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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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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

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

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

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

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60 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

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

16 **Design**

17 This study protocol has been drafted base on the literature review and following the
18 Consolidated Health Economic Evaluation Reporting Standards (CHEERS).³⁶ Medical
19 Research Council guidance³⁷ for complex interventions has been taken in account for
20 the RCT study.
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26 For the design of this economic evaluation study a CUA will be conducted from
27 a societal perspective, so indirect non-medical cost variables will be included. Also, a
28 temporal horizon of 12-month will be used with the purpose of assessing health
29 outcomes and costs at long-term. This methodological decision is based on the
30 characteristics of the symptoms of FMS, its consequences, its tendency to chronicity,
31 and the fact that its treatment is associated with on-going clinical management.
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36 The elements to be compared in this study are the UCC ^{21,33,38,39} for patients with
37 FMS and the UCC plus a MI provided in primary care centres.
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39 The MI consists in a 12-week group program of 2-hour weekly combining: 7
40 health education instructions, 11 trainings on physical activity and physical health, and
41 7 interventions of psychological therapy based on cognitive-behavioural strategies and
42 pain management. Group therapy is being delivered by the general practitioner
43 specialized in FMS, the physiotherapist, and the psychologist with the support of the
44 head nurses of each health centre involved.
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51 **Study population**

52 The patients recruited for the study sample are shortlisted from the electronic medical
53 records system eCAP (computerized medical history program) belonging to the Catalan
54 Health Service (CatSalut) and the Catalan Health Institute (CHI). Only the medical
55 records of the 11 primary care centres of the *Gerència Territorial Terres de L'Ebre* in
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3 Catalonia (Spain) are included. Allocation to study groups is randomized according to a
4 randomized list by centre. The inclusion criteria is detail in the RCT protocol study.³⁴
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8 Patient and Public Involvement

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10 Patients or the public will not be involved in the design, or conducting, or reporting, or
11 dissemination plans of our research.
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14 Outcomes measures and data collection

15 Health outcomes

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17 The utilities will be obtained based on the results of the QOL instrument SF-36
18 questionnaire⁴⁰ (Optum, Inc. license number QM048943) and QALYs will be
19 calculated. This measurement instrument is administrated to the study sample at
20 baseline, immediately after the intervention, and at 6 and 12 months of follow-up.
21 Sociodemographic and clinical data are collected at baseline and it is fully detail in the
22 RCT study protocol.³⁵ All these information is introduced in a software application that
23 has been designed for the purpose of this study and is available in the *Terres de l'Ebre*
24 CHI website, linked to the electronic medical records.
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34 Cost outcomes

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

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53 Direct costs include visits to primary care services, to other professional
54 referrals, and emergency, clinical tests for diagnosis and medical follow-up,
55 pharmacological treatments, and hospitalizations. The prices of each service unit for the
56 cost calculation will be obtained from the DOGC, except for the prices of the drugs for
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3 which the Council of Pharmaceutical Colleges of Catalonia will be considered as the
4 source of information.
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6 Indirect non-medical costs consist of losing of productivity including temporary
7 and permanent disability. These measurements will be estimated based on sick leave
8 days and months spent with permanent disability, respectively.
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10 Data collection is expected to be complete by December 2021.
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15 Sample size

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

25 The SPSS version 25 and the Stata version 15 for Windows will be used to the
26 statistical analysis. First, a descriptive analysis of the sample will be carried out
27 comparing its characteristics between the study arms.
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30 As an economic evaluation outcome measure, the incremental ratio of the cost-
31 utility will be estimated dividing the difference in total mean costs in both UCC and MI
32 by the differences in QALYs of each study arm. Moreover, 95% confidence intervals
33 will be calculated for all analyses.
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38 Regarding possible biases, the intention-to-treat principle will be applied in
39 order not to affect the random distribution. In addition, to address the loss of follow-up
40 and non-response, multiple imputation approaches to substitute missing values will be
41 implemented.
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47 Sensitivity analysis

48 A deterministic sensitivity analysis will be performed to assess the robustness of the
49 results.⁴² We will modify the items which have a most percentage about the cost, to
50 compare with new results.
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55 ETHICAL ASPECTS

56 This study was designed according to the Helsinki/Tokyo Declaration and it was
57 approved by the Clinical Research Ethics Committee of the *Fundació Institut*
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3 *Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina*
4 (IDIAPJGol), on 25/04/2018 (code P18/068). Furthermore, oral and written information
5 is delivered to participants and informed consents required. This project respects the
6 data protection law guaranteeing anonymity.
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10 11 12 **DISCUSSION**

