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Cost-utility analysis of a multicomponent intervention for Fibromyalgia syndrome in primary care versus usual clinical practise: study protocol for an economic evaluation of a randomized control trial

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Abstract (300/300)

Introduction Fibromyalgia syndrome (FMS) carries a high cost to society. The significant economic burden in the use of healthcare and, especially, social resources suggests prioritizing the revision of the usual clinical (UCC) care and improving the treatment strategies. FMS is potentially disabling due to its impact on quality of life (QOL) and loss of productivity, which greatly increases the indirect costs to society. The aim of this study is to perform an economic evaluation to compare the cost and health-benefits of a multicomponent intervention (MI) program for FMS and the UCC, for patients who attend to primary health care centres of the *Gerència Territorial Terres de L'Ebre* in Catalonia, Spain. This study is expected to support the effectiveness results of a randomized control trial study and the implementation of the MI in the UCC.

Method and analysis A cost-utility analysis will be conducted from the societal perspective. Quality-adjusted life years will be obtained from the results of the SF-36 questionnaire, a QOL measurement instrument. Direct and indirect healthcare costs will be estimated from official prices and reports of the public health and social security sectors. Incremental cost-utility ratio will be estimated to compare both healthcare practices. Deterministic sensitivity analysis will be also implemented to compare different scenarios modifying the elements of higher weight in the cost composition.

Ethics and dissemination This study has been designed according to the Helsinki/Tokyo Declaration and it was approved by the Clinical Research Ethics Committee of the *Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina* (IDIAPJGol), on 25/04/2018 (code P18/068). Furthermore, oral and written information will be delivered to participants and informed consents will be required guaranteeing anonymity. Dissemination strategy includes publications in scientific journals and through the local and national media, and conferences in academic events.

Clinical-Trials.gov registration: NCT04049006

Strengths and limitations of this study

- This study will provide relevant and accurate information about the economic impact and health benefits of a new treatment strategy for FMS.
- The results of the analysis will be helpful for decision-makers in order to supply the best healthcare option and considering stakeholders' opinions.
- The design of this study is based on a randomized control trial and it includes a wide perspective from society, and with a time horizon of 1-year which will allow assessing long-term changes.
- The cost-utility analysis is a popular participatory measurement tool but also controversial among experts since it has methodological limitations as well as the QOL variable.
- The indirect costs data collection strategy will only include those people who are linked to the social security system excluding people who work independently.

INTRODUCCION

Fibromyalgia is a chronic syndrome characterized by persistent and widespread musculoskeletal pain, but also associated with psychological and social factors, that remains medically unexplained.[1–4] Disability is one of the main consequences due to its impact on daily functioning, quality of life (QOL), and loss of productivity.[5] Furthermore, the prevalence of fibromyalgia syndrome (FMS) is significant in adults. An updated review has shown that its prevalence in the general population ranges between 0.2 and 6.6%, 2.45% particularly in Spain, being women the most affected group.[6,7] Therefore, healthcare for patients with this diagnosis is not only intricate from a clinical point of view, but also costly from an economic perspective for both the health and social security systems.[5,8–13]

Available evidence has shown that FMS implies a considerable cost to society associated, especially, with comorbidity and incapacity.[8,14–18] Among European countries, the total annual costs estimated for FMS were €7,900 (direct €910, indirect €6,990) for France, €7,256 (direct €1,765, indirect €5,491) for Germany, and €7,814 (direct €5,241, indirect €2,573) for Netherlands.[17,18] Additionally, FMS has the highest direct healthcare cost among other musculoskeletal conditions and illnesses widespread pain related,[14] and higher rates of unemployment and sick leave days.[19]

In the Spanish context, the global economic burden of FMS is robust and has been estimated at more than €12,993 million annually.[20] According to updated data published by the National Institute of Social Security of Spain (NISS), the number of assigned temporary disabilities due to FMS has increased in recent years, as well as the average number of days.[21] A cross-sectional and multicentre study, conducted from a retrospective review of medical outpatient records in Catalonia between 2006 and 2007, showed that patients with FMS had a considerably higher annual total costs in healthcare (included drugs, complementary tests, all types of medical visits, referrals, and hospitalizations) and non-health care (sick leave, and early retirement) resource utilization, under routine medical practice in the primary care setting, compared with a reference population. This study obtained an incremental adjusted per-patient per-year total cost of €5,010 for FMS patients, being €614 (12.3%) for direct costs and €4,394 (87.7%) for indirect costs.[10]

As well, another cross-sectional study conducted in Spain based on a face-to-face patient interview encountered a mean total cost per patient per year of €9,982, of which €3,245.8 (32.5%) corresponded to direct healthcare costs and €6,736.2 (67.5%) to indirect costs attributable to productivity losses.[11] Moreover, this study evidenced that: (i) non-pharmacological therapies accounted the highest cost of direct healthcare resources, and involved three times more than the cost of drug treatment; (ii) there was a significant association between disease severity and higher total costs; and (iii) patients with permanent working disability implies the highest use of resources.[11] However, all these findings were achieved over a decade ago and an update of the data is necessary for the Spanish health system.

Health economic evaluation is essential in policy decision-making since it provides evidence to identify the efficiency of an intervention, program, or project in order to optimize the benefits from limited resources.[22] Among the economic evaluation techniques, cost-utility analysis (CUA) estimates how much wellbeing is achieved for each monetary unit invested, involving both health outcomes and costs. This technique is an useful tool for comparing intervention strategies, especially for those with quite different health outcomes because of the standard utility units commonly used to measure all of them: the quality-adjusted life-year (QALY).[23] Despite its limitations, especially in measuring the value that society attaches to healthcare states, CUA is superior to other economic evaluation strategies and provides relevant information for resource allocation processes.[24]

Economic evaluation of interventions programs for FMS has been scarcely studied. According to the published findings, non-pharmacological strategies, especially psychology-based therapies, evidenced positive results in decreasing the economic burden of FMS.[19,25–31] In Spain, some cost-utility studies that compared alternative interventions (psychoeducational therapy, acceptance and commitment therapy, internet-delivered exposure therapy, and Mindfulness-Based Stress Reduction) with usual drug treatment have demonstrated the cost-utility from a healthcare and social perspective. [19,26–28,30] Nevertheless, only the FibroQoL study included a multicomponent intervention (MI) modality but with technical and methodological differences compare to actual proposal.[32,26]

The aim of this study is to perform a CUA on a MI (that consists of health education, physical activity, and cognitive-behavioral therapy) for patients with FMS compared to the usual clinical care (UCC),[33] provided with in the 11 primary health care

centres of the *Gerència Territorial Terres de L'Ebre* of the Catalan Institute of Health, Spain. The results of this economic assessment are expected to support the evidence of the randomized clinical trial (RCT) related to this project.[34] (Clinical-Trials.gov: NCT04049006).[35] With the support of the results, this new treatment proposal will likely improve the UCC and, with it, the QOL of patients with FMS as well as the efficiency of health and social allocation resources.

METHOD

Design

This study protocol has been drafted base on the literature review and following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[36] Medical Research Council guidance[37] for complex interventions has been taken in account for the RCT study.

For the design of this economic evaluation study a CUA will be conducted from a societal perspective, so indirect non-medical cost variables will be included. Also, a temporal horizon of 12-month will be used with the purpose of assessing health outcomes and costs at long-term. This methodological decision is based on the characteristics of the symptoms of FMS, its consequences, its tendency to chronicity, and the fact that its treatment is associated with on-going clinical management.

The elements to be compared in this study are the UCC [21,33,38,39] for patients with FMS and the UCC plus a MI provided in primary care centres.

The MI consists in a 12-week group program of 2-hour weekly combining: 7 health education instructions, 11 trainings on physical activity and physical health, and 7 interventions of psychological therapy based on cognitive-behavioural strategies and pain management. Group therapy is being delivered by the general practitioner specialized in FMS, the physiotherapist, and the psychologist with the support of the head nurses of each health centre involved.

Study population

The patients recruited for the study sample are shortlisted from the electronic medical records system eCAP (computerized medical history program) belonging to the Catalan Health Service (CatSalut) and the Catalan Health Institute (CHI). Only the medical records of the 11 primary care centres of the *Gerència Territorial Terres de L'Ebre* in

Catalonia (Spain) are included. Allocation to study groups is randomized according to a randomized list by centre. The inclusion criteria is detail in the RCT protocol study.[34]

Patient and Public Involvement

Patients or the public will not be involved in the design, or conducting, or reporting, or dissemination plans of our research.

Outcomes measures and data collection

Health outcomes

The utilities will be obtained based on the results of the QOL instrument SF-36 questionnaire[40] (Optum, Inc. license number QM048943) and QALYs will be calculated. This measurement instrument is administrated to the study sample at baseline, immediately after the intervention, and at 6 and 12 months of follow-up. Sociodemographic and clinical data are collected at baseline and it is fully detail in the RCT study protocol.[35] All these information is introduced in a software application that has been designed for the purpose of this study and is available in the *Terres de l'Ebre* CHI website, linked to the electronic medical records.

Cost outcomes

Direct and indirect costs related with the use of health and social resources, will be estimated in euros (€) according to the official prices for the public sector published in the *Diari Oficial de la Generalitat de Catalunya* (DOGC)[41] (updated to 2019), and the data from the Spanish Statistics National Institute (SNI), respectively. Table 1 shows the description of cost variables and data sources. These cost variables will be taken retrospectively 12-month before the start date of the MI and 12-month after the end of the MI.

---------- TABLE 1 ----------

Direct costs include visits to primary care services, to other professional referrals, and emergency, clinical tests for diagnosis and medical follow-up, pharmacological treatments, and hospitalizations. The prices of each service unit for the cost calculation will be obtained from the DOGC, except for the prices of the drugs for

which the Council of Pharmaceutical Colleges of Catalonia will be considered as the source of information.

Indirect non-medical costs consist of losing of productivity including temporary and permanent disability. These measurements will be estimated based on sick leave days and months spent with permanent disability, respectively.

Data collection is expected to be complete by December 2021.

Sample size

A total number of 260 participants has been calculated as the sample-size (130 subjects per study arm) for the RCT study.[34] Between 10 and 13 MI groups with their respective control groups (UCC), are required including 10-12 patients per group.

Statistical analysis

The SPSS version 25 and the Stata version 15 for Windows will be used to the statistical analysis. First, a descriptive analysis of the sample will be carried out comparing its characteristics between the study arms.

As an economic evaluation outcome measure, the incremental ratio of the cost-utility will be estimated dividing the difference in total mean costs in both UCC and MI by the differences in QALYs of each study arm. Moreover, 95% confidence intervals will be calculated for all analyses.

Regarding possible biases, the intention-to-treat principle will be applied in order not to affect the random distribution. In addition, to address the loss of follow-up and non-response, multiple imputation approaches to substitute missing values will be implemented.

Sensitivity analysis

A deterministic sensitivity analysis will be performed to assess the robustness of the results.[42] We will modify the items which have a most percentage about the cost, to compare with new results.

ETHICAL ASPECTS

This study was designed according to the Helsinki/Tokyo Declaration and it was approved by the Clinical Research Ethics Committee of the *Fundació Institut*

Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), on 25/04/2018 (code P18/068). Furthermore, oral and written information is delivered to participants and informed consents required. This project respects the data protection law guaranteeing anonymity.

DISCUSSION

This study intends to address FMS as a public health problem with economic repercussions.[10] Indeed, it compromises the health of a significant number of people, who are large consumers of health and social resources in the short and long-term. Therefore, the results of this study are expected to collaborate with the establishment of a multicomponent treatment for FMS in primary care settings, in order to reduce its economic burden and improve patients' QOL.

According to the literature review, the indirect costs attributable to sick leaves and permanent work disability, double the direct costs of healthcare. [8 10,11 14–18 19 20] As a result, efforts should be aimed at preventing the loss of productivity that represents the highest cost for the community and a significant impact on patients' health. From a societal perspective and taking this priority into account, this study incorporates indirect non-medical cost variables that will allow evaluating the impact of FMS burden in the social security system.

Another economic concern is the costs of the diagnosis process since it is purely clinical and it comes from discard.[43] Before a patient is diagnosed by FMS, other probable diseases must be ruled out through objective tests and different medical specialists. This path is often long and exhausting for patients, frustrating for doctors but also expensive from the perspective of the health system.[44] Furthermore, the presence of comorbidities can hinder and delay the diagnosis, as well as complicate the treatment strategy.[45] Considering this, the sample could show differences in the use of resources depending on the diagnostic year. However, it is assumed that the randomization will provide a balance between the study arms of patients with a more recent diagnosis and / or greater comorbidities weight.

Considering the evidence on the economic burden of FMS,[8,14–21] especially related to the loss of productivity, UCC does not seem to be completely helpful to reduce the effects of chronicity or prevent disability. Thus, FMS treatment should not be limited to short-term pain relief. It should also promote the acceptance of the condition,

the self-management of symptoms and the empowerment of patients to deal with FMS in their daily lives. The effective implementation of non-pharmacological approaches by patients at long-term and changes in lifestyle should be accomplished to avoid overprovision, overmedication, and the consequences of chronicity. The MI evaluated in this study aims to face with these goals by combining physical, psychological, and health education methods.

Findings on the efficacy of MI for patients with this condition have proved to be helpful in improving QOL, physical function, psychological variables, and/or pain after 3 to 12 months of follow-up.[46 47 48 49 50 51] However, more studies are required on the economic efficiency of this type of intervention and, particularly, in the context of the public health system in Spain.

Evidence on efficiency is essential for decision-making to prioritize the budgets in those treatment options that prove to be cost-efficient and cover patients' health-needs. Economic evaluation is key to overcoming the barrier of uncertainty about the true costs of carrying out an intervention and its sustainability.[52] The CUA selected for this study is a popular measurement tool that combines data on quantity and quality of life, valued by users of a health service, associated with a monetary cost. Therefore, it involves a participatory and economic evidence-based decision-making strategy that consider stakeholders' preferences.[53] Nevertheless, this methodology is also controversial.[54] The main highlights are: (i) the way to measure the value that society assign to a state of health. Although it is intended to guarantee transparency, the methodology for collecting and analysing this data is still questioned; (ii) the gain in health depends on the severity of the condition and, therefore, this value is affected by the characteristics of the patients and their health state; (iii) for long-term diseases such as FMS, where disability accumulates over time, this measurement tool is limited since it assumes that the utility of a health state is independent of the time spent in that health state, and the previous and subsequent health states.[24] Although these points pose challenges to overcome from a methodological point of view, CUA is still a valid and effective strategy to carry out economic evaluations in health and collaborate with decision-makers in selecting between different intervention alternatives.[24]

Other limitations related to the instruments and data collection is that the QOL is a multifactor variable that could be influenced by many circumstances not directly attached to the medical condition like family dynamic, working conditions, economic

and political context, among others.[55] Nonetheless, socio-demographic variables will be included in the analysis models trying to correct this possible effect.

On the other hand, all the health centres included in the study depend on the public health services of the region, so that both clinical care protocols and direct medical costs are standardized according to official publications and will be homogeneous for the entire sample. Considering the diversity of health centres included, it could be assumed that the population is representative for the community of Catalonia.

However, indirect costs will only include those people who are linked to the social security system and can access to its benefits. This excludes people who work independently of whom we will not have a record of their activity cedes or low productivity.

Although the 1-year time horizon is a strength of the study, since it will allow assessing long-term changes, it may also face the possible loss of follow-up. To minimize loss of sample, reminders for the interviews will be implemented, and even different strategies will be used for data collection, such as telephone calls.

If the results show to be utility-cost, this study will support, through efficiency evidence, the incorporation of a MI to the usual practise for FMS in units specialized in Central Sensitivity Syndromes located in primary care centres and in hospitals of Catalonia, Spain. What is more, improvement in patients' QOL and cost reduction of the healthcare services and social resources are expected. Finally, it is intended that this new intervention proposal can be replicated in other health areas of Catalonia and Spain, and considering as a guide for other European health systems.

AUTHOR CONTRIBUTIONS

VMA, **MC**, **CAM, AB**, **JFS** and **AQG** participated in the design of the study. **VMA** wrote the drafts versions with the review of all authors. **RCA**, **NCQ**, **GGS, MCS, IFA, AQG, AB, CAM, JFS, and VMA** are involved in the development of the general project and the RCT study from which this qualitative study is related.

