Impact Questionnaire (FIQR-Br): cross-cultural validation, reliability, and construct and structural validation. Disabil Rehabil. 2017 Aug;39(16):1650-1663. doi:10.1080/09638288.2016.1207106

1

PROTOCOLO DE PESQUISA PARA FIBRIOMIALGIA -
VERSÃO BRASILEIRA DA SCL-90-R– "ESCALA DE AVALIAÇÃO DE SINTOMAS -40"
Adaptado por Diana Tosello Laloni (2001)

Nome: _____

Idade:_____ **Data de nascimento:**_____

Sexo: **M** ☐ **F** ☐

Estado civil: **solteiro** ☐ **casado ou amigado** ☐ **separado** ☐ **viúvo** ☐

Grau de escolaridade: **analfabeto** ☐ **1ª. a 4ª.** ☐ **5ª. a 8ª.** ☐ **2º. Grau** ☐ **3º. Grau** ☐

Data _____/_____/_____

Orientações:
1- Preencha os dados da identificação na parte superior da folha.
2- Use um lápis preto para marcar a resposta.
3- Se você desejar alterar sua resposta, apague com cuidado a 1ª. marca e marque a nova resposta.
4- Não faça outras anotações fora dos círculos.

INSTRUÇÕES:

Olá prezado participante,

Será apresentada uma lista de problemas que as pessoas algumas vezes têm relacionadas com a fibromialgia. Por favor leia-os cuidadosamente e pinte, um círculo por resposta, que melhor descreve **o quanto algum problema o tem procurado ou angustiado durante os últimos tempos incluindo hoje.** Pinte o círculo em apenas 1 número para cada problema e não pule nenhum item. Se mudar de idéia, apague sua primeira resposta e remarque o círculo.

Nenhum pouco	Um pouco	Moderadamente	Bastante	Muito	EXEMPLO O quanto você está preocupado com:
0	1	2	3	4	Dores no corpo

2

Nenhum pouco	Um pouco	Moderadamente	Bastante	Muito	O quanto você está preocupado com:
0	1	2	3	4	Fraqueza ou tonturas
0	1	2	3	4	Dores do coração ou no peito
0	1	2	3	4	Sentir medo em espaço abertos ou nas ruas
0	1	2	3	4	Pensamentos de acabar com a própria vida
0	1	2	3	4	Repetidamente sentir medo sem razão
0	1	2	3	4	Ter medo de sair de casa sozinho
0	1	2	3	4	Dores nas costas e quadris
0	1	2	3	4	Sentir-se sem importância
0	1	2	3	4	Sentir medo
0	1	2	3	4	Náuseas, enjôos ou estômago ruim

3

Nenhum pouco	Um pouco	Moderadamente	Bastante	Muito	O quanto você está preocupado com:
0	1	2	3	4	Dores musculares (dor no corpo)
0	1	2	3	4	Sentir-se vigiado e comentado pelos outros
0	1	2	3	4	Ter que conferir e reconferir o que fez
0	1	2	3	4	Sentir medo de andar de ônibus, metro ou trens
0	1	2	3	4	Problemas para respirar
0	1	2	3	4	Ondas de calor ou frio
0	1	2	3	4	Ter que evitar certas coisas, lugares ou atividades que o amedrontam (dão medo)
0	1	2	3	4	Um “branco"na cabeça (ter incapacidade momentânea de raciocinar ou lembrar-se de algo)
0	1	2	3	4	Dormência ou formigamento em partes do corpo
0	1	2	3	4	Sentir-se sem esperança sobre o futuro

4

Nenhum pouco	Um pouco	Moderadamente	Bastante	Muito	O quanto você está preocupado com:
0	1	2	3	4	Dificuldade de concentração
0	1	2	3	4	Sentir fraqueza em partes do corpo
0	1	2	3	4	Sentir-se tenso ou travado
0	1	2	3	4	Sentir peso nos braços e pernas
0	1	2	3	4	Sentir-se desconfortável quando as pessoas o observam ou falam de você
0	1	2	3	4	Ter que repetir as mesmas ações como tocar, contar ou lavar
0	1	2	3	4	Ter desejos de quebrar ou destruir coisas
0	1	2	3	4	Sentir-se muito acanhado ou preocupado com os outros
0	1	2	3	4	Sentir-se inquieto numa multidão, fazendo compras ou no cinema
0	1	2	3	4	Sentir que tudo é um esforço

5

Nenhum pouco	Um pouco	Moderadamente	Bastante	Muito	O quanto você está preocupado com:
0	1	2	3	4	Ondas de terror ou pânico
0	1	2	3	4	Envolver-se freqüentemente em discussões
0	1	2	3	4	Sentir nervosismo quando é deixado sozinho
0	1	2	3	4	Sentir-se solitário mesmo quando está acompanhado
0	1	2	3	4	Sentir-se tão agitado que não é capaz de parar quieto (de movimentar-se)
0	1	2	3	4	Girar ou atirar coisas
0	1	2	3	4	Com medo de desmaiar em público
0	1	2	3	4	Nunca se sentir próximo a outra pessoa
0	1	2	3	4	Sentimentos de culpa
0	1	2	3	4	A idéia de que há algo errado com sua mente

Damásio, B. F., Andrade, T. F., & Koller, S. H. (2015). 12-Item Short-Form Health Survey Version 2 (SF-12v2).

APPENDIX A

Medical Outcomes 12-Item Short-Form Health Survey **(Versão 2) – SF-12v2**

Este questionário busca compreender a sua opinião em relação à sua saúde. Essas informações irão ajudar a avaliar como você se sente e o quão bem você está em relação às suas atividade diárias. Por favor, responda cada pergunta selecionando a resposta mais apropriada. Se você não tiver certeza sobre como responder à pergunta, por favor, dê a resposta que mais se aproxima do que você pensa.

1. Em geral, você diria que sua saúde é:

1	2	3	4	5
Excelente	Muito Boa	Boa	Ruim	Muito Ruim

2. Os seguintes itens são sobre atividades que você poderia fazer atualmente durante um dia comum. **Devido à sua saúde**, você tem dificuldade para fazer essas atividades? Neste caso, quanto?

ATIVIDADES	Sim. Dificulta muito.	Sim. Dificulta um pouco.	Não. Não dificulta de modo algum.
a. **Atividades moderadas,** tais como mover uma mesa, passar aspirador de pó, jogar bola, varrer a casa.	1	2	3
b. Subir **vários** lances de escada.	1	2	3

3. Durante as **últimas 4 semanas**, quanto do tempo você teve algum dos seguintes problemas com seu trabalho ou com alguma atividade diária regular, **como consequência de sua saúde física**?

	Todo o tempo	A maior parte do tempo	Alguma parte do tempo	Uma pequena parte do tempo	Nenhuma parte do tempo
a. Realizou menos tarefas do que você gostaria?	1	2	3	4	5
b. Esteve limitado no seu tipo de trabalho ou outras atividades?	1	2	3	4	5

4. Durante as **últimas 4 semanas**, quanto do tempo você teve algum dos seguintes problemas com seu trabalho ou outra atividade regular diária, **como consequência de algum problema emocional** (por exemplo, sentir-se deprimido ou ansioso)?

	Todo o tempo	A maior parte do tempo	Alguma parte do tempo	Uma pequena parte do tempo	Nenhuma parte do tempo
Realizou menos tarefas do que você gostaria?	1	2	3	4	5
Não trabalhou ou não fez qualquer das atividades com tanto cuidado como geralmente faz?	1	2	3	4	5

5. Durante as **últimas 4 semanas**, quanto a dor interferiu com seu trabalho normal (incluindo tanto o trabalho, fora de casa e dentro de casa)?

