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COST-UTILITY AND QUALITATIVE ASPECTS ON THE IMPLEMENTATION OF A COMPLEX INTERVENTION FOR FIBROMYALGIA SYNDROME: A PRAGMATIC RANDOMISED CONTROLLED TRIAL IN PRIMARY CARE

Victoria Mailen Arfuch Prezioso

Universitat Autònoma de Barcelona

Facultad de Medicina

Departamento de Pediatría, Obstetricia y Ginecología, y Medicina Preventiva y Salud Pública

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DOCTORAL THESIS:

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Coste-utilidad y aspectos cualitativos sobre la implementación de una intervención compleja para el tratamiento de la fibromialgia: un ensayo pragmático controlado aleatorizado en la atención primaria

Author:
Victoria Mailen Arfuch Prezioso

Supervisor:
Dra. Anna Berenguera Ossó

Co-supervisor:
Dra. Carina Aguilar Martín

Tutor:
Dr. Miquel Porta Serra

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*"**T**he most beautiful people we have known are those who have known defeat, known suffering, known struggle, known loss, and have found their way out of those depths".*

Elisabeth Kübler-Ross

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Summary

Resum

Introducció. La síndrome de fibromiàlgia (SFM) és una afecció musculoesquelètica crònica que comporta dolor corporal generalitzat, fatiga, alteracions del son i malestar emocional, entre altres símptomes, que redueixen la funcionalitat i la qualitat de vida. A causa del seu impacte significatiu en les esferes biopsicosocials i l'exercici laboral dels pacients, l'SFM és potencialment incapacitant. No existeix un consens científic respecte a la seva etiopatogènia, el diagnòstic es basa principalment en l'avaluació clínica; el tractament, i principalment en el maneig dels símptomes. Per tant, les decisions dels pacients sobre l'estil de vida i els comportaments de salut tenen un paper clau en el maneig d'aquesta condició. Tot i la seva aparença invisible, la seva prevalença i la seva creixent càrrega econòmica per a la societat són preocupants. Existeix un iniquitat de gènere, afectant més a les dones de mitjana edat, cosa que planteja un desafiament mèdic i una problemàtica de gènere. Tant la literatura com les guies de pràctica clínica nacionals i internacionals suggereixen utilitzar un enfocament multidisciplinari de tractament juntament amb l'abordatge farmacològic habitual. En aquesta línia, i seguint les directrius mèdiques de l'administració sanitària pública de Catalunya, es va desenvolupar un programa d'intervenció multicomponent (IMC) a la Unitat de Síndromes de Sensibilitat Central de la regió sanitària de les Terres de l'Ebre. Aquesta intervenció de salut va ser dissenyada per enfortir la pràctica clínica habitual a l'SFM i millorar la qualitat de vida dels pacients a través d'un programa que combina educació per a la salut, exercici físic aeròbic i teràpia cognitivoconductual.

Objectiu. Aquesta tesi doctoral té com a objectiu avaluar aquesta nova intervenció complexa per a l'SFM des de la perspectiva qualitativa i d'economia de la salut. Aquesta intervenció va ser administrada a pacients amb l'SFM a centres d'Atenció Primària a la Salut dins de la Gerència Territorial Terres de l'Ebre, pertanyent a l'Institut Català de la Salut (ICS), Espanya, des d'abril del 2017 fins al gener del 2020.

L'*Estudi I* tenia com a objectiu capturar les opinions dels pacients participants a la IMC sobre el format, els continguts i els beneficis a curt i llarg termini per a la salut del programa mitjançant l'exploració dels significats socialment construïts emergents en grups de pacients.

A l'*Estudi II* tenia com a objectiu comprendre les experiències viscudes, l'impacte personal, els aprenentatges i el desenvolupament subjectiu dels pacients que van participar de la IMC, des d'una perspectiva individual.

Finalment, l'*Estudi III* va avaluar el cost-utilitat de la nova intervenció en comparació de l'atenció clínica habitual a l'Atenció Primària a la Salut.

Mètodes. La metodologia implementada es va basar en una estratègia de mètodes mixtos, segons el que recomana el "Medical Researh Council" per avaluar intervencions complexes. Per fer-ho es van realitzar tres estudis, dos basats en una metodologia qualitativa i una avaluació econòmica.

Els *Estudis I* i *II* van adoptar una metodologia qualitativa a través les tècniques de grups focals de discussió (GFD) i entrevistes individuals, respectivament. Ambós casos, els informants van ser seleccionats intencionalment entre aquells pacients que van participar en almenys un 75% de la IMC durant els darrers 12 mesos. Així mateix, les dades van ser recollides mitjançant guies de preguntes semiestructurades i enregistraments d'àudio, que després van ser anonimitzades per emmagatzemar-les i analitzar-les. Els GFD es van dur a terme de forma presencial, mentre que les entrevistes individuals es van realitzar tant en aquesta mateixa modalitat com telefònicament a causa del brot de COVID-19. Les transcripcions literals i sistemàtiques (paraula per paraula) es van analitzar mitjançant anàlisi temàtica i des de l'enfocament de la fenomenologia hermenèutica, a partir del qual es van identificar, organitzar i interpretar codis, categories i temes. A més, es van realitzar triangulacions entre els investigadors per garantir el rigor i la qualitat científica dels estudis.

L'*Estudi III* presenta una anàlisi de cost-utilitat realitzada juntament amb un assaig controlat aleatori pragmàtic i es va dur a terme des d'una perspectiva social, un enfocament de capital humà i un horitzó temporal d'un any. Les dades es van recopilar des de l'abril del 2017 fins al març del 2021. La qualitat de vida dels pacients es va recollir mitjançant el qüestionari SF-36v2 i després es va transformar en Anys de Vida Ajustats per Qualitat (AVAC) utilitzant l'instrument SF-6Dv2. Les dades necessàries per estimar costos relacionats amb la utilització de serveis es van recollir del sistema d'història clínica electrònica (eCAP) i de l'informe oficial preus de serveis sanitaris i medicaments d'Espanya. Els costos totals van incloure costos mèdics directes (serveis sanitaris a Atenció Primària, atenció mèdica especialitzada, tècniques de diagnòstic per imatges i medicaments receptats) i pèrdues de productivitat (dies de baixa laboral per malaltia). A partir d'una anàlisi completa de casos, es van estimar les ràtios incrementals del cost-utilitat (RCU), crues i ajustades, per comparar les estratègies de tractament tenint en compte el llindar de cost-efectivitat estimat per al sistema nacional de salut espanyol. Finalment, es van fer anàlisis de

sensibilitat deterministes (d'una i dues vies) per contrastar els resultats obtinguts. La primera estratègia va incloure variacions als principals components de cost de l'atenció mèdica directa (metges generals i infermeres en atenció primària) en funció de la despesa sanitària ponderada de l'any 2021. A la segona anàlisi de sensibilitat, es va afegir una variació en l'adherència terapèutica , en eliminar de la mostra aquells pacients amb menys del 66% d'assistència a les sessions de la IMC (8 de 12 sessions totals), per avaluar l'esquema d'implementació del programa.

Resultats. A l'*Estudi I*, es van dur a terme dos GFDs al febrer i juliol de 2020 i van participar 19 dones (GFD1 n=12, ≥6 i 12 mesos després de la intervenció; GFD2 n=7, <6 mesos després de la intervenció) . Els resultats de l'anàlisi es van organitzar en cinc categories i temes. En general, els participants van coincidir que la IMC va ser una experiència positiva i beneficiosa quant al seu format i continguts temàtics, i en recomanarien la continuació. Es va destacar el paper del grup de parells i professionals en la legitimació de l'SFM, el suport a l'experiència de la malaltia i l'alleujament del patiment. Tot i que no es van reportar canvi significatius a nivell dels símptomes físics, els informants van destacar haver adquirit habilitats i estratègies per al maneig del dolor. Entre els suggeriments per millorar la IMC es van trobar: ampliar el cronograma i el contingut del programa en matèria de nutrició, suport psicològic, adaptacions individuals de l'exercici físic, orientació sobre la medicació i temes relacionats amb la sexualitat.

A l'*Estudi II*, es van entrevistar deu dones el juliol del 2020 entre 30 minuts i 1 hora. A partir de l'anàlisi es van identificar quatre temes principals: La legitimització de l'SFM a través de la IMC, La IMC com a experiència socialitzadora, Aprendre a viure amb l'SFM a través de la IMC, i suggeriments per millorar la IMC. Així mateix, les persones entrevistades van considerar que el programa d'intervenció va ser una experiència reveladora que va contribuir a millorar la salut i el benestar percebuts. Altres beneficis de la IMC destacats van ser la presa de consciència sobre el procés de malaltia, el desenvolupament d'habilitats d'afrontament i apoderament, l'autoperdó i l'automaneig dels símptomes. Com a l'Estudi I, els participants van suggerir la inclusió de psicoteràpia d'expressió.

Finalment, a l'*Estudi III* es van analitzar dades de 297 individus (161 subjectes del grup d'intervenció i 136 controls). Els RCUs obtinguts, 1,780.75 € per AVAC guanyat al model cru i 851.67 € al model ajustat, van suggerir que la millora en la qualitat de vida dels participants compensava l'augment del cost en caure per sota del preu màxim acceptat per una unitat extra

de qualitat de vida a Espanya. A més, aquestes troballes van ser recolzades per les anàlisis de sensibilitat en variar els costos mèdics directes de més pes i en corregir per adherència terapèutica. Aquest darrer cas, en augmentar l'assistència a la IMC, es va observar la dominància del programa sobre l'atenció clínica habitual i el potencial d'estalvi de costos, cosa que indicaria els beneficis del disseny de la intervenció.

Conclusió. Els resultats obtinguts indiquen que la IMC avaluada és cost-útil i valorable per millorar la qualitat de vida i el benestar dels pacients. En aquest sentit, levidència proporcionada per metodologies quantitatives i qualitatives utilitzades suggereix que la societat podria beneficiar-se de l' enfortiment de la pràctica clínica habitual per l'SFM a través de la implementació del programa terapèutic proposat. Això no obstant, s'han identificat possibles ajustaments necessaris a la intervenció per adaptar-la a les necessitats individuals dels pacients dins dels recursos disponibles i així per maximitzar-ne els beneficis. A més, l'avaluació de mètodes mixtos va demostrar que és una estratègia integral per a la triangulació de dades en avaluar intervencions complexes. En resum, aquest treball de tesi proporciona evidència científica per a la presa de decisions enfocades a millorar l'atenció sanitària de l'SFM, reduir-ne la càrrega per a la societat i millorar la qualitat de vida dels pacients en un context de falta d'evidència.

Resumen

Introducción. El síndrome de fibromialgia (SFM) es una afección musculoesquelética crónica que acarrea dolor corporal generalizado, fatiga, alteraciones del sueño y emocionales, entre otros síntomas somáticos, que reducen la funcionalidad y la calidad de vida. Debido a su significativo impacto en las esferas biopsicosociales y el desempeño laboral de los pacientes, el SFM es potencialmente incapacitante. Al no existir consenso científico respecto a su etiopatogenia, el diagnóstico se basa principalmente en la evaluación clínica; y su tratamiento, en el manejo de los síntomas. Por tanto, las decisiones de los pacientes sobre el estilo de vida y sus comportamientos de salud juegan un papel clave en el manejo de esta condición. A pesar de su apariencia invisible, su prevalencia y su creciente carga económica para la sociedad son preocupantes. Más aún, las mujeres de mediana edad son el grupo más afectado, lo que plantea un desafío médico y una problemática de género. Tanto la literatura como las guías clínicas nacionales e internacionales sugieren utilizar un enfoque multidisciplinario de tratamiento junto al abordaje farmacológico habitual. En esta línea, y siguiendo las directrices médicas de la administración sanitaria pública de Cataluña, se desarrolló un programa de intervención multicomponente (IMC) en la Unidad de Síndromes de Sensibilidad Central de la región sanitaria de las *Terres de L'Ebre*. Esta intervención de salud fue diseñada para fortalecer la práctica clínica habitual en el SFM y mejorar la calidad de vida de los pacientes a través de un programa que combina educación para la salud, ejercicio físico aeróbico y terapia cognitivo-conductual.

Objetivo. La presente tesis doctoral tiene como objetivo evaluar esta nueva intervención compleja para el SFM desde la perspectiva cualitativa y de economía de la salud. Esta intervención fue administrada a pacientes con el SFM en centros de Atención Primaria a la Salud dentro de la *Gerència Territorial Terres de L'Ebre*, perteneciente al *Institut Català de la Salut* (ICS), España, desde abril de 2017 hasta enero de 2020.

El *Estudio I* buscó capturar las opiniones de los pacientes participantes en la IMC sobre el formato, los contenidos y los beneficios a corto y largo plazo para la salud del programa mediante la exploración de los significados socialmente construidos emergentes en grupos de pacientes.

En el *Estudio II* se buscó comprender las experiencias vividas, el impacto personal, los aprendizajes y desarrollo subjetivo de los pacientes que participaron de la IMC, desde una perspectiva individual.

Por último, el *Estudio III* evaluó el coste-utilidad de la nueva intervención en comparación con la atención clínica habitual en la Atención Primaria a la Salud.

Métodos. La metodología implementada se basó en una estrategia de métodos mixtos, según lo recomendado por el "Medical Research Council" para evaluar intervenciones complejas. Para ello se realizaron tres estudios, dos de ellos basados en una metodología cualitativa y una evaluación económica.

Los *Estudios I* y *II* adoptaron una metodología cualitativa a través de diseños de grupos focales de discusión (GFD) y entrevistas individuales, respectivamente. En ambos casos, los informantes fueron seleccionados intencionalmente entre aquellos pacientes que participaron en al menos un 75% de la IMC durante los últimos 12 meses. Asimismo, los datos fueron recogidos mediante guías de preguntas semiestructuradas y grabaciones de audio, que luego fueron anonimizados para su almacenamiento y análisis. Los GFD se llevaron a cabo de forma presencial, mientras que las entrevistas individuales se realizaron tanto en esta misma modalidad como telefónicamente debido al brote de COVID-19. Las transcripciones textuales (palabra por palabra) se analizaron mediante análisis temático y desde el enfoque de la fenomenología hermenéutica, a partir del cual se identificaron, organizaron e interpretaron códigos, categorías y temas. Además, se realizaron triangulaciones entre los investigadores para garantizar el rigor y calidad científica de los estudios.

El *Estudio III* presenta un análisis de coste-utilidad realizado junto con un ensayo controlado aleatorio pragmático y fue llevado a cabo desde una perspectiva social, un enfoque de capital humano y un horizonte temporal de un año. Los datos se recopilaron desde abril de 2017 hasta marzo de 2021. La calidad de vida de los pacientes se recogió mediante el cuestionario SF-36v2 y luego se transformó en Años de Vida Ajustados por Calidad (AVAC) utilizando el instrumento SF-6Dv2. Los datos necesarios para estimar costes relacionados a la utilización de servicios, se recogieron del sistema de historia clínica electrónica (eCAP) y del informe oficial precios de servicios sanitarios y medicamentos de España. Los costes totales incluyeron costes médicos directos (servicios sanitarios en Atención Primaria, atención médica especializada, técnicas de diagnóstico por imágenes y medicamentos recetados) y pérdidas de productividad (días de baja laboral por enfermedad). A partir de un análisis completo de casos, se estimaron los ratios incrementales del coste-utilidad (RCU), crudos y ajustados, para comparar las estrategias de tratamiento teniendo en cuenta el umbral de coste-efectividad estimado para el sistema nacional

de salud español. Finalmente, se realizaron análisis de sensibilidad deterministas (de una y dos vías) para contrastar los resultados obtenidos. La primera estrategia incluyó variaciones en los principales componentes de coste de la atención médica directa (médicos generales y enfermeras en atención primaria) en función del gasto sanitario ponderado del año 2021. En el segundo análisis de sensibilidad, se añadió una variación en la adherencia terapéutica, al eliminar de la muestra aquellos pacientes con menos del 66% de asistencia a las sesiones de la IMC (8 de 12 sesiones totales), con el fin de evaluar el esquema de implementación del programa.

Resultados. En el *Estudio I*, se llevaron a cabo dos GFDs en febrero y julio de 2020 y participaron 19 mujeres (GFD1 n=12, ≥6 y 12 meses después de la intervención; GFD2 n=7, <6 meses después de la intervención). Los resultados del análisis se organizaron en cinco dominios y temas. En general, los participantes coincidieron en que la IMC fue una experiencia positiva y beneficiosa en cuanto a su formato y contenidos temáticos, y recomendarían su continuación. Se destacó el papel del grupo de pares y profesionales en la legitimación del SFM, el apoyo a la experiencia de la enfermedad y el alivio del padecimiento. Aunque no se reportaron cambios significativos a nivel de los síntomas físicos, los informantes destacaron haber adquirido habilidades y estrategias para el manejo del dolor. Entre las sugerencias para mejorar la IMC se hallaron: ampliar el cronograma y el contenido del programa en materia de nutrición, apoyo psicológico, adaptaciones individuales del ejercicio físico, orientación sobre la medicación y temas relacionados con la sexualidad.

En el *Estudio II*, se entrevistaron a diez mujeres en julio de 2020 entre 30 minutos y 1 hora. A partir del análisis se identificaron cuatro temas principales: La legitimización del SFM a través de la IMC, La IMC como una experiencia socializadora, Aprender a vivir con el SFM a través de la IMC, y Sugerencias para mejorar la IMC. Asimismo, los entrevistados consideraron que el programa de intervención fue una experiencia reveladora que contribuyó a mejorar la salud y el bienestar percibidos. Otros beneficios de la IMC destacados fueron la toma de conciencia sobre el proceso de enfermedad, el desarrollo de habilidades de afrontamiento y empoderamiento, el autoperdón y automanejo de los síntomas. Al igual que en el *Estudio I*, los participantes sugirieron la inclusión de psicoterapia de expresión.