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REFERENCES

1. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990;33(2):160–72.
2. Wolfe F, Clauw DJ, Fitzcharles MA, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. *J Rheumatol* 2011;38(6):1113–22.
3. Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum* 2016;46(3):319–29.
4. Helfenstein M, Goldenfum MA, Siena CAF. Fibromyalgia: Clinical and occupational aspects. *Rev Assoc Med Bras* 2012;58(3):358–65.
5. Skaer TL. Fibromyalgia: disease synopsis, medication cost effectiveness and economic burden. *Pharmacoeconomics* 2014;32(5):457–66.
6. Marques AP, Santo A de S do E, Berssaneti AA, et al. Prevalence of fibromyalgia: literature review update. *Rev Bras Reumatol* 2017;57(4):356–63.
7. Seoane-Mato D, Sanchez-Piedra C, Silva-Fernandez L, et al. Prevalence of rheumatic diseases in adult population in Spain (EPISER 2016 study): Aims and methodology. *Reumatol Clin* 2019;15(2):90–6.
8. Robinson RL, Birnbaum HG, Morley MA, Sisitsky T, Greenberg PE, Claxton AJ. Economic cost and epidemiological characteristics of patients with fibromyalgia claims. J Rheumatol. 2003;30(6):1318–25.
9. Spaeth M. Epidemiology, costs, and the economic burden of fibromyalgia. Arthritis Res Ther. 2009;11(3):2–3.

10. Sicras-Mainar A, Rejas J, Navarro R, et al. Treating patients with fibromyalgia in primary care settings under routine medical practice: a claim database cost and burden of illness study. *Arthritis Res Ther* 2009;11(2):1–14.
11. Rivera J, Rejas J, Esteve-Vives J, et al. Resource utilisation and health care costs in patients diagnosed with fibromyalgia in Spain. *Clin Exp Rheumatol* 2009;27(5 Suppl 56):S39-45.
12. Thompson JM, Luedtke CA, Oh TH, et al. Direct medical costs in patients with fibromyalgia: Cost of illness and impact of a brief multidisciplinary treatment program. *Am J Phys Med Rehabil* 2011;90(1):40–6.
13. Vervoort VM, Vriezekolk JE, Olde Hartman TC, et al. Cost of illness and illness perceptions in patients with fibromyalgia. *Clin Exp Rheumatol* 2016;34(2 Suppl 96):S74-82.
14. White KP, Speechley M, Harth M, et al. The London Fibromyalgia Epidemiology Study: direct health care costs of fibromyalgia syndrome in London, Canada. *J Rheumatol* 1999;26(4):885–9.
15. Berger A, Dukes E, Martin S, et al. Characteristics and healthcare costs of patients with fibromyalgia syndrome. *Int J Clin Pract* 2007;61(9):1498–508.
16. Berger A, Sadosky A, Dukes EM, et al. Patterns of healthcare utilization and cost in patients with newly diagnosed fibromyalgia. *Am J Manag Care* 2010;16(5 Suppl):S126-37.
17. Boonen A, Van Den Heuvel R, Van Tubergen A, et al. Large differences in cost of illness and wellbeing between patients with fibromyalgia, chronic low back pain, or ankylosing spondylitis. *Ann Rheum Dis* 2005;64(3):396–402.
18. Winkelmann A, Perrot S, Schaefer C, et al. Impact of fibromyalgia severity on health economic costs. *Appl Health Econ Health Policy* 2011;9(2):125–36.
19. Feliu-Soler A, Borràs X, Peñarrubia-María MT, et al. Cost-utility and biological underpinnings of Mindfulness-Based Stress Reduction (MBSR) versus a psychoeducational programme (FibroQoL) for fibromyalgia: A 12-month randomised controlled trial (EUDAIMON study). *BMC Complement Altern Med* 2016;16(1):1–16.
20. Cabo-Meseguer A, Cerda-Olmedo G, Trillo-Mata JL. Fibromyalgia: Prevalence, epidemiologic profiles and economic costs. *Med Clin (Barc)* 2017;149(10):441–8.
21. Instituto Nacional de la Seguridad social. Guia de actualización en la valoración de fibromialgia, sÍndrome de fatiga crónica, sensibilidad química múltiple y electrosensibilidad. Segunda Edición. 2019. https://www.semg.es/images/documentos/guia_fibromialgia_2019.pdf (accessed 22 Jun 2020)
22. Chisholm D, Evans DB. Economic evaluation in health: Saving money or improving care? *J Med Econ* 2007;10(3):325–37.
23. Franklin M. Cost utility analysis. *Ment Heal Econ Costs Benefits Psychiatr Care* 2017;307:89–119.
24. Mccabe C. What is cost-utility analysis? Newmarket, UK: *Hayward Medical Communications* 2009(February): 1-4. http://www.bandolier.org.uk/painres/download/whatis/What_is_cost-util.pdf (accessed 22 Jun 2020)
25. Goossens ME, Rutten-van Molken MP, Leidl RM, et al. Cognitive-educational treatment of fibromyalgia: a randomized clinical trial. II. Economic evaluation. *J Rheumatol* 1996;23(7):1246–54.
26. Luciano J V, Sabes-Figuera R, Cardenosa E, et al. Cost-utility of a psychoeducational intervention in fibromyalgia patients compared with usual care: an economic evaluation alongside a 12-month randomized controlled trial. *Clin J Pain* 2013;29(8):702–11.
27. Luciano J V., D'Amico F, Cerdà-Lafont M, et al. Cost-utility of cognitive behavioral therapy versus U.S. Food and Drug Administration recommended drugs and usual care in the treatment of patients with fibromyalgia: An economic evaluation alongside a 6-month randomized controlled trial. *Arthritis Res Ther* 2014;16(1):1–17.
28. Luciano J V, D'Amico F, Feliu-Soler A, et al. Cost-Utility of Group Acceptance and

Commitment Therapy for Fibromyalgia Versus Recommended Drugs: An Economic Analysis Alongside a 6-Month Randomized Controlled Trial Conducted in Spain (EFFIGACT Study). *J Pain* 2017;18(7):868–80.
29. Hedman-Lagerlof M, Hedman-Lagerlof E, Ljotsson B, et al. Cost-Effectiveness and Cost-Utility of Internet-Delivered Exposure Therapy for Fibromyalgia: Results From a Randomized, Controlled Trial. *J Pain* 2019;20(1):47–59.
30. Pérez-Aranda A, D'Amico F, Feliu-Soler A, et al. Cost–Utility of Mindfulness-Based Stress Reduction for Fibromyalgia versus a Multicomponent Intervention and Usual Care: A 12-Month Randomized Controlled Trial (EUDAIMON Study). *J Clin Med* 2019;8(7):1068.
31. Amico FD, Feliu-soler A. Cost-Utility of Attachment-Based Compassion Therapy (ABCT) for Fibromyalgia Compared to Relaxation: A Pilot Randomized Controlled Trial. *J Clin Med* 2020;9:726
32. Luciano J V, Martinez N, Penarrubia-Maria MT, et al. Effectiveness of a psychoeducational treatment program implemented in general practice for fibromyalgia patients: a randomized controlled trial. *Clin J Pain* 2011;27(5):383–91.
33. Salut D de. Guia per a l´avaluació de la fibromiàlgia i de la síndrome de fatiga crònica. Generalitat de Catalunya; 2017. http://canalsalut.gencat.cat/web/.content/_A-Z/F/fibromialgia/documents/guia_avaluacio_fibromialgia_fatiga_cronica.pdf (accessed 22 Jun 2020)
34. Caballol Angelats R, Gonçalves AQ, Aguilar Martín C, et al. Effectiveness, cost-utility, and benefits of a multicomponent therapy to improve the quality of life of patients with fibromyalgia in primary care: A mixed methods study protocol. *Med (United States)* 2019;98(41).
35. Caballol Angelats R, Gonçalves AQ, Aguilar Martín C, et al. Effectiveness, cost-utility, and benefits of a multicomponent therapy to improve the quality of life of patients with fibromyalgia in primary care. *Medicine (Baltimore)* 2019;98(41):e17289.
36. Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)-explanation and elaboration: A report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. *Value Heal* 2013;16(2):231–50.
37. Craig P, Dieppe P, Macintyre S, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. *Int J Nurs Stud* 2013;50(5):587–92.
38. Generaliat de Catalunya (Departament de Salut), Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS). Evaluació y abordaje de la fibromialgia y síndrome de fatiga crónica. 2017 http://aquas.gencat.cat/web/.content/minisite/aquas/publicacions/2017/evaluacion_fibromialgia_SFC_aquas2017es.pdf (accessed 22 Jun 2020)
39. Generalitat de Catalunya (Departament de Salut). Pla operatiu d'atenció a les persones afectades per les síndromes de senzibilització central: fibromiàlgia, síndrome de fatiga crònica i síndrome de sensibilitat química múltiple. 2016 https://canalsalut.gencat.cat/ca/salut-a-z/f/fibromialgia/ (accessed 22 Jun 2020)
40. Alonso J. Versión española de SF-36v2™ Health Survey © 1996, 2000 adaptada por J. Alonso y cols 2003. *Heal Surv* 2003;1–8. http://www.ser.es/wp-content/uploads/2015/03/SF36_CUESTIONARIOpdf.pdf (accessed 25 Jun 2020)
41. Catalunya G de. Diari Oficial de la Generalitat de Catalunya. https://dogc.gencat.cat/es (accessed 25 Jun 2020)
42. Andronis L, Barton P, Bryan S. Sensitivity analysis in economic evaluation: An audit of NICE current practice and a review of its use and value in decision-making. *Health Technol Assess* 2009;13(29).
43. Wang S-M, Han C, Lee S-J, et al. Fibromyalgia diagnosis: a review of the past, present and future. *Expert Rev Neurother* 2015;15(6):667–79.
44. Briones-Vozmediano E. The social construction of fibromyalgia as a health problem from the perspective of policies, professionals, and patients. *Glob Health Action* 2017;10(1).

45. Lichtenstein A, Tiosano S, Amital H. The complexities of fibromyalgia and its comorbidities. *Curr Opin Rheumatol* 2018;30(1):94–100.
46. Giusti EM, Castelnuovo G, Molinari E. Differences in Multidisciplinary and Interdisciplinary Treatment Programs for Fibromyalgia: A Mapping Review. *Pain Res Manag* 2017;2017:7261468.
47. Bourgault P, Lacasse A, Marchand S, et al. Multicomponent interdisciplinary group intervention for self-management of fibromyalgia: a mixed-methods randomized controlled trial. *PLoS One* 2015;10(5):e0126324.
48. Ollevier A, Vanneuville I, Carron P, et al. A 12-week multicomponent therapy in fibromyalgia improves health but not in concomitant moderate depression, an exploratory pilot study. *Disabil Rehabil* 2019;0(0):1–8.
49. Martin J, Torre F, Padierna A, et al. Six-and 12-month follow-up of an interdisciplinary fibromyalgia treatment programme: results of a randomised trial. *Clin Exp Rheumatol* 2012;30(6 Suppl 74):103–11.
50. Saral I, Sindel D, Esmaeilzadeh S, et al. The effects of long- and short-term interdisciplinary treatment approaches in women with fibromyalgia: a randomized controlled trial. *Rheumatol Int* 2016;36(10):1379–89.
51. Stein KF, Miclescu A. Effectiveness of multidisciplinary rehabilitation treatment for patients with chronic pain in a primary health care unit. *Scand J Pain* 2013;4(4):190–7.
52. Eisman AB, Kilbourne AM, Dopp AR, et al. Economic evaluation in implementation science: Making the business case for implementation strategies. *Psychiatry Res* 2020;283:112433.
53. Anneliese P, Hoch J. Understanding Cost-utility Analysis in Health Care. *Univ Toronto Med J* 2006: Jan 1
54. McGregor M. Cost-utility analysis: Use QALYs only with great caution. *Cmaj* 2003;168(4):433–4.
55. Tarter T, Johnson G, Johnson R. Neuropsychology of Cancer and Oncology. Chad A Noggle; Raymond S Dean: Springer Publishing Company 2013:3

Table 1. Cost outcomes measurements and data collection

Cost outcomes measurements and data collection				
Cost outcomes	**Cost outcomes description**	**Data source**	**Cost data source**	**Cost calculation**
Direct healthcare costs				
Primary care visits	-General Practitioner -Nurse -Physiotherapist -Psychologists	eCAP*	DOGC**	Number of visits × price
Professional referral visits	-Traumatology -Psychiatry -Rehabilitation -Other specialities	eCAP	DOGC	Number of visits × price
Clinical tests	-Blood test -Diagnostic imaging techniques -Other tests	eCAP	DOGC	Test done x price
Pharmacological prescriptions	-Muscle relaxants -Analgesics -Corticoids -Antidepressants -Anxiolytics -Anti-seizure -Gastric protectors -Other drugs	eCAP	Council of Pharmaceutical Colleges of Catalonia	Medicines bought × price
Emergency visits		eCAP	DOGC	Number of visits × price
Hospitalizations		eCAP	DOGC	Number of hospitalization days x price
Indirect non-medical costs: loss of productivity				
Temporary disability (TD)	Absenteeism	eCAP/SNI***		Number of sick leave days × salary
Permanente disability (PD)		e-CAP/INE		Number of months with PD x pension

*eCAP: computerized medical history program

**DOGC: *Diario Oficial de la Generalitat de Catalunya*

***SNI: Statistics National Institute

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Cost-utility analysis of a multicomponent intervention for Fibromyalgia syndrome in primary care versus usual clinical practice: study protocol for an economic evaluation of a randomized control trial

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Abstract (300/300)

Introduction Fibromyalgia syndrome (FMS) carries a high cost to society. The significant economic burden in the use of healthcare and, especially, social resources suggests the revision of the usual clinical care (UCC) and the improvement of the treatment strategies. FMS is potentially disabling due to its impact on the quality of life (QOL) and productivity loss, which greatly increases the indirect costs to society. This study aims to perform an economic evaluation to compare the cost and health-benefits between a multicomponent intervention (MI) program and the UCC, for FMS patients who attend to primary care centres (PCC) of the *Gerència Territorial Terres de L'Ebre* in Catalonia, Spain. This study is expected to support the effectiveness results of a randomized control trial study on the implementation of this program.

Method and analysis A cost-utility analysis will be conducted from a societal perspective. Quality-adjusted life years will be obtained from the results of the SF-36 questionnaire, a QOL measurement instrument. Direct and indirect healthcare costs will be obtained from official prices and reports published by the public health administration and the Statistics National Institute. The incremental cost-utility ratio will be estimated to compare both healthcare practices. Deterministic sensitivity analysis will be also implemented to compare different cost scenarios modifying the items with higher weight in the cost composition.

Ethics and dissemination This study has been designed according to the Helsinki/Tokyo Declaration and it was approved by the Clinical Research Ethics Committee of the *Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina* (IDIAPJGol), on 25/04/2018 (code P18/068). Furthermore, oral and written information will be delivered to participants, and informed consent will be required guaranteeing anonymity. Dissemination strategy includes publications in scientific journals and presentations through the local and national media and conferences in academic events.

ClinicalTrials.gov registration: NCT04049006

Strengths and limitations of this study

- This study will provide relevant and accurate information about the economic impact and health benefits of a new treatment strategy for FMS.
- The results of the analysis will be helpful for decision-makers in order to supply the best healthcare option and considering stakeholders' opinions.
- The design of this study is based on a randomized control trial and it includes a wide perspective from society, and with a time horizon of 1-year which will allow assessing long-term changes.
- The cost-utility analysis is a popular participatory measurement tool but also controversial among experts since it has methodological limitations as well as the QOL variable.
- The data source for indirect costs will only allow including data from patients who are linked to the social security system excluding independent and informal workers, unemployed people, and housewives.