13 This study intends to address FMS as a public health problem with economic
14 repercussions.¹⁰ Indeed, it compromises the health of a significant number of people,
15 who are large consumers of health and social resources in the short and long-term.
16 Therefore, the results of this study are expected to collaborate with the establishment of
17 a multicomponent treatment for FMS in primary care settings, in order to reduce its
18 economic burden and improve patients' QOL.
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24 According to the literature review, the indirect costs attributable to sick leaves
25 and permanent work disability, double the direct costs of healthcare.^{8 10,11 14–18 19 20} As a
26 result, efforts should be aimed at preventing the loss of productivity that represents the
27 highest cost for the community and a significant impact on patients' health. From a
28 societal perspective and taking this priority into account, this study incorporates indirect
29 non-medical cost variables that will allow evaluating the impact of FMS burden in the
30 social security system.
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36 Another economic concern is the costs of the diagnosis process since it is purely
37 clinical and it comes from discard.⁴³ Before a patient is diagnosed by FMS, other
38 probable diseases must be ruled out through objective tests and different medical
39 specialists. This path is often long and exhausting for patients, frustrating for doctors
40 but also expensive from the perspective of the health system.⁴⁴ Furthermore, the
41 presence of comorbidities can hinder and delay the diagnosis, as well as complicate the
42 treatment strategy.⁴⁵ Considering this, the sample could show differences in the use of
43 resources depending on the diagnostic year. However, it is assumed that the
44 randomization will provide a balance between the study arms of patients with a more
45 recent diagnosis and / or greater comorbidities weight.
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53 Considering the evidence on the economic burden of FMS,^{8,14–21} especially
54 related to the loss of productivity, UCC does not seem to be completely helpful to
55 reduce the effects of chronicity or prevent disability. Thus, FMS treatment should not be
56 limited to short-term pain relief. It should also promote the acceptance of the condition,
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3 the self-management of symptoms and the empowerment of patients to deal with FMS
4 in their daily lives. The effective implementation of non-pharmacological approaches by
5 patients at long-term and changes in lifestyle should be accomplished to avoid
6 overprovision, overmedication, and the consequences of chronicity. The MI evaluated
7 in this study aims to face with these goals by combining physical, psychological, and
8 health education methods.
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11 Findings on the efficacy of MI for patients with this condition have proved to be
12 helpful in improving QOL, physical function, psychological variables, and/or pain after
13 3 to 12 months of follow-up.^{46 47 48 49 50 51} However, more studies are required on the
14 economic efficiency of this type of intervention and, particularly, in the context of the
15 public health system in Spain.
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18 Evidence on efficiency is essential for decision-making to prioritize the budgets
19 in those treatment options that prove to be cost-efficient and cover patients' health-
20 needs. Economic evaluation is key to overcoming the barrier of uncertainty about the
21 true costs of carrying out an intervention and its sustainability.⁵² The CUA selected for
22 this study is a popular measurement tool that combines data on quantity and quality of
23 life, valued by users of a health service, associated with a monetary cost. Therefore, it
24 involves a participatory and economic evidence-based decision-making strategy that
25 consider stakeholders' preferences.⁵³ Nevertheless, this methodology is also
26 controversial.⁵⁴ The main highlights are: (i) the way to measure the value that society
27 assign to a state of health. Although it is intended to guarantee transparency, the
28 methodology for collecting and analysing this data is still questioned; (ii) the gain in
29 health depends on the severity of the condition and, therefore, this value is affected by
30 the characteristics of the patients and their health state; (iii) for long-term diseases such
31 as FMS, where disability accumulates over time, this measurement tool is limited since
32 it assumes that the utility of a health state is independent of the time spent in that health
33 state, and the previous and subsequent health states.²⁴ Although these points pose
34 challenges to overcome from a methodological point of view, CUA is still a valid and
35 effective strategy to carry out economic evaluations in health and collaborate with
36 decision-makers in selecting between different intervention alternatives.²⁴
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55 Other limitations related to the instruments and data collection is that the QOL is
56 a multifactor variable that could be influenced by many circumstances not directly
57 attached to the medical condition like family dynamic, working conditions, economic
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3 and political context, among others.⁵⁵ Nonetheless, socio-demographic variables will be
4 included in the analysis models trying to correct this possible effect.
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7 On the other hand, all the health centres included in the study depend on the
8 public health services of the region, so that both clinical care protocols and direct
9 medical costs are standardized according to official publications and will be
10 homogeneous for the entire sample. Considering the diversity of health centres
11 included, it could be assumed that the population is representative for the community of
12 Catalonia.
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17 However, indirect costs will only include those people who are linked to the
18 social security system and can access to its benefits. This excludes people who work
19 independently of whom we will not have a record of their activity cedes or low
20 productivity.
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24 Although the 1-year time horizon is a strength of the study, since it will allow
25 assessing long-term changes, it may also face the possible loss of follow-up. To
26 minimize loss of sample, reminders for the interviews will be implemented, and even
27 different strategies will be used for data collection, such as telephone calls.
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31 If the results show to be utility-cost, this study will support, through efficiency
32 evidence, the incorporation of a MI to the usual practise for FMS in units specialized in
33 Central Sensitivity Syndromes located in primary care centres and in hospitals of
34 Catalonia, Spain. What is more, improvement in patients' QOL and cost reduction of
35 the healthcare services and social resources are expected. Finally, it is intended that this
36 new intervention proposal can be replicated in other health areas of Catalonia and Spain,
37 and considering as a guide for other European health systems.
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45 **AUTHOR CONTRIBUTIONS**

46 **VMA, MC, CAM, AB, JFS** and **AQG** participated in the design of the study. **VMA**
47 wrote the drafts versions with the review of all authors. **RCA, NCQ, GGS, MCS, IFA,**
48 **AQG, AB, CAM, JFS, and VMA** are involved in the development of the general
49 project and the RCT study from which this qualitative study is related.
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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 × 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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Primary Subject Heading:	Health economics

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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

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3 (67.5%) to indirect costs attributable to productivity losses.¹¹ Moreover, this study
4 evidenced that: (i) non-pharmacological therapies accounted the highest cost of direct
5 healthcare resources, and involved three times more than the cost of drug treatment; (ii)
6 there was a significant association between disease severity and higher total costs; and
7 (iii) patients with permanent working disability implies the highest use of resources.¹¹
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12 However, all these findings were achieved over a decade ago and an update of the data
13 is necessary for the Spanish public health system.
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16 Health economic evaluation is essential in policy decision-making since it
17 provides evidence to identify the efficiency of an intervention, program, or project in
18 order to optimize the benefits from limited resources.²² Among the economic evaluation
19 techniques, cost-utility analysis (CUA) estimates how much wellbeing is achieved for
20 each monetary unit invested, involving both health outcomes and costs. This technique
21 is a useful tool for comparing intervention strategies, especially for those with quite
22 different health outcomes because of the standard utility units commonly used to
23 measure all of them: the quality-adjusted life-year (QALY).²³ Despite its limitations,
24 especially in measuring the value that society attaches to healthcare states, CUA is
25 superior to other economic evaluation strategies and provides relevant information for
26 resource allocation processes.²⁴
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35 The economic evaluation of intervention programs for FMS has been scarcely
36 studied. According to the published findings, non-pharmacological strategies, especially
37 psychology-based therapies, have evidenced positive results in decreasing the economic
38 burden of FMS.^{19,25-31} In Spain, some cost-utility studies that compare alternative
39 interventions (psychoeducational therapy, acceptance and commitment therapy,
40 internet-delivered exposure therapy, and Mindfulness-Based Stress Reduction) with
41 usual drug treatment have demonstrated the cost-utility from a healthcare and social
42 perspective.^{19,26-28,30} Nevertheless, only the FibroQoL study included a multicomponent
43 intervention (MI) modality but with technical and methodological differences compare
44 to the actual proposal.^{32,26}
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52 This study aims to perform a CUA on a MI (that consists of health education,
53 physical activity, and cognitive-behavioral therapy) for patients with FMS compared to
54 the usual clinical care (UCC),³³ provided within the 11 primary healthcare centres of the
55 *Gerència Territorial Terres de L'Ebre* of the Catalan Institute of Health, Spain. The
56 results of this economic assessment are expected to support the evidence of the
57 randomized clinical trial (RCT) related to this project.³⁴ (Clinical-Trials.gov:
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3 NCT04049006).³⁵ This new intervention proposal will hopefully reinforce the UCC,
4 enhance patients' QOL, and promote efficiency in health and social resources
5 allocation.
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10 **METHOD**