Por último, en el *Estudio III* se analizaron datos de 297 individuos (161 sujetos del grupo de intervención y 136 controles). Los RCUs obtenidos, 1,780.75 € por AVAC ganado en el modelo crudo y 851.67 € en el modelo ajustado, sugirieron que la mejora en la calidad de vida de los

participantes compensaba el aumento del coste al caer por debajo del precio máximo aceptado por una unidad extra de calidad de vida en España. Además, estos hallazgos fueron respaldados por los análisis de sensibilidad al variar los costes médicos directos de mayor peso y al corregir por adherencia terapéutica. Este último caso, al aumentar la asistencia a la IMC, se observó la dominancia del programa sobre la atención clínica habitual y su potencial de ahorro de costes lo que indicaría los beneficios del diseño de la intervención.

Conclusión. Los resultados obtenidos indican que la IMC evaluada es coste-útil y valorable para mejorar la calidad de vida y el bienestar de los pacientes. En este sentido, la evidencia proporcionada por metodologías cuantitativas y cualitativas utilizadas sugiere que la sociedad podría beneficiarse del fortalecimiento de la práctica clínica habitual para el SFM a través de la implementación del programa terapéutico propuesto. No obstante, se han identificado posibles ajustes necesarios a la intervención para adaptarla a las necesidades individuales de los pacientes dentro de los recursos disponibles y así para maximizar sus beneficios. Además, la evaluación de métodos mixtos demostró ser una estrategia integral para la triangulación de datos al evaluar intervenciones complejas. En resumen, este trabajo de tesis proporciona evidencia para la toma de decisiones enfocadas a mejorar la atención sanitaria del SFM, reducir su carga para la sociedad y mejorar la calidad de vida de los pacientes en un contexto de incertidumbre médica.

Abstract

Background. Fibromyalgia syndrome (FMS) is a chronic musculoskeletal condition that presents widespread pain, fatigue, sleep disturbances, and mental distress, among other somatic symptoms, that reduce functionality and quality of life. Due to its significant impact on patients' biopsychosocial spheres and work performance, FMS is potentially disabling. While there is no scientific consensus regarding its etiopathogenesis, the diagnosis is primarily based on clinical assessment and its treatment, on symptom management. Thus, patients' decisions on lifestyle and health behaviours play a key role in illness-management. Despite appearing as an invisible disease, its prevalence and increasing economic burden on society are worrisome. Remarkably, middle-aged females are the most affected group, raising a medical challenge and a gender concern. Literature and national and international guidelines suggest using a multidisciplinary approach alongside the usual pharmacological treatment. In this line and following the medical guideline from the Catalonian public health administration, a multicomponent intervention (MCI) programme was developed in the Central Sensitivity Syndromes Unit from *Terres de L'Ebre* health region. This health intervention was designed to strengthen the routine practice for FMS and improve patients' quality of life by combining health education, aerobic physical exercise and cognitive-behavioural therapy.

Objective. The present doctoral thesis aims to assess this new MCI programme for FMS from a qualitative and health economic perspective. The intervention was administrated to patients with this health condition in primary care centres within the *Gerència Territorial Terres de L'Ebre* health region, belonging to the *Institut Català de la Salut* (ICS), Spain, from April 2017 to January 2020.

Study I sought to capture patients' appraisals of the programme's format, contents, and health benefits in the short and long term by exploring the socially constructed meanings raised in groups of patients.

Moving forward, Study II pursued understanding patients' lived experiences, personal impact and subjective insights after participating in the MCI programme from an individual perspective.

Lastly, *Study III* evaluated the cost-utility of the new intervention compared to the usual clinical care in primary care settings.

Methods. The implemented research methodology involved a mixed-method strategy as

recommended for assessing complex interventions by the Medical Research Council. To this end, three studies were conducted, including two based on qualitative methodology and an economic evaluation.

Studies I and *II* adopted qualitative methodology through focus group and interview designs, respectively. In both cases, informers were purposively sampled from those patients who received the MCI at least 75% within the previous 12 months. Furthermore, data was collected using semi-structured discussion schedules and audio recordings, and was anonymised for storage and analysis. While the focus group discussions (FGD) were conducted face-to-face, the in-depth individual interviews were performed in-person and telephonically due to the COVID-19 outbreak. *Verbatim* transcriptions (word-for-word) were analysed using thematic analysis and through a hermeneutic phenomenology approach, from which codes, categories and themes were identified, organised and interpreted. Furthermore, analyst triangulations were performed to warrant the rigour of the studies.

Study III presents a cost-utility analysis conducted alongside a pragmatic randomised controlled trial from a societal perspective, a human capital approach and a one-year time horizon. Data was collected from April 2017 to March 2021. Quality of life was measured through the SF-36v2 questionnaire and mapped into quality-adjusted life years (QALYs) using the SF-6Dv2 instrument. Data for estimating cost outcomes was collected from the electronic medical record system (eCAP), and the official Spanish prices report for healthcare services and drugs. Total costs comprised direct medical costs (healthcare services in primary care, specialised medical care, diagnostic imaging techniques, and prescribed medications) and productivity losses (sick leave days). Based on a complete case analysis, unadjusted and adjusted incremental cost-utility ratios (ICUR) were estimated to compare the treatment strategies in light of the Spanish cost-effectiveness threshold. Finally, one- and two-way deterministic sensitivity analyses were performed to assess the robustness of the results. The former included variations on major cost components of direct medical care (general practitioners and nurses in primary care) based on the weighted health expenditure from 2021. The latter added a variation in therapeutic adherence by subtracting those patients with less than 66% of session attendance (8 out of 12 total sessions) in order to assess the programme implementation scheme.

Results. In *Study I*, two FGDs took place in February and July 2020 and involved 19 females participants (FGD1 n=12, ≥6 and 12-month post-intervention; FGD2 n=7, <6 months post-

intervention). Results from the analysis were organised into five domains and themes. Overall, participants agreed that the MCI programme was a positive and beneficial experience regarding its format and thematic contents and would recommend its continuation. Highlights were made on the role of peers and professionals in legitimising FMS, supporting the illness experience and mitigating suffering. Even though physical symptoms were not completely overcome, participants reported having gained skills in pain management. Additional suggestions for improving the MCI included broadening the programme timeframe and content regarding nutrition, psychological support, physical exercise adaptations, medication guidance and sexuality.

In *Study II*, ten females were interviewed in July 2020 between 30 minutes to 1 hour. Four themes were identified from the analysis: legitimising fibromyalgia through the MCI, the MCI as a socialising experience, learning how to live with FMS through the MCI, and room for improving the MCI. Likewise, interviewees found the intervention programme an insightful experience that contributed to improved perceived health and well-being. Gaining in illness awareness, coping skills, empowerment, self-forgiveness, and symptom self-management emerged as some of the most relevant benefits from the MCI during the interpretative analysis. As in Study I, the inclusion of expression psychotherapy was also suggested.

Lastly, in *Study III,* data from 297 individuals was analysed (161 subjects from the intervention group and 136 controls). The obtained crude ICUR of €1,780.75 per QALY gained and the adjusted ICUR of €851.67 suggested that the improvement in participants' quality of life outweighed the cost increase as it fell below the maximum price accepted for an extra unit of quality of life in Spain. Furthermore, these findings were supported by the sensitivity analyses when variating major direct medical costs and when correcting by therapeutic adherence. The latter indicated the dominance of the programme over the usual clinical care and its cost-saving potential when increasing session attendance, which suggests the benefits of the implemented intervention scheme.

Conclusion. The obtained results indicate that the assessed MCI is cost-effective and valuable for improving patients' quality of life and well-being. In this regard, the evidence provided by quantitative and qualitative methodologies suggests that society could benefit from strengthening the standard regional practice for FMS with the proposed MCI programme. Nevertheless, adjustments have been identified to tailor the intervention to patients' needs

within the available resources to maximise its benefits. In addition, the mixed-method evaluation implemented proves to be a comprehensive strategy for data triangulation when assessing complex interventions. In sum, this thesis work provides decision-makers with evidence to enhance the healthcare approach to FMS, reduce its social burden and improve patients' quality of life in a context of medical uncertainty.

1. Introduction

1.1. Fibromyalgia, chronicles of an invisible disease

Fibromyalgia is currently described as a clinical pain syndrome with roots in an altered central nervous system processing function and, possibly, neuropathic [1]. Accordingly, its name derives from "FIBROS", which means soft tissues; "MIOS", muscles; and "ALGIA", pain [2]. Presented through non-visible clinical symptoms, fibromyalgia syndrome (FMS) severely affects patients' quality of life and carries a significant economic burden on society [3]. To date, its physiopathology, aetiology and gold-standard treatment remain unclear. The medical uncertainty around FMS is accompanied by controversy, scepticism and prejudices in the scientific community and the public. In this context, FMS still finds its legitimacy under scrutiny and its patients stigmatised [4]. As repeatedly stated by patient-participants from this project: *"Fibromyalgia is only understood by those who suffer from it"*.

Physicians have reported FMS clinical manifestations since the early XIX century. But it was not until 1990, when the American College of Rheumatology published its classification criteria [5], that FMS was academically acknowledged. Historically, we find FMS's closest predecessor in 'fibrositis' or 'muscular rheumatism', a generalised and non-specific pain condition described as an "inflammatory change in the fibrous tissues" [6–8]. Furthermore, due to their symptomatic resemblance, FMS has been associated with the hysteria syndrome construct [9,10]. Based on its seemingly psychosomatic nature and high prevalence among females, FMS has been involved in the soma-physique dichotomy controversy and buried as a psychological self-driven affliction in the collective consciousness. This preconception could explain why patients' experience of illness is often associated with mental roots or is related to stress.

Yunus's contributions to criteria in 1981 broadened the definition and clinical focus of FMS, highlighting the relevance of somatic and psychiatric symptoms beyond the severity and location of the pain [11,12]. Yet, more than a century later, the scientific community still encounters challenges in defining, recognising and measuring what they cannot see. Citing Perrot's reflection (2012), *"If fibromyalgia did not exist, we should have invented it"* [13].

1.1.1. Fibromyalgia's clinical picture and diagnosis

As a **syndrome** [14], fibromyalgia presents through a complex of symptoms, including chronic widespread musculoskeletal pain, stiffness and tenderness of the muscles, fatigue, headaches,

sleep and bowel disturbances, cognitive dysfunctions, emotional distress and common mental disorders, particularly anxiety and depression, among other central sensitivity and somatic symptoms [15]. Given the lack of specific laboratory tests and biomarkers, FMS diagnosis relies entirely on patients' reports and physicians' expertise and judgment. Despite the development of diagnostic guidelines over the last 30 years [5,16–20] and the efforts made to objectify patients' subjective illness experience, their clinical implications are still limited regarding treatment options and patient outcomes [21,22]. In other words, FMS imposes clinical and life challenges that might explain the low rate of professional interest in this condition among rheumatologists (only 10% according to the latest survey conducted in Catalonia) [23] and patients frequently seeking disability pension and early retirement [24].

One of the major controversies around FMS is its **differential diagnosis** [25–28]. According to the International Classification of Diseases-10, FMS diagnosis is coded M79.7 [29] within the 'other soft tissue disorders, not elsewhere classified' category. Despite the widespread quality of pain, which primarily characterised FMS, its diagnosis was initially based on doctors' exploration of eighteen specifically located 'tender points' (Figure 1) by pressuring delimitated body areas (digital palpation) [5]. This criterion has been abandoned because of its low accuracy and reliability in clinical practice. Instead, the current criteria for diagnosed FMS in adults (2016 revision) [18] involve the following self-reported indicators:

Figure 1. Tender point locations for the 1990 classification criteria for FMS.
Source: *Wolfe, F., et. al (1990). The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis and rheumatism, 33(2), 160–172.*

"(1) Generalised pain, defined as pain in at least 4 of 5 regions, is present.

(2) Symptoms have been present at a similar level for at least 3 months.

(3) Widespread pain index (WPI) ≥ 7 and symptom severity scale (SSS) score ≥ 5 OR WPI of 4–6 and SSS score ≥ 9.

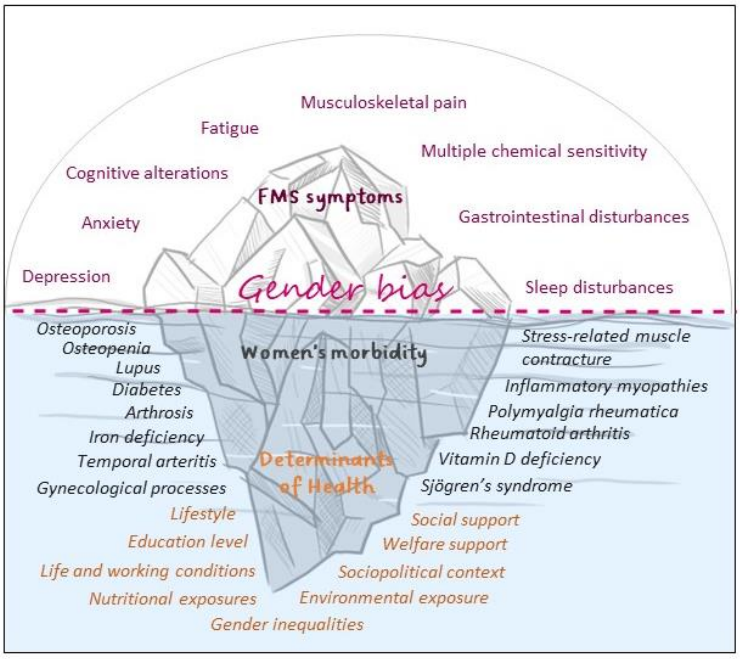
(4) A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses."

Beyond this categorical definition, discrepancies between the criteria and the actual clinical diagnosis have been reported [22,30,31], as there is no strict cut-point to identify FMS. Moreover, even though FMS is classified as a rheumatic disorder, most diagnoses are performed by primary care general practitioners (GP) [32]. In the words of Wolfe F. and colleagues: *"Clinical diagnosis is biased, variable and inaccurate"* [32]. The authors recently proposed a new diagnosis perspective by considering this condition a **dimensional disorder** [32]. Accordingly, approaching FMS as a continuum using the polysymptomatic distress (PSD) scale [17,33] would allow capturing patients with mild symptoms of FMS but who do not entirely fulfil the above diagnosis criteria. Following this line, FMS could be presented as an illness experience with a wide range of intensity and symptomatic phenotypes instead of a dichotomous condition.

1.1.2. Fibromyalgia on the tip of the iceberg

In addition to the lack of medical tests, FMS differential diagnosis is challenged by the **symptomatic overlap** with other rheumatic and non-rheumatic disorders and patients' **multimorbidity** [34,35]. FMS commonly presents concomitantly with other chronic conditions. Considering that FMS is most frequent among females, Valls L.C. [36,37] suggests that FMS symptoms could be rooted in other differential diagnoses in this group, as displayed in Figure 2. Furthermore, the author suggests that a gender bias could explain the sex difference of this condition. In her view, modern Medicine poorly addresses the particularities of females' health, disregarding their unique ways of experiencing illness and healing. Consequently, their pain may not receive the necessary health exploration. Therefore, the author proposes a thorough medical screening before diagnosing FMS.

Figure 2. The Fibromyalgia Iceberg

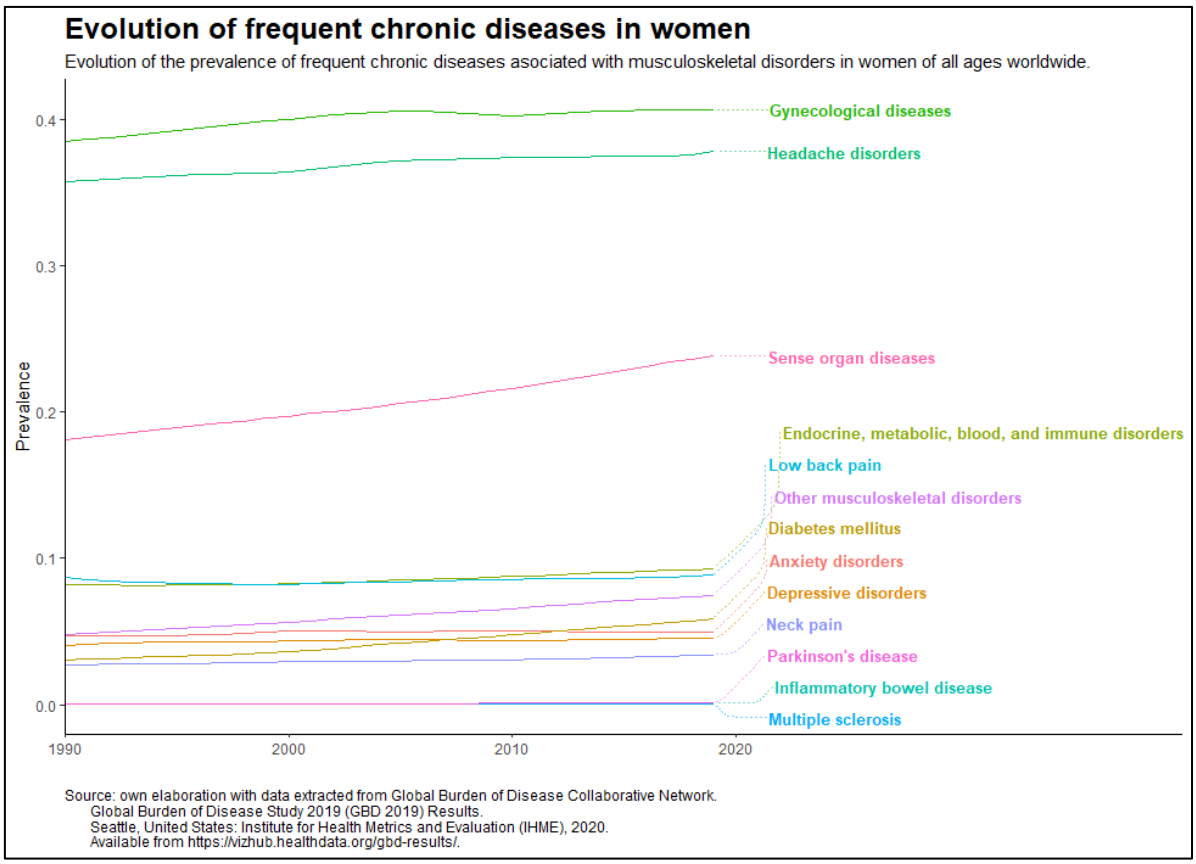


Source: own elaboration based on the original image (Creative Common Licence) from: https://commons.wikimedia.org/wiki/File:Iceberg_BW_illustration_Wiki_Warsha.png

Regarding FMS Epidemiology, this condition is highly frequent among rheumatic diseases, and its **prevalence** worldwide varies between 0.2 and 6.6% in the general population [38,39] and around 2.45% (95%CI, 2.06 - 2.90) in Spain [40]. Here, FMS is 10 times more likely in middle-aged females and is associated with obesity and lower education [40].