INTRODUCTION

Fibromyalgia is a chronic syndrome, medically unexplained, which is characterized by persistent and widespread musculoskeletal pain but also associated with psychological and social factors.[1–4] Disability is one of the main consequences due to its impact on daily functioning, quality of life (QOL), and productivity loss.[5] Furthermore, the prevalence of fibromyalgia syndrome (FMS) is significant in adults. An updated review has shown that its prevalence in the general population ranges between 0.2 and 6.6%, 2.45% particularly in Spain, and it is more frequent in women.[6,7] Therefore, healthcare for patients with this diagnosis is not only intricate from a clinical point of view but also costly from an economic perspective for both the health and social security systems.[5,8–13]

Available evidence has shown that FMS implies a considerable cost to society associated, especially, with comorbidity and incapacity.[8,14–18] Among European countries, the total annual costs estimated for FMS were €7,900 (direct €910, indirect €6,990) for France, €7,256 (direct €1,765, indirect €5,491) for Germany, and €7,814 (direct €5,241, indirect €2,573) for the Netherlands.[17,18] Additionally, FMS has the highest direct healthcare cost among other musculoskeletal conditions and illnesses chronic-pain related,[14] and higher rates of unemployment and sick leave days.[19]

In the Spanish context, the global economic burden of FMS is robust and has been estimated at more than €12,993 million annually.[20] According to updated data published by the National Institute of Social Security of Spain (NISS), the number of assigned temporary disabilities (short-term absenteeism because of sick leave days) due to FMS has increased in recent years, as well as the average number of days absent.[21] A cross-sectional and multicentre study, conducted from a retrospective review of medical outpatient records in Catalonia between 2006 and 2007, showed that patients with FMS had a considerably higher annual total costs in healthcare (included drugs, complementary tests, all types of medical visits, referrals, and hospitalizations) and non-healthcare resource utilization (sick leave days, and early retirement), under routine medical practice in the primary care setting, compared with a reference population. This study obtained an incremental adjusted per-patient per-year total cost of €5,010 for FMS patients, being €614 (12.3%) for direct costs and €4,394 (87.7%) for indirect costs.[10]

In line with this findings, another cross-sectional study conducted in Spain based on a face-to-face patient interview encountered a mean total cost per patient per year of €9,982, of which €3,245.8 (32.5%) corresponded to direct healthcare costs and €6,736.2

(67.5%) to indirect costs attributable to productivity losses.[11] Moreover, this study evidenced that: (i) non-pharmacological therapies accounted the highest cost of direct healthcare resources, and involved three times more than the cost of drug treatment; (ii) there was a significant association between disease severity and higher total costs; and (iii) patients with permanent working disability implies the highest use of resources.[11] However, all these findings were achieved over a decade ago and an update of the data is necessary for the Spanish public health system.

Health economic evaluation is essential in policy decision-making since it provides evidence to identify the efficiency of an intervention, program, or project in order to optimize the benefits from limited resources.[22] Among the economic evaluation techniques, cost-utility analysis (CUA) estimates how much wellbeing is achieved for each monetary unit invested, involving both health outcomes and costs. This technique is a useful tool for comparing intervention strategies, especially for those with quite different health outcomes because of the standard utility units commonly used to measure all of them: the quality-adjusted life-year (QALY).[23] Despite its limitations, especially in measuring the value that society attaches to healthcare states, CUA is superior to other economic evaluation strategies and provides relevant information for resource allocation processes.[24]

The economic evaluation of intervention programs for FMS has been scarcely studied. According to the published findings, non-pharmacological strategies, especially psychology-based therapies, have evidenced positive results in decreasing the economic burden of FMS.[19,25–31] In Spain, some cost-utility studies that compare alternative interventions (psychoeducational therapy, acceptance and commitment therapy, internet-delivered exposure therapy, and Mindfulness-Based Stress Reduction) with usual drug treatment have demonstrated the cost-utility from a healthcare and social perspective. [19,26–28,30] Nevertheless, only the FibroQoL study included a multicomponent intervention (MI) modality but with technical and methodological differences compare to the actual proposal.[32,26]

This study aims to perform a CUA on a MI (that consists of health education, physical activity, and cognitive-behavioral therapy) for patients with FMS compared to the usual clinical care (UCC),[33] provided within the 11 primary healthcare centres of the *Gerència Territorial Terres de L'Ebre* of the Catalan Institute of Health, Spain. The results of this economic assessment are expected to support the evidence of the randomized clinical trial (RCT) related to this project.[34] (Clinical-Trials.gov:

NCT04049006).[35] This new intervention proposal will hopefully reinforce the UCC, enhance patients' QOL, and promote efficiency in health and social resources allocation.

METHOD

Design

This study protocol has been drafted based on the literature review and following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[36] Medical Research Council guidance[37] for complex interventions has been taken into account for the RCT study.

For the design of this economic evaluation study a CUA will be conducted from a societal perspective, so indirect non-medical cost variables will be included. Also, a temporal horizon of 12-month will be used to assess health outcomes and costs in the long-term. This methodological decision is based on the clinical symptoms of FMS, its consequences, its tendency to chronicity, and the fact that its treatment is associated with on-going clinical management.

The human capital approach has been judged as the most suitable method for this study due to limitations in the data source since only full sick days, prescribed by the GP, and the period with a medical disability can be extracted from the computerized medical history program (eCAP).

The elements to be compared in this study are the UCC[21,33,38,39] for patients with FMS, and the UCC plus a MI provided in primary care centres. The MI consists of a 12-week group program of 2-hour weekly combining: 7 health education instructions, 11 pieces of training on physical activity and physical health, and 7 interventions of psychological therapy based on cognitive-behavioural strategies and pain management. Group therapy is being delivered by the general practitioner specialized in FMS, the physiotherapist, and the psychologist with the support of the head nurses of each health centre involved.

Study population

The patients recruited for the study sample are shortlisted from the electronic medical records system eCAP (computerized medical history program) belonging to the Catalan Health Service (CatSalut) and the Catalan Health Institute (CHI). Only the medical

records of the 11 primary care centres of the *Gerència Territorial Terres de L'Ebre* in Catalonia (Spain) are included. Allocation to study groups is randomized according to a randomized list by centre. This randomization strategy has been designed taking into account the possible variations in the sociodemographic and clinical variables of the primary care centres involved, due to the diversity of the territory, and in order to obtain a representative sample. The inclusion criteria are detailed in the RCT protocol study.[34]

Patient and Public Involvement

Patients or the public will not be involved in the design or conducting, or reporting, or dissemination plans of our research.

Outcomes measures and data collection

Health outcomes

The utilities will be obtained based on the results of the health-related QOL SF-36 questionnaire[40] (Optum, Inc. license number QM048943) and the estimation of quality-adjusted life years (QALYs). This measurement instrument is administrated to the study sample at baseline, immediately after the intervention, and at 6 and 12 months of follow-up. Sociodemographic and clinical variables are registered at baseline and are fully detailed in the RCT study protocol.[35] The collected data is introduced in a software application that has been specially designed for study and is available on the *Terres de l'Ebre* CHI website, linked to the electronic medical records.

Cost outcomes

Direct and indirect costs, related with the use of health and social resources, will be estimated in euros (€) according to the official prices for the public sector which are published in the *Diari Oficial de la Generalitat de Catalunya* (DOGC)[41] (updated to 2019), and in the Spanish Statistics National Institute (SNI), respectively. Table 1 shows the description of cost variables and data sources. These cost variables will be taken retrospectively 12-month before the start date of the MI and 12-month after the end of the MI.

Table 1. Cost outcomes measurements and data collection

Cost outcomes measurements and data collection				
Cost outcomes	**Cost outcomes description**	**Data source**	**Cost data source**	**Cost calculation**
Direct healthcare costs				
Primary care visits	-General Practitioner -Nurse -Physiotherapist -Psychologists	eCAP*	DOGC**	Number of visits × price
Professional referral visits	-Traumatology -Psychiatry -Rehabilitation -Other specialities	eCAP	DOGC	Number of visits × price
Clinical tests	-Blood test -Diagnostic imaging techniques -Other tests	eCAP	DOGC	Test performed x price
Pharmacological prescriptions	-Muscle relaxants -Analgesics -Corticoids -Antidepressants -Anxiolytics -Anti-seizure -Gastric protectors -Other drugs	eCAP	Council of Pharmaceutical Colleges of Catalonia	Medicines bought × price
Emergency visits		eCAP	DOGC	Number of visits × price
Hospitalizations		eCAP	DOGC	Number of hospitalization days x price
Indirect non-medical costs				
Temporary disability (TD)		eCAP/SNI***		Number of full sick leave days × salary
Permanent disability (PD)		eCAP/SNI		Number of months with PD x salary

*eCAP: computerized medical history program

**DOGC: *Diario Oficial de la Generalitat de Catalunya*

***SNI: Statistics National Institute

Direct costs include visits to primary care services, other professional referrals, and emergency services, clinical tests for diagnosis and medical follow-up, pharmacological treatments, and hospitalizations. The prices of each service unit for the cost calculation will be obtained from the DOGC, except for the prices of the drugs for which the Council of Pharmaceutical Colleges of Catalonia will be considered as the data source.

Indirect non-medical costs include temporary and permanent disability. In the Spanish context, the term "temporary disability" refers to the sick leave days due to common or professional illness in the short-term. On the other hand, "permanent

disability" refers to the impossibility to work due to the permanent and total or partial loss of working capacity in the long-term. In the first case, a GP determines if a patient is unable to work in the short-term. In the second case, a medical board assesses in depth the medical background and physical and mental condition of the person in order to determine if a permanent disability should be provided. The Spanish General Law of Social Security (Law 20/2014; Royal Legislative Decree 8/2015)[42] should be reviewed for further detail. These measurements will be estimated based on full sick leave days and months spent with disability, respectively.

For the purpose of this study and considering the access to the data available through the eCap, presenteeism and unpaid lost time will not be accounted in the data collection since it is not possible to get that kind of information from our data source.

The price weight of the social costs will be determined by the calculation of a total annual average salary (including ordinary and extra payments), for the Catalonia region, which is registered on the official records of the Statistics National Institute.[43] This estimation will be accounted for both part and full-time working schedules, and all activity sectors (industry, construction, and services except housework).

Data collection is expected to be completed by April 2021.

Sample size

A total number of 260 participants have been calculated as the sample-size (130 subjects per study arm) based on variations in the SF-36 questionnaire and in order to detect a score difference equal or higher than 5 points, assuming an alpha error of 0.05, a beta error of 0.05 in a bilateral contrast, and a dropout rate of 20%.[34] Consequently, between 10 and 13 MI groups with their respective control groups (UCC), are required including 10-12 patients per group.

Statistical analysis

The SPSS version 25 and the Stata version 15 for Windows will be used for the statistical analysis. First, a descriptive analysis of the sample will be carried out comparing its characteristics between the study arms.

As an economic evaluation outcome measure, the incremental ratio of the cost-utility will be estimated dividing the difference in total mean costs in both UCC and MI

by the differences in QALYs of each study arm. Moreover, 95% confidence intervals will be calculated for all analyses.

Regarding possible biases, the intention-to-treat principle will be applied in order not to affect the random distribution. In addition, to address the loss of follow-up and non-response, multiple imputation approaches to substitute missing values will be implemented.

Sensitivity analysis

A deterministic sensitivity analysis will be performed to assess the robustness of the results.[44] Items with a higher cost will be modified in order to compare them with the original results.

ETHICS AND DISSEMINATION

This study was designed according to the Helsinki/Tokyo Declaration and it was approved by the Clinical Research Ethics Committee of the *Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina* (IDIAPJGol), on 25/04/2018 (code P18/068). Furthermore, oral and written information is delivered to participants, and informed consent is required. This project respects the data protection law guaranteeing anonymity. Dissemination strategy includes publications in scientific journals and through the local and national media and conferences in academic events.

DISCUSSION

This study intends to address FMS as a public health problem with economic repercussions.[10] Indeed, it compromises the health of a significant number of people, who are large consumers of health and social resources in the short and long-term. Therefore, the results of this study are expected to collaborate with the inclusion of a MI for FMS in primary care settings in order to improve patients' QOL and reduce its economic burden.

According to the literature review, the indirect costs attributable to sick leaves and permanent work disability exceed the direct costs of healthcare.[8 10,11 14–18 19,20] As a result, efforts should be aimed at preventing productivity loss that represents the highest cost for the community and a significant impact on patients' health. From a societal

perspective and taking this priority into account, this study incorporates indirect non-medical cost variables that will allow assessing the impact of FMS burden on the social security system.

Even though more accurate methods, such as the friction cost approach, have been acknowledged by the literature for the estimation of the productivity costs, the human capital approach has been considered the most suitable for the characteristics of the data access in this study. Nevertheless, we do not underestimate the limitations of this approach, the reason why a sensitivity analysis will be performed to assess different possible cost scenarios. It will include different direct healthcare costs and, if necessary, the price weight of the social cost considering that the salary rate will be an overall annual average estimation without distinction neither of the type of activity nor the working schedule.

Another economic concern is the costs of the diagnosis process since it is purely clinical and it comes from discard.[45] Before a patient is diagnosed by FMS, other probable diseases must be ruled out through objective tests and different medical specialists. This path is often long and exhausting for patients, frustrating for doctors but also expensive from the perspective of the health system.[46] Furthermore, the presence of comorbidities can hinder and delay the diagnosis, as well as complicate the treatment strategy.[47] Considering this, the sample could show differences in the use of resources depending on the diagnostic year. However, it is assumed that the randomization will provide a balance between the study arms of patients with a more recent diagnosis and / or greater comorbidities weight.

Given the evidence on the economic burden of FMS,[8,14–21] especially related to the loss of productivity, UCC does not seem to be completely helpful to reduce the effects of chronicity or prevent disability. Thus, FMS treatment should not be limited to short-term pain relief. It should also promote the acceptance of the condition, the self-management of symptoms, and the empowerment of patients to deal with FMS in their daily lives. The effective implementation of non-pharmacological approaches by patients at long-term and lifestyle changes should be accomplished to avoid overprovision, overmedication, and the consequences of chronicity. The evaluated MI in this study aims to face with these goals by combining physical, psychological, and health education methods.

Findings on the efficacy of MI for patients with this condition have proved to help improve QOL, physical function, psychological variables, and/or pain after 3 to 12

months of follow-up.[48–53] However, more studies are required on the economic efficiency of this type of interventions and, particularly, in the context of the public health system in Spain.

Evidence on efficiency is essential for decision-making to prioritize the budgets in those treatment options that prove to be cost-efficient and cover patients' health needs. Economic evaluation is key to overcoming the barrier of uncertainty about the true costs of carrying out an intervention and its sustainability.[54] The CUA selected for this study is a popular measurement tool that combines data on quantity and quality of life, valued by users of a health service, and associated with a monetary cost. Therefore, it involves a participatory and economic evidence-based decision-making strategy that considers stakeholders' preferences.[55] Nevertheless, this methodology is also controversial.[56] The main highlights are: (i) the way to measure the value that society assigns to a state of health. Although it is intended to guarantee transparency, the methodology for collecting and analysing this data is still questioned; (ii) the gain in health depends on the severity of the condition and, therefore, this value is affected by the characteristics of the patients and their health state; (iii) for long-term diseases such as FMS, where disability accumulates over time, this measurement tool is limited since it assumes that the utility of a health state is independent of the time spent in that health state, and the previous and subsequent health states.[24] Although these points pose challenges to overcome from a methodological point of view, CUA is still a valid and effective strategy to carry out health economic evaluations and collaborate with decision-makers in selecting between different intervention alternatives.[24]

Other limitations related to the instruments and data collection is that the QOL is a multifactor variable that could be influenced by many circumstances not directly attached to the medical issue like family dynamic, working conditions, economic and political context, among others.[57] Nonetheless, socio-demographic variables will be included in the analysis models trying to correct these possible effects.

Although this health region comprises a wide and varied territory, all health centres involved in the study depend on the public health services of the region so that both clinical care protocols and direct medical costs are standardized according to official publications and will be homogeneous for the entire sample.

Regarding the indirect costs, only those people who are linked to the social security system and can access its benefits will be able to provide data about productivity costs. Therefore, it excludes independent and informal workers,

unemployed people, and housewives of whom we will not have any background of their productivity loss. In this sense, although the human capital approach could overestimate productivity costs, it could be compensated if we consider that there is no data recorded of these population subgroups that also represent a productivity loss for society due to the side effects of their illness processes.