11 **Design**

12 This study protocol has been drafted based on the literature review and following the
13 Consolidated Health Economic Evaluation Reporting Standards (CHEERS).³⁶ Medical
14 Research Council guidance³⁷ for complex interventions has been taken into account for
15 the RCT study.
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20 For the design of this economic evaluation study a CUA will be conducted from
21 a societal perspective, so indirect non-medical cost variables will be included. Also, a
22 temporal horizon of 12-month will be used to assess health outcomes and costs in the
23 long-term. This methodological decision is based on the clinical symptoms of FMS, its
24 consequences, its tendency to chronicity, and the fact that its treatment is associated
25 with on-going clinical management.
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30 The human capital approach has been judged as the most suitable method for
31 this study due to limitations in the data source since only full sick days, prescribed by
32 the GP, and the period with a medical disability can be extracted from the computerized
33 medical history program (eCAP).
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38 The elements to be compared in this study are the UCC^{21,33,38,39} for patients with
39 FMS, and the UCC plus a MI provided in primary care centres. The MI consists of a 12-
40 week group program of 2-hour weekly combining: 7 health education instructions, 11
41 pieces of training on physical activity and physical health, and 7 interventions of
42 psychological therapy based on cognitive-behavioural strategies and pain management.
43 Group therapy is being delivered by the general practitioner specialized in FMS, the
44 physiotherapist, and the psychologist with the support of the head nurses of each health
45 centre involved.
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52 **Study population**

53 The patients recruited for the study sample are shortlisted from the electronic medical
54 records system eCAP (computerized medical history program) belonging to the Catalan
55 Health Service (CatSalut) and the Catalan Health Institute (CHI). Only the medical
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3 records of the 11 primary care centres of the *Gerència Territorial Terres de L'Ebre* in
4 Catalonia (Spain) are included. Allocation to study groups is randomized according to a
5 randomized list by centre. This randomization strategy has been designed taking into
6 account the possible variations in the sociodemographic and clinical variables of the
7 primary care centres involved, due to the diversity of the territory, and in order to obtain
8 a representative sample. The inclusion criteria are detailed in the RCT protocol study.³⁴
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15 Patient and Public Involvement

16 Patients or the public will not be involved in the design or conducting, or reporting, or
17 dissemination plans of our research.
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22 Outcomes measures and data collection

23 Health outcomes

24 The utilities will be obtained based on the results of the health-related QOL SF-36
25 questionnaire⁴⁰ (Optum, Inc. license number QM048943) and the estimation of quality-
26 adjusted life years (QALYs). This measurement instrument is administrated to the study
27 sample at baseline, immediately after the intervention, and at 6 and 12 months of
28 follow-up. Sociodemographic and clinical variables are registered at baseline and are
29 fully detailed in the RCT study protocol.³⁵ The collected data is introduced in a software
30 application that has been specially designed for study and is available on the *Terres de*
31 *l'Ebre* CHI website, linked to the electronic medical records.
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41 Cost outcomes

42 Direct and indirect costs, related with the use of health and social resources, will be
43 estimated in euros (€) according to the official prices for the public sector which are
44 published in the *Diari Oficial de la Generalitat de Catalunya* (DOGC)⁴¹ (updated to
45 2019), and in the Spanish Statistics National Institute (SNI), respectively. Table 1 shows
46 the description of cost variables and data sources. These cost variables will be taken
47 retrospectively 12-month before the start date of the MI and 12-month after the end of
48 the MI.
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58 Table 1. Cost outcomes measurements and data collection
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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

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

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

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

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22 Data collection is expected to be completed by April 2021.

23 24 25 Sample size

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

33 34 35 Statistical analysis

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

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

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3 by the differences in QALYs of each study arm. Moreover, 95% confidence intervals
4 will be calculated for all analyses.
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6 Regarding possible biases, the intention-to-treat principle will be applied in
7 order not to affect the random distribution. In addition, to address the loss of follow-up
8 and non-response, multiple imputation approaches to substitute missing values will be
9 implemented.
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13 14 15 Sensitivity analysis

16 A deterministic sensitivity analysis will be performed to assess the robustness of the
17 results.⁴⁴ Items with a higher cost will be modified in order to compare them with the
18 original results.
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23 24 **ETHICS AND DISSEMINATION**

25 This study was designed according to the Helsinki/Tokyo Declaration and it was
26 approved by the Clinical Research Ethics Committee of the *Fundació Institut*
27 *Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina*
28 *(IDIAPJGol)*, on 25/04/2018 (code P18/068). Furthermore, oral and written information
29 is delivered to participants, and informed consent is required. This project respects the
30 data protection law guaranteeing anonymity. Dissemination strategy includes
31 publications in scientific journals and through the local and national media and
32 conferences in academic events.
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40 41 **DISCUSSION**