De maneira alguma	Um pouco	Moderadamente	Bastante	Extremamente
1	2	3	4	5

6. Estas questões são sobre como você se sente e como tudo tem acontecido com você durante as **últimas 4 semanas**. Para cada questão, por favor, dê uma resposta que mais se aproxime da maneira como você se sente. Em relação **às últimas 4 semanas**:

	Todo o tempo	A maior parte do tempo	Alguma parte do tempo	Uma pequena parte do tempo	Nenhuma parte do tempo
a. Quanto tempo você tem se sentido calmo ou tranquilo?	1	2	3	4	5
b. Quanto tempo você tem se sentido com muita energia?	1	2	3	4	5
c. Quanto tempo você tem se sentido desanimado e abatido?	1	2	3	4	5

7. Durante as últimas **4 semanas**, quanto do seu tempo a sua saúde física ou problemas emocionais interferiram com suas atividades sociais (como visitar amigos, parentes, etc.)?

Todo o tempo	A maior parte do tempo	Alguma parte do tempo	Uma pequena parte do tempo	Nenhuma parte do tempo
1	2	3	4	5

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**Page 1 (Title-page)**
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	**Page 2 (Trial registration number)**
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	**Page 2 (Trial registration number)**
Protocol version	#3	Date and version identifier	**Page 2**
Funding	#4	Sources and types of financial, material, and other support	**Page 9 (Funding statement)**

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	**Page 9 (Author's Contributions)**
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	**N/A**
Roles and responsibilities: sponsor and funder	#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	**N/A**
Roles and responsibilities: committees	#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)	**Page 6**
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	**Page 3**
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	**Page 3**
Objectives	#7	Specific objectives or hypotheses	**Page 3**

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, non-inferiority, exploratory)	**Page 3**
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	**Page 4**
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)	**Page 4**
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**Page 4-5**
Interventions: modifications	#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)	**Page 4**
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	**Page 5-6**

Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**Page 6**
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	**Page 6**
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)	**Page 10 (figure 1)**
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	**Page 6-7**
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	**Page 4**
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated	**Page 4**

		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	**Page 4**
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**Page 4**
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**Page 4**
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**N/A**
Methods: Data collection, management, and analysis			
Data collection plan	#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)	**Page 6**

		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	
Data collection plan: retention	#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	**Page 6**
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	**Page 6**
Statistics: outcomes	#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	**Page 7**
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**Page 7**
Statistics: analysis population and missing data	#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)	**Page 7**
Methods: Monitoring			

Data monitoring: formal committee	#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	**Page 6**
Data monitoring: interim analysis	#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	**Page 6**
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	**Page 5**
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**N/A**
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	**Page 7**
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)	**N/A**

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**Page 4-5**
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**N/A**
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	**Page 6**
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	**Page 9**
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**Page 6**
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	**Page 5**
Dissemination policy: trial results	#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	**Page 6**
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	**Page 9**

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**Page 6**
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	**Attached a file**
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	**N/A**

Fig. 1: Participant progression flowchart. HOT: Hyperbaric oxygen therapy.

Fig. 2: Enrolment flowchart. HOT: Hyperbaric oxygen therapy; FIQ-Br: Brazilian Portuguese Version-Fibromyalgia Impact Questionnaire; EAS-40: psychopathological symptoms questionnaire; SF-12: short-form quality of life questionnaire; VAS: Visual Analogue Score.

BMJ Open

Protocol of HOTFy: randomised clinical trial to hyperbaric oxygen therapy in fibromyalgia.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-069153.R1
Article Type:	Protocol
Date Submitted by the Author:	08-Dec-2022
Complete List of Authors:	da Mota Neto, José; Universidade Federal de Juiz de Fora, Núcleo de Pesquisa e Inovação em Ciências da Saúde (NUPICS) Mendes Jr., Adriano; Universidade Federal de Juiz de Fora Hospital Universitário, Serviço de Ortopedia e Traumatologia Magalhães Martins, Anita ; Universidade Federal de Juiz de Fora Teixeira de Landa, Aline; Universidade Federal de Juiz de Fora, Departamento de Reumatologia de Oliveira Fraga, Rafael; Universidade Federal de Juiz de Fora, Departamento de Reumatologia de Souza, Viviane ; Universidade Federal de Juiz de Fora, Departamento de Reumatologia Raposo, Nádia ; Universidade Federal de Juiz de Fora, Núcleo de Pesquisa e Inovação em Ciências da Saúde (NUPICS)
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Neurology, General practice / Family practice, Public health
Keywords:	Rheumatology < INTERNAL MEDICINE, IMMUNOLOGY, GENERAL MEDICINE (see Internal Medicine)

Protocol of HOTFy: randomised clinical trial to hyperbaric oxygen therapy in fibromyalgia.

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Competing interests: None declared.

Word count: 2.802 (excluding title page, abstract, references and figures)

ARTICLE SUMMARY

Abstract:

Introduction: Fibromyalgia is a polysymptomatic syndrome with a prevalence between 0.2 and 13% of the population and causes work disabilities in approximately half of affected patients. Several treatments to fibromyalgia have been proposed with partial improvement. This study aims to evaluate the efficacy of hyperbaric oxygen therapy and when it should be introduced to fibromyalgia.

Methods and Analysis: This is a protocol for an open-label, crossover, randomised clinical trial comparing treatment with hyperbaric oxygen therapy and standardised treatment to fibromyalgia. In the proposed study, 56 individuals with fibromyalgia will be randomised in a 1:1 ratio into a single, fixed, random block, in which one group will receive hyperbaric oxygen therapy and another will receive standard treatment. Subsequently, the groups will be crossed. Participants will be evaluated at baseline, eight and 16 weeks based on functional impairment assessed with the Fibromyalgia Impact Questionnaire - Brazilian Portuguese version, psychopathological symptoms questionnaire and short-form quality of life questionnaire. The improvement of symptoms concerning the moment of therapy used will be compared between groups. For sample size calculation, a moderate effect size, 80% power and 95% confidence will be estimated, in a total of 46 patients. Considering a dropout of 20%, 56 patients should be recruited.

Ethics and dissemination: The study was approved by the Universidade Federal de Juiz de Fora Teaching Hospital ethics committee and assigned the number 53058421.9.0000.5133 (version 3). The results will be disseminated via publications in peer-reviewed journals and presentations in medical meetings.

Trial registration number: This study is registered in REBEC (RBR-6prps8g)/UTN U1111-1278-3224.

Strengths and limitations of the study:

- Analysis of treatment in the same group and between treatment and no treatment in different groups.
- Assess the impact of hyperbaric oxygen therapy on the quality of life of fibromyalgia patients.
- Sample size was previously statistically calculated.
- The protocol was previously published, minimizing publication bias.
- Due to the long-term nature of the treatment (40 sessions), participants may be lost to follow-up.

Keywords

fibromyalgia; hyperbaric oxygen therapy; chronic pain; fibromyalgia treatment; chronic fatigue; oxygenation.