Finally, and even though a 1-year time horizon is a strength of the study since it will allow assessing long-term changes, it may also face a possible sample loss during the follow-up. To minimize sample loss, reminders for the interviews will be implemented, and even different strategies will be used for data collection, such as telephone calls and online survey platforms.

If the results show to be utility-cost, this study will support, through efficiency evidence, the incorporation of a MI to the usual practice for FMS in primary care centres of Catalonia, Spain. What is more, health improvements and cost reductions on sanitary and social resources are expected. To conclude, it is intended that this new intervention proposal be replicated in other health areas of Catalonia and Spain, and considered as a guide for other European health systems.

AUTHOR CONTRIBUTIONS

VMA, **MC**, **CAM**, **AB**, **JFS**, and **AQG** participated in the design of the study. **VMA** wrote the draft versions with the review of all authors. **RCA**, **NCQ**, **GGS**, **MCS**, **IFA**, **AQG**, **AB**, **CAM**, **JFS**, **and VMA** are involved in the development of the general project and the RCT study from which this qualitative study is related.

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REFERENCES

1. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum [Internet]. 1990/02/01. 1990;33(2):160–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2306288
2. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Hauser W, Katz RS, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol [Internet]. 2011/02/03. 2011;38(6):1113–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21285161
3. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Hauser W, Katz RL, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum [Internet]. 2016/12/06. 2016;46(3):319–29. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27916278
4. Helfenstein M, Goldenfum MA, Siena CAF. Fibromyalgia: Clinical and occupational aspects. Rev Assoc Med Bras. 2012;58(3):358–65.
5. Skaer TL. Fibromyalgia: disease synopsis, medication cost effectiveness and economic burden. Pharmacoeconomics. 2014 May;32(5):457–66.
6. Marques AP, Santo A de S do E, Berssaneti AA, Matsutani LA, Yuan SLK. Prevalence of fibromyalgia: literature review update. Rev Bras Reumatol (English Ed. 2017;57(4):356–63.
7. Seoane-Mato D, Sanchez-Piedra C, Silva-Fernandez L, Sivera F, Blanco FJ, Perez Ruiz F, et al. Prevalence of rheumatic diseases in adult population in Spain (EPISER 2016 study): Aims and methodology. Reumatol Clin. 2019 Mar;15(2):90–6.
8. Robinson RL, Birnbaum HG, Morley MA, Sisitsky T, Greenberg PE, Claxton AJ. Economic cost and epidemiological characteristics of patients with fibromyalgia claims. J Rheumatol. 2003;30(6):1318–25.
9. Spaeth M. Epidemiology, costs, and the economic burden of fibromyalgia. Arthritis Res Ther. 2009;11(3):2–3.
10. Sicras-Mainar A, Rejas J, Navarro R, Blanca M, Morcillo A, Larios R, et al. Treating patients with fibromyalgia in primary care settings under routine medical practice: a claim database cost and burden of illness study. Arthritis Res Ther. 2009;11(2):1–14.
11. Rivera, J.; Rejas, J.; Esteve-Vives, J.; Vallejo MA. GI. Resource utilisation and health care costs in patients diagnosed with fibromyalgia in Spain. Clin Exp Rheumatol

[Internet]. 2009;27(5 Suppl 56):S39-45. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed9&NEWS=N&AN=20074438

12. Thompson JM, Luedtke CA, Oh TH, Shah ND, Long KH, King S, et al. Direct medical costs in patients with fibromyalgia: Cost of illness and impact of a brief multidisciplinary treatment program. Am J Phys Med Rehabil. 2011 Jan;90(1):40–6.
13. Vervoort VM, Vriezekolk JE, Olde Hartman TC, Cats HA, van Helmond T, van der Laan WH, et al. Cost of illness and illness perceptions in patients with fibromyalgia. Clin Exp Rheumatol. 2016;34(2 Suppl 96):S74-82.
14. White KP, Speechley M, Harth M, Ostbye T. The London Fibromyalgia Epidemiology Study: direct health care costs of fibromyalgia syndrome in London, Canada. J Rheumatol. 1999 Apr;26(4):885–9.
15. Berger A, Dukes E, Martin S, Edelsberg J, Oster G. Characteristics and healthcare costs of patients with fibromyalgia syndrome. Int J Clin Pract. 2007;61(9):1498–508.
16. Berger A, Sadosky A, Dukes EM, Edelsberg J, Zlateva G, Oster G. Patterns of healthcare utilization and cost in patients with newly diagnosed fibromyalgia. Am J Manag Care. 2010 May;16(5 Suppl):S126-37.
17. Boonen A, Van Den Heuvel R, Van Tubergen A, Goossens M, Severens JL, Van Der Heijde D, et al. Large differences in cost of illness and wellbeing between patients with fibromyalgia, chronic low back pain, or ankylosing spondylitis. Ann Rheum Dis. 2005;64(3):396–402.
18. Winkelmann A, Perrot S, Schaefer C, Ryan K, Chandran A, Sadosky A, et al. Impact of fibromyalgia severity on health economic costs. Appl Health Econ Health Policy [Internet]. 2011;9(2):125–36. Available from: https://doi.org/10.2165/11535250-000000000-00000
19. Feliu-Soler A, Borràs X, Peñarrubia-María MT, Rozadilla-Sacanell A, D'Amico F, Moss-Morris R, et al. Cost-utility and biological underpinnings of Mindfulness-Based Stress Reduction (MBSR) versus a psychoeducational programme (FibroQoL) for fibromyalgia: A 12-month randomised controlled trial (EUDAIMON study). BMC Complement Altern Med [Internet]. 2016;16(1):1–16. Available from: http://dx.doi.org/10.1186/s12906-016-1068-2
20. Cabo-Meseguer A, Cerda-Olmedo G, Trillo-Mata JL. Fibromyalgia: Prevalence, epidemiologic profiles and economic costs. Med Clin (Barc). 2017 Nov;149(10):441–8.
21. Instituto Nacional de la Seguridad social. Guia de actualización en la valoración de fibromialgia, sÍndrome de fatiga crónica, sensibilidad química múltiple y electrosensibilidad. Segunda E dición [Internet]. 2019. Available from: https://www.semg.es/images/documentos/guia_fibromialgia_2019.pdf
22. Chisholm D, Evans DB. Economic evaluation in health: Saving money or improving care? J Med Econ. 2007;10(3):325–37.
23. Franklin M. Cost utility analysis. Ment Heal Econ Costs Benefits Psychiatr Care. 2017;307(October):89–119.
24. Mccabe C. What is cost-utility analysis? 2009;(February):1–6.
25. Goossens ME, Rutten-van Molken MP, Leidl RM, Bos SG, Vlaeyen JW, Teeken-Gruben NJ. Cognitive-educational treatment of fibromyalgia: a randomized clinical trial. II. Economic evaluation. J Rheumatol. 1996 Jul;23(7):1246–54.
26. Luciano J V, Sabes-Figuera R, Cardenosa E, T Penarrubia-Maria M, Fernandez-Vergel R, Garcia-Campayo J, et al. Cost-utility of a psychoeducational intervention in fibromyalgia patients compared with usual care: an economic evaluation alongside a 12-month randomized controlled trial. Clin J Pain. 2013 Aug;29(8):702–11.
27. Luciano J V., D'Amico F, Cerdà-Lafont M, Peñarrubia-María MT, Knapp M, Cuesta-Vargas AI, et al. Cost-utility of cognitive behavioral therapy versus U.S. Food and Drug Administration recommended drugs and usual care in the treatment of patients with fibromyalgia: An economic evaluation alongside a 6-month randomized controlled trial. Arthritis Res Ther. 2014;16(1):1–17.
28. Luciano J V, D'Amico F, Feliu-Soler A, McCracken LM, Aguado J, Peñarrubia-María

MT, et al. Cost-Utility of Group Acceptance and Commitment Therapy for Fibromyalgia Versus Recommended Drugs: An Economic Analysis Alongside a 6-Month Randomized Controlled Trial Conducted in Spain (EFFIGACT Study). J Pain [Internet]. 2017 Jul 1;18(7):868–80. Available from: https://doi.org/10.1016/j.jpain.2017.03.001

29. Hedman-Lagerlof M, Hedman-Lagerlof E, Ljotsson B, Wicksell RK, Flink I, Andersson E. Cost-Effectiveness and Cost-Utility of Internet-Delivered Exposure Therapy for Fibromyalgia: Results From a Randomized, Controlled Trial. J Pain. 2019 Jan;20(1):47–59.
30. Pérez-Aranda A, D'Amico F, Feliu-Soler A, McCracken LM, Peñarrubia-María MT, Andrés-Rodríguez L, et al. Cost–Utility of Mindfulness-Based Stress Reduction for Fibromyalgia versus a Multicomponent Intervention and Usual Care: A 12-Month Randomized Controlled Trial (EUDAIMON Study). J Clin Med. 2019;8(7):1068.
31. Amico FD, Feliu-soler A. Cost-Utility of Attachment-Based Compassion Therapy (ABCT) for Fibromyalgia Compared to Relaxation : A Pilot Randomized Controlled Trial. 2020;
32. Luciano J V, Martinez N, Penarrubia-Maria MT, Fernandez-Vergel R, Garcia-Campayo J, Verduras C, et al. Effectiveness of a psychoeducational treatment program implemented in general practice for fibromyalgia patients: a randomized controlled trial. Clin J Pain [Internet]. 2011/02/15. 2011;27(5):383–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21317775
33. Salut D de. Guia per a l´avaluació de la fibromiàlgia i de la síndrome de fatiga crònica. Generalitat de Catalunya; 2017.
34. Caballol Angelats R, Gonçalves AQ, Aguilar Martín C, Sancho Sol MC, González Serra G, Casajuana M, et al. Effectiveness, cost-utility, and benefits of a multicomponent therapy to improve the quality of life of patients with fibromyalgia in primary care: A mixed methods study protocol. Med (United States). 2019;98(41).
35. Caballol Angelats R, Gonçalves AQ, Aguilar Martín C, Sancho Sol MC, González Serra G, Casajuana M, et al. Effectiveness, cost-utility, and benefits of a multicomponent therapy to improve the quality of life of patients with fibromyalgia in primary care. Medicine (Baltimore). 2019;98(41):e17289.
36. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS)-explanation and elaboration: A report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. Value Heal [Internet]. 2013;16(2):231–50. Available from: http://dx.doi.org/10.1016/j.jval.2013.02.002
37. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. Int J Nurs Stud [Internet]. 2012/11/20. 2013;50(5):587–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23159157
38. Celaya M, Ibáñez D, Laseca N, López À, Romero C, Valls E, et al. Guia per a l'avaluació de la fibromiàlgia i de la síndrome de fatiga crònica. 2017;37. Available from: http://canalsalut.gencat.cat/web/.content/home_canal_salut/ciutadania/la_salut_de_la_a_a_la_z/f/fibromialgia/documents/guia_avaluacio_fibromialgia_fatiga_cronica.pdf
39. Gándara M, Muñoz G. Evaluación y abordaje de la fibromialgia y el síndrome de fatiga crónica. Día Mund la Fibromialgia y el Síndrome Fatiga. 2017;115.
40. Alonso J. Versión española de SF-36v2™ Health Survey © 1996, 2000 adaptada por J. Alonso y cols 2003. Heal Surv [Internet]. 2003;1–8. Available from: http://www.ser.es/wp-content/uploads/2015/03/SF36_CUESTIONARIOpdf.pdf
41. Catalunya G de. Diari Oficial de la Generalitat de Catalunya [Internet]. Available from: https://dogc.gencat.cat/es
42. Gobierno de España. Real Decreto 8/2015 por el que se aprueba el texto refundido de la Ley General de la Seguridad Social. Boletín Of del Estado [Internet]. 2015;1–157. Available from: http://www.boe.es/boe/dias/1994/06/29/pdfs/A20658-20708.pdf
43. INE. Coste laboral por trabajador, comunidad autónoma, sectores de actividad [Internet].

Available from: https://www.ine.es/jaxiT3/Tabla.htm?t=6061
44. Andronis L, Barton P, Bryan S. Sensitivity analysis in economic evaluation: An audit of NICE current practice and a review of its use and value in decision-making. Health Technol Assess (Rockv). 2009;13(29).
45. Wang S-M, Han C, Lee S-J, Patkar AA, Masand PS, Pae C-U. Fibromyalgia diagnosis: a review of the past, present and future. Expert Rev Neurother. 2015 Jun;15(6):667–79.
46. Briones-Vozmediano E. The social construction of fibromyalgia as a health problem from the perspective of policies, professionals, and patients. Glob Health Action [Internet]. 2017;10(1). Available from: http://dx.doi.org/10.1080/16549716.2017.1275191
47. Lichtenstein A, Tiosano S, Amital H. The complexities of fibromyalgia and its comorbidities. Curr Opin Rheumatol. 2018 Jan;30(1):94–100.
48. Giusti EM, Castelnuovo G, Molinari E. Differences in Multidisciplinary and Interdisciplinary Treatment Programs for Fibromyalgia: A Mapping Review. Pain Res Manag [Internet]. 2017/06/18. 2017;2017:7261468. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28620267
49. Bourgault P, Lacasse A, Marchand S, Courtemanche-Harel R, Charest J, Gaumond I, et al. Multicomponent interdisciplinary group intervention for self-management of fibromyalgia: a mixed-methods randomized controlled trial. PLoS One [Internet]. 2015/05/16. 2015;10(5):e0126324. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25978402
50. Ollevier A, Vanneuville I, Carron P, Baetens T, Goderis T, Gabriel L, et al. A 12-week multicomponent therapy in fibromyalgia improves health but not in concomitant moderate depression, an exploratory pilot study. Disabil Rehabil [Internet]. 2019/01/31. 2019;0(0):1–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30696285
51. Martin J, Torre F, Padierna A, Aguirre U, Gonzalez N, Garcia S, et al. Six-and 12-month follow-up of an interdisciplinary fibromyalgia treatment programme: results of a randomised trial. Clin Exp Rheumatol [Internet]. 2013/02/27. 2012;30(6 Suppl 74):103–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23261008
52. Saral I, Sindel D, Esmaeilzadeh S, Sertel-Berk HO, Oral A. The effects of long- and short-term interdisciplinary treatment approaches in women with fibromyalgia: a randomized controlled trial. Rheumatol Int [Internet]. 2016/04/09. 2016;36(10):1379–89. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27055444
53. Stein KF, Miclescu A. Effectiveness of multidisciplinary rehabilitation treatment for patients with chronic pain in a primary health care unit. Scand J Pain. 2013;4(4):190–7.
54. Eisman AB, Kilbourne AM, Dopp AR, Saldana L, Eisenberg D. Economic evaluation in implementation science: Making the business case for implementation strategies. Psychiatry Res [Internet]. 2020;283(June 2019):112433. Available from: https://doi.org/10.1016/j.psychres.2019.06.008
55. Anneliese P, Hoch J. Understanding Cost-utility Analysis in Health Care. Univ Toronto Med J. 2006 Jan 1;
56. McGregor M. Cost-utility analysis: Use QALYs only with great caution. Cmaj. 2003;168(4):433–4.
57. Tarter T, Johnson G, Johnson R. Neuropsychology of Cancer and Oncology. Chad A Noggle; Raymond S Dean, editor. New York: Springer Publishing Company; 2013. 3 p.

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Cost-utility analysis of a multicomponent intervention for Fibromyalgia syndrome in primary care versus usual clinical practice: study protocol for an economic evaluation of a randomized control trial

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Cost-utility analysis of a multicomponent intervention for Fibromyalgia syndrome in primary care versus usual clinical practice: study protocol for an economic evaluation of a randomized control trial

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Abstract (293/300)

Introduction Fibromyalgia syndrome (FMS) carries a high cost to society. The significant economic burden in the use of healthcare and, especially, social resources suggests the revision of the usual clinical care (UCC) and the improvement of the treatment strategies. FMS is potentially disabling due to its impact on the quality of life (QOL) and productivity loss, which considerably increases the indirect costs to society. This study aims to perform an economic evaluation to compare the cost and health-benefits between a multicomponent intervention (MI) program and the UCC, for FMS patients who attend to primary care centres (PCC) of the *Gerència Territorial Terres de L'Ebre* in Catalonia, Spain. This study is expected to support the effectiveness results of a randomized control trial study on the implementation of this program. This study protocol is linked to the pre-results of a Clinical Trial (ClinicalTrials.gov: NCT04049006).