42 This study intends to address FMS as a public health problem with economic
43 repercussions.¹⁰ Indeed, it compromises the health of a significant number of people,
44 who are large consumers of health and social resources in the short and long-term.
45 Therefore, the results of this study are expected to collaborate with the inclusion of a MI
46 for FMS in primary care settings in order to improve patients' QOL and reduce its
47 economic burden.
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53 According to the literature review, the indirect costs attributable to sick leaves
54 and permanent work disability exceed the direct costs of healthcare.^{8 10,11 14–18 19,20} As a
55 result, efforts should be aimed at preventing productivity loss that represents the highest
56 cost for the community and a significant impact on patients' health. From a societal
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3 perspective and taking this priority into account, this study incorporates indirect non-
4 medical cost variables that will allow assessing the impact of FMS burden on the social
5 security system.
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8 Even though more accurate methods, such as the friction cost approach, have
9 been acknowledged by the literature for the estimation of the productivity costs, the
10 human capital approach has been considered the most suitable for the characteristics of
11 the data access in this study. Nevertheless, we do not underestimate the limitations of
12 this approach, the reason why a sensitivity analysis will be performed to assess different
13 possible cost scenarios. It will include different direct healthcare costs and, if necessary,
14 the price weight of the social cost considering that the salary rate will be an overall
15 annual average estimation without distinction neither of the type of activity nor the
16 working schedule.
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24 Another economic concern is the costs of the diagnosis process since it is purely
25 clinical and it comes from discard.⁴⁵ Before a patient is diagnosed by FMS, other
26 probable diseases must be ruled out through objective tests and different medical
27 specialists. This path is often long and exhausting for patients, frustrating for doctors
28 but also expensive from the perspective of the health system.⁴⁶ Furthermore, the
29 presence of comorbidities can hinder and delay the diagnosis, as well as complicate the
30 treatment strategy.⁴⁷ Considering this, the sample could show differences in the use of
31 resources depending on the diagnostic year. However, it is assumed that the
32 randomization will provide a balance between the study arms of patients with a more
33 recent diagnosis and / or greater comorbidities weight.
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41 Given the evidence on the economic burden of FMS,^{8,14-21} especially related to
42 the loss of productivity, UCC does not seem to be completely helpful to reduce the
43 effects of chronicity or prevent disability. Thus, FMS treatment should not be limited to
44 short-term pain relief. It should also promote the acceptance of the condition, the self-
45 management of symptoms, and the empowerment of patients to deal with FMS in their
46 daily lives. The effective implementation of non-pharmacological approaches by
47 patients at long-term and lifestyle changes should be accomplished to avoid
48 overprovision, overmedication, and the consequences of chronicity. The evaluated MI
49 in this study aims to face with these goals by combining physical, psychological, and
50 health education methods.
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58 Findings on the efficacy of MI for patients with this condition have proved to
59 help improve QOL, physical function, psychological variables, and/or pain after 3 to 12
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3 months of follow-up.^{48–53} However, more studies are required on the economic
4 efficiency of this type of interventions and, particularly, in the context of the public
5 health system in Spain.
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8 Evidence on efficiency is essential for decision-making to prioritize the budgets
9 in those treatment options that prove to be cost-efficient and cover patients' health
10 needs. Economic evaluation is key to overcoming the barrier of uncertainty about the
11 true costs of carrying out an intervention and its sustainability.⁵⁴ The CUA selected for
12 this study is a popular measurement tool that combines data on quantity and quality of
13 life, valued by users of a health service, and associated with a monetary cost. Therefore,
14 it involves a participatory and economic evidence-based decision-making strategy that
15 considers stakeholders' preferences.⁵⁵ Nevertheless, this methodology is also
16 controversial.⁵⁶ The main highlights are: (i) the way to measure the value that society
17 assigns to a state of health. Although it is intended to guarantee transparency, the
18 methodology for collecting and analysing this data is still questioned; (ii) the gain in
19 health depends on the severity of the condition and, therefore, this value is affected by
20 the characteristics of the patients and their health state; (iii) for long-term diseases such
21 as FMS, where disability accumulates over time, this measurement tool is limited since
22 it assumes that the utility of a health state is independent of the time spent in that health
23 state, and the previous and subsequent health states.²⁴ Although these points pose
24 challenges to overcome from a methodological point of view, CUA is still a valid and
25 effective strategy to carry out health economic evaluations and collaborate with
26 decision-makers in selecting between different intervention alternatives.²⁴
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41 Other limitations related to the instruments and data collection is that the QOL is
42 a multifactor variable that could be influenced by many circumstances not directly
43 attached to the medical issue like family dynamic, working conditions, economic and
44 political context, among others.⁵⁷ Nonetheless, socio-demographic variables will be
45 included in the analysis models trying to correct these possible effects.
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50 Although this health region comprises a wide and varied territory, all health
51 centres involved in the study depend on the public health services of the region so that
52 both clinical care protocols and direct medical costs are standardized according to
53 official publications and will be homogeneous for the entire sample.
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56 Regarding the indirect costs, only those people who are linked to the social
57 security system and can access its benefits will be able to provide data about
58 productivity costs. Therefore, it excludes independent and informal workers,
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3 unemployed people, and housewives of whom we will not have any background of their
4 productivity loss. In this sense, although the human capital approach could overestimate
5 productivity costs, it could be compensated if we consider that there is no data recorded
6 of these population subgroups that also represent a productivity loss for society due to
7 the side effects of their illness processes.
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11 Finally, and even though a 1-year time horizon is a strength of the study since it
12 will allow assessing long-term changes, it may also face a possible sample loss during
13 the follow-up. To minimize sample loss, reminders for the interviews will be
14 implemented, and even different strategies will be used for data collection, such as
15 telephone calls and online survey platforms.
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20 If the results show to be utility-cost, this study will support, through efficiency
21 evidence, the incorporation of a MI to the usual practice for FMS in primary care
22 centres of Catalonia, Spain. What is more, health improvements and cost reductions on
23 sanitary and social resources are expected. To conclude, it is intended that this new
24 intervention proposal be replicated in other health areas of Catalonia and Spain, and
25 considered as a guide for other European health systems.
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32 **AUTHOR CONTRIBUTIONS**

33 **VMA, MC, CAM, AB, JFS, and AQG** participated in the design of the study. **VMA**
34 wrote the draft versions with the review of all authors. **RCA, NCQ, GGS, MCS, IFA,**
35 **AQG, AB, CAM, JFS, and VMA** are involved in the development of the general
36 project and the RCT study from which this qualitative study is related.
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46 *l'Ebre*, and the *Unitat de Sistemes d'informació de la Gerència Territorial Terres de*
47 *l'Ebre*. Likewise, the participation and support of all healthcare and non-healthcare
48 professionals who collaborate in the implementation of this study and data collection
49 are appreciated.
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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

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3 (67.5%) to indirect costs attributable to productivity losses.¹¹ Moreover, this study
4 evidenced that: (i) non-pharmacological therapies accounted the highest cost of direct
5 healthcare resources, and involved three times more than the cost of drug treatment; (ii)
6 there was a significant association between disease severity and higher total costs; and
7 (iii) patients with permanent working disability implies the highest use of resources.¹¹
8 However, all these findings were achieved over a decade ago, and an update of the data
9 is necessary for the Spanish public health system.