FMS prevalence has not increased significantly in Spain during the last 20 years [40]. However, data shows that many other **chronic diseases** have risen worldwide in the previous decades, particularly among females (Figure 3), representing the leading cause of death. Seemingly, FMS is an invisible disorder contributing to an invisible epidemic [41].

Figure 3. Evolution of the prevalence of frequent chronic disease associated with musculoskeletal disorders in women worldwide.



Note Figure 2: Fibromyalgia syndrome would be included in the *"Other musculoskeletal disorders"* category.

Despite the increase in lifespan, a large part of the European population lives with poor health in terms of morbidity and functionality [42]. A global burden of disease study from 2012 highlighted the increasing gap between **life expectancy at birth (LE)** and **healthy life expectancy (HALE)** [43].

Table 1 supports these findings, looking at LE and HALE worldwide and in Spain in the last three decades. On the one hand, although LE and HALE are higher for females, the changing rate throughout the years is lower compared to males. On the other hand, the gap between LE and HALE has decreased by almost 16% for females globally. Nevertheless, this trend is not observed in Spain, where it rose by 28.5% (more than 10 points higher than for males). Authors have called this phenomenon the male-female health-survival paradox [44–46] and emphasised the presence of high morbidity among females as an explanatory alternative.

Table 1. Life expectancy at birth and Healthy life expectancy around the world and Spain from 1990 to 2019 (mean years and 95% confidence intervals)

	Males				*Females*			
	1990	**2019**	**change**	**change %**	**1990**	**2019**	**change**	**change %**
Global LE	62.8 *(62.3-63.3)*	71.3 *(70.4-72.3)*	8.54	13.60%	68.1 *(67.6-68.6)*	72.8 *(71.7-73.8)*	4.69	6.89%
Global HALE	54.8 *(53.2-56.3)*	62.6 *(60.2-64.9)*	7.75	14.14%	58.7 *(56.9-60.3)*	64.88 *(61.7-67.8)*	6.18	10.53%
Spanish LE	73.3 *(73.2-73.4)*	80.7 *NA*	7.38	10.07%	80.5 *(80.4-80.6)*	85.68 *NA*	5.18	6.43%
Spanish HALE	64.8 *(63.1-66.3)*	70.8 *(67.9-73.2)*	6.01	9.27%	70.1 *(68.2-71.9)*	72.32 *(68.2-75.8)*	2.22	3.17%
Global LE-HALE	8	8.79	0.79	**9.88%**	9.4	7.91	-1.49	**-15.85%**
Spanish LE-HALE	8.5	9.87	1.37	**16.12%**	10.4	13.36	2.96	**28.46%**

References: NA = Not available; **LE** = Life expectancy; **HALE** = Healthy life expectancy
Source = own elaboration based on data extracted from: (i) Salomon, Joshua A et al. Healthy life expectancy for 187 countries, 1990-2010: a systematic analysis for the Global Burden Disease Study 2010. Lancet. 2012, 380,9859: 2144-62. doi:10.1016/S0140-6736(12)61690-0, and Wang, Haidong et al. Age-specific and sex-specific mortality in 187 countries, 1970-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012, 380,9859: 2071-94. doi:10.1016/S0140-6736(12)61719-X; (ii) https://vizhub.healthdata.org/gbd/results/ (iii) https://www.who.int/data/gho/data/indicators/indicator-details/GHO/gho-ghe-hale-healthy-life-expectancy-at-birth

According to the latest report from the World Health Organization (WHO, 2018) on **noncommunicable diseases (NCD)**, these are responsible for 74% of all deaths globally [47]. Therefore, the WHO recommends focussing on preventing the NCDs that contribute the most to death: cardiovascular diseases, cancers, diabetes, and chronic respiratory conditions [47]. However, other chronic diseases, including musculoskeletal and mental disorders, other non-communicable diseases, sense organ diseases, and neurological disorders, were associated with 9% of all deaths globally [48]. These NCDs lead the rank of **Years Lived with Disability (YLD)** [49,50], and indicator that focuses on the loss of healthy years rather than lifetime. The YLD rate change from 1990 to 2019 in all age groups and sexes worldwide shows a substantial increase.

Additionally, a recent study on the global estimation of the need for rehabilitation has confirmed that musculoskeletal, especially low-back pain, contributes the most to the YLDs burden [51]. In Spain, it has been estimated that 20 million people experience conditions that could benefit from rehabilitation (approximately 40% of the total Spanish population), which entails 3 out of 7 individuals. In the last thirty years, YLDs have increased by 38.2% in Spain [51]. Furthermore, females have been the most affected group (with 7.8 points of difference compared to 0.4 in males), showing a 0.8% annual rate change in YLD during this period. The social costs of covering these needs are massive and urge for intervention.

1.2. The Fibromyalgia Scientific Puzzle

FMS aetiopathogenesis is yet to be fully understood and has become a debated scientific puzzle. Paradoxically, the literature on unexplained chronic musculoskeletal pain is vast, and the hypotheses are varied. From a somatic functional disorder to a genetic condition, efforts to unveil the FMS mystery cover multiple and not mutually exclusive approaches [52]. Indeed, researchers have become raiders of the lost biomarker to provide a biological explanation for FMS that improves diagnostic accuracy and treatment efficacy [53]. Table 2 summarises some of the most prominent paradigms around the origin of this condition:

Table 2. Summary of explanatory theories behind Fibromyalgia syndrome

Central sensitisation
Central sensitivity syndromes present a disturbed pain processing with an amplified response to stimuli by the central nervous system (CNS) [54]. To date, this is the most widespread explanation for FMS, as it has been supported by neuroimaging studies [55]. However, new evidence may overturn this theory, indicating multiple origins for FMS [56]. In addition, the mechanism behind this CNS abnormal functionality has not been entirely elucidated. Some studies have shown that possible associated factors involve D vitamin deficiency and serotonin and dopamine neurotransmission dysfunctions [57–62].
Peripheral neuropathy
In this case, the origin of FMS is located not in the brain's core but in the outer nerve fibres that transmit signals through the spinal cord to and from the CNS to the rest of the body. Consequently, patients may experience pins and needles, tingling, numbness, and weakness. Yet, these symptoms may not always be constant in patients with FMS and nerve tests usually do not show any damage. Furthermore, other conditions share a similar sensory phenomenon, such as diabetes, but with a different aetiology mechanism [63]. Even though this theory seemed to have been overruled, a systematic review with meta-analysis from 2019 has put it once again on the table. This study found a prevalence of small fibre pathology of 49% in FMS cases, which has opened the research gate to explore further the relationship between these two conditions [1,64].
Experience of traumatic events and life stressors
There is accumulative evidence regarding the association between traumatic events, life stressors and FMS [52]. For instance, Kaleycheva and colleagues (2021) [65] showed through a systematic review and meta-analysis that physical abuse is strongly related to adult FMS. There is also similar evidence regarding childhood maltreatment, intimate partner violence, and challenging socioeconomic conditions [66–69]. However, the evidence on stress biomarkers may not completely back these findings [70]. Yet, Martínez-Lavín seemed to have found a biomedical explanation for how stress triggers chronic pain. The author has proposed FMS as a stress-induced neuropathic pain syndrome rather than a mental somatic disorder (the somatisation paradigm related to the traditional hysteria construct) [71]. In this line, environmental, psychological and physical stressors could produce neuroinflammation by altering biochemical and electric impulses that damage the dorsal root ganglia structure, which lies along the spinal column, and impact the pain-transmitting nerve response [72]. Furthermore, this proposal also covers the high prevalence of FMS among females by a sexually

dimorphic disorder related to the hormone system. But despite the efforts to adopt a biopsychosocial model to explain FMS aetiology, this paradigm remains forgotten, as recently highlighted by Pontes-Silva (2023) [73].

Neuroendocrine dysfunction

The hypothesis of a possible association between the endocrine system function and FMS has been scientifically considered since the early days. The literature indicates an interconnection between hormones, muscles, and joint tissue inflammation. For instance, it is known that low levels of oestrogen (typical during the menopause period) can reduce the connective tissue, which results in musculoskeletal pain and stiffness. Furthermore, imbalances in cortisol serum levels, also recognised as a stress hormone, could similarly affect the body. Nevertheless, the association between endocrine dysfunction and FMS needs further research to understand its mechanism and neurobiological characteristics [74,75].

Autoimmune response

Other interesting physiological pathways propose an immune response linked to FMS. In this regard, there is some evidence of the overlap of this condition with infectious diseases such as Epstein bar virus [76–78], hepatitis C [79–81], HIV [82,83], and even Covid-19 [84–86]. Moreover, FMS symptomatology has been observed in post-vaccination syndromes [87,88]. Accordingly, the infection would trigger a cytokine-induced response mechanism responsible for the unspecific symptoms exhibited in patients with FMS [74].

In this line, Goebel and colleagues discovered in a study with mice that a type of antibody, immunoglobulin G (IgG), plays a key role in FMS symptomatology by sensitising peripheral nociceptive nerves. The authors suggested that targeting IgG could be a new treatment strategy to reduce FMS symptoms [89].

Furthermore, given the high prevalence of bowel distortions in patients with FMS, emerging research lines in the gut–muscle axis have explored the possible involvement of the gut microbiome in this condition [90]. The gut microbiome is implicated in immune inflammatory responses that have been shown to impact muscular function and even mental health [91,92]. A recent systematic review supported the potential role of gut microbiota on FMS and suggested further research in this line. This approach, for instance, could lead to focusing on nutrition when treating FMS [93].

In addition, FMS could be partially inheritable [94]. However, genetic studies have not yet found the specific genes involved [52]. In any case, the FMS scientific puzzle faces a causality dilemma. Most of the presented mechanisms may not be incorrect and still do not necessarily solve the FMS aetiology enigma as it is difficult to prove if they play a primary or secondary role. In other words, the previous hypotheses could represent either the origin or consequence of this syndrome. Meanwhile, patients require healthcare and social support, which imposes a significant burden on society.

1.3. The Socioeconomic burden of Fibromyalgia syndrome

The financial impact of FMS has been proven to be substantial [95]. The iceberg nature of FMS has also been observed regarding its economic burden. In this regard, a study from 2015 alerted the underestimation of indirect costs and the hidden direct medical costs related to comorbidities and disability in patients with FMS [96].

According to a recent systematic literature review on the economic burden of FMS, annual direct costs per patient ranged from US$1,250 to US$8,504 in Europe, for which pharmacological coverage was the most significant contributor [95]. Nevertheless, studies have found that indirect costs, which entail productivity losses due to sick leave days and disability pension, could trigger the largest expenses from a societal perspective [97–100].

Few cost-of-illness studies on FMS have been performed in Spain. A study from 2009 estimated that the average annual cost per patient was €9,982, from which €3,245.8 (32.5%) corresponded to direct medical costs and €6,736.2 (67.5%) to indirect costs [101]. In addition, a study conducted in Catalonia's primary care settings found an excess cost of €5,010 for patients with FMS compared to a reference population. In this case, €614 (12.3%) were attributable to direct healthcare expenses and €4,394 (87.7%) to indirect costs [102]. These figures have been supported by a report from the Spanish National Institute of Social Security in 2019, which remarked on the increasing trend in absenteeism from work and temporary disability in patients with FMS [103].

Furthermore, Cabo-Menseguer and colleagues estimated in 2017 that FMS imposed an annual economic cost of about 13,000 million euros in Spain [3]. To appreciate this amount in context, the total Spanish public health expenditure from that year was about 68,500 million euros (€1,472 per capita), from which €9,675 million were allocated to primary care services [104]. Thus, the FMS burden estimation would represent almost 19% of the total health budget, and its economic consequences would be above the financial resources dedicated to the whole primary care sector.

1.4. The art of treating Fibromyalgia syndrome

Treating FMS is undoubtedly challenging and has boosted healthcare providers' creativity, particularly in primary care settings where most cases are handled. Being the FMS pathophysiology unclear, treatment strategies aim to mitigate patients' symptomatology and safeguard their quality of life. However, there is no specific medication for treating FMS. As mentioned in section 1.1.2, the most widely accepted theory about the origin of this condition is the central sensitisation model. Hence, the usual clinical practice (UCC) for this syndrome is frequently based -but not exclusively- on administering antidepressants (ATD), which are meant to regulate neurotransmitters. Yet, the literature and the clinical experience may have found shortcomings in this therapeutic strategy either for its limited effectiveness, short therapeutic adherence or the emerging side effects [105]. A systematic review published in 2018 [62] showed that the serotonin and noradrenaline reuptake inhibitors (SNRIs) duloxetine and milnacipran had no significant clinical benefits over placebo in treating FMS symptoms, while their potential harms were considerable. Even though patients may experience an initial positive impact on pain and mood management, the long-term benefits and its mechanism are still under research [106]. In addition, being FMS of a chronic nature, it would not be sustainable to administrate ATD for life, which urges therapeutic alternatives.

The latest clinical guidelines and research regarding FMS agree on addressing this condition pharmacologically and non-pharmacologically by covering several health domains such as education, psychological needs, and physical activity [52,107–112]. Nonetheless, there is less consensus about how this therapeutic approach should be put into practice as novel interventions are being developed and examined.

Furthermore, non-pharmacological interventions entail a broad category that involves any non-drug-derived therapy. The CEPS Platform defines this concept as: *"A non-pharmacological intervention is an efficient and effective method for human health. This non-invasive method takes the form of a product, programme or service. It has an observable action (measurable benefits and risks going beyond simple consumer opinion) on indicators of health and quality of life and can be linked to identified biological mechanisms and/or psychological processes. It can also have a positive impact on health behaviours and socio-economic indicators"* [113]. In addition, this organisation classifies non-pharmacological interventions into five groups: psychological, physical, nutritional, digital (e-health programmes), and other alternative interventions [114]. Within this framework, there is a large scope for therapeutic intervention development.

To date, several intervention strategies have been explored for FMS, including Mindfulness [115], Yoga [116], Pilates [117], Taichi [118], Acupuncture [119], aquatic activities [120], walking programmes [121], strength training [122], psychotherapy [123], among others. However, the evidence remains inconclusive regarding the gold standard of these therapies. Instead, an individualised assessment of each patient's health needs and preferences has been recommended to physicians [112].

From a biopsychosocial model, multidisciplinary approaches have shown promising results for FMS, particularly when combining patients' education in health self-management, cognitive behavioural therapy (CBT) and physical activity [124]. Previous experiences have demonstrated improving FMS symptoms and patients' quality of life [124]. Nonetheless, this therapeutic approach is at its onset, and more examination of each new intervention is needed.

In 2008, resolution 203/VII from the Catalonian Parliament commended the Government for developing a clinical guideline for FMS and chronic fatigue and creating specialised service units within the public health administration. This resolution was regulated by the order SLT/115/2010 published in the *Diari Oficial de la Generalitat de Catalunya* (DOGC) in 2010 [125], in which it was established that the specialised units were to be of regional action, multidisciplinary approach and in connection with primary care. This plan has been conducted since 2016 by operationalising Central Sensitivity Syndromes Units in primary care centres throughout Catalonia [126]. Since then, several initiatives have been developed to follow the official clinical guidelines and address regional health needs.