Method and analysis A cost-utility analysis will be conducted from a societal perspective. Quality-adjusted life years will be obtained from the results of the SF-36 questionnaire, a QOL measurement instrument. Direct and indirect healthcare costs will be obtained from official prices and reports published by the public health administration and the Statistics National Institute. The incremental cost-utility ratio will be estimated to compare both healthcare practices. Deterministic sensitivity analysis will also be implemented to compare different cost scenarios modifying the items with higher weight in the cost composition.

Ethics and dissemination The Clinical Research Ethics Committee from the IDIAPJGol Institute, has approved this study on 25/04/2018 (code P18/068) according to the Helsinki/Tokyo Declaration. Furthermore, oral and written information will be delivered to participants, and informed consent will be required guaranteeing anonymity. Dissemination strategy includes publications in scientific journals and presentations through the local and national media and conferences in academic events.

Strengths and limitations of this study

- This study will provide relevant and accurate information about the economic impact and health benefits of a new treatment strategy for FMS.
- The results of the analysis will be helpful for decision-makers in order to supply the best healthcare option and to consider stakeholders' opinions.
- The design of this study is based on a randomized control trial, and it includes a broad perspective from society, and with a time horizon of 1-year, which will allow assessing long-term changes.
- The cost-utility analysis is a popular participatory measurement tool but also controversial among experts since it has methodological limitations as well as the QOL variable.
- The data source for indirect costs will only allow including data from patients who are linked to the social security system, excluding independent and informal workers, unemployed people, and homemakers.

INTRODUCTION

Fibromyalgia is a chronic syndrome, medically unexplained, which is characterized by persistent and widespread musculoskeletal pain but also associated with psychological and social factors.[1–4] Disability is one of the main consequences due to its impact on daily functioning, quality of life (QOL), and productivity loss.[5] Furthermore, the prevalence of fibromyalgia syndrome (FMS) is significant in adults. An updated review has shown that its prevalence in the general population ranges between 0.2 and 6.6%, 2.45% particularly in Spain, and it is more frequent in women.[6,7] Therefore, healthcare for patients with this diagnosis is not only intricate from a clinical point of view but also costly from an economic perspective for both the health and social security systems.[5,8–13]

Available evidence has shown that FMS implies a considerable cost to society associated, especially, with comorbidity and incapacity.[8,14–18] Among European countries, the total annual costs estimated for FMS were €7,900 (direct €910, indirect €6,990) for France, €7,256 (direct €1,765, indirect €5,491) for Germany, and €7,814 (direct €5,241, indirect €2,573) for the Netherlands.[17,18] Additionally, FMS has the highest direct healthcare cost among other musculoskeletal conditions and illnesses chronic-pain related,[14] and higher rates of unemployment and sick leave days.[19]

In the Spanish context, the global economic burden of FMS is robust and has been estimated at more than €12,993 million annually.[20] According to updated data published by the National Institute of Social Security of Spain (NISS), the number of assigned temporary disabilities (short-term absenteeism because of sick leave days) due to FMS has increased in recent years, as well as the average number of days absent.[21] A cross-sectional and multicentre study, conducted from a retrospective review of medical outpatient records in Catalonia between 2006 and 2007, showed that patients with FMS had a considerably higher annual total costs in healthcare (included drugs, complementary tests, all types of medical visits, referrals, and hospitalizations) and non-healthcare resource utilization (sick leave days, and early retirement), under routine medical practice in the primary care setting, compared with a reference population. This study obtained an incremental adjusted per-patient per-year total cost of €5,010 for FMS patients, being €614 (12.3%) for direct costs and €4,394 (87.7%) for indirect costs.[10]

In line with this findings, another cross-sectional study conducted in Spain based on a face-to-face patient interview encountered a mean total cost per patient per year of €9,982, of which €3,245.8 (32.5%) corresponded to direct healthcare costs and €6,736.2

(67.5%) to indirect costs attributable to productivity losses.[11] Moreover, this study evidenced that: (i) non-pharmacological therapies accounted the highest cost of direct healthcare resources, and involved three times more than the cost of drug treatment; (ii) there was a significant association between disease severity and higher total costs; and (iii) patients with permanent working disability implies the highest use of resources.[11] However, all these findings were achieved over a decade ago, and an update of the data is necessary for the Spanish public health system.

Health economic evaluation is essential in policy decision-making since it provides evidence to identify the efficiency of an intervention, program, or project in order to optimize the benefits from limited resources.[22] Among the economic evaluation techniques, cost-utility analysis (CUA) estimates how much wellbeing is achieved for each monetary unit invested, involving both health outcomes and costs. This technique is a useful tool for comparing intervention strategies, especially for those with quite different health outcomes because of the standard utility units commonly used to measure all of them: the quality-adjusted life-year (QALY).[23] Despite its limitations, especially in measuring the value that society attaches to healthcare states, CUA is superior to other economic evaluation strategies and provides relevant information for resource allocation processes.[24]

The economic evaluation of intervention programs for FMS has been scarcely studied. According to the published findings, non-pharmacological strategies, especially psychology-based therapies, have evidenced positive results in decreasing the economic burden of FMS.[19,25–31] In Spain, some cost-utility studies that compare alternative interventions (psychoeducational therapy, acceptance and commitment therapy, internet-delivered exposure therapy, and Mindfulness-Based Stress Reduction) with usual drug treatment have demonstrated the cost-utility from a healthcare and social perspective. [19,26–28,30] Nevertheless, only the FibroQoL study included a multicomponent intervention (MI) modality but with technical and methodological differences compare to the actual proposal.[32,26]

This study aims to perform a CUA on a MI (that consists of health education, physical activity, and cognitive-behavioural therapy) for patients with FMS compared to the usual clinical care (UCC),[33] provided within the 11 primary healthcare centres of the *Gerència Territorial Terres de L'Ebre* of the Catalan Institute of Health, Spain. The results of this economic assessment are expected to support the evidence of the randomized clinical trial (RCT) related to this project.[34] (ClinicalTrials.gov:

NCT04049006).[35] This new intervention proposal will hopefully reinforce the UCC, enhance patients' QOL, and promote efficiency in health and social resources allocation.

METHOD

Design

This study protocol has been drafted based on the literature review and following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[36] Medical Research Council guidance[37] for complex interventions has been taken into account for the RCT study.

For the design of this economic evaluation study, a CUA will be conducted from a societal perspective so that indirect non-medical cost variables will be included. Also, a temporal horizon of 12-month will be used to assess health outcomes and costs in the long-term. This methodological decision is based on the clinical symptoms of FMS, its consequences, its tendency to chronicity, and the fact that its treatment is associated with on-going clinical management.

The human capital approach has been judged as the most suitable method for this study due to limitations in the data source since only full sick days, prescribed by the General Practitioner (GP), and the period with a medical disability can be extracted from the computerized medical history program (eCAP).

The elements to be compared in this study are the UCC[21,33,38,39] for patients with FMS, and the UCC plus a MI provided in primary care centres. The MI consists of a 12-week group program of 2-hour weekly combining: 7 health education instructions, 11 pieces of training on physical activity and physical health, and 7 interventions of psychological therapy based on cognitive-behavioural strategies and pain management. Group therapy is being delivered by the general practitioner specialized in FMS, the physiotherapist, and the psychologist with the support of the head nurses of each health centre involved.

Study population

The patients recruited for the study sample are shortlisted from the electronic medical records system eCAP (computerized medical history program) belonging to the Catalan Health Service (CatSalut) and the Catalan Health Institute (CHI). Only the medical

records of the 11 primary care centres of the *Gerència Territorial Terres de L'Ebre* in Catalonia (Spain) are included. Allocation to study groups is randomized according to a randomized list by health centre. The randomized strategy has been designed in order to obtain a representative sample giving patient's sociodemographic diversity throughout the territory. The inclusion criteria are detailed in the RCT protocol study.[34]

Patient and Public Involvement

Patients or the public will not be involved in the design or conducting, or reporting, or dissemination plans of our research.

Outcomes measures and data collection

Health outcomes

The utilities will be obtained based on the results of the health-related QOL SF-36 questionnaire[40] (Optum, Inc. license number QM048943) and the estimation of quality-adjusted life years (QALYs). This measurement instrument is administrated to the study sample at baseline, immediately after the intervention, and at 6 and 12 months of follow-up. Sociodemographic and clinical variables are registered at baseline and are fully detailed in the RCT study protocol.[35] The collected data is introduced in a software application that has been specially designed for study and is available on the *Terres de l'Ebre* CHI website, linked to the electronic medical records.

Cost outcomes

Direct and indirect costs, related with the use of health and social resources, will be estimated in euros (€) according to the official prices for the public sector which are published in the *Diari Oficial de la Generalitat de Catalunya* (DOGC)[41] (updated to 2019), and in the Spanish Statistics National Institute (SNI), respectively. Table 1 shows the description of cost variables and data sources which will be taken retrospectively 12-month before the start date of the MI and 12-month after the end of the MI.

Table 1. Cost outcomes measurements and data collection

Cost outcomes measurements and data collection				
Cost outcomes	**Cost outcomes description**	**Data source**	**Cost data source**	**Cost calculation**
Direct healthcare costs				
Primary care visits	-General Practitioner -Nurse -Physiotherapist -Psychologists	eCAP*	DOGC**	Number of visits × price
Professional referral visits	-Traumatology -Psychiatry -Rehabilitation -Other specialities	eCAP	DOGC	Number of visits × price
Clinical tests	-Blood test -Diagnostic imaging techniques -Other tests	eCAP	DOGC	Test performed x price
Pharmacological prescriptions	-Muscle relaxants -Analgesics -Corticoids -Antidepressants -Anxiolytics -Anti-seizure -Gastric protectors -Other drugs	eCAP	Council of Pharmaceutical Colleges of Catalonia	Medicines bought × price
Emergency visits		eCAP	DOGC	Number of visits × price
Hospitalizations		eCAP	DOGC	Number of hospitalization days x price
Indirect non-medical costs				
Temporary disability (TD)		eCAP/SNI***		Number of full sick leave days × salary
Permanent disability (PD)		eCAP/SNI		Number of months with PD x salary

*eCAP: computerized medical history program

**DOGC: *Diario Oficial de la Generalitat de Catalunya*

***SNI: Statistics National Institute

Direct costs include visits to primary care services, other professional referrals, and emergency services, clinical tests for diagnosis and medical follow-up, pharmacological treatments, and hospitalizations. Cost calculation will be based on unit service prices which will be obtained from the DOGC. Additionally, drugs prices will be extracted from the Council of Pharmaceutical Colleges of Catalonia.

Indirect non-medical costs include temporary and permanent disability. As it has been stated in the Spanish General Law of Social Security (Law 20/2014; Royal Legislative Decree 8/2015)[42], the term "temporary disability" refers to the sick leave days due to common or professional illness in the short-term. On the other hand, "permanent disability" refers to the impossibility to work due to the permanent and total

or partial loss of working capacity in the long-term. In the first case, a GP determines if a patient is unable to work in the short-term. In the second case, a medical board assesses in depth the medical background and physical and mental condition of the person in order to determine if a permanent disability should be provided. These measurements will be estimated based on full sick leave days and months spent with a disability, respectively.

We will not include other non-medical costs in the data collection, such as presenteeism and unpaid lost time, due to the limitations in the data available through our data source eCap.

The price weight of the social costs will be determined by the calculation of a total annual average salary (including regular and extra payments), for the Catalonia region, which is registered on the official records of the Statistics National Institute.[43] This estimation will be accounted for both part and full-time working schedules, and all activity sectors (industry, construction, and services except housework).

Data collection is expected to be completed by April 2021.

Sample size

A total number of 260 participants have been calculated as the sample-size (130 subjects per study arm) based on variations in the SF-36 questionnaire and in order to detect a score difference equal or higher than 5 points, assuming an alpha error of 0.05, a beta error of 0.05 in a bilateral contrast, and a dropout rate of 20%.[34] Consequently, between 10 and 13 MI groups with their respective control groups (UCC) are required, including 10-12 patients per group.

Statistical analysis

The SPSS version 25 and the Stata version 15 for Windows will be used for the statistical analysis. First, a descriptive analysis of the sample will be carried out comparing its characteristics between the study arms.

As an economic evaluation outcome measure, the incremental ratio of the cost-utility will be estimated, dividing the difference in total mean costs in both UCC and MI by the differences in QALYs of each study arm. Moreover, 95% confidence intervals will be calculated for all analyses.

Regarding possible biases, the intention-to-treat principle will be applied in order not to affect the random distribution. In addition, to address the loss of follow-up and non-response, multiple imputation approaches to substitute missing values will be implemented.

Sensitivity analysis

A deterministic sensitivity analysis will be performed to assess the robustness of the results.[44] Items with a higher cost will be modified in order to compare them with the first results.

DISCUSSION

This study intends to address FMS as a public health problem with economic repercussions.[10] Indeed, it compromises the health of a significant number of people, who are large consumers of health and social resources in the short and long-term. Therefore, this study is expected to collaborate with the inclusion of a MI for FMS in primary care settings in order to improve patients' QOL and reduce its economic burden.

According to the literature review, the indirect costs attributable to sick leaves and permanent work disability exceed the direct costs of healthcare.[8 10,11 14–18 19,20] As a result, efforts should be aimed at preventing productivity loss that represents the highest cost for the community and a significant impact on patients' health. From a societal perspective and taking this priority into account, this study incorporates indirect non-medical cost variables that will allow assessing the impact of FMS burden on the social security system.

More accurate methods, such as the friction cost approach, have been acknowledged by the literature for the estimation of the productivity costs. However, the human capital approach has been considered the most suitable for this study considering the data available. Nevertheless, a sensitivity analysis will be performed to assess alternative cost scenarios considering the limitations of this methodological approach. It will include different direct healthcare costs and, if necessary, the price weight of the social cost considering that the salary rate will be an overall annual average estimation without distinction neither of the type of activity nor the working schedule.

Another economic concern is the costs of the diagnosis process since it is purely clinical, and it comes from discard.[45] Before FMS diagnosis, other probable diseases must be ruled out through objective tests and different medical specialists. This path is often long and exhausting for patients, frustrating for doctors but also expensive from the perspective of the health system.[46] Furthermore, the presence of comorbidities can hinder and delay the diagnosis, as well as complicate the treatment strategy.[47] Considering this, the sample could show differences in the use of resources depending on the diagnostic year. However, it is assumed that the randomization will provide a balance between the study arms of patients with a more recent diagnosis and or greater comorbidities weight.

Given the evidence on the economic burden of FMS,[8,14–21] particularly related to the loss of productivity, UCC does not seem to be completely helpful to reduce the effects of chronicity or prevent disability. Thus, FMS treatment should not be limited to short-term pain relief. It should also promote the acceptance of the condition, the self-management of symptoms, and the empowerment of patients to deal with FMS in their daily lives. The effective implementation of non-pharmacological approaches by patients at long-term and lifestyle changes should be accomplished to avoid overprovision, overmedication, and the consequences of chronicity. The evaluated MI in this study aims to face with these goals by combining physical, psychological, and health education methods.

Findings on the efficacy of MI for patients with this condition have proved to help improve QOL, physical function, psychological variables, and or pain after 3 to 12 months of follow-up.[48–53] However, more studies are required on the economic efficiency of this type of interventions and, particularly, in the context of the public health system in Spain.