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

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

51 This study aims to perform a CUA on a MI (that consists of health education,
52 physical activity, and cognitive-behavioural therapy) for patients with FMS compared to
53 the usual clinical care (UCC),³³ provided within the 11 primary healthcare centres of the
54 *Gerència Territorial Terres de L'Ebre* of the Catalan Institute of Health, Spain. The
55 results of this economic assessment are expected to support the evidence of the
56 randomized clinical trial (RCT) related to this project.³⁴ (ClinicalTrials.gov:
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3 NCT04049006).³⁵ This new intervention proposal will hopefully reinforce the UCC,
4 enhance patients' QOL, and promote efficiency in health and social resources
5 allocation.
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10 **METHOD**

11 **Design**

12 This study protocol has been drafted based on the literature review and following the
13 Consolidated Health Economic Evaluation Reporting Standards (CHEERS).³⁶ Medical
14 Research Council guidance³⁷ for complex interventions has been taken into account for
15 the RCT study.
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20 For the design of this economic evaluation study, a CUA will be conducted from
21 a societal perspective so that indirect non-medical cost variables will be included. Also,
22 a temporal horizon of 12-month will be used to assess health outcomes and costs in the
23 long-term. This methodological decision is based on the clinical symptoms of FMS, its
24 consequences, its tendency to chronicity, and the fact that its treatment is associated
25 with on-going clinical management.
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30 The human capital approach has been judged as the most suitable method for
31 this study due to limitations in the data source since only full sick days, prescribed by
32 the General Practitioner (GP), and the period with a medical disability can be extracted
33 from the computerized medical history program (eCAP).
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38 The elements to be compared in this study are the UCC^{21,33,38,39} for patients with
39 FMS, and the UCC plus a MI provided in primary care centres. The MI consists of a 12-
40 week group program of 2-hour weekly combining: 7 health education instructions, 11
41 pieces of training on physical activity and physical health, and 7 interventions of
42 psychological therapy based on cognitive-behavioural strategies and pain management.
43 Group therapy is being delivered by the general practitioner specialized in FMS, the
44 physiotherapist, and the psychologist with the support of the head nurses of each health
45 centre involved.
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53 **Study population**

54 The patients recruited for the study sample are shortlisted from the electronic medical
55 records system eCAP (computerized medical history program) belonging to the Catalan
56 Health Service (CatSalut) and the Catalan Health Institute (CHI). Only the medical
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3 records of the 11 primary care centres of the *Gerència Territorial Terres de L'Ebre* in
4 Catalonia (Spain) are included. Allocation to study groups is randomized according to a
5 randomized list by health centre. The randomized strategy has been designed in order to
6 obtain a representative sample giving patient's sociodemographic diversity throughout
7 the territory. The inclusion criteria are detailed in the RCT protocol study.³⁴
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13 Patient and Public Involvement

14 Patients or the public will not be involved in the design or conducting, or reporting, or
15 dissemination plans of our research.
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20 Outcomes measures and data collection

22 Health outcomes

23 The utilities will be obtained based on the results of the health-related QOL SF-36
24 questionnaire⁴⁰ (Optum, Inc. license number QM048943) and the estimation of quality-
25 adjusted life years (QALYs). This measurement instrument is administrated to the study
26 sample at baseline, immediately after the intervention, and at 6 and 12 months of
27 follow-up. Sociodemographic and clinical variables are registered at baseline and are
28 fully detailed in the RCT study protocol.³⁵ The collected data is introduced in a software
29 application that has been specially designed for study and is available on the *Terres de*
30 *l'Ebre* CHI website, linked to the electronic medical records.
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40 Cost outcomes

41 Direct and indirect costs, related with the use of health and social resources, will be
42 estimated in euros (€) according to the official prices for the public sector which are
43 published in the *Diari Oficial de la Generalitat de Catalunya* (DOGC)⁴¹ (updated to
44 2019), and in the Spanish Statistics National Institute (SNI), respectively. Table 1 shows
45 the description of cost variables and data sources which will be taken retrospectively
46 12-month before the start date of the MI and 12-month after the end of the MI.
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54 Table 1. Cost outcomes measurements and data collection
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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

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3 or partial loss of working capacity in the long-term. In the first case, a GP determines if
4 a patient is unable to work in the short-term. In the second case, a medical board
5 assesses in depth the medical background and physical and mental condition of the
6 person in order to determine if a permanent disability should be provided. These
7 measurements will be estimated based on full sick leave days and months spent with a
8 disability, respectively.
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13 We will not include other non-medical costs in the data collection, such as
14 presenteeism and unpaid lost time, due to the limitations in the data available through
15 our data source eCap.
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18 The price weight of the social costs will be determined by the calculation of a
19 total annual average salary (including regular and extra payments), for the Catalonia
20 region, which is registered on the official records of the Statistics National Institute.⁴³
21 This estimation will be accounted for both part and full-time working schedules, and all
22 activity sectors (industry, construction, and services except housework).
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25 Data collection is expected to be completed by April 2021.
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28 29 30 31 Sample size

32 A total number of 260 participants have been calculated as the sample-size (130
33 subjects per study arm) based on variations in the SF-36 questionnaire and in order to
34 detect a score difference equal or higher than 5 points, assuming an alpha error of 0.05,
35 a beta error of 0.05 in a bilateral contrast, and a dropout rate of 20%.³⁴ Consequently,
36 between 10 and 13 MI groups with their respective control groups (UCC) are required,
37 including 10-12 patients per group.
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44 45 Statistical analysis