INTRODUCTION

Fibromyalgia (FM) is a polysymptomatic syndrome that consists of diffuse chronic pain, fatigue, sleep disturbances and autonomic disturbances, cognitive dysfunction, hypersensitivity to stimuli, somatic symptoms, and psychiatric disorders.[1] The prevalence of FM in the general population is distinct in each country [2] and affects between 0.2 and 13% of the population and causes work disability in approximately half of affected patients.[3,4]

Due to the absence of accurate diagnostic tools and adequate biomarkers, a diagnosis based on constantly evolving clinical criteria remains the best option.[1] Treatment and prevention constitute knowledge gaps and move towards multimodal therapies.[5–12] According to the American College of Rheumatology, generalised bilateral pain above and below the waist for at least 3 months or 11 tender points are diagnostic criteria for FM.[13,14,15]

Several factors are related to the results of the treatment of FM, such as genetic predisposition, personal experiences of pain, emotional-cognitive factors, mind-body relationships, and psychological capacity to deal with stress. According to the European Alliance of Rheumatology Associations (EULAR), the ideal treatment of FM must contain at least four pillars and may also utilise new adjuvant modalities.[1] It should begin with a pharmacotherapeutic modality with antidepressants, anticonvulsants, analgesics, and adjuvant nonpharmacological measures, such as patient education about the disease, regular physical activity at least three times per week, psychotherapy modalities, such as relaxation techniques, hypnosis, and cognitive-behavioural therapy. With respect to adjuvant treatment modalities, positive results have been observed with the use of medical cannabis, low laser therapy, nature activity therapies, transcutaneous electrical nerve stimulation (TENS), acupuncture and hyperbaric oxygen therapy (HOT).[6,8,9,16]

The HOT treatment modality involves patients breathing nearly 100% oxygen while inside a closed chamber in which the pressure is two to three times higher than the atmospheric pressure at sea level.[12,17,18] HOT has led to promising results in pre-clinical models of nociceptive, inflammatory, and neuropathic pain and clinical benefits in the treatment of chronic pain, stroke sequelae, traumatic brain injury, spinal cord trauma and autism.[16,17,19] HOT may play a role in modulating the inflammatory response after tissue injury, resulting in a decrease in the nociceptive response by 80-95% for up to 90 minutes after exposure to HOT. However, the antinociceptive effect of HOT in pre-clinical models appear to be unrelated to oxidative stress.[20] Randomised clinical trials on HOT for FM have shown reduction of pain, number of tender points, improvement of functional and neuropsychiatric questionnaires and quality of life.[16]

Several protocols for the treatment of FM with HOT have been applied with different pressure values, total number of sessions and time to begin the therapy.[16] Although the effectiveness of HOT has already been evaluated in other studies, doubts remain about the ideal time to introduce the technology and about the consistency of the results. This study aims to evaluate the efficacy of HOT and when it should be introduced for fibromyalgia.

MATERIALS AND METHODS

Study design and settings

This protocol was written according to the SPIRIT guidelines.[21] This work utilises a randomised, crossover primary study protocol to conduct a clinical trial comparing treatment with hyperbaric oxygen and standardised treatment at a single research centre in the rheumatology department of a tertiary teaching hospital.

Recruitment

All participants will be referred from the Teaching Hospital Rheumatology outpatient clinic, after being diagnosed with fibromyalgia according to the American College of Rheumatology diagnostic criteria [13,14,15] and enrol in the study according to the inclusion and exclusion criteria identified by a rheumatologist (Fig. 1). After being considered eligible as a participant, the patient will be informed verbally about the study and its objectives. Those who consent to participate will be offered the consent form (Appendix I); they will then be asked to sign the consent form, and a registration number will be incepted for the participant.

Inclusion and exclusion criteria

Patients will be included if they meet the following criteria: adults aged between ≥18 years and ≤70 years; diagnosis of fibromyalgia at least 2 years before inclusion based on one of two criteria – bilateral symptoms of generalised pain occurring above and below the waist for at least 3 months without another somatic disorder that warrants the symptoms and/or the presence of at least 11 of the 18 tender points.[13,14,15] The exclusion criteria included the following: HOT contraindications (pregnancy, use of bleomycin, cisplatin, disulfiram, and doxorubicin, middle ear surgery, untreated pneumothorax or pneumomediastinum, claustrophobia);[22] associated autoimmune rheumatologic disease (rheumatoid arthritis, systemic lupus erythematosus, scleroderma, and others) to avoid interference in the primary outcome due to the autoimune disease and inability to sign the consent form.

Withdraw from the study

The participants who wish to withdraw from the study before the completion of 32 sessions and/or interrupt the treatment for more than 5 consecutive sessions will be able to continue their assistance treatment without interruption at the rheumatology outpatient clinic and without prejudice to the usual recommended treatment, according to the orientation of the preparticipation recommendations.

Randomisation

All patients who give written consent to participate and meet the eligibility criteria, as assessed by a rheumatologist, will be randomised in a 1:1 ratio. Each participant will receive a number in sequential order. The randomisation sequence will be generated using computer software (randomizer.org). Participants will be allocated with equal probability to the intervention and will be randomised into a single, fixed, random block. The list will be prepared by an individual not belonging to the research group based in the musculoskeletal unit of the university hospital. This individual will prepare a sequence of opaque envelopes identified with the participant's registration number, containing only one intervention to be performed, according to the computer-generated sequence. In the participant researcher's allocation request, that independent individual will access the envelope and disclose its contents.

Blinding

Clinical findings will be assessed by a rheumatologist evaluator blinded to treatment allocation. Due to the nature of the intervention, evaluators, data collectors, and care providers will be blinded.

Intervention

The participants will receive daily HOT sessions 5 times per week, totalling between 32-40 procedures at the end of the protocol. Each treatment will consist of 90 minutes of oxygen therapy with an inspired fraction of medicinal oxygen (FiO2) (purity >99%) [23] at 2.3 ATA

(absolute atmospheres) of pressure in individualized hyperbaric equipment registered according to ECO BAR 800 (serial number: E4-034, manufactured in April 2015 and ECO BAR 800, serial number: E4-033, manufactured in November 2014). Each chamber will be up to date on maintenance.

The standard treatment will be offered by a rheumatologist and will consist of simultaneous patient education, physical activity, and pharmacological treatment (antidepressants, anticonvulsants, analgesics, and myorelaxants).[1] Both groups will complete the functional impairment questionnaire assessed with the visual analogue scale (VAS), [24] Fibromyalgia Impact Questionnaire - Brazilian Portuguese version (FIQR-Br), [25] psychopathological symptoms questionnaire (EAS-40) [26] and short-form quality of life questionnaire (SF-12) [27] initially after randomisation. Consecutively, they will receive the same HOT protocol at different times. The early group will receive 40 sessions of HOT for 8 weeks and will be reassessed by the same rheumatologist and applied the same baseline questionnaires and will be crossed over to the standardised group, which will receive the standardised treatment alone now. The standardised group will now be crossed over to the delayed group will receive HOT for 8 weeks according to the same protocol and will be reassessed at 16 weeks by the same rheumatologist and the same baseline questionnaires will be applied (Fig. 2).

Follow-up

Enrolled patients will undergo assessments by a blinded rheumatologist at baseline, 8 weeks, and 16 weeks (Fig. 2). In addition, during the baseline, 8-week, and 16-week appointments, they will be subjected to additional pain assessment with the VAS, [24] functional evaluation using the FIQR-Br, [25] psychopathological evaluation using the EAS-40 [26] and the SF-12 quality of life questionnaire. [27]

Risks and modifications

The risks described in the literature in decreasing order of frequency will be considered those related to the treatment with hyperbaric oxygen therapy: hypoglycaemia in diabetic patients, barotraumas, central nervous system intoxication by oxygen (convulsive seizures), pulmonary toxicity related to a long time of exposure to oxygen, temporary changes in eye refraction, and acceleration of the lens opacification process.[28–33] Before each HOT session, medical and nursing evaluations specialized in hyperbaric medicine will be carried out as risk reduction and control measures. The patient will be asked about possible side effects and situations that could trigger them, which will be recorded in a form preestablished by qualified professionals in hyperbaric medicine who will perform the treatment.

Adherence

Daily reminders are performed by the hyperbaric medicine team for adherence purposes and with the following approach: education on the importance of following study guidelines for treatment adherence; instructions on equalisation manoeuvres and their effects; guidelines in the first session on adverse effects and how to identify them; notification of exclusion from the study if there are more than 5 consecutive days of absence of treatment; importance of notifying the hyperbaric medicine team quickly about possible adverse effects reported in the informed consent; instruction on the flowchart of care in case of intercurrences in the first care of the hyperbaric medicine team.

Concomitant care

The use of antibiotic, hormonal and non-hormonal anti-inflammatory drugs for less than 10 days due to adverse effects should not be considered as a covariate, as well as the use of topical drugs in the ear, for example.