1.5. A new Multicomponent Intervention Programme in Catalonia, Spain

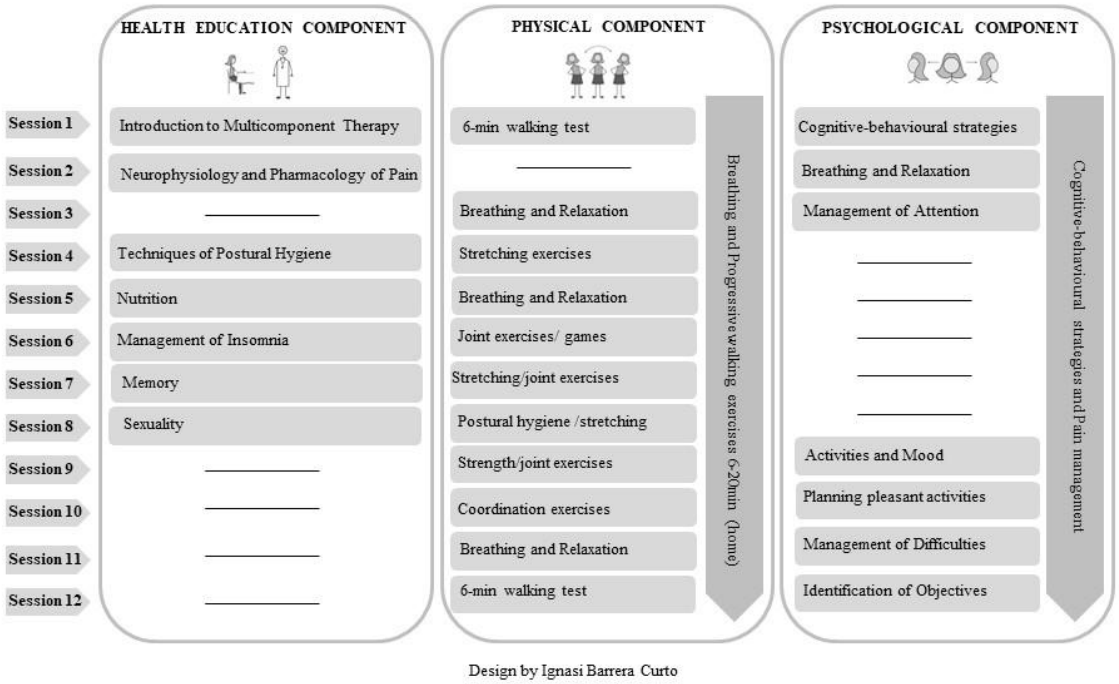
This doctoral thesis assesses a novel multicomponent intervention (MCI) programme for patients with FMS developed in the Central Sensitivity Syndromes Unit from the health region *Gerència Territorial Terres de L'Ebre*, belonging to the *Institut Català de la Salut* (ICS), Spain.

This MCI consists of a 12-week (3-month) and 2-hour/session group-based programme (24 h. total) that includes health education, physical exercise, and CBT. A multidisciplinary team consisting of a GP, a nurse, a physiotherapist and a psychologist delivered the MCI in addition to the UCC, with the purpose of strengthening the routine practice for FMS.

Primary health care in Catalonia is Universal and is the first point of access to health care. Individuals can access the rest of the public system services by referral from primary care, except for *061/Salut Respon* or medical emergencies, which can be reached directly in a crisis. Furthermore, primary care services offer diagnosis and attention to the main acute and chronic health problems, health and social assistance, health promotion services, preventive interventions, curative and rehabilitative care, home care service, urgent or continued care and attention to sexual and reproductive health. All these services are guaranteed by the regional health administration (CatSalut) and publicly funded.

The MCI was conducted in groups of 8 to 15 patients from April 2017 to January 2020 and in five waves (see Annexe, Pending Publications, Study III, Supplementary Material S1). This initiative focused on addressing FMS symptoms and improving patients' quality of life by providing non-pharmacological therapeutic strategies. Figure 4 displays the thematic content of the MCI sessions as presented in this project's published general study protocol [127].

Figure 4. Content of the multicomponent therapy sessions



Source: Caballol Angelats R, Gonçalves AQ, Aguilar Martín C, et al. Effectiveness, cost-utility, and benefits of a multicomponent therapy to improve the quality of life of patients with fibromyalgia in primary care: A mixed methods study protocol [published correction appears in Medicine (Baltimore). 2019 Nov;98(48):e18263]. Medicine (Baltimore). 2019;98(41):e17289. doi:10.1097/MD.0000000000017289

2. Justification

Despite guidelines' recommendations for a multidisciplinary approach to FMS, there is room for more robust evidence on this therapeutic strategy's efficacy, cost-efficacy and impact on patients' well-being. Previous studies differ in the intervention format and content designs, target population, or methodology, limiting the extrapolation of their results to other contexts. In light of developing a new MCI programme for FMS in primary care settings within the Catalonian regional public health administration, a broad evaluation of this therapeutic initiative was needed.

According to the Medical Research Council guidance [128], **complex interventions** require comprehensive strategies and mixed methodologies to assess beyond the intended health outcomes. In this line, context elements, stakeholders' acceptability, feasibility, implementation aspects and economic impact should be included in evaluating new health technologies to capture their benefits and blind spots in real-world scenarios.

Complexity in interventions could be related to the health problem itself, the multidimensional impact of the condition, the multidisciplinary treatment approach, its potential large-scale impact, the profile of the target population, the lack of scientific knowledge, or the number of components involved in the intervention, among other factors [128]. **FMS complexity** has been widely explained in the previous sections. It covers the debated scientific evidence of its aetiopathogenesis, the difficulties in the differential diagnosis, the lack of medical consensus on the best treatment option, the potential gender bias, its significant societal impact and economic burden, and the multidisciplinary therapeutic approach recommended to support patients' health needs.

Mixed-method evaluations provide a methodological strategy to systematically assess new health interventions by studying quantitative and qualitative data. In this regard, qualitative methods allow for exploring patients' lived experiences, health benefits, acceptability, and suggestions for tailoring programmes to their health needs. Inventions can be adapted to real-world scenarios by including stakeholders' perspectives to boost therapeutic adherence, applicability and health benefits. Furthermore, health economic evaluations provide relevant evidence for health resource allocation and management decision-making. Conducting studies using these methodologies facilitates complex intervention research on new health programmes.

3. Research Hypothesis and Aims

3.1. Hypothesis

A new Multicomponent Intervention programme for FMS administrated in the *Gerència Territorial Terres de L'Ebre*, ICS (Spain), which includes health education, physical activity and cognitive-behavioural therapy, would improve patient-participants' quality of life and well-being and would result cost-effective for society.

3.2. Aims

3.2.1. General aim

The present doctoral thesis aims to assess a complex and multicomponent intervention programme for patients with FMS, developed and conducted in the *Gerència Territorial Terres de L'Ebre*, ICS (Spain), by implementing qualitative and health-economic methodologies to comprehensively evaluate its benefits on patients' quality of life, well-being and cost-effectiveness.

3.2.2. Specific aims

I) To qualitatively assess patients' acceptability and appraisals on the MCI content, format, benefits, and shortcomings and explore their lived experiences and subjective impact. Furthermore, this thesis seeks to identify the intervention's facilitators, barriers, and aspects to be improved and adapted to meet patients' health needs and reduce FMS social burden.

II) To perform a cost-utility analysis to compare the new MCI programme with the UCC provided in the primary care setting form the regional public health administration.

4. Methods

4.1. Qualitative studies

"Not everything that can be counted counts, and not everything that counts can be counted". (Albert Einstein)

4.1.1. Design

Studies I and *II* [129–131] adopted a **qualitative research methodology** [132] according to the Medical Research Council guidance [133]. In addition, these studies were designed following the Consolidated criteria for reporting qualitative research (COREQ) [134] and the Standards for Reporting Qualitative Research (SRQR) [135].

4.1.2. Participants and Recruitment

Patients registered in any of the 11 **primary care centres** (PCCs) from the *Gerència Territorial Terres de L'Ebre* regional health administration belonging to the ICS were eligible to participate in the MCI programme. The inclusion criteria involved:

- Being diagnosed with FMS in the electronic medical record system (eCAP) (International Classification of Diseases-10 codes: M79.0, M79.7) [29].
- Being an adult (over 18 years old).
- Having Catalan and/or Spanish oral and written communication skills.
- Having a phone number.
- Signing informed consent.

Moreover, patients were not considered for inclusion in the presence of:

- Active psychotic episode.
- Intellectual impairment.
- Severe depression and personality disorder.
- Auto/hyperaggressive behaviour.
- Abuse of psychoactive substances.
- Rejecting to be part of the programme and sign the informed consent.

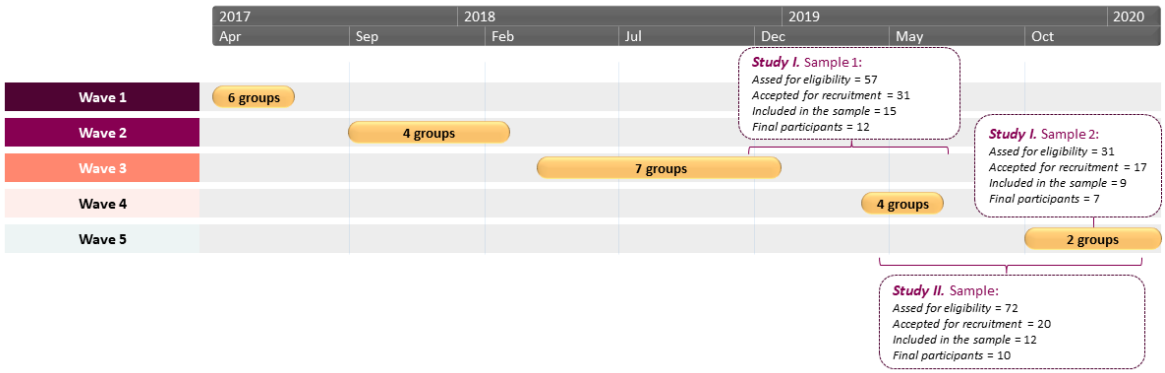
In addition to the above criteria, patients who received at least 75% (9 out of 12 sessions) of the MCI programme within the last 12 months were recruited to participate in the qualitative studies to prevent memory bias. Following a purposive heterogeneous sampling strategy,

sociodemographic variables (age, sex, birth country, educational level, occupational class, working condition, and registered PCC) were considered to achieve maximum discourse variability.

In *Study I*, candidates were sampled according to their follow-up to assess the MCI benefits in the short and middle-long term. Accordingly, two groups were considered: candidates with 6 to 12 months post-intervention and those with less than 6 months. Based on the trial scheme, patients registered in 7 out of 11 PCCs were eligible for recruitment. During recruitment, the first telephonic contact was made three weeks before the data collection day, in which patients received key information about the study (goals, time, location, and data protection measures). Those who accepted to participate were sent a reminder via text message a week and a day before the event.

Study II identified patients from 5 out of 11 PCCs as potential candidates. Those who had participated in the data collection from *Study I* were not eligible for recruitment in *Study II*. Figure 5 describes the sampling process in both qualitative studies.

Figure 5. Qualitative studies' sampling strategy.



4.1.3. Data collection

Data in *Study I* was collected by conducting two **focus group discussions (FGDs)**, while 10 **in-depth individual interviews** were carried out in *Study II*. In both cases, informants involved patients with FMS diagnosis who received the MCI programme and fulfilled the described inclusion criteria. The author of the present thesis partook as a facilitator in the FGDs fieldwork with the support of her thesis main supervisor, PhD Anna Berenguera, as a co-facilitator and research assistant, PhD Alessandra Queiroga Gonçalves, as an observer who took field notes. Furthermore, the author conducted all the one-on-one interviews in *Study II*.

FGDs are a social-based technique to gain insights into socially constructed perceptions about a specific shared topic. From a community level, FGDs are particularly suitable to identify the group's perspective and needs [132]

In-depth interviews facilitate obtaining detailed personal perspectives of the matter under investigation by providing a more private, individual-centred discussion. In this regard, interviewees have the opportunity to express their opinions and perceptions in their own words. Therefore, in-depth interviews are suitable for exploring lived experiences [132]

Data collection for *Study I* and *II* was carried out during the first semester of 2020, and the setting was the PCC Baix Ebre from Tortosa city. The first was conducted in February (FGD1 n=12 participants with 6 to 12 months of follow-up) and the second in July (FGD2 n=7 participants with less than 6 months of follow-up). Both FGDs were performed face-to-face. The individual interviews were also conducted during July of the same year, but only four were in person, while the rest were telephonic, as preferred by the interviewees. Hence, the first data collection phase occurred before the COVID-19 pandemic outbreak and the second after the first pandemic wave. In this context, some health security measures were adopted, such as reducing the number of participants, wearing face masks, ensuring ventilation, providing alcohol gel, and facilitating physical distancing. In addition, as some of the participants in the FGDs did not accept to be video-recorded, all meetings and interviews were audio-recorded.

In both studies, **semi-structured interview schedules** (Annexe, Supplementary materials S1 and S2), with open-ended and follow-up questions, were developed to guide the discussions and thoroughly reviewed by the research team.

On the one hand, the interview guide from *Study I* covered the informants' overall perception of the effectiveness of the MCI, its health benefits and impact on daily life, their appraisals of its features such as timeframe, setting, staff performances, group-based approach, and thematic contents, and their suggestions for improvement. On the other hand, the discussion in *Study II* was orientated towards the personal impact of the MCI. In this regard, interviewees were asked about their general opinion on the MCI, its benefits, the perceived psychological and emotional impact, the development of coping skills and self-symptom management, the impact on their social network and the feedback they received from their closer ones, the transferability of knowledge on lifestyle, the feasibility of implementing the MCI in the UCC, and suggestions.

In addition to the discussion schedules and active listening, other **interview techniques** were implemented to obtain quality data, such as summarising, clarification, validation and redirection. When summarising, the facilitator or interviewer wraps up the interviewee/s' accounts when it diversifies or after covering several topics in order to condense the information and visualise the progress of the dialogue. Clarification entails the interviewer describing the informant/s' responses in a simplified manner to confirm that the interviewee's message has been interpreted correctly. Validation involves supporting the interviewee/s' responses by showing understanding, empathy and opening for disclosing their perspectives. Finally, redirecting occurs when the facilitator switches the direction of the discussion either by changing the subject and helping the interviewee/s to focus on the question or by boosting the group dynamic in a FGD when one or few participants tend to monopolise the conversation.

4.1.4. Data analysis

Verbatim transcriptions (word-for-word) were analysed using thematic analysis [136] from a hermeneutic phenomenological perspective [137–139].

Thematic analysis is a flexible qualitative analytical method that can be used across different epistemological or theoretical approaches [136]. For instance, when applied conjointly with **hermeneutic phenomenology**. According to Ken H.M. Ho [137], this is a popular duet when researchers intend to interpret a phenomenon beyond taken-for-granted thinking and superficial descriptions, particularly in modest samples. The goal is to capture the narratives' essence through meaningful themes and not just patterns of words and phrases [140]. Researchers may question the semantic content of the data by reading the interviewee/s' unspoken words or latent content [136] and finding the validity of their interpretations in data and analyst triangulations.

To this end, researchers must immerse themselves in the data and embrace their own theoretical and subjective position towards their research. Consistently, hermeneutic phenomenology does not disregard researchers' preunderstandings but incorporates them as part of their **reflexivity** [141], which is defined as *"a researcher's insight into their own biases and rationale for decision-making as the study progress"* in the words of Johnson J. et al. (2020) [142].

From this non-linear and circular analytical approach, researchers move back and forth, comparing and articulating texts, coding, and researchers' perspectives throughout the analytical

process and reaching higher levels of understanding alongside this interpretive path. Hence, texts are not just singular units of data but crucial pieces of the informational puzzle that gain sense in the context of a whole set of units.

Historically, hermeneutic phenomenology originates in Husserl's philosophy work on phenomenology, which focuses on uncovering the meaning of lived experiences as perceptual and individual phenomena [138,139]. Intrinsically descriptive, this methodology proposes to capture the essence of the embodied world experience by bracketing or suspending one's judgement and pre-understanding. According to Husserl, conscious awareness was inseparable from the world where it arose, which opposed the prevailing Cartesian dualism of that time. Nevertheless, the knowing subject and the object to be known must have still been kept apart to achieve true knowledge.

His disciple, Martin Heidegger, developed his master's premises towards a more contextual and interpretative approach by situating the lived human experience and reconciling the subject and the object through a hermeneutic twist. Under his concept of *Dasein*, Heidegger focused on the human experience in the world, not from an individual perspective but a social one that shapes an intentional conscience. A consciousness that signifies the world while being interpellated by time, history, culture, and all their possibilities, particularly the inexorable death. Therefore, humans would not be fixed realities that can abstract themselves from the world in which they live but beings in constant but finite development. According to the author, questioning and interpreting phenomena from our pre-conceptions are the vehicle for understanding the lived experience in the world, assuming a dialectic dynamic between the whole and the parts of the phenomena [138,139].

In this context, thematic analysis provides an operational structure for conducting recursive interpretive efforts [138]. Based on the literature [136,143,144] and the thesis author's fieldwork experience, conducting thematic analysis step-by-step is described in Table 3.

Table 3. The thematic analysis method: a practical summary.

Phase	*Description*	*Procedure*
Preanalytical intuitions	From a holistic approach, preanalytical intuitions entail familiarisation and identification of preliminary thoughts about the data and the examination of the researcher's subjective position towards the study matter, the informants, the research project, and the research team (academic paradigms, knowledge gaps, level of involvement in the project, relationship with the informers, preconceptions, previous experiences, prejudices, beliefs, feelings, etc.). In a theoretical or deductive approach, this phase may include engaging with the conceptual literature framework and previous research. Even though this first step might be disregarded in practice, it is strongly recommended not to as it is paramount for grasping a first overall perception of the material from a subjective point of view. When overlooking subjectivity in qualitative research, it is more likely to fall into researcher bias. Reflexivity goes beyond a single step; it entails a research attitude and behaviour contributing to transparency throughout the qualitative methodological path.	Reading the data several times, immersing in the data, reflecting on initial insights and personal perspectives, and taking notes. If applicable, review the literature and theoretical background. It is also important to question yourself about your beliefs on the study matter and your position regarding the informants, the project, and your colleagues to identify any possible bias in the next steps of the analysis.
Initial coding	Fragmentation of each separate case/text in small units of analysis ('codes'). A code is the most basic segment or item that emerges from the raw data and serves to systematically compare the data set in a manageable, trackable, and transparent way.	Identifying and labelling simple but relevant units of meaning within the text (words or short phrases) that explain what has been said and how the researcher has interpreted it. A code could refer to anything from values, emotions, beliefs, behaviours, perspectives, experiences, events, and the informer's attitudes or reactions during the data collection, among other possibilities.