46 The SPSS version 25 and the Stata version 15 for Windows will be used for the
47 statistical analysis. First, a descriptive analysis of the sample will be carried out
48 comparing its characteristics between the study arms.
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51 As an economic evaluation outcome measure, the incremental ratio of the cost-
52 utility will be estimated, dividing the difference in total mean costs in both UCC and MI
53 by the differences in QALYs of each study arm. Moreover, 95% confidence intervals
54 will be calculated for all analyses.
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3 Regarding possible biases, the intention-to-treat principle will be applied in
4 order not to affect the random distribution. In addition, to address the loss of follow-up
5 and non-response, multiple imputation approaches to substitute missing values will be
6 implemented.
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10 11 Sensitivity analysis

12 A deterministic sensitivity analysis will be performed to assess the robustness of the
13 results.⁴⁴ Items with a higher cost will be modified in order to compare them with the
14 first results.
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20 **DISCUSSION**

21 This study intends to address FMS as a public health problem with economic
22 repercussions.¹⁰ Indeed, it compromises the health of a significant number of people,
23 who are large consumers of health and social resources in the short and long-term.
24 Therefore, this study is expected to collaborate with the inclusion of a MI for FMS in
25 primary care settings in order to improve patients' QOL and reduce its economic
26 burden.
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32 According to the literature review, the indirect costs attributable to sick leaves
33 and permanent work disability exceed the direct costs of healthcare.^{8 10,11 14–18 19,20} As a
34 result, efforts should be aimed at preventing productivity loss that represents the highest
35 cost for the community and a significant impact on patients' health. From a societal
36 perspective and taking this priority into account, this study incorporates indirect non-
37 medical cost variables that will allow assessing the impact of FMS burden on the social
38 security system.
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45 More accurate methods, such as the friction cost approach, have been
46 acknowledged by the literature for the estimation of the productivity costs. However,
47 the human capital approach has been considered the most suitable for this study
48 considering the data available. Nevertheless, a sensitivity analysis will be performed to
49 assess alternative cost scenarios considering the limitations of this methodological
50 approach. It will include different direct healthcare costs and, if necessary, the price
51 weight of the social cost considering that the salary rate will be an overall annual
52 average estimation without distinction neither of the type of activity nor the working
53 schedule.
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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

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3 collection and analysis to measure the value that society assigns to a state of health; (ii)
4 the gain in health depends on the severity of the condition and, therefore, this value is
5 affected by patients' pain perception and health status; (iii) for long-term diseases such
6 as FMS, where disability accumulates over time, this measurement tool is limited since
7 it assumes that the utility of a health state is independent of the time spent with it, and
8 the previous and subsequent health conditions.²⁴ Although these points pose challenges
9 to overcome from a methodological point of view, CUA is still a valid and effective
10 strategy to carry out health economic evaluations and collaborate with decision-makers
11 in selecting between different intervention alternatives.²⁴
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19 Other limitations related to the instruments and data collection is that the QOL is
20 a multifactor variable that could be influenced by many circumstances not directly
21 attached to the medical issue like family dynamic, working conditions, economic and
22 political context, among others.⁵⁷ Nonetheless, sociodemographic variables will be
23 included in the analysis models trying to correct these possible effects.
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27 Although this health region comprises a wide and varied territory, all health
28 centres involved in the study depend on the public health services of the region so that
29 both clinical care protocols and direct medical costs are standardized according to
30 official publications and will be homogeneous for the entire sample.
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34 Regarding the indirect costs, only those people who are linked to the social
35 security system and can access its benefits will be able to provide data about
36 productivity costs. Therefore, it excludes independent and informal workers,
37 unemployed people, and homemakers of whom we will not have any background of
38 their productivity loss. In this sense, although the human capital approach could
39 overestimate productivity costs, it could be compensated if we consider that there is no
40 data recorded of these population subgroups that also represent a productivity loss for
41 society due to the side effects of their illness processes.
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48 Finally, and even though a 1-year time horizon is a strength of the study since it
49 will allow assessing long-term changes, it may also face a possible sample loss during
50 the follow-up. In order to minimize sample loss, reminders for the interviews will be
51 implemented, and even different strategies will be employed for data collection, such as
52 telephone calls and online survey platforms.
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56 If the results show to be utility-cost, this study will support, through efficiency
57 evidence, the incorporation of a MI to the usual practice for FMS in primary care
58 centres of Catalonia, Spain. What is more, health improvements and cost reductions on
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3 sanitary and social resources are expected. To conclude, it is intended that this new
4 intervention proposal be replicated in other health areas of Catalonia and Spain, and
5 considered as a guide for other European health systems.
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10 **ETHICS AND DISSEMINATION**

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

28 **VMA, MC, CAM, AB, JFS, and AQG** participated in the design of the study. **VMA**
29 wrote the draft versions with the review of all authors. **RCA, NCQ, GGS, MCS, IFA,**
30 **AQG, AB, CAM, JFS, and VMA** are involved in the development of the general
31 project and the RCT study from which this qualitative study is related.
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41 *l'Ebre*, and the *Unitat de Sistemes d'informació de la Gerència Territorial Terres de*
42 *l'Ebre*. Likewise, the participation and support of all healthcare and non-healthcare
43 professionals who collaborate in the implementation of this study and data collection
44 are appreciated.
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51 **COMPETING INTERESTS** The authors have no conflicts of interest to disclose.
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58 Action 2017–2020 within the National Research Program; the Technical, Scientific and
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BMJ Open