Evidence on efficiency is essential for decision-making to prioritize the budgets in those treatment options that prove to be cost-efficient and cover patients' health needs. Economic evaluation is key to overcoming the barrier of uncertainty about the real costs of carrying out an intervention and its sustainability.[54] The CUA selected for this study is a popular measurement tool that combines data on quantity and quality of life, valued by users of a health service, and associated with a monetary cost. Therefore, it involves a participatory and economic evidence-based decision-making strategy that considers stakeholders' preferences.[55] Nevertheless, this methodology is also controversial.[56] The main highlights are: (i) the lack of transparency in the data

collection and analysis to measure the value that society assigns to a state of health; (ii) the gain in health depends on the severity of the condition and, therefore, this value is affected by patients' pain perception and health status; (iii) for long-term diseases such as FMS, where disability accumulates over time, this measurement tool is limited since it assumes that the utility of a health state is independent of the time spent with it, and the previous and subsequent health conditions.[24] Although these points pose challenges to overcome from a methodological point of view, CUA is still a valid and effective strategy to carry out health economic evaluations and collaborate with decision-makers in selecting between different intervention alternatives.[24]

Other limitations related to the instruments and data collection is that the QOL is a multifactor variable that could be influenced by many circumstances not directly attached to the medical issue like family dynamic, working conditions, economic and political context, among others.[57] Nonetheless, sociodemographic variables will be included in the analysis models trying to correct these possible effects.

Although this health region comprises a wide and varied territory, all health centres involved in the study depend on the public health services of the region so that both clinical care protocols and direct medical costs are standardized according to official publications and will be homogeneous for the entire sample.

Regarding the indirect costs, only those people who are linked to the social security system and can access its benefits will be able to provide data about productivity costs. Therefore, it excludes independent and informal workers, unemployed people, and homemakers of whom we will not have any background of their productivity loss. In this sense, although the human capital approach could overestimate productivity costs, it could be compensated if we consider that there is no data recorded of these population subgroups that also represent a productivity loss for society due to the side effects of their illness processes.

Finally, and even though a 1-year time horizon is a strength of the study since it will allow assessing long-term changes, it may also face a possible sample loss during the follow-up. In order to minimize sample loss, reminders for the interviews will be implemented, and even different strategies will be employed for data collection, such as telephone calls and online survey platforms.

If the results show to be utility-cost, this study will support, through efficiency evidence, the incorporation of a MI to the usual practice for FMS in primary care centres of Catalonia, Spain. What is more, health improvements and cost reductions on

sanitary and social resources are expected. To conclude, it is intended that this new intervention proposal be replicated in other health areas of Catalonia and Spain, and considered as a guide for other European health systems.

ETHICS AND DISSEMINATION

This study was designed according to the Helsinki/Tokyo Declaration, and it was approved by the Clinical Research Ethics Committee of the *Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina* (IDIAPJGol), on 25/04/2018 (code P18/068). Furthermore, oral and written information is delivered to participants, and informed consent is required. This project respects the data protection law guaranteeing anonymity. Dissemination strategy includes publications in scientific journals and through the local and national media and conferences in academic events.

AUTHOR CONTRIBUTIONS

VMA, **MC**, **CAM**, **AB**, **JFS**, and **AQG** participated in the design of the study. **VMA** wrote the draft versions with the review of all authors. **RCA**, **NCQ**, **GGS**, **MCS**, **IFA**, **AQG**, **AB**, **CAM**, **JFS**, **and VMA** are involved in the development of the general project and the RCT study from which this qualitative study is related.

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REFERENCES

1. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990;33(2):160–72.
2. Wolfe F, Clauw DJ, Fitzcharles MA, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. *J Rheumatol* 2011;38(6):1113–22.
3. Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum* 2016;46(3):319–29.
4. Helfenstein M, Goldenfum MA, Siena CAF. Fibromyalgia: Clinical and occupational aspects. *Rev Assoc Med Bras* 2012;58(3):358–65.
5. Skaer TL. Fibromyalgia: disease synopsis, medication cost effectiveness and economic burden. *Pharmacoeconomics* 2014;32(5):457–66.
6. Marques AP, Santo A, Berssaneti AA, et al. Prevalence of fibromyalgia: literature review update. *Rev Bras Reumatol* 2017;57(4):356–63.
7. Seoane-Mato D, Sanchez-Piedra C, Silva-Fernandez L, et al. Prevalence of rheumatic diseases in adult population in Spain (EPISER 2016 study): Aims and methodology. *Reumatol Clin* 2019;15(2):90–6.
8. Robinson RL, Birnbaum HG, Morley MA, et al. Economic cost and epidemiological characteristics of patients with fibromyalgia claims. *J Rheumatol* 2003;30(6):1318–25.
9. Spaeth M. Epidemiology, costs, and the economic burden of fibromyalgia. *Arthritis Res Ther* 2009;11(3):2–3.
10. Sicras-Mainar A, Rejas J, Navarro R, et al. Treating patients with fibromyalgia in primary care settings under routine medical practice: a claim database cost and burden of illness study. *Arthritis Res Ther* 2009;11(2):1–14.
11. Rivera J, Rejas J, Esteve-Vives J, et al. Resource utilisation and health care costs in patients diagnosed with fibromyalgia in Spain. *Clin Exp Rheumatol* 2009;27(5 Suppl 56):S39-45.
12. Thompson JM, Luedtke CA, Oh TH, Shah ND, Long KH, King S, et al. Direct medical costs in patients with fibromyalgia: Cost of illness and impact of a brief multidisciplinary treatment program. *Am J Phys Med Rehabil* 2011;90(1):40–6.
13. Vervoort VM, Vriezekolk JE, Olde Hartman TC, et al. Cost of illness and illness perceptions in patients with fibromyalgia. *Clin Exp Rheumatol* 2016;34(2 Suppl 96):S74-82.
14. White KP, Speechley M, Harth M, et al. The London Fibromyalgia Epidemiology Study: direct health care costs of fibromyalgia syndrome in London, Canada. *J Rheumatol* 1999;26(4):885–9.
15. Berger A, Dukes E, Martin S, et al. Characteristics and healthcare costs of patients with fibromyalgia syndrome. *Int J Clin Pract* 2007;61(9):1498–508.
16. Berger A, Sadosky A, Dukes EM, et al. Patterns of healthcare utilization and cost in patients with newly diagnosed fibromyalgia. *Am J Manag Care* 2010;16(5 Suppl):S126-

37.
17. Boonen A, Van Den Heuvel R, Van Tubergen A, et al. Large differences in cost of illness and wellbeing between patients with fibromyalgia, chronic low back pain, or ankylosing spondylitis. *Ann Rheum Dis* 2005;64(3):396–402.
18. Winkelmann A, Perrot S, Schaefer C, et al. Impact of fibromyalgia severity on health economic costs. *Appl Health Econ Health Policy* 2011;9(2):125–36.
19. Feliu-Soler A, Borràs X, Peñarrubia-María MT, et al. Cost-utility and biological underpinnings of Mindfulness-Based Stress Reduction (MBSR) versus a psychoeducational programme (FibroQoL) for fibromyalgia: A 12-month randomised controlled trial (EUDAIMON study). *BMC Complement Altern Med* 2016;16(1):1–16.
20. Cabo-Meseguer A, Cerda-Olmedo G, Trillo-Mata JL. Fibromyalgia: Prevalence, epidemiologic profiles and economic costs. *Med Clin (Barc)* 2017;149(10):441–8.
21. Instituto Nacional de la Seguridad social. Guia de actualización en la valoración de fibromialgia, sÍndrome de fatiga crónica, sensibilidad química múltiple y electrosensibilidad. Segunda E dición 2019. https://www.semg.es/images/documentos/guia_fibromialgia_2019.pdf (Accessed 25 May 2020)
22. Chisholm D, Evans DB. Economic evaluation in health: Saving money or improving care? *J Med Econ* 2007;10(3):325–37.
23. Franklin M. Cost utility analysis. Ment Heal Econ Costs Benefits. *Psychiatr Care* 2017;307:89–119.
24. Mccabe C. What is cost-utility analysis? *Hayward Medical Communications* 2009;(February):1–6. http://www.bandolier.org.uk/painres/download/whatis/What_is_cost-util.pdf (Accessed 25 May 2020)
25. Goossens ME, Rutten-van Molken MP, Leidl RM, et al. Cognitive-educational treatment of fibromyalgia: a randomized clinical trial. II. Economic evaluation. *J Rheumatol* 1996;23(7):1246–54.
26. Luciano J V, Sabes-Figuera R, Cardenosa E, et al. Cost-utility of a psychoeducational intervention in fibromyalgia patients compared with usual care: an economic evaluation alongside a 12-month randomized controlled trial. *Clin J Pain* 2013;29(8):702–11.
27. Luciano J V, D'Amico F, Cerdà-Lafont M, et al. Cost-utility of cognitive behavioral therapy versus U.S. Food and Drug Administration recommended drugs and usual care in the treatment of patients with fibromyalgia: An economic evaluation alongside a 6-month randomized controlled trial. *Arthritis Res Ther* 2014;16(1):1–17.
28. Luciano J V, D'Amico F, Feliu-Soler A, et al. Cost-Utility of Group Acceptance and Commitment Therapy for Fibromyalgia Versus Recommended Drugs: An Economic Analysis Alongside a 6-Month Randomized Controlled Trial Conducted in Spain (EFFIGACT Study). *J Pain* 2017;18(7):868–80.
29. Hedman-Lagerlof M, Hedman-Lagerlof E, Ljotsson B, et al. Cost-Effectiveness and Cost-Utility of Internet-Delivered Exposure Therapy for Fibromyalgia: Results From a Randomized, Controlled Trial. *J Pain* 2019;20(1):47–59.
30. Pérez-Aranda A, D'Amico F, Feliu-Soler A, et al. Cost–Utility of Mindfulness-Based Stress Reduction for Fibromyalgia versus a Multicomponent Intervention and Usual Care: A 12-Month Randomized Controlled Trial (EUDAIMON Study). *J Clin Med* 2019;8(7):1068.
31. Amico FD, Feliu-soler A. Cost-Utility of Attachment-Based Compassion Therapy (ABCT) for Fibromyalgia Compared to Relaxation : A Pilot Randomized Controlled Trial. *J Clin Med* 2020; 9(3):726.
32. Luciano J V, Martinez N, Penarrubia-Maria MT, et al. Effectiveness of a psychoeducational treatment program implemented in general practice for fibromyalgia patients: a randomized controlled trial. *Clin J Pain* 2011;27(5):383–91.
33. Celaya M, Ibáñez D, Laseca N, et al. Guia per a l´avaluació de la fibromiàlgia i de la síndrome de fatiga crònica. *Generalitat de Catalunya* 2017. https://canalsalut.gencat.cat/web/.content/_A-

Z/F/fibromialgia/documents/guia_avaluacio_fibromialgia_fatiga_cronica.pdf (Accessed 20 Feb 2020)
34. Caballol Angelats R, Gonçalves AQ, Aguilar Martín C, et al. Effectiveness, cost-utility, and benefits of a multicomponent therapy to improve the quality of life of patients with fibromyalgia in primary care: A mixed methods study protocol. *Med (United States)* 2019;98(41).
35. Caballol Angelats R, Gonçalves AQ, Aguilar Martín C, et al. Effectiveness, cost-utility, and benefits of a multicomponent therapy to improve the quality of life of patients with fibromyalgia in primary care. *Medicine (Baltimore)* 2019;98(41):e17289.
36. Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)-explanation and elaboration: A report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. *Value Heal* 2013;16(2):231–50.
37. Craig P, Dieppe P, Macintyre S, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. *Int J Nurs Stud* 2013;50(5):587–92.
38. Nishishinya Aquino B, Requeijo Lorenzo C, Roqué Fíguls M, et al. Evaluación y abordaje de la fibromialgia. Actualización de las evidencias científicas. Barcelona. Ministerio de Sanidad, Servicios Sociales e Igualdad. Agència de Qualitat i Avaluació Sanitàries de Catalunya. Departament de Salut. *Generalitat de Catalunya* 2017 (Informes de Evaluación de Tecnologías Sanitarias). https://aquas.gencat.cat/web/.content/minisite/aquas/publicacions/2017/Fibromialgia_actualizacion_RedETS2017.pdf (Accessed 27 Feb 2020)
39. Gándara M, Muñoz G. Evaluación y abordaje de la fibromialgia y el síndrome de fatiga crónica. Día Mund la Fibromialgia y el Síndrome Fatiga. Oficial Nacional de Salud Pública-AEMPPI Ecuador 2017. https://www.elsevier.com/es-es/connect/actualidad-sanitaria/dia-mundial-de-la-fibromialgia-y-el-sindrome-de-fatiga-cronica?aaref=https%3A%2F%2Fwww.google.com%2F (Accessed 27 Feb 2020)
40. Alonso J, et al. Versión española de SF-36v2™ Health Survey © 1996, 2000 adaptada por J. Alonso et al. *Heal Surv* 2003;1–8. http://www.ser.es/wp-content/uploads/2015/03/SF36_CUESTIONARIOpdf.pdf (Accessed 1 Mar 2020)
41. Generalitat de Catalunya. Diari Oficial de la Generalitat de Catalunya. https://dogc.gencat.cat/es
42. Gobierno de España. Real Decreto 8/2015 por el que se aprueba el texto refundido de la Ley General de la Seguridad Social. *Boletín Of del Estado* 2015;1–157. http://www.boe.es/boe/dias/1994/06/29/pdfs/A20658-20708.pdf (Accessed 1 Mar 2020)
43. Instituto Nacional de Estadística (INE). Coste laboral por trabajador, comunidad autónoma, sectores de actividad. https://www.ine.es/jaxiT3/Tabla.htm?t=6061 (Accessed 20 Mar 2020)
44. Andronis L, Barton P, Bryan S. Sensitivity analysis in economic evaluation: An audit of NICE current practice and a review of its use and value in decision-making. *Health Technol Assess (Rockv)* 2009;13(29).
45. Wang S-M, Han C, Lee S-J, et al. Fibromyalgia diagnosis: a review of the past, present and future. *Expert Rev Neurother* 2015;15(6):667–79.
46. Briones-Vozmediano E. The social construction of fibromyalgia as a health problem from the perspective of policies, professionals, and patients. *Glob Health Action* 2017;10(1).
47. Lichtenstein A, Tiosano S, Amital H. The complexities of fibromyalgia and its comorbidities. *Curr Opin Rheumatol* 2018;30(1):94–100.
48. Giusti EM, Castelnuovo G, Molinari E. Differences in Multidisciplinary and Interdisciplinary Treatment Programs for Fibromyalgia: A Mapping Review. *Pain Res Manag* 2017;2017:7261468.
49. Bourgault P, Lacasse A, Marchand S, et al. Multicomponent interdisciplinary group intervention for self-management of fibromyalgia: a mixed-methods randomized controlled trial. *PLoS One* 2015;10(5):e0126324.
50. Ollevier A, Vanneuville I, Carron P, et al. A 12-week multicomponent therapy in

fibromyalgia improves health but not in concomitant moderate depression, an exploratory pilot study. *Disabil Rehabil* 2019;0(0):1–8.
51. Martin J, Torre F, Padierna A, et al. Six-and 12-month follow-up of an interdisciplinary fibromyalgia treatment programme: results of a randomised trial. *Clin Exp Rheumatol* 2012;30(6 Suppl 74):103–11.
52. Saral I, Sindel D, Esmaeilzadeh S, et al. The effects of long- and short-term interdisciplinary treatment approaches in women with fibromyalgia: a randomized controlled trial. *Rheumatol Int* 2016;36(10):1379–89.
53. Stein KF, Miclescu A. Effectiveness of multidisciplinary rehabilitation treatment for patients with chronic pain in a primary health care unit. *Scand J Pain* 2013;4(4):190–7.
54. Eisman AB, Kilbourne AM, Dopp AR, et al. Economic evaluation in implementation science: Making the business case for implementation strategies. *Psychiatry Res* 2020;283(June 2019):112433.
55. Anneliese P, Hoch J. Understanding Cost-utility Analysis in Health Care. *Univ Toronto Med J* 2006;83(2) http://utmj.org/index.php/UTMJ/article/view/734 (Accessed 25 May 2020)
56. McGregor M. Cost-utility analysis: Use QALYs only with great caution. *Cmaj* 2003;168(4):433–4.
57. Tarter T, Johnson G, Johnson R. Neuropsychology of Cancer and Oncology. Chad A Noggle; Raymond S Dean, editor. New York: Springer Publishing Company 2013:3-5

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Cost-utility analysis of a multicomponent intervention for fibromyalgia syndrome in primary care versus usual clinical practice: Study protocol for an economic evaluation of a randomized control trial

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Cost-utility analysis of a multicomponent intervention for fibromyalgia syndrome in primary care versus usual clinical practice: Study protocol for an economic evaluation of a randomized control trial

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Abstract (282/300)

Introduction Fibromyalgia syndrome (FMS) imposes a high cost on society. The significant economic burden from the use of healthcare and, especially, social resources is a spur to revising the usual clinical care (UCC) and to improving treatment strategies. FMS has a deleterious effect on the quality of life (QOL) and productivity, which considerably increase the indirect costs to society. This study reports an economic evaluation comparing the cost and health benefits in a multicomponent intervention (MI) program and UCC of FMS patients who attend primary health care centres of the Gerència Territorial Terres de L'Ebre region of Catalonia, Spain. This study is expected to obtain evidence supporting the results of a randomized control trial study linked to the implementation of this program. (ClinicalTrials.gov: NCT04049006).