Creating categories	Categorising is a method to classify codes into topic groups. It helps to organise the codebook, provide structure, and reach a first level of abstraction in the analysis. When analysing large data sets, codes and categories extracted for the first cases give rise to the working analytical framework for indexing subsequent data. This initial framework will be enriched with emergent codes throughout the analysis process.	Clustering codes into meaningful groups with a descriptive label. There is no rule about how many codes should be included in each category, but researchers should remember that it is meant to systematise the analysis process. It is recommended to have an extra category for miscellaneous codes that may not fit anywhere but may become relevant in the following phases. At this stage, figures, diagrams, and mind maps could help to present preliminary results graphically.
Analyst triangulation	Exchanging preliminary results with at least two other qualitative researchers to compare analytical approaches, codebooks and the working analytical framework to safeguard the study's rigour.	Finding similarities and differences between researchers' codebooks. Sharing perspectives and reaching a consensus on the working analytical framework. When the latter is not possible, discrepancies may need to be thoroughly addressed before the analysis progresses. An external qualitative researcher occasionally audits the analysis process to support the research team in finding consensus.
Identification of themes	Finding patterns of meaning throughout the analysis and the data set. Themes represent the highest level of abstraction when reporting results in thematic analysis, by collating the interactions between codes and categories, themes bridge between data and interpretation.	Clustering categories into meaningful and broader data items summarising the data set's content and interpretation. The number of categories within a theme could vary as long as a logical and trackable research decision supports it.
Reviewing and naming themes	Seeking internal coherence within the analysis. Finding and solving incongruencies.	Checking the articulation between code extracts, categories, themes and the whole data set.
Analyst triangulation	At this stage, a second analyst triangulation is recommended to check	The same research team shares their codebook intending to revise the

	on the emerging themes.	consistency of the thematic analysis. External qualitative researchers might be invited to participate in this phase to guarantee the transparency of the results. Audit trails can be useful to illustrate the rationale and research path between data items. Additionally, it helps to guarantee the confirmability of the analysis, which means that the findings can be tracked on the informants' responses. Audit trails can be presented through spreadsheet matrices or figures, including codes, categories, themes, and representative quotes.
Reporting	Recreating and communicating the data from the scholars' analytical glances in order to answer the research questions through an organic synthesis of the main finding.	Written presentation of the most significant findings. Explaning each theme and sub-themes and selecting representative and vivid quotes from the raw data to exemplify them.

Coding in thematic analysis can be performed in two different ways: deductively or inductively. The former, adopted in *Study I*, means that the analysis is theory-driven as the investigator is interested in answering specific research questions or following the literature. Consequently, themes may be closer to the questions from the discussion schedule and/or organised in broad domains. In the latter, also called open coding and adopted in *Study II*, analysis is data-driven as no previous coding frame, categories or topics are meant to structure it. Given its emergent nature, the analysis results and the identified themes may have less connection with the questions from the interview guide [136].

Furthermore, coding can be supported by Computer Assisted Qualitative Data Analysis Software (CAQDAS). In *Study II,* NVIVO12 [145] was used to conduct the analysis. Microsoft Excel (version 2019) was the adopted digital tool in Study I. Noteworthy, CAQDAS do not perform analysis but facilitates storing and managing data, which is particularly useful when working with large data sets.

Lastly, the sample sizes in these qualitative studies were not driven by the **saturation** [146] of the data but by the availability of potential candidates after applying the inclusion criteria. Instead, saturation was sought from the depth of the analysis and assumed by the qualitative research team when no more codes and themes were captured from the data based on the study questions. Yet, saturation in qualitative research is a controversial and in-development rigour standard as it does not offer clear guidance on sample size for this research methodology [147].

Table 4 provides an example of one of the audit trials that resulted from the analysis process in *Study II*.

Table 4. Example of audit trail from *Study II*

	Codes	***Categories***	***Themes***
1	Educational benefits	The MCI: an educational experience	Legitimising Fibromyalgia through the multicomponent intervention
2	Learning new techniques		
3	Highlighting the relaxation component		
4	Professionals promoting physical exercise		
5	Useful contents		
6	New learnings		
7	Gaining insight into one's health		
8	Having a place to vent	Receiving psychological support during the MCI	
9	Psychological support from professionals		
10	Psychological and emotional benefits		
11	Professionals and peers understand FMS		
12	MCI promoting autonomy		
13	MCI promotes mental health		
14	Participating with people who understand you		
23	Patients reducing medication	The MCI as a game changer	
24	Following exercises guidelines		
25	Exercising daily		
26	MCI gives patients something to do		
27	Learning how to keep a routine		
28	*"I can say now that I have a real health problem"* (IVC)	Experiencing Fibromyalgia as a real health problem	
29	Professional follow-up has a legitimating effect		
30	*"What it does is give it a face"* (IVC)		
31	MCI backing up FMS		

References: IVC= In Vivo code

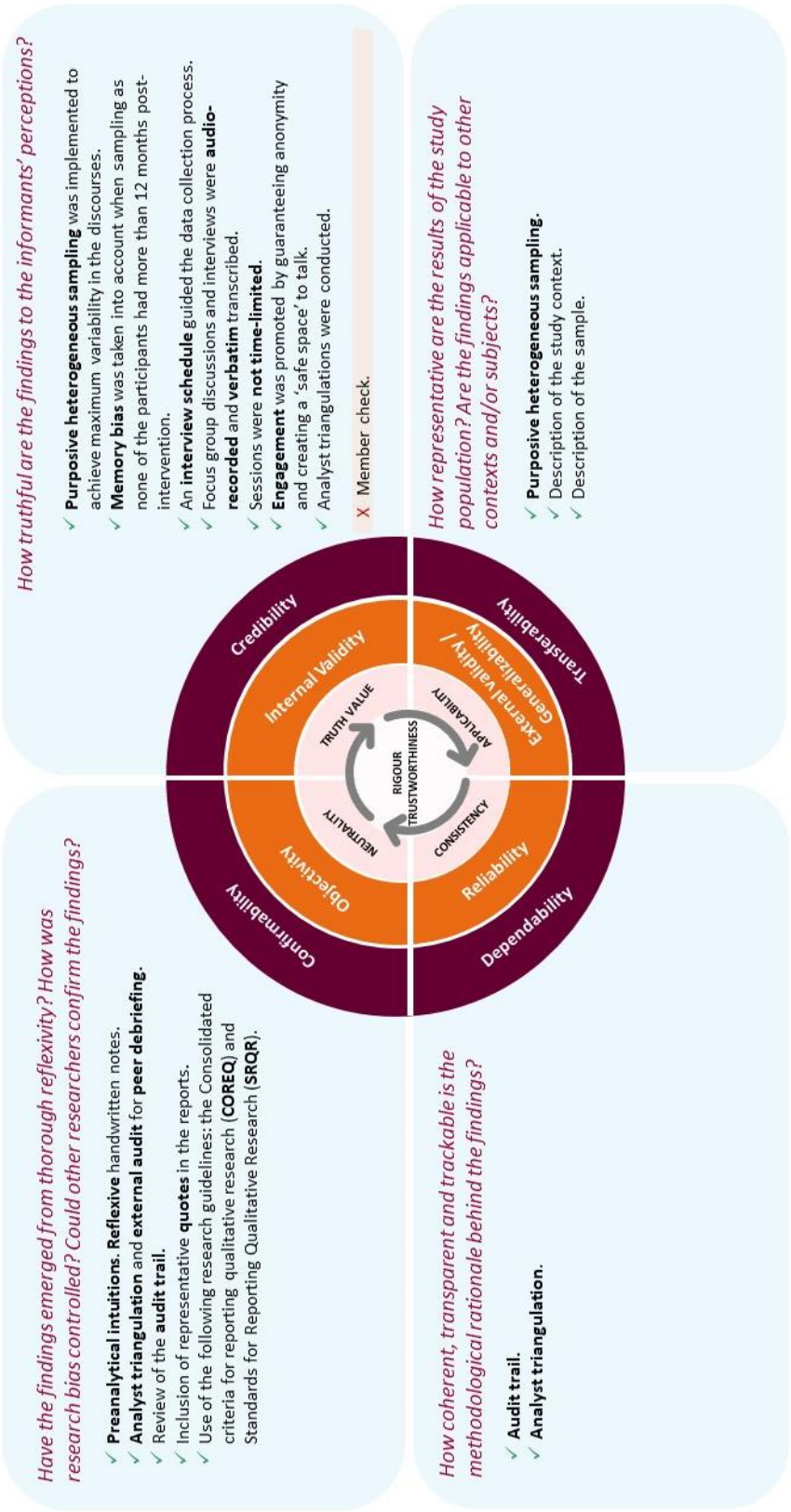
4.1.5. Trustworthiness

Rigour standards in qualitative research aim to ensure good practices and quality data production [148]. However, given its humanistic nature and naturalistic inquiry, qualitative methodology faces challenges in meeting the traditional positivistic criteria of reliability and validity. Indeed, the qualitative research approach is non-linear, reflexive, interpretative, and hardly generalisable. From the quantitative lance, the potential impact of subjectivity in the research process makes qualitative methodology particularly treacherous.

In an attempt to adjust the concept of rigour to the qualitative framework, Lincoln and Guba [149] proposed the term' *trustworthiness'* in the 80s to refer to four leading indicators to assess quality, transparency, and truthfulness. Despite the criticism for its equivalence and resemblance with the rationalistic paradigm, this model offers an interesting and still-in-force proposal to address rigour in the qualitative method and bridge the gap within the scientific community. Other proposals have been developed since then, including checklist guidelines, COREQ and SRQR, and more generic approaches [142].

Figure 6 displays the relationship between the concepts of rigour (rationalistic paradigm) and trustworthiness (naturalistic inquiry) according to Lincoln and Guba [149] and how the latter has been addressed in the qualitative studies of this thesis work.

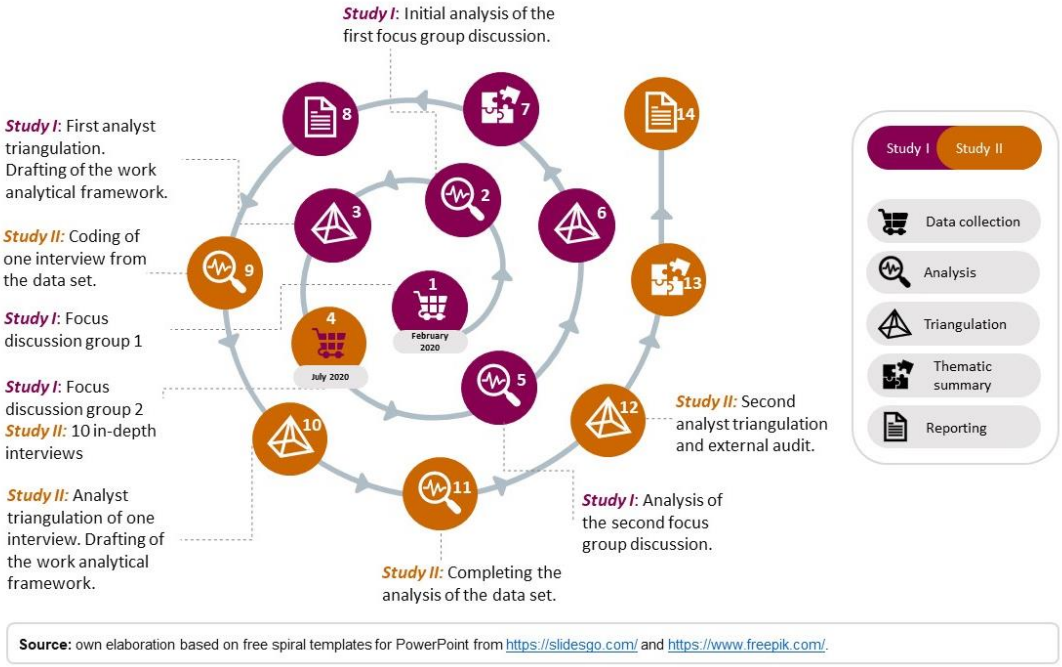
Figure 6. Trustworthiness in Studies I and II.



4.1.6. A Qualitative Research Journey

Figure 7 summarises the qualitative research process conducted in this doctoral thesis.

Figure 7. Diagram of the qualitative research journey of this doctoral thesis.



Source: own elaboration based on free spiral templates for PowerPoint from https://slidesgo.com/ and https://www.freepik.com/.

4.2. Economic evaluation study

"Nowadays people know the price of everything and the value of nothing". (Oscar Wilde)

4.2.1. Design

Study III [150] encompasses a **cost-utility analysis (CUA)** [151] conducted alongside a double-arm and 12-month **pragmatic randomised controlled trial (PRCT)** [152] (ClinicalTrials.gov: NCT04049006) [127]. PRCTs are conducted in real-world scenarios and populations, using a convenient comparison arm, prioritising relevant outcomes and keeping randomisation standards [153].

Economic evaluations provide a quantitative method to evaluate and compare health technologies' costs and benefits jointly. In this regard, they are a powerful strategy for providing decision-makers with integrated evidence to allocate resources in healthcare services. In this way, CUA informs about health technologies' contextual value for money by moving beyond prices and showing the incremental cost of acquiring an additional unit of health benefit. Indeed, it expresses the opportunity cost of allocating resources by comparing the costs and health benefits of adopting a new treatment strategy in a natural or simulated healthcare scenario where other options will be forgone.

CUA is a type of cost-effectiveness analysis which uses **quality-adjusted life years (QALYs)** [154,155] as the health benefit component of the analysis. This method is particularly recommended to assess the burden of chronic diseases in the long term as individuals' functionality is usually more affected than the length of life.

Metaphorically speaking, QALYs work as a 'currency' to measure the impact of an intervention on patients' quality of life over time as they can be gained or lost by incorporating a new health technology compared to the second-best option. In this regard, they are especially useful for comparing different types of interventions, such as cardiovascular surgery and a tabaco dishabituation programme. QALYs are obtained by multiplying a health state obtained using health-related quality of life (HRQOL) and self-reported instrument [156] per the assigned utility value and the time of the intervention effect also called the time horizon. In the case of *Study III*, a one-year time horizon was adopted due to the chronic nature of FMS.

QALYs take values from 0, representing death, to 1, representing perfect health. The values in between are based on stakeholders' preferences (weights/utilities) for a particular health state, which might change between populations. For instance, five years of perfect health or ten years with half of that quality of life due to living with a chronic condition equals 5 QALYs in both cases.

Furthermore, this study adopted a **societal perspective** [157], meaning that all registered and available costs incurred by the patient, the healthcare funder, and society as a whole were considered. Unfortunately, this approach may face challenges in accounting for non-registered information such as out-of-the-counter drug consumption, informal care, informal labour market, time and out-of-pocket expenses dedicated to medical visits (such as transportation) and/or private healthcare services and alternative medicines, loss in consumption, and productivity losses in children, homemakers and pensioners. This limitation on data availability may lead to underestimating actual costs for society.

Additionally, a **human capital approach** [151] guided the data collection and estimation of indirect costs, given that only full sick leave days were recorded in our data source. The human capital approach in health economics assumes workers are valued for their earnings. Hence, productivity losses are measured in terms of lost wages (gross salary in days of absence from work). The main drawback of this method is the potential overestimation of indirect costs. According to the friction cost approach [158], when workers cannot assume their responsibilities due to illness, someone else generally compensates for the tasks and prevents production loss, which may actually reduce companies' costs if co-workers replace the job. In this sense, only the time passed until the sick worker is replaced, the so-called 'friction period', would be advisable to be counted as productivity losses. Counterargued, this approach might not be feasible nor realistic in all labour market scenarios [159]. Yet, from a societal perspective, productivity losses adopt an Insurance Medicine approach [160]. Whether the social welfare or the employer assumes the paid sick time, it is counted as part of the indirect cost derived from the disease that represents the societal production loss. The Spanish General Law of Social Security (Law 2072014; Royal Legislative Decree 8/2015) [161] establishes that 'temporary disability' refers to short-term absenteeism from work due to common or work-related illness. It is measured by sick leave days prescribed by a GP and financed between the National Social Security System, the Social Security Mutual Society Partner and the employers depending on the number of days.

Lastly, *Study III* was designed following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [162].