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

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3 year of €9,982, comprising €3,245.8 (32.5%) of direct healthcare costs and €6,736.2
4 (67.5%) of indirect costs attributable to productivity losses.¹¹ This study also showed that:
5 (i) non-pharmacological therapies accounted for the highest costs of direct healthcare
6 resources, involving three times more than the cost of drug treatments; (ii) there was a
7 significant direct association between disease severity and total costs; and (iii) patients
8 with a permanent working disability made the most extensive use of resources.¹¹
9 However, these findings were collated over a decade ago, and are in need of updating
10 with reference to the Spanish public health system.
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17 Health economic evaluation is essential in policy decision-making since it
18 provides evidence enabling the efficiency of an intervention, program, or project to be
19 determined, thereby making it possible to optimize the benefits from limited resources.²²
20 Of the economic evaluation techniques, cost-utility analysis (CUA) estimates how much
21 wellbeing is achieved for each monetary unit invested, taking into account both health
22 outcomes and costs. This technique is a useful tool for comparing intervention strategies,
23 especially those with quite different health outcomes because a standard utility unit is
24 commonly used to measure all of them: the quality-adjusted life year (QALY).²³ Despite
25 its limitations, especially in measuring the value that society attaches to different health
26 status, CUA is better than other economic evaluation strategies and provides useful
27 information for resource allocation processes.²⁴
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36 The economic evaluation of intervention programs for FMS has been little studied.
37 According to the published findings, non-pharmacological strategies, especially
38 psychology-based therapies, have yielded positive results in terms of reducing the
39 economic burden of FMS.^{19,25-31} In Spain, some cost-utility studies comparing alternative
40 interventions (i.e., psychoeducational therapy, acceptance and commitment therapy,
41 internet-delivered exposure therapy, and mindfulness-based stress reduction) with usual
42 drug treatment have demonstrated the cost-utility from a healthcare and social
43 perspective.^{19,26-28,30} However, only the FibroQoL study has included a multicomponent
44 intervention (MI) modality, and it had significant technical and methodological
45 differences compared with the current proposal.^{32,26}
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53 This study aims to perform a CUA on an MI consisting of health education,
54 physical activity, and cognitive-behavioural therapy, for patients with FMS compared
55 with their treatment under usual clinical care (UCC),³³ provided within the 11 primary
56 care centres of the Gerència Territorial Terres de L'Ebre of the Institut Català de la Salut,
57 Spain. The results of this economic assessment are expected to support the evidence of
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3 the randomized clinical trial (RCT) related to this project.³⁴ (ClinicalTrials.gov:
4 NCT04049006).³⁵ It is hoped that this new proposed intervention will reinforce the UCC,
5 enhance patients' QOL, and promote the efficient allocation of health and social
6 resources.
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10 11 **METHOD**

12 13 **Design**

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15 This study protocol has been drafted based on a literature review and following the
16 recommendations of the Consolidated Health Economic Evaluation Reporting Standards
17 (CHEERS)³⁶ about preliminary results. The UK Medical Research Council guidance³⁷
18 for complex interventions has been taken into account in planning the RCT study.
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22 The design of this economic evaluation study requires a CUA to be conducted
23 from a societal perspective so that indirect non-medical cost variables are included.
24 Health outcomes and costs will be assessed over a 12-month duration to ensure that long-
25 term outcomes are measured. This methodological decision is based on the clinical
26 symptoms of FMS, its consequences, its tendency to chronicity, and the fact that its
27 treatment is associated with on-going clinical management.
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31 The human capital approach has been judged the most suitable method for this
32 study due to the limitations of the data source, given that only full sick days, prescribed
33 by the general practitioner (GP), and the period with a medical disability can be extracted
34 from the computerized medical history program (eCAP).
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38 The elements to be compared in this study are the UCC^{21,33,38,39} for patients with
39 FMS, and the UCC plus an MI provided in primary care centres. The MI consists of a 12-
40 week group program of 2 hours per week combining: 7 health education instructions, 11
41 items of physical activity and physical health training, and 7 interventions of
42 psychological therapy based on cognitive-behavioural strategies and pain management.
43 Group therapy is being delivered by the general practitioner specialized in FMS, the
44 physiotherapist, and the psychologist, with the support of the head nurses of each health
45 centre involved.
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54 55 **Study population**

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57 The patients recruited for the study sample are shortlisted from the electronic medical
58 records system eCAP (computerized medical history program) of the Catalan Health
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3 Service (CatSalut) and the Institut Català de la Salut. Only the medical records of the 11
4 primary care centres of the Gerència Territorial Terres de L'Ebre in Catalonia, Spain, are
5 included. Patients are allocated at random to study groups from lists provided by the
6 health centres in order to obtain a representative sample giving patient's
7 sociodemographic diversity throughout the territory. The inclusion criteria are set out in
8 detail in the RCT protocol study.³⁴
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15 Patient and Public Involvement

16 Neither patients nor the public will be involved in the design or execution of our research,
17 or the reporting and dissemination of its results.
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22 Outcomes measures and data collection

23 Health outcomes

24 The utilities will be obtained based on the results of the health-related QOL SF-36
25 questionnaire⁴⁰ (Optum, Inc., license number QM048943) and the QALY estimates. This
26 measurement instrument is administered to the study sample at baseline, immediately
27 after the intervention, and at 6 and 12 months of follow-up. Sociodemographic and
28 clinical variables are registered at baseline and are fully described in the RCT study
29 protocol.³⁵ A software application, specially designed for the study and linked to digital
30 medical records, is employed to register the collected data.
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40 Cost outcomes

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

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

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

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

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22 Data collection is expected to be completed by April 2021.

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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.