Method and analysis A cost-utility analysis (CUA) will be conducted from a societal perspective. Quality-adjusted life years will be calculated from the results of the SF-36 questionnaire, a QOL measurement instrument. Direct and indirect healthcare costs will be obtained from official prices and reports published by the Spanish Public Health Administration and the National Statistics Institute. The incremental cost-utility ratio will be estimated to compare the two healthcare practices. Deterministic sensitivity analysis will also be used to compare different cost scenarios, modifying the items with the highest weight in the cost composition.

Ethics and dissemination The Clinical Research Ethics Committee of the IDIAPJGol Institute approved this study on 25/04/2018 (code P18/068) in accordance with the Helsinki/Tokyo Declaration. Information will be provided orally and in writing to participants, and their informed consent will be required. Participant anonymity will be guaranteed. The dissemination strategy includes publications in scientific journals and presentations in local and national media and at academic conferences.

Strengths and limitations of this study

- This study will produce important and accurate information about the economic impact and health benefits of a new treatment strategy for FMS.
- The results of the analysis will help decision-makers to provide the best healthcare options and to consider stakeholders' opinions.
- The design of this study protocol is linked to a randomized control trial; it includes a broad perspective from society, and a one-year horizon, which will enable long-term changes to be assessed.
- Although cost-utility analysis is a popular measurement tool, its methodological limitations make it controversial among some experts.
- The indirect-cost data source only includes patients who are linked to the social security system, which excludes self-employed and unemployed people, homemakers, and workers in the informal economy.

INTRODUCTION

Fibromyalgia is a chronic, medically unexplained syndrome that is characterized by persistent and widespread musculoskeletal pain, and that is also associated with psychological and social factors.[1–4] Disability is one of the main consequences of its impact on daily functioning, quality of life (QOL), and loss of productivity.[5] The prevalence of fibromyalgia syndrome (FMS) is significant in adults. A recent review suggests its prevalence in the general population of many countries ranges between 0.2 and 6.6%, and it is more frequent in women.[6] Specifically, it is present in 2.45% of the Spanish population.[7] Therefore, healthcare for patients with this diagnosis is not only complicated from a clinical point of view but also costly from an economic perspective for both the health and social security systems.[5,8–13]

Available evidence has shown that FMS imposes a considerable cost on society, especially those associated with comorbidity and incapacity.[8,14–18] Among European countries, the estimated total annual costs of FMS were €7,900 (direct €910, indirect €6,990) for France, €7,256 (direct €1,765, indirect €5,491) for Germany, and €7,814 (direct €5,241, indirect €2,573) for the Netherlands.[17,18] Additionally, FMS is responsible for the highest direct healthcare costs of all musculoskeletal conditions and chronic pain-related illnesses,[14] and higher rates of unemployment and number of days sick leave.[19]

In the Spanish context, the overall economic burden of FMS is considerable and has been estimated at more than €12,993 million annually.[20] According to the most recent data published by the Spanish National Institute of Social Security (NISS), the number of assigned temporary disabilities (short-term absenteeism because of days off sick) due to FMS has increased in recent years, as well as the average number of days of absence.[21] A cross-sectional and multicentre study involving a retrospective review of medical outpatient records in Catalonia between 2006 and 2007 showed that patients with FMS had considerably higher annual total costs of healthcare (including drugs, complementary tests, all types of medical visits, referrals, and hospitalizations) and non-healthcare resource utilization (sick leave days, and early retirement), under routine medical practice in the primary care setting, compared with a reference population. The study obtained an incremental adjusted per-patient per-year total cost of €5,010 for FMS patients, being €614 (12.3%) for direct costs and €4,394 (87.7%) for indirect costs.[10]

In line with these findings, another cross-sectional study conducted in Spain, based on face-to-face patient interviews, encountered a mean total cost per patient per

year of €9,982, comprising €3,245.8 (32.5%) of direct healthcare costs and €6,736.2 (67.5%) of indirect costs attributable to productivity losses.[11] This study also showed that: (i) non-pharmacological therapies accounted for the highest costs of direct healthcare resources, involving three times more than the cost of drug treatments; (ii) there was a significant direct association between disease severity and total costs; and (iii) patients with a permanent working disability made the most extensive use of resources.[11] However, these findings were collated over a decade ago, and are in need of updating with reference to the Spanish public health system.

Health economic evaluation is essential in policy decision-making since it provides evidence enabling the efficiency of an intervention, program, or project to be determined, thereby making it possible to optimize the benefits from limited resources.[22] Of the economic evaluation techniques, cost-utility analysis (CUA) estimates how much wellbeing is achieved for each monetary unit invested, taking into account both health outcomes and costs. This technique is a useful tool for comparing intervention strategies, especially those with quite different health outcomes because a standard utility unit is commonly used to measure all of them: the quality-adjusted life year (QALY).[23] Despite its limitations, especially in measuring the value that society attaches to different health status, CUA is better than other economic evaluation strategies and provides useful information for resource allocation processes.[24]

The economic evaluation of intervention programs for FMS has been little studied. According to the published findings, non-pharmacological strategies, especially psychology-based therapies, have yielded positive results in terms of reducing the economic burden of FMS.[19,25–31] In Spain, some cost-utility studies comparing alternative interventions (i.e., psychoeducational therapy, acceptance and commitment therapy, internet-delivered exposure therapy, and mindfulness-based stress reduction) with usual drug treatment have demonstrated the cost-utility from a healthcare and social perspective.[19,26–28,30] However, only the FibroQoL study has included a multicomponent intervention (MI) modality, and it had significant technical and methodological differences compared with the current proposal.[32,26]

This study aims to perform a CUA on an MI consisting of health education, physical activity, and cognitive-behavioural therapy, for patients with FMS compared with their treatment under usual clinical care (UCC),[33] provided within the 11 primary care centres of the Gerència Territorial Terres de L'Ebre of the Institut Català de la Salut, Spain. The results of this economic assessment are expected to support the evidence of

the randomized clinical trial (RCT) related to this project.[34] (ClinicalTrials.gov: NCT04049006).[35] It is hoped that this new proposed intervention will reinforce the UCC, enhance patients' QOL, and promote the efficient allocation of health and social resources.

METHOD

Design

This study protocol has been drafted based on a literature review and following the recommendations of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)[36] about preliminary results. The UK Medical Research Council guidance[37] for complex interventions has been taken into account in planning the RCT study.

The design of this economic evaluation study requires a CUA to be conducted from a societal perspective so that indirect non-medical cost variables are included. Health outcomes and costs will be assessed over a 12-month duration to ensure that long-term outcomes are measured. This methodological decision is based on the clinical symptoms of FMS, its consequences, its tendency to chronicity, and the fact that its treatment is associated with on-going clinical management.

The human capital approach has been judged the most suitable method for this study due to the limitations of the data source, given that only full sick days, prescribed by the general practitioner (GP), and the period with a medical disability can be extracted from the computerized medical history program (eCAP).

The elements to be compared in this study are the UCC[21,33,38,39] for patients with FMS, and the UCC plus an MI provided in primary care centres. The MI consists of a 12-week group program of 2 hours per week combining: 7 health education instructions, 11 items of physical activity and physical health training, and 7 interventions of psychological therapy based on cognitive-behavioural strategies and pain management. Group therapy is being delivered by the general practitioner specialized in FMS, the physiotherapist, and the psychologist, with the support of the head nurses of each health centre involved.

Study population

The patients recruited for the study sample are shortlisted from the electronic medical records system eCAP (computerized medical history program) of the Catalan Health

Service (CatSalut) and the Institut Català de la Salut. Only the medical records of the 11 primary care centres of the Gerència Territorial Terres de L'Ebre in Catalonia, Spain, are included. Patients are allocated at random to study groups from lists provided by the health centres in order to obtain a representative sample giving patient's sociodemographic diversity throughout the territory. The inclusion criteria are set out in detail in the RCT protocol study.[34]

Patient and Public Involvement

Neither patients nor the public will be involved in the design or execution of our research, or the reporting and dissemination of its results.

Outcomes measures and data collection

Health outcomes

The utilities will be obtained based on the results of the health-related QOL SF-36 questionnaire[40] (Optum, Inc., license number QM048943) and the QALY estimates. This measurement instrument is administered to the study sample at baseline, immediately after the intervention, and at 6 and 12 months of follow-up. Sociodemographic and clinical variables are registered at baseline and are fully described in the RCT study protocol.[35] A software application, specially designed for the study and linked to digital medical records, is employed to register the collected data.

Cost outcomes

Direct and indirect costs, related to the use of health and social resources, will be estimated in euros (€) based on the official prices for the public sector, which are published in the Diari Oficial de la Generalitat de Catalunya (DOGC)[41] (updated in 2019), and in the Spanish National Statistics Institute (NSI), respectively. Table 1 shows the cost variables and data sources that will be collected retrospectively, 12 months before the start date, and 12 months after the end of the MI.

Table 1. Cost outcome measurements and data collection.

Cost outcomes				
Cost outcome	**Cost outcome description**	**Data source**	**Cost data source**	**Cost calculation**
Direct healthcare costs				
Primary care visits	-General practitioner -Nurse -Physiotherapist -Psychologists	eCAP*	DOGC**	Number of visits × price
Professional referral visits	-Traumatology -Psychiatry -Rehabilitation -Other specialities	eCAP	DOGC	Number of visits × price
Clinical tests	-Blood test -Diagnostic imaging techniques -Other tests	eCAP	DOGC	Test performed x price
Pharmacological prescriptions	-Muscle relaxants -Analgesics -Corticoids -Antidepressants -Anxiolytics -Anti-seizure -Gastric protectors -Other drugs	eCAP	Council of Pharmaceutical Colleges of Catalonia	Medicines bought × price
Emergency visits		eCAP	DOGC	Number of visits × price
Hospitalizations		eCAP	DOGC	Number of hospitalization days x price
Indirect non-medical costs				
Temporary disability (TD)		eCAP	NSI***	Number of full sick leave days × salary
Permanent disability (PD)		eCAP	NSI***	Number of months with PD x salary

*eCAP: computerized medical history program

**DOGC: Diario Oficial de la Generalitat de Catalunya

***NSI: Spanish National Statistics Institute

Direct costs include visits to primary care services, other professional referrals, and emergency services, clinical tests for diagnosis and medical follow-up, pharmacological treatments, and hospitalizations. Costs will be calculated based on unit service prices, which will be obtained from the DOGC. Additionally, drug prices will be obtained from the Council of Pharmaceutical Colleges of Catalonia.

Indirect non-medical costs include temporary and permanent disability. As stated in the Spanish General Law of Social Security (Law 20/2014; Royal Legislative Decree 8/2015)[42], the term 'temporary disability' refers to sick leave days due to short-term

common or professional illness, whereas 'permanent disability' refers to the impossibility of working due to the permanent and total or partial loss of working capacity in the long-term. In the former case, a GP determines whether a patient is unable to work in the short-term. In the latter case, a medical board conducts an in-depth assessment of the medical background, including the physical and mental condition of the person, in order to determine whether a permanent disability should be declared. These measurements will be estimated from the number of full sick leave days and the months spent with a disability, respectively.

We will not collect data on other non-medical costs, such as presenteeism and unpaid lost time, because of the limitations of the data available from our data source (eCap).

The weighted price of the social costs will be determined by calculating a total annual average salary (including regular and extra payments) for the Catalonia region, based on the official records of the NSI.[43] This estimate will take into account part-time and full-time working schedules, and all activity sectors (industry, construction, and all services except housework).

Data collection is expected to be completed by April 2021.

Sample size

In order to detect a score difference of at least 5 points in the SF-36 questionnaire, it has been calculated that 260 participants (130 subjects per study arm) are needed to ensure an adequate sample size, assuming an alpha error of 0.05, a beta error of 0.05 in a bilateral contrast, and a dropout rate of 20%.[34] Consequently, between 10 and 13 MI groups, with their respective control groups (UCC), including 10-12 patients per group, are required.

Statistical analysis

SPSS version 25 and Stata version 15 for Windows will be used for the statistical analyses. First, a descriptive analysis of the sample will be carried out that will compare the characteristics of the two study arms.

As an economic evaluation outcome measure, the incremental ratio of the cost-utility will be estimated, dividing the difference in total mean costs in both UCC and MI by the differences in QALYs of each study arm. 95% confidence intervals will be calculated for all parameter estimates.

To avoid possible biases as far as possible, the intention-to-treat principle will be applied in order not to affect the random distribution. In addition, to address the loss of follow-up and non-response, multiple imputation approaches to substitute missing values will be implemented.

Sensitivity analysis

A deterministic sensitivity analysis will be performed to assess the robustness of the results.[44] Items with a higher cost will be modified in order to compare them with the initial results.

DISCUSSION

This study aims to address FMS as a public health problem with economic repercussions.[10] FMS compromises the health status of a considerable number of people, who consequently consume substantial health and social resources in the short and long terms. Therefore, this study is expected to support the inclusion of an MI for FMS in primary care settings in order to improve patient QOL and to reduce its economic burden.

The literature review indicates that the indirect costs attributable to sick leave and permanent work disability exceed the direct costs of healthcare.[8-11,14-20] Therefore, preventing productivity loss should be prioritized since this imposes the highest cost on the community. This study adopts a societal perspective, including indirect non-medical cost variables that will allow us to assess the impact of the burden of FMS on the social security system.

More accurate methods, such as the friction cost approach, have been acknowledged as being effective for estimating productivity costs. However, the human capital approach has been considered the most suitable for this study, given the data available. However, a sensitivity analysis will be performed to assess alternative cost scenarios that take into account the limitations of this methodological approach. It will include different direct healthcare costs and, if necessary, the weighted price of the social cost, considering that the salary rate will be an overall annual average estimate without distinction between the type of activity or the working schedule.

Additionally, another economic concern involves the costs of the diagnostic process since it is purely clinical.[45] Before FMS is diagnosed, other possible diseases must be ruled out with objective tests and by a variety of medical specialists. This process is often long and exhausting for patients, frustrating for doctors, and expensive from the

perspective of the health system.[46] Furthermore, the presence of comorbidities can hinder and delay the diagnosis, as well as complicating the choice of a treatment strategy.[47] Hence, the study sample could show differences in the use of resources between patients depending on the year of diagnosis and the medical records. However, it is expected that the randomized allocation will balance these differences between the study arms.

Given the evidence about the economic burden of FMS,[8,14–21] particularly related to the loss of productivity, UCC does not seem to be entirely helpful for reducing the effects of chronicity or for preventing disability. Thus, FMS treatment should not be limited to short-term pain relief. It should also promote the acceptance of the condition, the self-management of symptoms, and empowering patients to deal with FMS in their daily lives. Non-pharmacological approaches could address the consequences of chronicity, reducing healthcare overprovision and overmedication. Indeed, the proposed MI aims to address these challenges by combining physical, psychological, and health educational methods.

Findings regarding the efficacy of MI for patients with this condition have proved helpful for improving QOL, physical function, psychological variables, and or pain after 3 to 12 months of follow-up.[48–53] However, more studies are required to address the economic efficiency of this type of intervention, particularly in the context of the Spanish public health system.