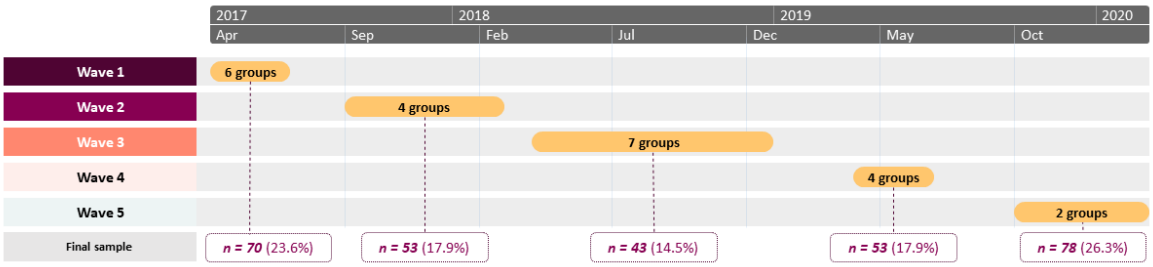
4.2.2. Participants and Recruitment

Sampling and recruitment in *Study III* were based on the associated PRCT designed for evaluating the MCI programme. Inclusion and exclusion criteria have been detailed above in section 2.1.2. In addition, only those individuals who have completed at least the baseline and the 12-month post-intervention follow-up were included in the sample of *Study III*.

Commonly called piggyback evaluations [163], economic studies rooted in a trial designed under clinical criteria may face limitations regarding sample size, follow-up, or data collection. Consequently, the results obtained from the associated economic study could not fully capture the actual costs and benefits of the assessed health technology [164], given that the study design is primarily intended to meet the PRCT needs. However, in this case, the sample estimation was performed based on the same primary outcome: the results obtained from the adopted quality-of-life instrument. Accordingly, 260 individuals (130 per study arm) were calculated to detect a difference of at least five points in the Spanish version of the SF-36v2 questionnaire [150], assuming an α error of 0.05, a β error of 0.05 (bilateral contrast), and a 20% of dropout rate. Figure 1 from the *Study III* results manuscript (Annexe, Pending publications) displays the respective sample flow diagram, which can be found in the result section of this thesis work.

As mentioned in section 1.5, the MCI programme was carried out in five waves from 2017 to 2020 by delivering the intervention in different PCCs throughout the health region according to availability. Initially, individuals with FMS who fulfilled the inclusion criteria were shortlisted from the eCAP system and telephonically contacted to participate in the MCI. A first meeting at the patient's registered PCC was scheduled for baseline assessment when further information about the programme was delivered. Additionally, individual-based random allocation to intervention and control (waiting list) was conducted following the Efron procedure [165]. Both researchers and patients were kept blind during the first encounter and until the next contact call, when patients were informed if they were recruited for the intervention or control group. Those allocated to the control group were offered to participate in the MCI once their 12-month follow-up was ended. Figure 8 shows the number of individuals finally included in the *Study III* sample from each MCI wave, where a group represents one PCC.

Figure 8. Study III sampling



4.2.3. Data collection

Primary data was collected by administrating questionaries and extracting information from the eCAP system from the beginning of the study in April 2017 to the end of the follow-up period in March 2021. Face-to-face interviews were the primary data collection strategy until the COVID-19 outbreak. Given the pragmatic nature of the project, these visits provide patients with a clinical follow-up. In most cases, an online platform (SurveyMonkey Audience[1]) and phone calls replaced the visits to the PCC during the pandemic. All data were documented in a software application specially developed for this project within the ICS digital system. Data collection from *Study III* encompassed sociodemographic, clinical, health-related quality of life and cost variables (v.).

Sociodemographic data was collected during the first interview at baseline and included sex (dichotomous v.), age (continuous v.), birth country (nominal v.), maximum achieved educational level (ordinal v.), marital status (nominal v.), cohabitation (each possibility was treated as a dichotomous v. as they were not mutually exclusive), current working condition (nominal v.) and occupational class (ordinal v.).

In addition, **clinical variables** covered: years after FMS diagnosis (continuous v.); family history of FMS (dichotomous v.); trigger factors associated with FMS onset, including physical, exercise, psychological, and stress (dichotomous v.); a count of common self-reported cognitive and physical symptoms (continuous v.) including attention, memory and sleep disturbances, paraesthesia, low back pain, fatigue, dried mucus, Raynaud syndrome, sensory sensitivity, cephalexin stability, and drug intolerance; the Hospital Anxiety and Depression Scale (HADS) [166,167] (discrete v.); the Revised Fibromyalgia Impact Questionnaire (FIQR) [168,169]

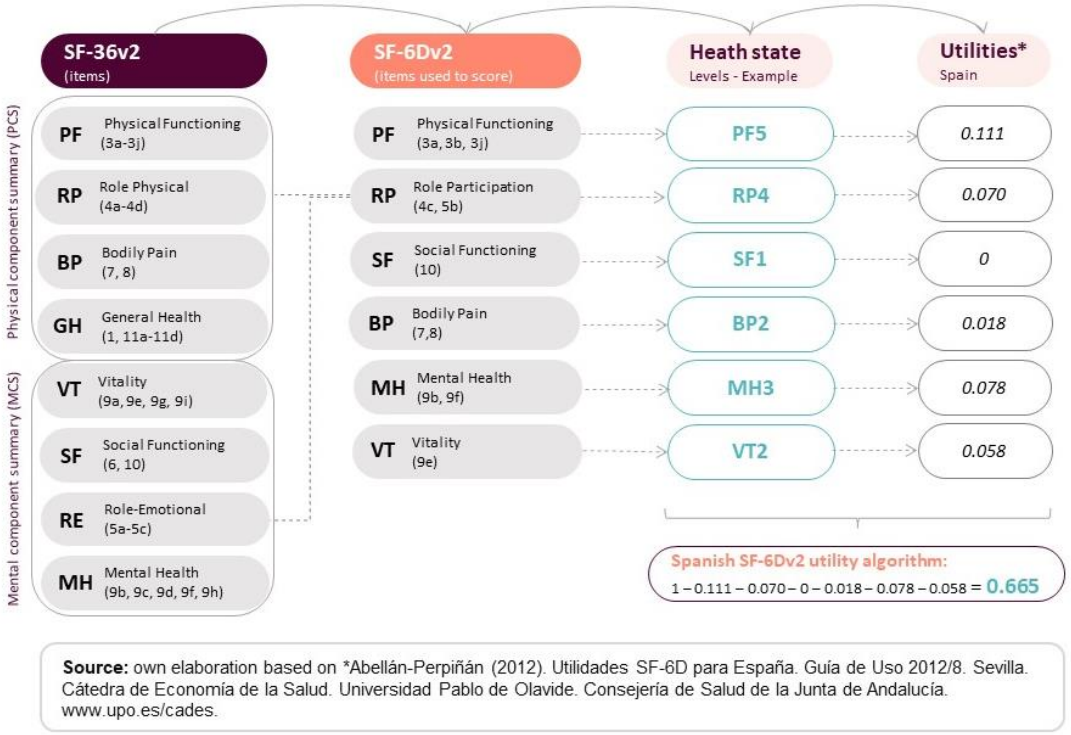
[1] www.surveymonkey.com/mp/audience

(continuous v.); and presence of comorbidities recorded in the eCAP system (dichotomous v.). The latter was explored following the literature [36] regarding diagnoses with similar symptoms to FMS, as explained in the introduction section and represented by 'The Fibromyalgia Iceberg' in Figure 2. Table S5, presented in the *Study III* results manuscript (Annexe, Pending publications, Study III, Supplementary Material S5), shows the explored diagnoses. Finally, session attendance at the MCI was also included for those in the intervention group.

Regarding the **health outcome**, data collected through the SF-36v2 health survey [150] in Catalan or Spanish (Optum, Inc., license number QM048943) at baseline and 12 months post-intervention were included in *Study III*. This HRQOL instrument measures self-reported functional health and well-being using 36 questions comprising 8 multi-item dimensions. On the one hand, the physical component score (PCS) includes the dimensions of Physical Functioning (PF), Role-physical (RP), Bodily Pain (BP), and General Health (GH). On the other hand, the mental health component score (MCS) addresses Vitality (VT), Social Functioning (SF), Role-Emotional (RE), and Mental Health (MH). Scores are presented by means of each subscale or dimension and summaries of the PCS and MCS ranging from 0 to 100, in which the higher the score, the better HRQOL reported.

As previously remarked, economic evaluations derived from clinical trials may face challenges when analysing data that does not meet the methodological needs. Administrating instruments to assess patients' quality of life does not necessarily inform about QALYs, which is the case of the SF-36v2. **'Mapping'** is a statistical technique that converts clinical outcomes into utility values through preference-based algorithms from similar data sets [170]. To this end, the results obtained from the SF-36v2 questionnaire [171] were mapped into the SF-6Dv2 index [172] based on Spanish preference weights [173] and using the corresponding scoring software (QualityMetric, non-commercial license, order 240835D) [174]. The following diagram (Figure 9) explains the mapping process:

Figure 9. Mapping SF-36v2 scores into the SF-6Dv2 index



Source: own elaboration based on *Abellán-Perpiñán (2012). Utilidades SF-6D para España. Guía de Uso 2012/8. Sevilla. Cátedra de Economía de la Salud. Universidad Pablo de Olavide. Consejería de Salud de la Junta de Andalucía. www.upo.es/cades.

Noteworthy, the Spanish utility bottom threshold is significantly smaller than the one from the United Kingdom [173]. Therefore, it is possible to obtain results close to or even below 0 (which theoretically means worse than death).

Concerning the **cost variables** included in *Study III*, data was collected 12 months before and after the MCI programme for each participant and control. Costs were estimated in euros (€) based on units of consumption registered in the eCAP system and multiplied by the corresponding official Spanish prices for health services, drugs and average wages in 2021 [175–177]. Table S2 in ***Study III*** results manuscript (Annexe, Pending publications, Study III, Supplementary Material, S2) describes variables, prices, and data sources for cost estimations.

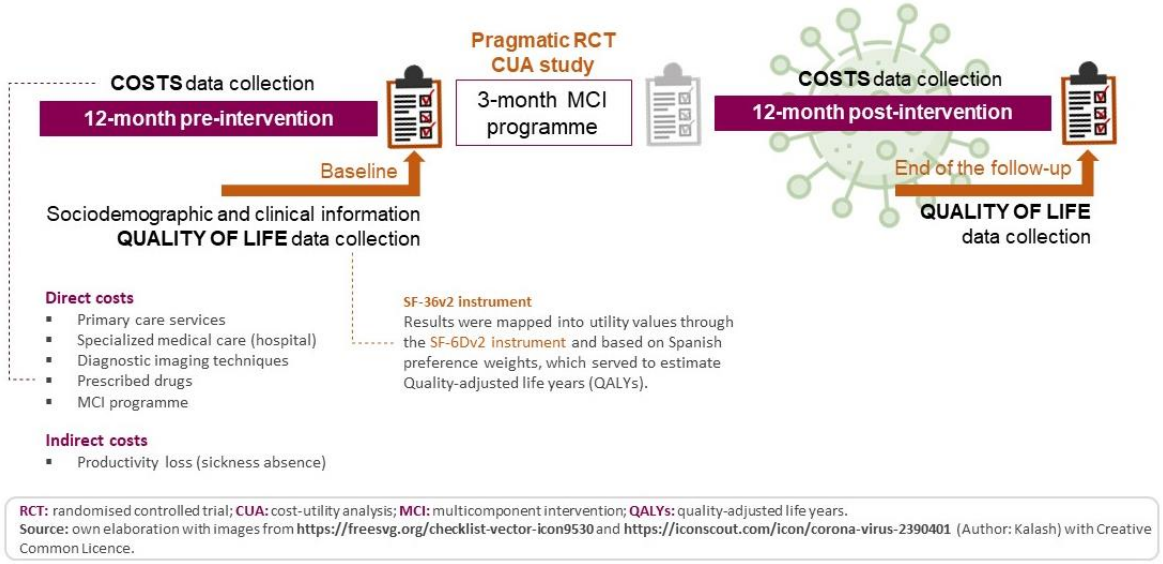
Costs are categorised into two big groups: direct medical costs and indirect costs. The former covers healthcare services through inpatient and outpatient treatments, including visits in primary care to the general practitioner, nurse, rehabilitation, and physiotherapist (low complexity), as well as simple blood tests and non-urgent emergency services (without a stay); specialised medical care or referrals to the regional hospital *Verge de la Cinta* which included traumatology, psychiatry, rehabilitation, non-urgent emergency (without a stay), other practices (external referrals) and hospital discharge; diagnostic imaging techniques (all kinds), and

pharmacological treatment (all types). As for drugs, costs were estimated by multiplying the number of active days of prescription (as it was the only data registered in the eCAP system) by the cost of treatment per day (CTD) related to each different national registered drug code or, when not available, the international Anatomical Therapeutic Chemical (ATC) Classification. Noteworthy, the CTD data had to be specially requested by post to the Spanish National Minister of Health. All prices were considered before tax deductions as they better represented the socioeconomic burden of FMS on the use of direct medical services. In the case of drugs, the official final market prices were used for estimations. In Spain, pharmaceutical co-payment is implemented by the National Health System based on individuals' income, age and degree of illness and divided into three categories that publicly finance 100%, 60% or 40% of the total cost, respectively [178].

Indirect costs consisted of productivity losses incurred during the follow-up period. They were measured as sickness absence by multiplying the number of prescribed sick leave days per the average salary per day in Catalonia for the third trimester of 2021. Wages were obtained from the Spanish National Statistics Institute [177] and comprised part-time and full-time work, regular and extra payments, and were endorsed to all activity sectors (industry, construction, and all services except housework).

Lastly, the cost of the MCI programme was estimated per person based on actual expenditure dedicated to professionals' wages. As the healthcare providers were paid per hour of service, regardless of the number of participants in each MCI, a mean of 10 participants was taken into account to estimate the individual MCI cost. Figure 10 summarises the data collection process in *Study III*.

Figure 10. Cost-utility analysis: data collection diagram.



RCT: randomised controlled trial; **CUA:** cost-utility analysis; **MCI:** multicomponent intervention; **QALYs:** quality-adjusted life years.
Source: own elaboration with images from **https://freesvg.org/checklist-vector-icon9530** and **https://iconscout.com/icon/corona-virus-2390401** (Author: Kalash) with Creative Common Licence.

4.2.4. Data analysis

A **complete case analysis** was carried out given the attained sample size, the expected level of participant drop-out/non-response (25%), and the pragmatic nature of the study design for which real-world data was prioritised. Therefore, only those individuals who did not drop out from the study and were not lost during the follow-up period were included in the final study sample regardless of the number of sessions attended. Accordingly, the randomisation was preserved, non-compliance with the offered MCI schedule was considered, and the sample size was monitored according to estimations.

Analyses were performed using R Studio software [179]. Initially, the sample was described to assess its homogeneity at baseline. The study groups were compared by sociodemographic and clinical characteristics using bivariate analysis and independence tests (T-test, Fisher's and Pearson's chi-squared tests). Secondly, the interested outcome variables were explored pre- and post-intervention among the study groups. QALYs and costs per major component were described using means, bootstrap confidence intervals (10,000 replications), paired and independent mean differences and p-values (T-test, Wilcoxon signed-rank and rank-sum tests).

Thirdly, the main outcome of a CUA was estimated: the **incremental cost-utility ratio (ICUR)**. This measurement results from the quotient between the difference of mean costs and benefits between the health technologies to be compared:

$$ICUR = \frac{\bar{X}\ (\text{Costs\_new intervention}) - \bar{X}(Costs\_comparator)}{\bar{X}(QALYS\_new\ intervention) - \bar{X}(QALYs\_comparator)}$$

In *Study III*, the ICUR mathematical operation was performed using a difference-in-differences technique which considered the costs and benefits incurred during the pre-intervention period in order to correct for possible baseline imbalances between the study groups:

$$ICURmean = \frac{\Delta\bar{X}(\text{CostsMCIpost} - \text{CostsMCIpre}) - \Delta\bar{X}(CostsUCCpost - CostsUCCpre)}{\Delta\bar{X}(\text{QALYsMCIpost} - \text{QALYsMCIpre}) - \Delta\bar{X}\ (QALYsUCCpost - QALYsUCCpre)}$$

Where:

$\Delta\bar{X}$ = mean difference
post = post-intervention
pre = pre-intervention
MCI = Multicomponent Intervention
UCC = Usual Clinical Care
QALYs = Quality-adjusted life years

The ratio obtained is interpreted by means of the cost-effectiveness plane (Figure 11) and the cost-effectiveness threshold. The ICUR could fall within four decision-making scenarios depending on the incremental costs and benefits obtained. Quadrants II (northwest corner) and IV (southeast corner) provide straightforward information regarding the new intervention. While the former only entails losses in terms of health and resources, the latter increases QALYs and results in cost-savings. Nevertheless, in quadrants I (northeast) and III (southwest), the decision-making is uncertain as both cases have gains and losses. The cost-effectiveness threshold (CET) indicates the maximum monetary value the funder is willing to pay to gain one QALY. Hence, everything above the CET should be rejected and accepted otherwise [180].

Figure 11. The Cost-effectiveness plane.

ICER: Incremental cost-effectiveness ratio; **QALY:** quality-adjusted life year.
Source: own elaboration.

Furthermore, the ICURs from *Study III* were estimated using **Seemingly unrelated regression (SUR) models** [181] (systemfit R package) in order to account for the correlation between costs and effects [182]. This method estimates equations for costs and effects so that these variables can be correlated through error terms. Furthermore, non-parametric bootstrapping was applied to the mean differences of these outcomes between the study groups, given the skewed distribution trend of costs. As a result, crude and adjusted ICURs were estimated by considering the following covariates: age, education level, cohabitation (living alone), years since diagnostic, reported symptoms, having a family history of FMS, presence of comorbidities, HADS, and FIQR total scores.