Concomitant drugs or therapies that will be considered prohibited will be potent analgesic drugs that are introduced during the research without justification or prior evaluation by the rheumatology medical team or other treatment methodology that was not introduced before randomisation such as hypnotherapy.

Outcomes

The primary outcome will be the improvement in the pain VAS, the functional impairment FIQR-Br and the psychopathological symptoms EAS-40 evaluations of patients with fibromyalgia and to identify the best moment of application through the analysis of the results of the questionnaires applied at different times and in different groups conducted by the same rheumatologist at different times evaluation (0-8-16 weeks).

The improvement in the quality of life of the participants after the intervention will be assessed by a blinded rheumatologist through the analysis of the SF-12 score as a secondary outcome.

Data collection and management

Participant data will be collected through the study forms (Appendices II, III, IV) and stored on the RedCap platform, which will be used as the study repository. The original study forms will be inserted and kept on file with the principal investigator. Participants' files must be stored in numerical order and in a safe and accessible place. Participant files will be kept in storage for a period of 5 years after the conclusion of the study. The principal investigator will supervise the completion of the electronic spreadsheet and will be responsible for its security and correct completion. Incorrect or missing data will be evaluated by the principal investigator and corrected where necessary. During the study, a committee consisting of the main researcher, a coresearcher, the cosupervisor, and the main supervisor will monitor the data. The verification by one of the coresearchers of the adequate completion of the questionnaires that will be used may contribute to a strategy to avoid data loss. A loss of up to 20% of the sample was estimated, and patients considered dropouts will be analysed in the groups in which they were initially allocated.

Confidentiality

Each participant will receive a number upon inclusion in the study, which will be used for their identification in the trial. All data will be stored in the RedCap repository, and only the main researchers will have access to it. The set of data for statistical analysis will not use personalized identifications, thereby protecting the patient's individuality. All the data of the participants will be protected in the dissemination of the results, both in publication and at academic conferences. All information collected will be used only for this research and will not be exchanged with other institutions.

Data access and dissemination

The study protocol will be available upon request. Study data will be collected for academic and noncommercial use, and any participant will have access to their data per their request. The researchers involved in the study will have access to the summary data of the research at the end, and they will be able to publish the study and present it at a scientific event. To ensure confidentiality, data dispersed to project team members will be masked from any information identifying the participants. This work will be disseminated by the publication of

peer-reviewed manuscripts, presentation in abstract form at national and international scientific meetings and data sharing with other investigators.

Patient and public involvement

Patients participating in the study will not be involved in the development of this protocol. The results of the study will be made available to patients upon request.

Sample size

The software G*Power 3.1[34] was used to calculate the sample size. The study by Efrati et al.[16] guided the calculation when considering the hypothesis for a clinical improvement of the somatic and neuropsychiatric symptoms of fibromyalgia, associated with a moderate effect size (f = 0.25); [35] the correlation between measurements (r = 0.30), correction for nonsphericity (ε = 1.0), 80% power and 95% confidence were also included in the calculation. Ultimately, a total of 46 patients will be required. Considering a loss to follow-up ("dropout") of 20%, 56 patients should be recruited, with 28 patients in each group.

Statistical analysis

Descriptive statistics will be expressed as the mean ± standard deviation (continuous data) or numbers and percentages (categorical data). Data will be analysed with the SPSS software (version 24.0, IBM Inc.). To test differences between groups (early vs. delayed), a 2x3 ANOVA of repeated measures will be performed based on a crossover design with a sequence effect. *Post hoc* comparisons will be performed with unpaired t tests for intergroup comparisons and paired t tests for intragroup comparisons. The significance level adopted will be 5% ($p<0.05$).[35]

DISCUSSION

The presented protocol intends to study the adjuvant effect of hyperbaric oxygen therapy (HOT) in patients with fibromyalgia (FM). The hypotheses about the pathogenic mechanism of FM lead to the multifactorial comprehension of the disease and still has points to clarify; but data shows that genetic factors, stressful events, peripheral (inflammatory) and central (cognitive-emotional) mechanisms are associated with neuromorphological and nociplastic changes, leading to pain misperception.[1]

The multimodal treatment has been rapidly growing as the ideal option for FM.[9] In this strategy, the combination of pharmacological and nonpharmacological treatment strategies, such as education in pain neuroscience, physical activity, psychological support, physical therapy techniques and nature exposure, offers option that may improve the adherence of the treatment. In this sense, the introduction of other adjuvant therapeutic modality as oxygen therapy improves the effectiveness.

HOT consists of a treatment modality with a low risk of complications and few contraindications,[28,31] that can greatly reduce the pain symptoms of FM patients, due to its immunomodulatory action on several cells of the immune system and by acting on the inflammatory pathways of different tissues. Furthermore, the role of HOT in inducing neuroplasticity in FM patients was endorsed by studies showing clinical and brain functionality improvement through single photon emission computed tomography (SPECT).[16,18,19]

The strengths of this study are the possibility of evaluating the best time to apply HOT based on functional and neuropsychiatric scores, in addition to ratifying the effectiveness of the method as an adjuvant treatment for FM at Brazilian population. The risk of losing participants due to the long period of the intervention and the moderate power of the sample size ratio for the primary outcome should be mentioned as limitations. The study may generate new

hypotheses for the application of HOT in FM and its effects on neuroplasticity and the modulation of the inflammatory process.

Ethics and dissemination

This protocol and the model of the informed consent form contained in Appendix I were reviewed and approved by the Research Ethics Committee of the Universidade Federal de Juiz de Fora Teaching Hospital ethics committee according to the protocol 53058421.9.00005133 and by the Brazilian Clinical Trials Registry (ReBEC) as registered RBR-6prps8g, UTN U1111-1278-3224.

Author's Contributions: JMN was the main researcher involved in the study concept and design, data collection, and drafting of the manuscript. VAS, AFMJ, AFMM, ATL, ROF and NRBR initiated the study design. ATL, ROF, VAS, and AFMM will take part in the implementation and data collection. JMN, VAS, AFMJ, AFMM, and NRBR provided statistical insights into the clinical trial design. VAS, AFMJ, AFMM, ATL, ROF and NRBR will perform primary statistical analysis. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Funding statement: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
Competing interests statement: None declared.
Trial status: This trial is not recruiting patients at the time of submission of this manuscript.
Word Count: 2.802
Protocol version: protocol V3, from September/2022.
Patient consent for publication will be obtained.

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Fig. 1: Participant progression flowchart. HOT: Hyperbaric oxygen therapy.

Fig. 2: Enrolment flowchart. HOT: Hyperbaric oxygen therapy; FIQ-Br: Brazilian Portuguese Version-Fibromyalgia Impact Questionnaire; EAS-40: psychopathological symptoms questionnaire; SF-12: short-form quality of life questionnaire; VAS: Visual Analogue Score.