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3 To avoid possible biases as far as possible, the intention-to-treat principle will be
4 applied in order not to affect the random distribution. In addition, to address the loss of
5 follow-up and non-response, multiple imputation approaches to substitute missing values
6 will be implemented.
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10 11 Sensitivity analysis

12 A deterministic sensitivity analysis will be performed to assess the robustness of the
13 results.⁴⁴ Items with a higher cost will be modified in order to compare them with the
14 initial results.
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20 21 **DISCUSSION**

22 This study aims to address FMS as a public health problem with economic
23 repercussions.¹⁰ FMS compromises the health status of a considerable number of people,
24 who consequently consume substantial health and social resources in the short and long
25 terms. Therefore, this study is expected to support the inclusion of an MI for FMS in
26 primary care settings in order to improve patient QOL and to reduce its economic burden.
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30 The literature review indicates that the indirect costs attributable to sick leave and
31 permanent work disability exceed the direct costs of healthcare.^{8-11,14-20} Therefore,
32 preventing productivity loss should be prioritized since this imposes the highest cost on
33 the community. This study adopts a societal perspective, including indirect non-medical
34 cost variables that will allow us to assess the impact of the burden of FMS on the social
35 security system.
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41 More accurate methods, such as the friction cost approach, have been
42 acknowledged as being effective for estimating productivity costs. However, the human
43 capital approach has been considered the most suitable for this study, given the data
44 available. However, a sensitivity analysis will be performed to assess alternative cost
45 scenarios that take into account the limitations of this methodological approach. It will
46 include different direct healthcare costs and, if necessary, the weighted price of the social
47 cost, considering that the salary rate will be an overall annual average estimate without
48 distinction between the type of activity or the working schedule.
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55 Additionally, another economic concern involves the costs of the diagnostic
56 process since it is purely clinical.⁴⁵ Before FMS is diagnosed, other possible diseases must
57 be ruled out with objective tests and by a variety of medical specialists. This process is
58 often long and exhausting for patients, frustrating for doctors, and expensive from the
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3 perspective of the health system.⁴⁶ Furthermore, the presence of comorbidities can hinder
4 and delay the diagnosis, as well as complicating the choice of a treatment strategy.⁴⁷
5 Hence, the study sample could show differences in the use of resources between patients
6 depending on the year of diagnosis and the medical records. However, it is expected that
7 the randomized allocation will balance these differences between the study arms.
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12 Given the evidence about the economic burden of FMS,^{8,14–21} particularly related
13 to the loss of productivity, UCC does not seem to be entirely helpful for reducing the
14 effects of chronicity or for preventing disability. Thus, FMS treatment should not be
15 limited to short-term pain relief. It should also promote the acceptance of the condition,
16 the self-management of symptoms, and empowering patients to deal with FMS in their
17 daily lives. Non-pharmacological approaches could address the consequences of
18 chronicity, reducing healthcare overprovision and overmedication. Indeed, the proposed
19 MI aims to address these challenges by combining physical, psychological, and health
20 educational methods.
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24 Findings regarding the efficacy of MI for patients with this condition have proved
25 helpful for improving QOL, physical function, psychological variables, and or pain after
26 3 to 12 months of follow-up.^{48–53} However, more studies are required to address the
27 economic efficiency of this type of intervention, particularly in the context of the Spanish
28 public health system.
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32 Evidence of efficiency is essential for decision-making in order to allow budgets
33 to be prioritized for those treatment options that prove to be cost-efficient and to fulfil
34 patients' health needs. Economic evaluation is key to overcoming the obstacles arising
35 from the uncertainty about the real costs and the sustainability of particular
36 interventions.⁵⁴ The CUA is a popular measurement tool that combines quantity data and
37 QOL, based on the opinions of the healthcare users, associated with a monetary cost. It
38 involves a participatory and economic evidence-based decision-making strategy that
39 considers stakeholders' preferences.⁵⁵ However, this methodology is controversial,⁵⁶ the
40 main points of contention being: (i) the lack of transparency about data collection and
41 analysis regarding the measurement of the value that society assigns to a state of health;
42 (ii) that the gain in health depends on the severity of the condition, so the value is affected
43 by patients' perception of their pain and health status; (iii) the limited value of this
44 measurement tool for long-term diseases such as FMS, where disability accumulates over
45 time since it assumes that the utility of a health state is independent of the time the patient
46 has experienced it, and the influence of previous and subsequent health conditions.²⁴
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3 Although all these factors pose methodological challenges, CUA is still a valid and
4 effective strategy for carrying out health economic evaluations and collaborating with
5 decision-makers in choosing between intervention alternatives.²⁴
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8 Another limitation related to the instruments and the data collection stems from
9 the QOL being a multifactorial variable that could be influenced by non-medical
10 circumstances such as family dynamics, working conditions, and economic and political
11 contexts, among others.⁵⁷ Sociodemographic variables will therefore be analysed in the
12 models in order to control for these possible effects.
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17 This health region covers a wide and varied territory. However, all the primary
18 care centres participating in the study are run by the public health administration, meaning
19 that clinical care protocols and direct medical costs are both standardized according to
20 official regulations and will be homogeneous for the entire sample.
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24 Regarding the indirect costs, only those people who are linked to the social
25 security system and who have access to its benefits will be able to provide data about
26 productivity costs. The study sample, therefore, excludes self-employed and unemployed
27 people, homemakers, and workers in the informal economy. In this sense, although the
28 human capital approach could overestimate productivity costs, it could be offset by the
29 missed data of these population subgroups that contribute to the productivity loss to
30 society due to the side effects of their illness.
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36 Finally, this study could be affected by sample loss-to-follow-up given the one-
37 year time horizon. This methodological characteristic is also a strength of the study since
38 it will allow long-term changes to be assessed. In order to minimize the number of
39 participants abandoning the study, reminders of upcoming interviews will be sent, and
40 different data collection methods, such as telephone calls and online survey platforms,
41 may even be used.
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46 If the results indicate that the intervention is utility-cost-effective, this study will
47 support, through efficiency evidence, the inclusion of an MI as part of the usual practice
48 for FMS in primary care centres in Catalonia, Spain. Additionally, enhancements of
49 patient QOL and cost reductions for health and social resources are expected. We hope
50 that this new proposed intervention could be replicated throughout the rest of Catalonia
51 and Spain, and used more extensively as a guide within other European health systems.
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58 **ETHICS AND DISSEMINATION**

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3 This study was designed in accordance with the Helsinki/Tokyo Declaration. It was
4 approved by the Clinical Research Ethics Committee of the Fundació Institut Universitari
5 per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), on
6 25/04/2018 (code P18/068). Information is delivered to participants orally and in writing
7 before their necessary informed consent is obtained. This project respects the data
8 protection laws guaranteeing participant anonymity. Dissemination strategy includes
9 publications in scientific journals and through presentations in the local and national
10 media and at academic conferences.
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19 **AUTHOR CONTRIBUTIONS**

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