Lastly, **sensitivity analyses (SA)** were performed deterministically in one- and tow-ways to account for uncertainty and assess the robustness of the results [183,184]. First, primary healthcare costs (GP and nursing) were accommodated according to the actual regional weighted health expenditure from 2021 as they entailed a major economic cost. Further details can be found in the *Study III* results manuscript (Annexe, Pending publications, Study III, Supplementary material, S3). Secondly, those participants with a session attendance <66% (minimum of 8 out of 12 sessions) were excluded from the sample to assess the implementation scheme of the MCI programme.

4.3. Ethical considerations

All the studies in this doctoral thesis were conducted in accordance with the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of the IDIAPJGol Institute (codes P17/069 and P18/068 on 25 April 2018). Furthermore, written informed consent was obtained from the participants to use their anonymous information for research and publication.

The project entailed a minimal risk of the possibility of personal integrity violation as all collected data was anonymized before analysis to prevent individual identification. In the case of qualitative data, names and identification signs were removed from the verbatim transcriptions and documents were anonymously coded. In addition, contact information support was offered to informants, considering the potential emotional repercussions of digging into their illness experiences and perceptions, which could have caused anxiety and sadness.

5. Results

This doctoral thesis encompasses four peer-reviewed publications, including two study protocols (one related to *Studies I* and *II* and the second one regarding *Study III*) and two original research articles on the results of *Study I* and *Study II*. In addition, the results of *Study III* are presented in its manuscript version in the Annexe section (Pending publicationts), which is currently under a peer-review process in an international journal.

5.1. Study Protocol for Studies I and II

Title: Assessing the benefits on quality of life of a multicomponent intervention for fibromyalgia syndrome in primary care: patients' and health professionals' appraisals: a qualitative study protocol

Reference: Arfuch, V. M., Caballol Angelats, R., Aguilar Martín, C., Carrasco-Querol, N., Sancho Sol, M. C., González Serra, G., Fusté Anguera, I., Gonçalves, A. Q., & Berenguera, A. (2020). Assessing the benefits on quality of life of a multicomponent intervention for fibromyalgia syndrome in primary care: patients' and health professionals' appraisals: a qualitative study protocol. BMJ open, 10(11), e039873. https://doi.org/10.1136/bmjopen-2020-039873

Summary

Introduction: This study protocol presents the qualitative assessment design for evaluating a multicomponent intervention (MCI) programme for patients with fibromyalgia syndrome (FMS). This programme was delivered in primary care settings from the *Gerència Territorial Terres de L'Ebre* in south Catalonia, Spain. It covered a 12-session scheme which combined health education, physical activity and cognitive-behavioural therapy. The proposed goals of this protocol covered exploring patient and healthcare staff participants' opinions and lived experiences about the MCI programme. The present doctoral thesis only covers the qualitative assessment from patients' perspectives.

Methods: Four focus group discussions (FGDs) were planned, including 8-12 informants. Two FGDs would focus on patient-participants from the MCI, and two would be focused on healthcare staff involved in this therapeutic initiative. Furthermore, data gathering comprised 10-12 individual interviews with patients. Data would be verbatim transcribed and analysed through thematic analysis.

BMJ Open

Assessing the benefits on quality of life of a multicomponent intervention for fibromyalgia syndrome in primary care: patients' and health professionals' appraisals: a qualitative study protocol

Victoria Mailen Arfuch ,[1,2] Rosa Caballol Angelats,[3,4] Carina Aguilar Martín,[1,5] Noèlia Carrasco-Querol,[1] Maria Cinta Sancho Sol,[1,4] Gemma González Serra,[1,4] Immaculada Fusté Anguera,[3,4] Alessandra Queiroga Gonçalves,[1,6] Anna Berenguera [2,7]

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For numbered affiliations see end of article.

Correspondence to
Dr Anna Berenguera; aberenguera@idiapjgol.org

ABSTRACT

Introduction Fibromyalgia syndrome (FMS) is a complex condition still scarcely understood and with ambiguity when prescribing treatment. Both patients and healthcare providers can supply valuable information for the development of new treatment strategies. The qualitative narrative analysis of participant's accounts is potentially helpful to reveal new insights about their opinions, needs, and experiences and, consequently, to model healthcare interventions accurately. International treatment guidelines suggest a promising future for multicomponent intervention (MI) approaches for FMS. This study aims to assess the benefits of a MI for patients with FMS in the context of primary care (PC) in *Terres de L'Ebre,* Catalonia (Spain). Furthermore, it is intended to detect the overall perception of effectiveness and to understand patients' lived experience and its impact on the quality of life.

Method and analysis Qualitative research from a socioconstructivism paradigm perspective and a Hermeneutic Phenomenological method. For data collection, four focus group discussions (FGDs) of 8–12 people (2 FGDs of patients and 2 of professionals) and 10–12 key informant interviews with the participants in the MI group will be carried out. All the information will be recorded and verbatim transcribed to perform an interpretive thematic analysis.

Ethics and dissemination This study protocol has been approved by the Clinical Research Ethics Committee from the IDIAPJGol Institute, on 25 April 2018 (code P18/068), according to the Declaration of Helsinki/Tokyo. All participants will receive oral/written information about the study, and they will be required to sign an informed consent sheet. Data anonymity will be guaranteed. Dissemination will be carried out through publications in scientific journals, presentations in academic meetings, workshops and through the local and national media.

Trial registration number ClinicalTrials.gov: NCT04049006; Pre-results.

Strengths and limitations of this study

- This study will provide information on barriers and facilitators about the multicomponent intervention (MI) programme for fibromyalgia syndrome to design more flexible treatment strategies adapted to patients' health needs.
- The results of this study will help to improve the contents of a MI considering patients' and professionals' opinions and the available resources in primary care.
- In-depth patient interviews will contribute to a richer understanding of their health needs, lived experiences and the subjective benefits of the MI to provide accurate and higher quality health services.
- A pre-implementation phase through qualitative methodology has not been conducted before the MI started.
- The results of this study will not be generalisable to other contexts due to the limitations of the method.

INTRODUCTION

Fibromyalgia is a long-term condition, potentially disabling characterised especially by an atypical perception of pain. This syndrome disrupts patients' biopsychosocial universe compromising personal and occupational aspects, plans and relationships.[1] Consequently, global health status and quality of life (QOL) could be distorted.[2]

Fibromyalgia syndrome (FMS) is a complex condition associated with several symptoms and comorbidities, such as rheumatological and psychiatric disorders.[3] FMS diagnosis is based on clinical criteria where the most frequent manifestations are: generalised musculoskeletal pain, fatigue, sleep disturbance, gastrointestinal disorders, psychological distress which can trigger anxiety and depression, loss of functioning, low tolerance to physical effort, migraines and dizziness.[4–6]

The worldwide prevalence of FMS in the general population is estimated between

0.2% and 6.6% and, 2.45% on average in Spain.[7 8] It is usually diagnosed in middle-aged people,[2 9] and it is more frequent in women with a prevalence ranged between 2.4% and 6.8% and with a female/male ratio of 21:1.[10] Although this difference in prevalence between women and men cannot be fully explained yet, studies suggest that these rates are overestimated for women and underestimated for men due to diagnostic criteria bias.[11 12] Moreover, another study identifies the existence of gender bias in healthcare towards patients with chronic pain, which helps to demystify the FMS as a predominantly female condition due to intrinsic factors.[13]

Although FMS is classified as a central sensitivity syndrome,[14 15] its pathogenesis, aetiology and evolution are still medically unexplained. Some experts suggest an interaction between neurophysiological, genetic, epigenetics and psychosocial factors.[16–19] This knowledge gap complexes and delays the diagnosis process, discrediting the authenticity of the fibromyalgia, and generating ambivalence about the provision of healthcare.[20 21]

Diverse treatment strategies have been tested focusing on severity symptom management, QOL improvement and the prevention of chronicity. Physical exercise, psychological approaches such as cognitive–behavioural therapy (CBT), health education and complementary medicine have demonstrated some clinical improvement in symptom control.[22–27] Nevertheless, the evidence remains uncertain, and there is scope for further research to determine the best treatment option. In this context, users' and professionals' opinions become a strategic resource for the design of treatments tailored to health needs. A qualitative analytic approach to understanding their point of views and necessities is a valuable method which reveals novel insights about how people make sense of this condition and how they experience treatments.[28]

There are few published qualitative studies about the effectiveness of interventions in patients suffering from FMS. According to the evidence, qualitative methodology is a useful approach to assess in-depth participants' treatment experience and detect patients' global impression of change regarding pain management, functionality and QOL.[29–34] However, authors acknowledged that it would be important to include the clinicians' appraisals as well.[30]

Multidisciplinary interventions that combine pharmacological and non-pharmacological treatments have shown to be effective in some clinical trial studies after 3–12 months of follow-up.[30 35–39] A recent study, based on a comprehensive 8-week group-based multidisciplinary rehabilitation programme that included CBT and graduated activity training, showed significant improvements in health-related QoL at the end of the intervention, at 6 months and one year of follow-up.[40] Regarding the Spanish population, a study of similar characteristics was conducted in the Basque Country in 2012, about a 6-week interdisciplinary treatment in the hospital context. This programme that combined psychological, medical, educational and physiotherapeutic components demonstrated significant improvements in QOL, physical function and pain at a 6-month follow-up. Although these results were maintained at 12 months, they were not compared with a control group, nor were they studied in the context of primary care (PC).[41]

Multicomponent intervention (MI) programmes have been recommended in international treatment guidelines.[42–45] Nevertheless, this intervention strategy for FMS is in its infancy in the usual clinical care[46] into the Spanish public health sector. In Catalonia, and since 2016, 18 accredited units specialised in Central Sensitivity Syndromes located in PC centres and hospitals[47] provide multidisciplinary healthcare to patients with FMS.[48]

This study aims to search out, through qualitative research methodology and from patients with FMS and healthcare providers' points of view, the overall perception of effectiveness about a MI and its benefits on patients' QOL. Moreover, the specific objectives of the study are:

- To assess the subjective benefits on patients' functional impact, mood and pain management.
- To assess professionals' experience about the MI and their appraisal regarding the benefits of the programme for patients' health.
- To detect improvable aspects of the MI, based on the opinions and experiences of participants (users and professionals), in order to standardise the programme so that it can be replicated in other health settings.
- To explore the subjective benefits and the impact of the MI on patients' daily life and to understand the structure of their lived experiences.

This MI programme is provided within the 11 PC centres of the *Gerència Territorial Terres de L'Ebre* of the Catalan Institute of Health. It consists of a 3-month group programme combining: health education, physical activity and CBT. The purpose of this proposal is to promote patients' QOL by increasing control over their health in order to improve it.

It is expected that the results will support and extend the results of the randomized clinical trial (RCT) from which this project arises (ClinicalTrials.gov: NCT04049006).[49] The contents of each MI session and other details of the design are fully described in the published protocol of the RCT study.[50]

METHOD

Design

This protocol has been drafted based on the literature review and following the protocol guidance for qualitative research of the Health Research Authority.[51] Furthermore, this study will be reported following the Consolidated Criteria for Reporting Qualitative Research[52] and the Standards for Reporting Qualitative Research: A Synthesis of Recommendations.[53] Finally, the evaluation of the intervention will be founded on the constructs and guidelines suggested by experts of implementation research.[54 55]

For the design of this study, interpretive qualitative research will be carried out based on the theoretical framework of the socioconstructivism paradigm[56] and a Hermeneutic Phenomenological method.[57] This perspective aims to answer what are the meanings that give sense to our individual and collective existence, and how they come to be constituted.[58] In this way, the narrative occurs and evolves in the process of social interaction, where the discourse does not pre-exist but is constructed in the intersubjective setting. Therefore, socially constructed narrative realities give significance and structure to our existence, and the interpretation of this experience challenges the way of being in a particular context.[59] This study design is also accurate since it incorporates the preunderstanding of the researcher as part of the experience and so it is not necessary bracketing particular beliefs about the phenomena in order to explore it.

The multiperspective research approach collects data from informants with different positioning regarding the study phenomenon, expanding not only the narrative themes of the accounts but also enriching the understanding of the structure and dynamics of interaction between them.[60 61]

Intervention strategy

The MI consists of a 12-week group programme of 2 hours weekly combining: 7 health education instructions delivered by a general practitioner and a nurse, 11 pieces of training on physical activity delivered by a physiotherapist, and 7 interventions of CBT delivered by a psychologist.

Regarding the contents of the programme, the health education component includes an introduction to multicomponent therapy, neurophysiology and pharmacology of pain, techniques of postural hygiene, nutrition, insomnia management, memory and sexuality. The physical activity component focuses on breathing and relaxation, stretching, strength/joint and coordination exercises, and the 6 min walking test. Finally, the psychological component works on CBT strategies, pain and attention management, mood and emotional management, strategies for coping with difficulty, and the planning of goals and pleasant activities.

This MI programme aims to: the patients' acquisition of knowledge, skills and attitudes for the daily management of the FMS; the improvement of their physical condition; the relief of their emotional distress, and to provide skills to overcome psychological difficulties.

Participants and setting

This study will include patients who have had a minimum of participation in the MI group and PC professionals involved in some stage of the programme. All participants will be recruited from any of the 11 PC centres belonging to the *Gerència Territorial Terres de l'Ebre* (Catalan Health Institute).

The inclusion criteria for patients are: have a clinical diagnosis of FMS (International Classification of Diseases-10 codes: M79.0, M79.7), being over 18 years, be able to communicate (orally and written) effectively in Catalan or Spanish, have a phone number, have participated in a minimum of 75% of the intervention programme (equal to or more than 9 out of 12 sessions), accept participation in the qualitative study, sign the informed consent. On the other hand, the exclusion criteria involve: having an actively psychotic episode, having an intellectual impairment, having severe depression and personality disorder, registering auto/hyperaggressive behaviour, detecting use of psychoactive substances, having not attended to a minimum of 75% of the MI group sessions (less than 9 out of 12 sessions), not sign the informed consent.

The criteria for professional recruitment include sign the informed consent sheet, have participated in some stage of the MI in the last 6 months, not having declared conflicts of interest.

Group and individual interviews with patients and professionals will be carried out in a PC centre from *Terres de L'Ebre* area. Sound insulation criteria will be considered to guarantee the confidentiality of the information.

Patient and public involvement

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

Sampling and recruitment

Theoretical sampling will be used to achieve maximum discursive variability. First, two lists of possible candidates among patients will be drafted based on time criteria (up to <6 months of follow-up after the intervention and, between ≥6 and 12 months of follow-up) in order to assess the perception of the benefits in the short and medium-long term. Second, those patients who accomplish with a minimum attendance of 75% to the intervention group will be included in the recruitment sample. Then, criteria based on gender, age, working status and geographical area will be applied to draft a list of possible candidates. Finally, patients will be contacted by phone, and only those who accept participating in the qualitative study will be included in the final data collection sample. Regarding PC professionals, general practitioners and nurses of different genders, age groups, geographical areas of work will be included.

Additionally, and in order to understand the reasons for MI dropout and the possible lack of adherence, 4–6 phone calls will be done to patients who have been recruited to participate in the study and have signed the informed consent but who, finally, did not start the programme or wanted to leave it early. Members of the research group will carry out these phone calls according to the data protection low.

Informants will be invited to participate in the study through telephone contact. They will be informed about the characteristics and objectives of the study, the audio–video recording of the interviews, and they will be guaranteed with the anonymity of the data management.

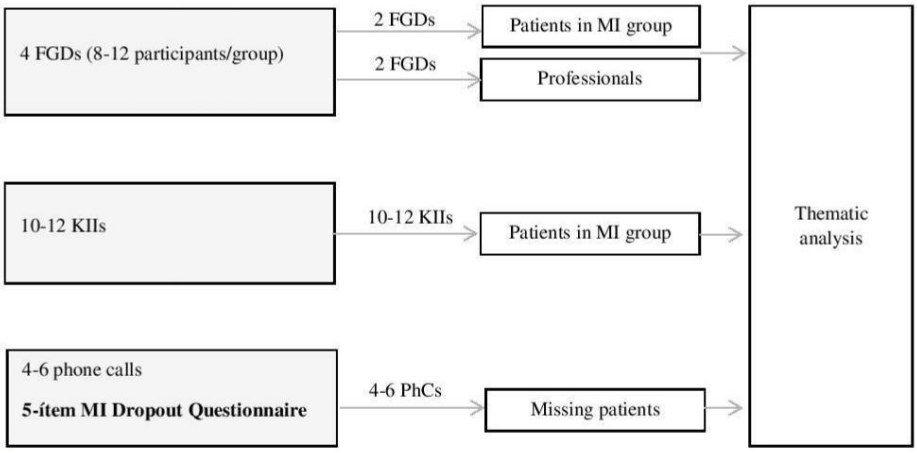

Figure 1 Flow diagram of the qualitative study. FGD, focus group discussions; KII, key informant interview; MI, multicomponent intervention; PhCs, phone calls.

People who have participated in both study groups because of an ethical requirement (first control and then intervention group) will be recruited for some of the individual interviews. Although this subsample cannot be included in the quantitative study for methodological reasons, they could provide valuable information for the qualitative analysis since they will have experienced both treatment interventions.

Data collection

Data collection includes four focus group discussions (FGDs) of 8–12 people (2 FGDs of patients and 2 of professionals) and 10–12 key informant interviews (KIIs) with patients that have participated in the MI group. FGDs and KIIs will be carried out through different samples. When necessary, additional discussion groups and personal interviews will be conducted to achieve discourse saturation. Data collection is expected to be complete by January 2021. Figure 1 describes the design and methodology of data collection.

The FGDs and KIIs will be audio and video recorded, prior informed consent, and will be literally and systematically transcribed. Identifying data of the informants in the transcripts will be anonymised.