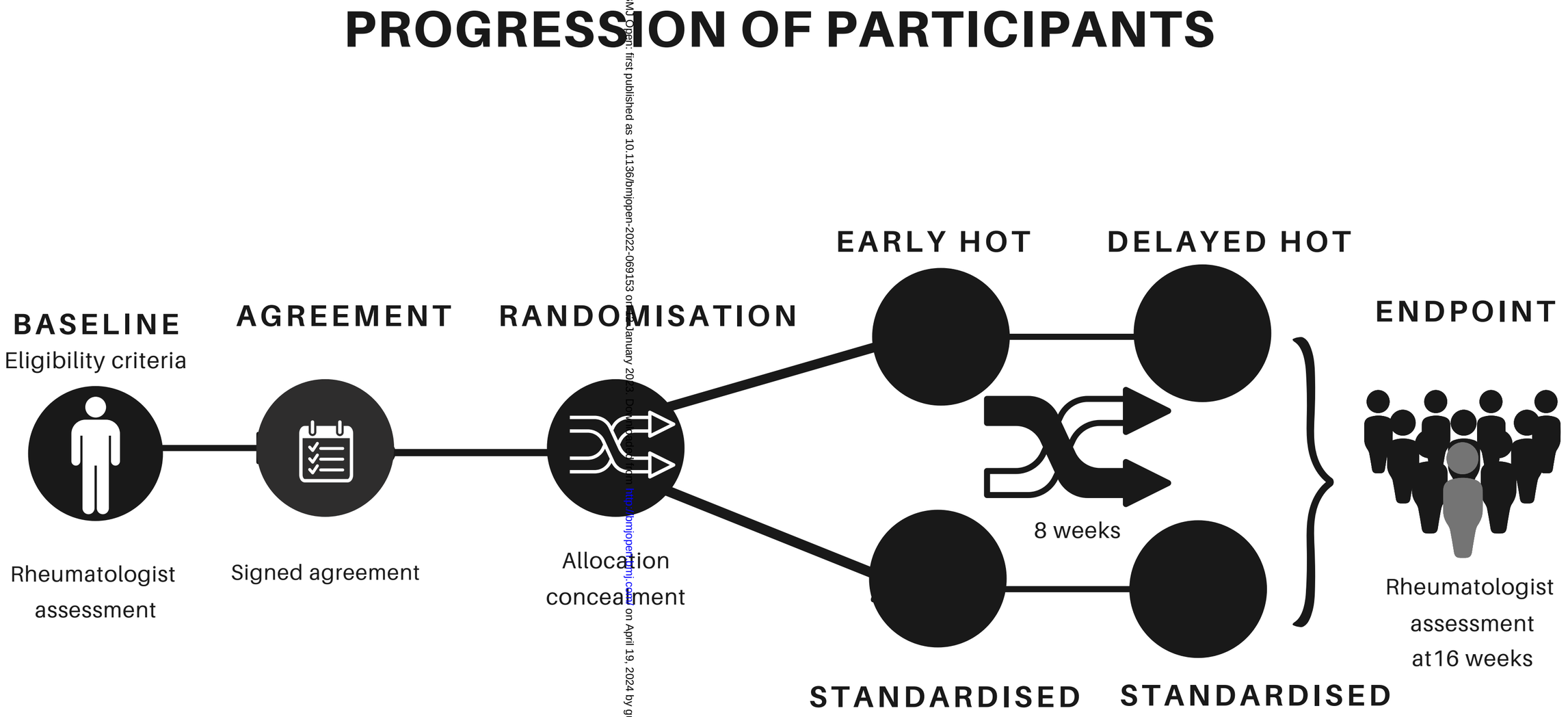

Fig. 1: Participant progression flowchart. HOT: Hyperbaric oxygen therapy.

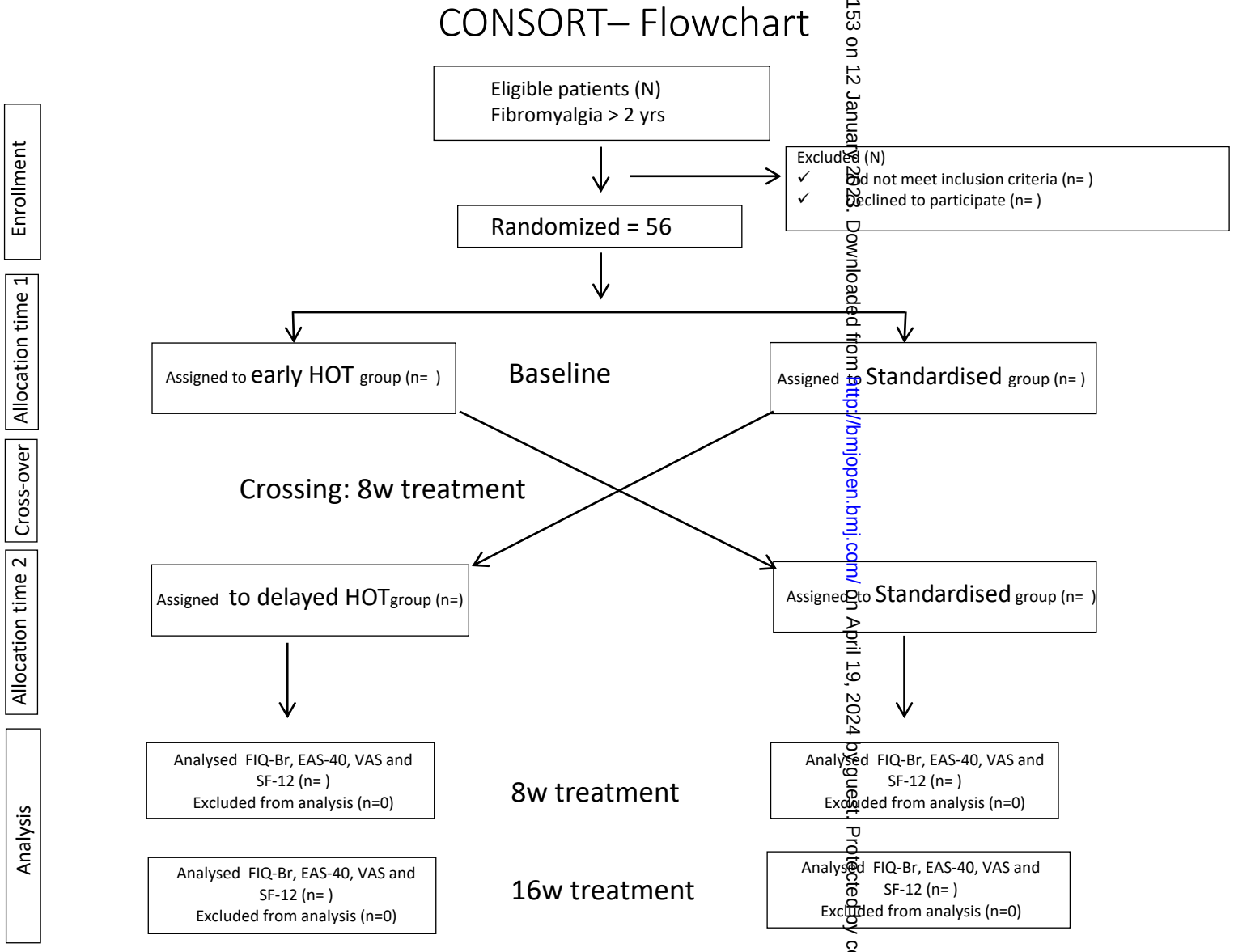

Fig. 2: Enrolment flowchart. HOT: Hyperbaric oxygen therapy; FIQ-Br: Brazilian Portuguese Version-Fibromyalgia Impact Questionnaire; EAS-40: psychopathological symptoms questionnaire; SF-12: short-form quality of life questionnaire; VAS: Visual Analogue Score.

HU Hospital Universitário - UFJF	**HOSPITAL UNIVERSITÁRIO DA UNIVERSIDADE FEDERAL DE JUIZ DE FORA** Comitê de Ética em Pesquisa com Seres Humanos do HU-UFJF	EBSERH HOSPITAIS UNIVERSITÁRIOS FEDERAIS

Ambulatório de Reumatologia
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E-mail: motadort@gmail.com

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

O Senhor (a) está sendo convidado (a) como voluntário (a) a participar da pesquisa **"HOTFy: ensaio clínico randomizado para oxigenoterapia hiperbárica na fibromialgia"**. Neste estudo pretendemos "avaliar o efeito agudo e residual da oxigenoterapia hiperbárica (OHB) sobre sintomas físicos e mentais, bem como o impacto da tecnologia na qualidade de vida de pacientes portadores de fibromialgia." O motivo que nos leva a estudar "consiste na dificuldade de tratamento da fibromialgia, necessitando de novas tecnologias ou metodologias que reduzam sintomas e melhorem a qualidade de vida dos pacientes".