Evidence of efficiency is essential for decision-making in order to allow budgets to be prioritized for those treatment options that prove to be cost-efficient and to fulfil patients' health needs. Economic evaluation is key to overcoming the obstacles arising from the uncertainty about the real costs and the sustainability of particular interventions.[54] The CUA is a popular measurement tool that combines quantity data and QOL, based on the opinions of the healthcare users, associated with a monetary cost. It involves a participatory and economic evidence-based decision-making strategy that considers stakeholders' preferences.[55] However, this methodology is controversial,[56] the main points of contention being: (i) the lack of transparency about data collection and analysis regarding the measurement of the value that society assigns to a state of health; (ii) that the gain in health depends on the severity of the condition, so the value is affected by patients' perception of their pain and health status; (iii) the limited value of this measurement tool for long-term diseases such as FMS, where disability accumulates over time since it assumes that the utility of a health state is independent of the time the patient has experienced it, and the influence of previous and subsequent health conditions.[24]

Although all these factors pose methodological challenges, CUA is still a valid and effective strategy for carrying out health economic evaluations and collaborating with decision-makers in choosing between intervention alternatives.[24]

Another limitation related to the instruments and the data collection stems from the QOL being a multifactorial variable that could be influenced by non-medical circumstances such as family dynamics, working conditions, and economic and political contexts, among others.[57] Sociodemographic variables will therefore be analysed in the models in order to control for these possible effects.

This health region covers a wide and varied territory. However, all the primary care centres participating in the study are run by the public health administration, meaning that clinical care protocols and direct medical costs are both standardized according to official regulations and will be homogeneous for the entire sample.

Regarding the indirect costs, only those people who are linked to the social security system and who have access to its benefits will be able to provide data about productivity costs. The study sample, therefore, excludes self-employed and unemployed people, homemakers, and workers in the informal economy. In this sense, although the human capital approach could overestimate productivity costs, it could be offset by the missed data of these population subgroups that contribute to the productivity loss to society due to the side effects of their illness.

Finally, this study could be affected by sample loss-to-follow-up given the one-year time horizon. This methodological characteristic is also a strength of the study since it will allow long-term changes to be assessed. In order to minimize the number of participants abandoning the study, reminders of upcoming interviews will be sent, and different data collection methods, such as telephone calls and online survey platforms, may even be used.

If the results indicate that the intervention is utility-cost-effective, this study will support, through efficiency evidence, the inclusion of an MI as part of the usual practice for FMS in primary care centres in Catalonia, Spain. Additionally, enhancements of patient QOL and cost reductions for health and social resources are expected. We hope that this new proposed intervention could be replicated throughout the rest of Catalonia and Spain, and used more extensively as a guide within other European health systems.

ETHICS AND DISSEMINATION

This study was designed in accordance with the Helsinki/Tokyo Declaration. It was approved by the Clinical Research Ethics Committee of the Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), on 25/04/2018 (code P18/068). Information is delivered to participants orally and in writing before their necessary informed consent is obtained. This project respects the data protection laws guaranteeing participant anonymity. Dissemination strategy includes publications in scientific journals and through presentations in the local and national media and at academic conferences.

AUTHOR CONTRIBUTIONS

VMA, **MC**, **CAM**, **AB**, **JFS**, and **AQG** designed the study. **VMA** wrote the draft versions, which all the other authors reviewed. **RCA**, **NCQ**, **GGS**, **MCS**, **IFA**, **AQG**, **AB**, **CAM**, **JFS**, **and VMA** are involved in the development of the general project and the RCT study from which this qualitative study is related.

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REFERENCES

1. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990;33(2):160–72.
2. Wolfe F, Clauw DJ, Fitzcharles MA, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. *J Rheumatol* 2011;38(6):1113–22.
3. Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum* 2016;46(3):319–29.
4. Helfenstein M, Goldenfum MA, Siena CAF. Fibromyalgia: Clinical and occupational aspects. *Rev Assoc Med Bras* 2012;58(3):358–65.
5. Skaer TL. Fibromyalgia: disease synopsis, medication cost effectiveness and economic burden. *Pharmacoeconomics* 2014;32(5):457–66.
6. Marques AP, Santo A, Berssaneti AA, et al. Prevalence of fibromyalgia: literature review update. *Rev Bras Reumatol* 2017;57(4):356–63.
7. Seoane-Mato D, Sanchez-Piedra C, Silva-Fernandez L, et al. Prevalence of rheumatic diseases in adult population in Spain (EPISER 2016 study): Aims and methodology. *Reumatol Clin* 2019;15(2):90–6.
8. Robinson RL, Birnbaum HG, Morley MA, et al. Economic cost and epidemiological characteristics of patients with fibromyalgia claims. *J Rheumatol* 2003;30(6):1318–25.
9. Spaeth M. Epidemiology, costs, and the economic burden of fibromyalgia. *Arthritis Res Ther* 2009;11(3):2–3.
10. Sicras-Mainar A, Rejas J, Navarro R, et al. Treating patients with fibromyalgia in primary care settings under routine medical practice: a claim database cost and burden of illness study. *Arthritis Res Ther* 2009;11(2):1–14.
11. Rivera J, Rejas J, Esteve-Vives J, et al. Resource utilisation and health care costs in patients diagnosed with fibromyalgia in Spain. *Clin Exp Rheumatol* 2009;27(5 Suppl 56):S39-45.
12. Thompson JM, Luedtke CA, Oh TH, Shah ND, Long KH, King S, et al. Direct medical costs in patients with fibromyalgia: Cost of illness and impact of a brief multidisciplinary treatment program. *Am J Phys Med Rehabil* 2011;90(1):40–6.
13. Vervoort VM, Vriezekolk JE, Olde Hartman TC, et al. Cost of illness and illness perceptions in patients with fibromyalgia. *Clin Exp Rheumatol* 2016;34(2 Suppl 96):S74-82.
14. White KP, Speechley M, Harth M, et al. The London Fibromyalgia Epidemiology Study: direct health care costs of fibromyalgia syndrome in London, Canada. *J Rheumatol* 1999;26(4):885–9.
15. Berger A, Dukes E, Martin S, et al. Characteristics and healthcare costs of patients with fibromyalgia syndrome. *Int J Clin Pract* 2007;61(9):1498–508.
16. Berger A, Sadosky A, Dukes EM, et al. Patterns of healthcare utilization and cost in patients with newly diagnosed fibromyalgia. *Am J Manag Care* 2010;16(5 Suppl):S126-37.
17. Boonen A, Van Den Heuvel R, Van Tubergen A, et al. Large differences in cost of illness and wellbeing between patients with fibromyalgia, chronic low back pain, or ankylosing spondylitis. *Ann Rheum Dis* 2005;64(3):396–402.
18. Winkelmann A, Perrot S, Schaefer C, et al. Impact of fibromyalgia severity on health economic costs. *Appl Health Econ Health Policy* 2011;9(2):125–36.
19. Feliu-Soler A, Borràs X, Peñarrubia-María MT, et al. Cost-utility and biological underpinnings of Mindfulness-Based Stress Reduction (MBSR) versus a

psychoeducational programme (FibroQoL) for fibromyalgia: A 12-month randomised controlled trial (EUDAIMON study). *BMC Complement Altern Med* 2016;16(1):1–16.
20. Cabo-Meseguer A, Cerda-Olmedo G, Trillo-Mata JL. Fibromyalgia: Prevalence, epidemiologic profiles and economic costs. *Med Clin (Barc)* 2017;149(10):441–8.
21. Instituto Nacional de la Seguridad social. Guia de actualización en la valoración de fibromialgia, sÍndrome de fatiga crónica, sensibilidad química múltiple y electrosensibilidad. Segunda Edición 2019. https://www.semg.es/images/documentos/guia_fibromialgia_2019.pdf (Accessed 25 May 2020)
22. Chisholm D, Evans DB. Economic evaluation in health: Saving money or improving care? *J Med Econ* 2007;10(3):325–37.
23. Franklin M. Cost utility analysis. In: Mental Health Economics: The Costs and Benefits of Psychiatric Care. Cham. Springer International Publishing 2017:89–119 https://doi.org/10.1007/978-3-319-55266-8_6
24. Mccabe C. What is cost-utility analysis? *Hayward Med Commun* 2009;(February):1–6. http://www.bandolier.org.uk/painres/download/whatis/What_is_cost-util.pdf (Accessed 25 May 2020)
25. Goossens ME, Rutten-van Molken MP, Leidl RM, et al. Cognitive-educational treatment of fibromyalgia: a randomized clinical trial. II. Economic evaluation. *J Rheumatol* 1996;23(7):1246–54.
26. Luciano J V, Sabes-Figuera R, Cardenosa E, et al. Cost-utility of a psychoeducational intervention in fibromyalgia patients compared with usual care: an economic evaluation alongside a 12-month randomized controlled trial. *Clin J Pain* 2013;29(8):702–11.
27. Luciano J V, D'Amico F, Cerdà-Lafont M, et al. Cost-utility of cognitive behavioral therapy versus U.S. Food and Drug Administration recommended drugs and usual care in the treatment of patients with fibromyalgia: An economic evaluation alongside a 6-month randomized controlled trial. *Arthritis Res Ther* 2014;16(1):1–17.
28. Luciano J V, D'Amico F, Feliu-Soler A, et al. Cost-utility of group acceptance and commitment therapy for fibromyalgia versus recommended drugs: An economic analysis alongside a 6-month randomized controlled trial conducted in Spain (EFFIGACT Study). *J Pain* 2017;18(7):868–80.
29. Hedman-Lagerlof M, Hedman-Lagerlof E, Ljotsson B, et al. Cost-effectiveness and cost-utility of internet-delivered exposure therapy for fibromyalgia: Results from a randomized, controlled trial. *J Pain* 2019;20(1):47–59.
30. Pérez-Aranda A, D'Amico F, Feliu-Soler A, et al. Cost-utility of mindfulness-based stress reduction for fibromyalgia versus a multicomponent intervention and usual care: A 12-month randomized controlled trial (EUDAIMON Study). *J Clin Med* 2019;8(7):1068.
31. Amico FD, Feliu-soler A. Cost-utility of attachment-based compassion therapy (ABCT) for fibromyalgia compared to relaxation : A pilot randomized controlled trial. *J Clin Med* 2020; 9(3):726.
32. Luciano J V, Martinez N, Penarrubia-Maria MT, et al. Effectiveness of a psychoeducational treatment program implemented in general practice for fibromyalgia patients: a randomized controlled trial. *Clin J Pain* 2011;27(5):383–91.
33. Celaya M, Ibáñez D, Laseca N, et al. Guia per a l´avaluació de la fibromiàlgia i de la síndrome de fatiga crònica. *Generalitat de Catalunya* 2017. https://canalsalut.gencat.cat/web/.content/_A-Z/F/fibromialgia/documents/guia_avaluacio_fibromialgia_fatiga_cronica.pdf (Accessed 20 Feb 2020)
34. Caballol Angelats R, Gonçalves AQ, Aguilar Martín C, et al. Effectiveness, cost-utility, and benefits of a multicomponent therapy to improve the quality of life of patients with fibromyalgia in primary care: A mixed methods study protocol. *Medicine* 2019;98(41).
35. Caballol Angelats R, Gonçalves AQ, Aguilar Martín C, et al. Effectiveness, cost-utility, and benefits of a multicomponent therapy to improve the quality of life of patients with fibromyalgia in primary care. *Medicine (Baltimore)* 2019;98(41):e17289.
36. Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation

reporting standards (CHEERS)-explanation and elaboration: A report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. *Value Heal* 2013;16(2):231–50.
37. Craig P, Dieppe P, Macintyre S, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. *Int J Nurs Stud* 2013;50(5):587–92.
38. Nishishinya Aquino B, Requeijo Lorenzo C, Roqué Fíguls M, et al. Evaluación y abordaje de la fibromialgia. Actualización de las evidencias científicas. Barcelona. Ministerio de Sanidad, Servicios Sociales e Igualdad. Agència de Qualitat i Avaluació Sanitàries de Catalunya. Departament de Salut. *Generalitat de Catalunya* 2017 (Informes de Evaluación de Tecnologías Sanitarias). https://aquas.gencat.cat/web/.content/minisite/aquas/publicacions/2017/Fibromialgia_actualizacion_RedETS2017.pdf (Accessed 27 Feb 2020)
39. Gándara M, Muñoz G. Evaluación y abordaje de la fibromialgia y el síndrome de fatiga crónica. Día Mundial de la Fibromialgia y el Síndrome de Fatiga Crónica. Oficial Nacional de Salud Pública-AEMPPI Ecuador 2017. https://www.elsevier.com/es-es/connect/actualidad-sanitaria/dia-mundial-de-la-fibromialgia-y-el-sindrome-de-fatiga-cronica?aaref=https%3A%2F%2Fwww.google.com%2F (Accessed 27 Feb 2020)
40. Alonso J, et al. Versión española de SF-36v2™ Health Survey © 1996, 2000, adapted by J. Alonso et al. *Heal Surv* 2003;1–8. http://www.ser.es/wp-content/uploads/2015/03/SF36_CUESTIONARIOpdf.pdf (Accessed 1 Mar 2020)
41. Generalitat de Catalunya. Diari Oficial de la Generalitat de Catalunya. https://dogc.gencat.cat/es
42. Gobierno de España. Real Decreto 8/2015 por el que se aprueba el texto refundido de la Ley General de la Seguridad Social. *Boletín Oficial del Estado* 2015;1–157. http://www.boe.es/boe/dias/1994/06/29/pdfs/A20658-20708.pdf (Accessed 1 Mar 2020)
43. Instituto Nacional de Estadística (INE). Coste laboral por trabajador, comunidad autónoma, sectores de actividad. https://www.ine.es/jaxiT3/Tabla.htm?t=6061 (Accessed 20 Mar 2020)
44. Andronis L, Barton P, Bryan S. Sensitivity analysis in economic evaluation: An audit of NICE current practice and a review of its use and value in decision-making. *Health Technol Assess (Rockv)* 2009;13(29).
45. Wang S-M, Han C, Lee S-J, et al. Fibromyalgia diagnosis: a review of the past, present and future. *Expert Rev Neurother* 2015;15(6):667–79.
46. Briones-Vozmediano E. The social construction of fibromyalgia as a health problem from the perspective of policies, professionals, and patients. *Glob Health Action* 2017;10(1).
47. Lichtenstein A, Tiosano S, Amital H. The complexities of fibromyalgia and its comorbidities. *Curr Opin Rheumatol* 2018;30(1):94–100.
48. Giusti EM, Castelnuovo G, Molinari E. Differences in multidisciplinary and interdisciplinary treatment programs for fibromyalgia: A mapping review. *Pain Res Manag* 2017;2017:7261468.
49. Bourgault P, Lacasse A, Marchand S, et al. Multicomponent interdisciplinary group intervention for self-management of fibromyalgia: a mixed-methods randomized controlled trial. *PLoS One* 2015;10(5):e0126324.
50. Ollevier A, Vanneuville I, Carron P, et al. A 12-week multicomponent therapy in fibromyalgia improves health but not in concomitant moderate depression, an exploratory pilot study. *Disabil Rehabil* 2019;0(0):1–8.
51. Martin J, Torre F, Padierna A, et al. Six-and 12-month follow-up of an interdisciplinary fibromyalgia treatment programme: results of a randomised trial. *Clin Exp Rheumatol* 2012;30(6 Suppl 74):103–11.
52. Saral I, Sindel D, Esmaeilzadeh S, et al. The effects of long- and short-term interdisciplinary treatment approaches in women with fibromyalgia: a randomized controlled trial. *Rheumatol Int* 2016;36(10):1379–89.
53. Stein KF, Miclescu A. Effectiveness of multidisciplinary rehabilitation treatment for patients with chronic pain in a primary health care unit. *Scand J Pain* 2013;4(4):190–7.

54. Eisman AB, Kilbourne AM, Dopp AR, et al. Economic evaluation in implementation science: Making the business case for implementation strategies. *Psychiatry Res* 2020;283(June 2019):112433.
55. Anneliese P, Hoch J. Understanding cost-utility analysis in health care. *Univ Toronto Med J* 2006;83(2) http://utmj.org/index.php/UTMJ/article/view/734 (Accessed 25 May 2020)
56. McGregor M. Cost-utility analysis: Use QALYs only with great caution. *Can Med Assoc J* 2003;168(4):433–4.
57. Tarter T, Johnson G, Johnson R. Neuropsychology of Cancer and Oncology. Chad A Noggle; Raymond S Dean, editor. New York: Springer Publishing Company 2013:3-5