Para este estudo adotaremos os seguintes procedimentos: **"os pacientes serão distribuídos por sorteio em dois grupos: grupo 1 - receberá oxigenoterapia hiperbárica inicialmente e grupo 2 - receberá oxigenoterapia hiperbárica após período inicial de 2 meses. Esses grupos serão avaliados pelos critérios estabelecidos, nos seguintes momentos: inicio da pesquisa e no final dos 4 meses da inclusão."**. Os riscos envolvidos na pesquisa consistem nos " riscos relacionados com a oxigenoterapia hiperbárica: hipoglicemia (queda de glicemia) em pacientes diabéticos; dor no ouvido; crises convulsivas devido ao excesso de oxigênio; problemas pulmonares relacionados com longo tempo de exposição ao oxigênio (>120 sessões); agravamento transitório da função cardíaca em pacientes com insuficiência cardíaca grave antes de 20 sessões; alterações temporárias de refração do olho, podendo melhorar ou piorar, transitoriamente

por exemplo, miopia prévia; aceleração do processo de opacificação do cristalino (catarata). Como medidas de minimização e controle dos riscos, a avaliação médica e de enfermagem, criteriosa, pré-tratamento, questionando o paciente sobre os riscos mencionados acima, será realizada por formulário pré-estabelecido e pelos profissionais qualificados das clinicas de oxigenoterapia hiperbárica. No caso de intercorrências, será seguido fluxograma de atendimento de intercorrências aprovado por entidades certificadoras de qualidade de atendimento como Instituto de Certificação Qualidade Brasil (ICQ), respeitando padrão de certificação Organização Nacional de Acreditação (ONA) e realizado de imediato e gratuitamente."

A pesquisa poderá contribuir para **"melhoria dos sintomas físicos e mentais relacionados com a fibromialgia, além de melhorar a qualidade de vida desses pacientes".**

Para participar deste estudo você não terá nenhum custo, nem receberá qualquer vantagem financeira. Apesar disso, caso sejam identificados e comprovados danos provenientes desta pesquisa, o Senhor (a) tem assegurado o direito a indenização. O Sr. (a) será esclarecido (a) sobre o estudo em qualquer aspecto que desejar e estará livre para participar ou recusar-se a participar. Poderá retirar seu consentimento ou interromper a participação a qualquer momento. A sua participação é voluntária e a recusa em participar não acarretará qualquer penalidade ou modificação na forma em que o Sr. (a) é atendido (a) é atendido pelo pesquisador, que tratará a sua identidade com padrões profissionais de sigilo, atendendo a legislação brasileira (Resolução Nº 466/12 do Conselho Nacional de Saúde), utilizando as informações somente para os fins acadêmicos e científicos.

Os resultados da pesquisa estarão à sua disposição quando finalizada. Seu nome ou o material que indique sua participação não será liberado sem a sua permissão. O (A) Senhor (a) não será identificado (a) em nenhuma publicação que possa resultar deste estudo, mantendo a confidencialidade e a anonimização do participante. Os dados e instrumentos utilizados na pesquisa ficarão arquivados com o pesquisador responsável por um período de 5 (cinco) anos, e após esse tempo serão destruídos. Este termo de consentimento encontra-se impresso em duas vias originais, sendo que uma via será

arquivada pelo pesquisador responsável, na Unidade Músculo-esquelética do Hospital Universitário da Universidade Federal de Juiz de Fora (HU-UFJF) e a outra será fornecida ao Senhor (a).

Eu, _____, portador do documento de Identidade _____ fui informado (a) dos objetivos do estudo **"HOTFy: ensaio clínico randomizado para oxigenoterapia hiperbárica na fibromialgia**", de maneira clara e detalhada e esclareci minhas dúvidas. Sei que a qualquer momento poderei solicitar novas informações e modificar minha decisão de participar se assim o desejar.

Declaro que concordo em participar desse estudo. Recebi uma via deste termo de consentimento livre e esclarecido e me foi dada à oportunidade de ler e esclarecer as minhas dúvidas.

Juiz de Fora, _____ de _____ de _____.

_____ _____

Nome e assinatura do (a) participante (a) Data

ou responsável legal

_____ _____

Pesquisador Data

_____ _____

Nome e assinatura da testemunha Data

Em caso de dúvidas com respeito aos aspectos éticos deste estudo, você poderá consultar o Comitê de Ética em Pesquisa HU-UFJF:

Rua Catulo Breviglieri, s/nº - Bairro Santa Catarina
CEP.: 36036-110 - Juiz de Fora – MG

Telefone: 4009-5167

E-mail: cep.hu@ufjf.edu.br

Revised Fibromyalgia Impact Questionnaire (FIQR-Br)

Questionário do Impacto de Fibromialgia Revisado

Sobrenome: Primeiro nome: Idade:

Instruções: Para cada questão, marque um "X" no quadrado que melhor indica o quanto a fibromialgia dificultou a realização das seguintes atividades nos últimos 7 dias.

Escovar ou pentear seus cabelos	Sem dificuldade □□□□□□□□□□ Muita dificuldade
Caminhar continuamente por 20 minutos	Sem dificuldade □□□□□□□□□□ Muita dificuldade
Preparar uma refeição em casa	Sem dificuldade □□□□□□□□□□ Muita dificuldade
Passar o aspirador, esfregar com a mão ou varrer o chão	Sem dificuldade □□□□□□□□□□ Muita dificuldade
Erguer e carregar uma sacola cheia de compras	Sem dificuldade □□□□□□□□□□ Muita dificuldade
Subir um lance de escadas	Sem dificuldade □□□□□□□□□□ Muita dificuldade
Trocar a roupa de cama	Sem dificuldade □□□□□□□□□□ Muita dificuldade
Ficar sentado por 45 minutos	Sem dificuldade □□□□□□□□□□ Muita dificuldade
Fazer compras no supermecado	Sem dificuldade □□□□□□□□□□ Muita dificuldade

Sub-total do domínio função (somente para uso interno) ☐

Lupi JB, Carvalho de Abreu DC, Ferreira MC, Oliveira RDR, Chaves TC. Brazilian Portuguese version of the Revised Fibromyalgia Impact Questionnaire (FIQR-Br): cross-cultural validation, reliability, and construct and structural validation. Disabil Rehabil. 2017 Aug;39(16):1650-1663. doi:10.1080/09638288.2016.1207106

Instruções: Para cada questão, marque um "X" no quadrado que melhor descreve o impacto global da sua fibromialgia em sua vida, nos últimos 7 dias:

A fibromialgia me impediu de realizar as atividades da semana	Nunca □□□□□□□□□□ Sempre
Eu fiquei completamente esgotado pelos meus sintomas de fibromialgia	Nunca □□□□□□□□□□ Sempre

Sub-total do domínio impacto global
(somente para uso interno) ☐

Instruções: Para cara uma das 10 questões seguintes, marque um "X" no quadrado que melhor indica a intensidade dos seus sintomas de fibromialgia nos últimos 7 dias:

Por favor, indique o seu nível de dor	Sem dor □□□□□□□□□□ Dor insuportável
Por favor,indique o seu nível de energia	Muita energia □□□□□□□□□□ Sem energia
Por favor,indique o seu nível de rigidez	Sem rigidez □□□□□□□□□□ Muitarigidez
Por favor,indique a qualidade do seu sono	Acordo bem descansado □□□□□□□□□□ Acordo muito cansado
Por favor,indique o seu nível de depressão	Sem depressão □□□□□□□□□□ Muito deprimido
Por favor, indique a qualidade de sua memória	Boa memória □□□□□□□□□□ Memória muito ruim
Por favor,indique o seu nível de ansiedade	Sem ansiedade □□□□□□□□□□ Muito ansioso

Lupi JB, Carvalho de Abreu DC, Ferreira MC, Oliveira RDR, Chaves TC. Brazilian Portuguese version of the Revised Fibromyalgia Impact Questionnaire (FIQR-Br): cross-cultural validation, reliability, and construct and structural validation. Disabil Rehabil. 2017 Aug;39(16):1650-1663. doi:10.1080/09638288.2016.1207106

Por favor,indique o seu nível de sensibilidade ao toque	Sem sensibilidade □□□□□□□□□□ Muita sensibilidade
Por favor, indique o nível de equilíbrio do seu corpo	Sem desequilíbrio □□□□□□□□□□ Muito desequilíbrio
Por favor, indique o seu nível de sensibilidade a barulhos altos, luzes fortes, odores e frio	Sem sensibilidade □□□□□□□□□□ Muita sensibilidade

Sub-total do domínio sintomas (somente para uso interno) ☐

PONTUAÇÃO TOTAL – FIQR (somente para uso interno) ☐

Pontuação do FIQR

O Questionário do Impacto da Fibromialgia Revisado, é composto por 21 itens que investigam 3 domínios.

Domínios e Conjuntos

Domínios	Número de itens	Conjuntos de itens	Item invertido	Orientação para os Domínios
Função	9	1-9	Não	Pontuação mais baixa = Melhor qualidade de vida
Impacto global	2	10, 11	Não	
Sintomas	10	12-21	Não	

Lupi JB, Carvalho de Abreu DC, Ferreira MC, Oliveira RDR, Chaves TC. Brazilian Portuguese version of the Revised Fibromyalgia Impact Questionnaire (FIQR-Br): cross-cultural validation, reliability, and construct and structural validation. Disabil Rehabil. 2017 Aug;39(16):1650-1663. doi:10.1080/09638288.2016.1207106

Pontuação dos Domínios

Itens da escala	Cada item é graduado em uma escala numérica de 0 a 10
Ponderação/ coeficiente dos itens	Não
Faixa de pontuação	- A pontuação para o domínio da função varia de 0 a 90 - A pontuação para a gama do domínio impacto global varia de 0 a 20 - A pontuação para a faixa do domínio sintomas varia de 0 a 100 e - O alcance total FIQR de 0 a 100
Pontuação dos domínios	O FIQR é pontuado em três etapas: - Para cada item, a escala numérica é pontuada entre 0 e 10 - A pontuação para cada um dos três domínios é obtido somando-se a pontuação de cada item neste domínio - Um fator de normalização é aplicado a cada uma das três pontuações dos domínios: a pontuação do domínio função deve ser dividida por 3, o conjunto de pontuação do domínio impacto global é dividido por 1 (ou seja, ele é deixado inalterado), e o escore do domínio sintoma é dividido por 2 - O FIQR pontuação total é a soma das três pontuações dos domínios normalizados
Interpretação e análise de questões não respondidas	No caso do paciente deixar de responder alguma questão, o seguinte sistema de ponderação precisa ser utilizado para minimizar esse problema: se apenas X questões do primeiro domínio (função) forem respondidas o escore final das X questões deve ser multiplicado por 9/x (uma vez que existem 9 itens para o domínio função). De modo semelhante deve ser realizado para o segundo domínio (Impacto Global) que contém apenas 2 itens. Assim, o escore final deve ser multiplicado por 2/x e o terceiro domínio (Sintomas) com 10 itens deve ter uma ponderação de 10/x. O questionário deve

Lupi JB, Carvalho de Abreu DC, Ferreira MC, Oliveira RDR, Chaves TC. Brazilian Portuguese version of the Revised Fibromyalgia Impact Questionnaire (FIQR-Br): cross-cultural validation, reliability, and construct and structural validation. Disabil Rehabil. 2017 Aug;39(16):1650-1663. doi:10.1080/09638288.2016.1207106

	ser considerado inválido se três ou mais questões individuais não forem respondidas.
Interpretação de múltiplas respostas para um item	Se o sujeito faz várias respostas para um item, o item não pode ser pontuado. O questionário deve ser considerado inválido se o sujeito faz várias respostas para três ou mais itens individuais
Interpretação e análise das respostas de itens não representativos	No caso de alguns itens do primeiro domínio (ou seja, o domínio função) não puderem ser respondidos, porque não realizou essa atividade nos últimos 7 dias ou é fisicamente incapaz de realizar essa atividade, a seguinte alteração deve ser usada para a questão sentinela deste domínio *"Marque o quadrado que melhor indica o quanto a fibromialgia dificultou na realização de cada um dos 9 itens e atividades durante os últimos 7 dias. Se você não executou uma atividade particular nos últimos 7 dias, marque a taxa de dificuldade para a última vez que realizou esta atividade. Se você não pode realizar essa atividade, marque a última caixa de opções"* O domínio pode ser marcado como descrito no procedimento de pontuação

Lupi JB, Carvalho de Abreu DC, Ferreira MC, Oliveira RDR, Chaves TC. Brazilian Portuguese version of the Revised Fibromyalgia Impact Questionnaire (FIQR-Br): cross-cultural validation, reliability, and construct and structural validation. Disabil Rehabil. 2017 Aug;39(16):1650-1663. doi:10.1080/09638288.2016.1207106

1

PROTOCOLO DE PESQUISA PARA FIBRIOMIALGIA -
VERSÃO BRASILEIRA DA SCL-90-R– "ESCALA DE AVALIAÇÃO DE SINTOMAS -40"
Adaptado por Diana Tosello Laloni (2001)

Nome: _____

Idade:_____ **Data de nascimento:**_____

Sexo: **M** ☐ **F** ☐

Estado civil: **solteiro** ☐ **casado ou amigado** ☐ **separado** ☐ **viúvo** ☐

Grau de escolaridade: **analfabeto** ☐ **1ª. a 4ª.** ☐ **5ª. a 8ª.** ☐ **2º. Grau** ☐ **3º. Grau** ☐

Data _____/_____/_____

Orientações:
1- Preencha os dados da identificação na parte superior da folha.
2- Use um lápis preto para marcar a resposta.
3- Se você desejar alterar sua resposta, apague com cuidado a 1ª. marca e marque a nova resposta.
4- Não faça outras anotações fora dos círculos.

INSTRUÇÕES:

Olá prezado participante,

Será apresentada uma lista de problemas que as pessoas algumas vezes têm relacionadas com a fibromialgia. Por favor leia-os cuidadosamente e pinte, um círculo por resposta, que melhor descreve **o quanto algum problema o tem procurado ou angustiado durante os últimos tempos incluindo hoje.** Pinte o círculo em apenas 1 número para cada problema e não pule nenhum item. Se mudar de idéia, apague sua primeira resposta e remarque o círculo.

Nenhum pouco	Um pouco	Moderadamente	Bastante	Muito	EXEMPLO O quanto você está preocupado com:
0	1	2	3	4	Dores no corpo

2

Nenhum pouco	Um pouco	Moderadamente	Bastante	Muito	O quanto você está preocupado com:
0	1	2	3	4	Fraqueza ou tonturas
0	1	2	3	4	Dores do coração ou no peito
0	1	2	3	4	Sentir medo em espaço abertos ou nas ruas
0	1	2	3	4	Pensamentos de acabar com a própria vida
0	1	2	3	4	Repetidamente sentir medo sem razão
0	1	2	3	4	Ter medo de sair de casa sozinho
0	1	2	3	4	Dores nas costas e quadris
0	1	2	3	4	Sentir-se sem importância
0	1	2	3	4	Sentir medo
0	1	2	3	4	Náuseas, enjôos ou estômago ruim

3

Nenhum pouco	Um pouco	Moderadamente	Bastante	Muito	O quanto você está preocupado com:
0	1	2	3	4	Dores musculares (dor no corpo)
0	1	2	3	4	Sentir-se vigiado e comentado pelos outros
0	1	2	3	4	Ter que conferir e reconferir o que fez
0	1	2	3	4	Sentir medo de andar de ônibus, metro ou trens
0	1	2	3	4	Problemas para respirar
0	1	2	3	4	Ondas de calor ou frio
0	1	2	3	4	Ter que evitar certas coisas, lugares ou atividades que o amedrontam (dão medo)
0	1	2	3	4	Um “branco"na cabeça (ter incapacidade momentânea de raciocinar ou lembrar-se de algo)
0	1	2	3	4	Dormência ou formigamento em partes do corpo
0	1	2	3	4	Sentir-se sem esperança sobre o futuro

4

Nenhum pouco	Um pouco	Moderadamente	Bastante	Muito	O quanto você está preocupado com:
0	1	2	3	4	Dificuldade de concentração
0	1	2	3	4	Sentir fraqueza em partes do corpo
0	1	2	3	4	Sentir-se tenso ou travado
0	1	2	3	4	Sentir peso nos braços e pernas
0	1	2	3	4	Sentir-se desconfortável quando as pessoas o observam ou falam de você
0	1	2	3	4	Ter que repetir as mesmas ações como tocar, contar ou lavar
0	1	2	3	4	Ter desejos de quebrar ou destruir coisas
0	1	2	3	4	Sentir-se muito acanhado ou preocupado com os outros
0	1	2	3	4	Sentir-se inquieto numa multidão, fazendo compras ou no cinema
0	1	2	3	4	Sentir que tudo é um esforço

5

Nenhum pouco	Um pouco	Moderadamente	Bastante	Muito	O quanto você está preocupado com:
0	1	2	3	4	Ondas de terror ou pânico
0	1	2	3	4	Envolver-se freqüentemente em discussões
0	1	2	3	4	Sentir nervosismo quando é deixado sozinho
0	1	2	3	4	Sentir-se solitário mesmo quando está acompanhado
0	1	2	3	4	Sentir-se tão agitado que não é capaz de parar quieto (de movimentar-se)
0	1	2	3	4	Girar ou atirar coisas
0	1	2	3	4	Com medo de desmaiar em público
0	1	2	3	4	Nunca se sentir próximo a outra pessoa
0	1	2	3	4	Sentimentos de culpa
0	1	2	3	4	A idéia de que há algo errado com sua mente

Damásio, B. F., Andrade, T. F., & Koller, S. H. (2015). 12-Item Short-Form Health Survey Version 2 (SF-12v2).

APPENDIX A

Medical Outcomes 12-Item Short-Form Health Survey **(Versão 2) – SF-12v2**

Este questionário busca compreender a sua opinião em relação à sua saúde. Essas informações irão ajudar a avaliar como você se sente e o quão bem você está em relação às suas atividade diárias. Por favor, responda cada pergunta selecionando a resposta mais apropriada. Se você não tiver certeza sobre como responder à pergunta, por favor, dê a resposta que mais se aproxima do que você pensa.

1. Em geral, você diria que sua saúde é:

1	2	3	4	5
Excelente	Muito Boa	Boa	Ruim	Muito Ruim

2. Os seguintes itens são sobre atividades que você poderia fazer atualmente durante um dia comum. **Devido à sua saúde**, você tem dificuldade para fazer essas atividades? Neste caso, quanto?

ATIVIDADES	Sim. Dificulta muito.	Sim. Dificulta um pouco.	Não. Não dificulta de modo algum.
a. **Atividades moderadas,** tais como mover uma mesa, passar aspirador de pó, jogar bola, varrer a casa.	1	2	3
b. Subir **vários** lances de escada.	1	2	3

3. Durante as **últimas 4 semanas**, quanto do tempo você teve algum dos seguintes problemas com seu trabalho ou com alguma atividade diária regular, **como consequência de sua saúde física**?

	Todo o tempo	A maior parte do tempo	Alguma parte do tempo	Uma pequena parte do tempo	Nenhuma parte do tempo
a. Realizou menos tarefas do que você gostaria?	1	2	3	4	5
b. Esteve limitado no seu tipo de trabalho ou outras atividades?	1	2	3	4	5

4. Durante as **últimas 4 semanas**, quanto do tempo você teve algum dos seguintes problemas com seu trabalho ou outra atividade regular diária, **como consequência de algum problema emocional** (por exemplo, sentir-se deprimido ou ansioso)?

	Todo o tempo	A maior parte do tempo	Alguma parte do tempo	Uma pequena parte do tempo	Nenhuma parte do tempo
Realizou menos tarefas do que você gostaria?	1	2	3	4	5
Não trabalhou ou não fez qualquer das atividades com tanto cuidado como geralmente faz?	1	2	3	4	5

5. Durante as **últimas 4 semanas**, quanto a dor interferiu com seu trabalho normal (incluindo tanto o trabalho, fora de casa e dentro de casa)?

De maneira alguma	Um pouco	Moderadamente	Bastante	Extremamente
1	2	3	4	5

6. Estas questões são sobre como você se sente e como tudo tem acontecido com você durante as **últimas 4 semanas**. Para cada questão, por favor, dê uma resposta que mais se aproxime da maneira como você se sente. Em relação **às últimas 4 semanas**:

	Todo o tempo	A maior parte do tempo	Alguma parte do tempo	Uma pequena parte do tempo	Nenhuma parte do tempo
a. Quanto tempo você tem se sentido calmo ou tranquilo?	1	2	3	4	5
b. Quanto tempo você tem se sentido com muita energia?	1	2	3	4	5
c. Quanto tempo você tem se sentido desanimado e abatido?	1	2	3	4	5

7. Durante as últimas **4 semanas**, quanto do seu tempo a sua saúde física ou problemas emocionais interferiram com suas atividades sociais (como visitar amigos, parentes, etc.)?

Todo o tempo	A maior parte do tempo	Alguma parte do tempo	Uma pequena parte do tempo	Nenhuma parte do tempo
1	2	3	4	5

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**Page 1 (Title-page)**
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	**Page 2 (Trial registration number)**
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	**Page 2 (Trial registration number)**
Protocol version	#3	Date and version identifier	**Page 2**
Funding	#4	Sources and types of financial, material, and other support	**Page 9 (Funding statement)**

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	**Page 9 (Author's Contributions)**
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	**N/A**
Roles and responsibilities: sponsor and funder	#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	**N/A**
Roles and responsibilities: committees	#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)	**Page 6**
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	**Page 3**
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	**Page 3**
Objectives	#7	Specific objectives or hypotheses	**Page 3**

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, non-inferiority, exploratory)	**Page 3**
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	**Page 4**
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)	**Page 4**
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**Page 4-5**
Interventions: modifications	#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)	**Page 4**
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	**Page 5-6**

Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**Page 6**
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	**Page 6**
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)	**Page 10 (figure 1)**
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	**Page 6-7**
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	**Page 4**
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated	**Page 4**

		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	**Page 4**
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**Page 4**
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**Page 4**
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**N/A**
Methods: Data collection, management, and analysis			
Data collection plan	#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)	**Page 6**

		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	
Data collection plan: retention	#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	**Page 6**
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	**Page 6**
Statistics: outcomes	#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	**Page 7**
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**Page 7**
Statistics: analysis population and missing data	#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)	**Page 7**
Methods: Monitoring			

Data monitoring: formal committee	#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	**Page 6**
Data monitoring: interim analysis	#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	**Page 6**
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	**Page 5**
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**N/A**
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	**Page 7**
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)	**N/A**

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**Page 4-5**
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**N/A**
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	**Page 6**
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	**Page 9**
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**Page 6**
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	**Page 5**
Dissemination policy: trial results	#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	**Page 6**
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	**Page 9**

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**Page 6**
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	**Attached a file**
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	**N/A**