An experienced moderator will conduct the FGDs using a semistructured guide. A comoderator and an observer will also participate as part of the research team. The FGDs are expected to last no more than 95 min. The guide will cover the following topics: the overall opinion about the MI effectiveness, an evaluation of the elements of the framework (time, space, professionals and beneficiaries), improvable aspects, and the benefits of the intervention on patients' QOL.

KIIs will be delivered by an experienced qualitative researcher and will be based on open-ended structured questions. The objective is to assess the patients' personal lived experience in the intervention programme and exploring their subjective impact. The interviews are expected to last no more than 65 min.

The question protocols for the FGDs and the KIIs will include open-ended questions aimed to cover the research objectives: patients' experiences during the MI and the subjective benefits, its impact on QOL and daily life, patients' and professionals' overall perception of effectiveness, and barriers and facilitators on the intervention implementation.

Data analysis

A thematic analysis will be carried out to identify, interpret and report patterns (themes) within data. First, literal transcripts of the audio recordings will be included in a text corpus according to a published guide, which enlists the steps for thematic analysis.[62] Secondly, successive readings of the text corpus will be completed as well as the formulation of pre-analytical intuitions. Thirdly, the coding process will be delivered, organising the data into the most basic meaningful elements (codes). Consecutively, the emergent themes from the interpretative analysis will be registered and clustered where appropriate under superordinate themes or salient phrases. In this way, all the relevant coded data extracts will be organised within the identified themes to catch the essential attributes of the participants' accounts. These themes will be reviewed and named checking the existence of coherent patterns. Finally, a report will be drafted writing up the results of the analysis and the interpretation of it.

Furthermore, a triangulation process of this first thematic analysis will be fulfilled between two or more members of the research team.[63] Discrepancies in the data analysis triangulation process will be resolved primarily through consensus. In case this is not achieved, the majority criteria will be implemented, if applicable.

If none of these strategies worked, the external expert opinion would be appealed to solve the struggle. Nevertheless, an attempt will be made to reach agreements between researchers that include all points of view, fulfilling the criterion of internal coherence. The meanings extract from the triangulation will be interpreted, and an explanatory framework will be created with the contributions of each type of informant (users and professionals participating in the FGDs and the KIIs).

DISCUSSION

FMS has become a challenge for health providers due to its heterogeneity, unclear aetiopathogenesis and the particularities of the patients' profile.[20] Faced with this scenario, it is vital to incorporate a holistic perspective of all those involved in the development and implementation of treatment strategies, including people suffering from this condition.

From a methodological perspective and according to the Medical Research Council, the qualitative approach provides relevant information for the validation and modelling of new intervention programmes in order to effectively implement them in the real world and to identify and understand the main barriers.[64 65] Moreover, the communication with stakeholder groups informs if the intervention addresses the priority issues for the people involved and uses appropriate, feasible and acceptable methods.[66]

Accordingly, the qualitative assessment is expected to reveal key details of the MI implementation, from patients' and professionals' points of view involved. This information will allow adjusting the setting elements (timeline, number of participants in the group), therapeutic components and thematic contents that cover patients' health needs. Additionally, the results of this study will likely improve the adherence to the MI, the adequacy of health centres and the impact on family members. Consequently, healthcare services for FMS, provided on the recently established units specialised in Central Sensitivity Syndromes in the area, will increase their effectiveness and efficiency. As well, this programme will be hopefully replicated and considering as an intervention model in other healthcare systems.

A triangulation technique will be implemented to achieve complex analysis. The multiperspective qualitative approach can also help to study relationships and dynamics between patients and professionals and to explore similarities and differences in their perceptions.

Furthermore, in-depth patient interviews will contribute to a richer understanding of their real health needs, lived experiences and the subjective benefits of the MI. This information is crucial for providing accurate and high-quality health services and collaborates with FMS acceptance and self-management.

Even though the qualitative approach is considered a weak method to achieve reliable evidence, it can also be successful in seeking little studied and controversial topics related to FMS. Patients' experiences could guide researchers on the path to resolve the FMS dilemma. Understanding the experience of illness and how this syndrome impacts at different levels such as work, social, physical, psychological and sexual functionality could help to determine how to approach it from the healthcare services to improve patients' QOL and overcome its legitimacy debate.

Attending the limitations of the qualitative methodology, the results of this study will not be generalisable to other contexts. Moreover, due to the nature of self-reported data, the results could be affected by memory, group effect, overestimation or underestimation, selection, or attribution biases. In addition to the intrinsic limitations of the method, this qualitative study also presents shortcomings. Firstly, any pre-implementation phase was conducted. Secondly, inclusion criteria in the FGDs and KIIs will be limited only to those people who agree to participate in the qualitative study so that they could have a greater interest and a more positive perception of the MI. Another limitation is that, initially, no external expert in qualitative methodology will be included in the triangulation analysis process to avoid investigator bias. It will only be considered in case of major discrepancies between the researchers. Finally, there will be no FGDs according to sex due to the lack of a necessary sample of male patients.

Regarding the healthcare context, PC services could address this issue, providing support to their patients, preventing health decline, and motivating these people to feel empowered in coping with FMS. Effective management actions in PC could reduce the costs of specialised professional care, overprovision and overmedication, avoiding system overload, and providing more holistic care to the needs of patients with FMS.

Equally important, new health policies and specialised training programmes that increase knowledge and sensitisation of health providers are needed to resolve fibromyalgia's lack of recognition and stigma based on social construction in the Spanish context.[67] A comprehensive assessment of the FMS symptomatology and its impact on the QoL of patients should be part of the usual clinical care.[68]

ETHICS AND DISSEMINATION

The Clinical Research Ethics Committee from the *Fundació Institut Universitariper a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina* (IDIAPJGol), has approved this study protocol on 25/04/2018 (code P18/068), according to the Declaration of Helsinki/Tokyo. All participants will receive oral/written information about the study, and they will be required to sign an informed consent sheet. Data anonymity will be guaranteed. Dissemination will be carried out through publications in scientific journals, presentations in academic meetings, workshops and through the local and national media.

Author affiliations
[1]Unitat de Suport a la Recerca Terres de l'Ebre, IDIAP Jordi Gol, Barcelona, Catalunya, Spain
[2]Department of Pediatrics, Obstetrics and Gynecology, and Preventive Medicine, Universitat Autonoma de Barcelona, Barcelona, Catalunya, Spain
[3]Equip d'Atenció Primària Tortosa Est, Institut Català de la Salut, Tortosa, Catalunya, Spain
[4]Unitat d'Expertesa en Síndromes de Sensibilització Central Terres de l'Ebre, Institut Català de la Salut, Tortosa, Catalunya, Spain
[5]Unitat d'Avaluació, Direcció d'Atenció Primària Terres de l'Ebre, Institut Català de la Salut, Tortosa, Catalunya, Spain
[6]Unitat Docent de Medicina de Família i Comunitària Tortosa-Terres de L'Ebre, Institut Català de la Salut, Tortosa, Catalunya, Spain
[7]Central Research Unit, IDIAP Jordi Gol, Barcelona, Catalunya, Spain

Twitter Anna Berenguera @ABerenguera

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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ORCID iDs
Victoria Mailen Arfuch http://orcid.org/0000-0001-5935-6907
Anna Berenguera http://orcid.org/0000-0002-0889-2002

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5.2. Study I

Title

Patients' appraisals about a multicomponent intervention for fibromyalgia syndrome in primary care: a focus group study

Reference

Arfuch, V. M., Queiroga Gonçalves, A., Caballol Angelats, R., Aguilar Martín, C., Carrasco-Querol, N., Sancho Sol, M. C., González Serra, G., Fusté Anguera, I., & Berenguera, A. (2021). Patients' appraisals about a multicomponent intervention for fibromyalgia syndrome in primary care: a focus group study. International journal of qualitative studies on health and well-being, 16(1), 2005760. https://doi.org/10.1080/17482631.2021.2005760

Summary

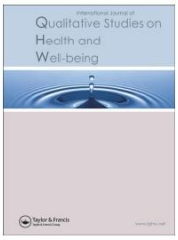
Introduction: This study presents the results of qualitative research aimed at exploring patients' experiences and appraisals on the format, content, health impact, and perceived benefits in the short (≤6-month) and long (>6-month) term of a multicomponent intervention (MCI) programme for patients with Fibromyalgia (FMS). The MCI was delivered in primary care settings from the *Gerència Territorial Terres de L'Ebre* in south Catalonia, Spain. It covered a 12-session programme which combined health education, physical activity and cognitive-behavioural therapy.

Methods: Two focus group discussions (FGDs) were conducted in February and July 2020, respectively, and they involved 19 patient-participants total (FGD1= 12; FGD2= 7) who were purposively sampled. A semi-structured discussion schedule with open-ended questions guided the data collection. Discussions were audio-recorded, and thematic analysis was performed on verbatim transcriptions from a phenomenological hermeneutic approach. In addition, two analyst triangulations were carried out to guarantee the study's trustworthiness.

Results: Five themes defined the main explored domains in this study, including: *'A positive but improvable experience'* regarding user satisfaction, *'Health improvements and suffering relief'* in users' overall perception of MCI effectiveness, *'Correct but limited'* concerning the programmes' format and framework, *'Relevant topics but psychological support should be reinforced'* described the MCI thematic content, and lastly, *'Supporting material reorganisation, social backing and prevention strategies'* as users' proposals for improvement. Overall, participants reported being satisfied with the programme compared to the usual clinical care (UCC), even though suggestions for improvement were expressed. The MCI was described as a positive and enriching experience

due to its benefits on illness acceptance and legitimacy, quality of life and well-being, and social bonding. Peer encounters and support were found to be facilitators of this therapeutic initiative. Furthermore, no substantial differences were observed between the FGDs regarding the programme's short- and long-term benefits. In addition, all participants approved recommending this intervention to other patients with FMS and found it suitable for supporting the UCC.

Conclusion: The study findings suggest that the MCI could boost the routine practice for FMS from the patients' perspective. Benefits on patients' biopsychological spheres confirm the multilevel impact of this multidisciplinary therapeutic strategy. However, adjustments to the intervention design are needed to meet patients' reported health needs in order to increase therapeutic adherence and maximise its benefits.



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Patients' appraisals about a multicomponent intervention for fibromyalgia syndrome in primary care: a focus group study

Victoria Mailen Arfuch[a,b,c], Alessandra Queiroga Gonçalves[a,d], Rosa Caballol Angelats[e,f], Carina Aguilar Martín[a,g], Noèlia Carrasco-Querol[a], Maria Cinta Sancho Sol[f,h], Gemma González Serra[f,i], Immaculada Fusté Anguera[e,f] and Anna Berenguera[b,j,k]

[a]Unitat de Suport a La Recerca Terres de l'Ebre, Institut Universitari d'Investigació En Atenció Primària Jordi Gol (Idiap Jordi Gol), Tortosa, Spain; [b]Department of Pediatrics, Obstetrics and Gynecology, and Preventive Medicine, Universitat Autònoma de Barcelona, Spain; [c]Insurance Medicine Division, Department of Neuroscience, Karolinska Institutet, Sweden; [d]Unitat Docent de Medicina de Família I Comunitària Tortosa-Terres de L'Ebre, Institut Català de La Salut (Ics), Spain; [e]Centre d'Atenció Primària Baix Ebre Tortosa Est, Gerència Territorial de Terres de l'Ebre, Institut Català de La Salut (Ics), Tortosa, Spain; [f]Unitat d'Expertesa En Sindromes de Sensibilització Central Terres de l'Ebre, Gerència Territorial de Terres de l'Ebre, Institut Català de La Salut (Ics), Tortosa, Spain; [g]Unitat d'Avaluació, Direcció d'Atenció Primària Terres de l'Ebre, Gerència Territorial de Terres de l'Ebre, Institut Català de La Salut (Ics), Tortosa, Spain; [h]Centro de Salut Mental Adultos (Csma) de Fundació Pere Mata Terres de l'Ebre, Tortosa, Spain; [i]Servei de Rehabilitació I Medicina Física, Hospital Verge de La Cinta, Gerència Territorial de Terres de l'Ebre, Institut Català de La Salut (Ics), Tortosa, Spain; [j]Central Research Unit, Institut Universitari per a La Recerca a l'Atenció Primària de Salut Jordi Gol I Gurina (Idiapjgol), Barcelona, Spain; [k]Departament d'Infermeria, Universitat de Girona, Girona, Spain

ABSTRACT

Purpose: To assess fibromyalgia patients' experiences and appraisals about a multidisciplinary intervention programme, in Catalonia's primary care, regarding its format and contents, benefits, and health impact in the short and long term.

Method: Qualitative interpretative research design through hermeneutic phenomenology perspective. Two focus groups discussions were conducted in February and July 2020. The purposive heterogeneous sample included 19 fibromyalgia patients who attended a multicomponent programme. In addition, thematic analysis on the verbatims was performed.

Results: Findings were organized into five main domains with an explanatory theme each. Overall, the informants valued the programme as a positive experience due to its holistic approach, health benefits, suffering relief, group effect, and fibromyalgia legitimacy promotion. Detected improvable aspects focused on extending the timeframe, including family members as beneficiaries, deepening the thematic contents, and getting regular access to this healthcare service. Furthermore, the intervention was considered feasible to be incorporated into usual clinical care.

Conclusion: the programme fulfilled users' expectations about results and procedure and showed promise as a treatment strategy to reinforce the usual practice. Our findings suggest a broad perspective on fibromyalgia patients' suffering, which urges us to adjust the intervention programme to their real health needs.

ARTICLE HISTORY

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KEYWORDS

Fibromyalgia syndrome; primary care; multicomponent intervention; qualitative research; focus group discussions

1 Introduction

Fibromyalgia syndrome (FMS) remains medically unexplained (Alciati et al., 2021), for what its gold-standard treatment is debated, and there is scope for high-quality evidence (Mascarenhas et al., 2021). Being classified as a central sensitivity syndrome (Fleming & Volcheck, 2015), FMS significantly compromises patients' quality of life (QOL) and functionality, leading to disability (Wuytack & Miller, 2011). Therefore, healthcare strategies need to provide biopsychological and multimodal treatment approaches in order to face FMS impact (Bair & Krebs, 2020).

Given FMS high prevalence among rheumatic illnesses, representing 2.45% in Spain (Cabo-Meseguer et al., 2017; Seoane-Mato et al., 2019), the usual clinical care (UCC) may not be sufficient to address patients' suffering. In this context, primary care professionals, including nurses, physiotherapists, and psychologists, could strengthen the usual medical practice.

Clinically, FMS involves somatic, psychological, and social factors (Sarzi-Puttini et al., 2020). It is characterized by chronic widespread musculoskeletal pain associated with multiple unspecific symptoms such as insomnia, fatigue, depression and anxiety. As a result, patients' social and work performance can be deteriorated leading to sickness absence and early retirement (Isomeri et al., 2020; Mas et al., 2008). Even though the evolution of its diagnostic criteria (F Wolfe et al., 1990, 2016; Frederick, 2010), both

CONTACT Anna Berenguera aberenguera@idiapjgol.org Fundació Institut Universitari per a La Recerca a l'Atenció Primària de Salut Jordi Gol I Gurina (Idiapjgol), Barcelona, Spain

Supplemental data for this article can be accessed here.

professionals and patients still struggle when searching for an accurate diagnosis and treatment approach (Galvez-s & Reyes, 2020).

Recent studies highlight the disruptive effect of the diagnosis experience and the treatment process on patients' daily life (Ashe et al., 2017; Briones-Vozmediano et al., 2015; Taylor et al., 2016). This is especially true for middle-aged women, who are the most impacted population group showing a substantially higher rate than men (Marques et al., 2017; Mas et al., 2008; Villanueva et al., 2004). Even though this major sex difference is not fully understood, it could be explained by a diagnostic criteria bias (Häuser et al., 2019; Samulowitz et al., 2018; Frederick Wolfe et al., 2018). On the other hand, Martínez-Lavín (2021) proposes considering fibromyalgia as a stress-induced, sex-dimorphic neuropathic pain syndrome rather than a mental somatic symptom disorder, which may explain why it is more frequent in women due to the prevalence of this phenomenon in this population group.

According to the qualitative literature, the most frequent themes on patients' accounts related to their living experience with FMS are poor functional performance, distress, lack of credibility, uncertainty, pain acceptance, poor sleep, and social stigma (Climent-Sanz et al., 2021; Johnson et al., 2006; LaChapelle et al., 2008; Quintner, 2020; Sim & Madden, 2008; Taylor et al., 2016)

Lempp et al. (2009) explain that the knowledge gap on FMS etiopathogenesis creates uncertainty about the best treatment option and foments FMS inauthenticity. In this scenario, patients' voices reach a strategic value in the development of healthcare approaches.

The UCC for FMS in Spain is generally based on the administration of a medical record, the delivery of information about the condition, the prescription of pharmacological treatment, and the referral to specialists if necessary (Celaya et al., 2017; Gándara & Muñoz, 2017; Instituto Nacional de la Seguridad social, 2019). However, its purely biomedical approach seems limited as a healthcare strategy. Alternatively, non-pharmacological therapies such as physical activity, psychological therapy, and health education interventions have been demonstrated to improve symptom management and QOL (Aman et al., 2018; Baranowsky et al., 2009; Bernardy et al., 2013; Bush et al., 2013; García-Ríos et al., 2019; Luciano et al., 2014; Prabhakar et al., 2019; Sosa-Reina et al., 2017).

Furthermore, multicomponent interventions (MCI) have been proven beneficial in the short and long-term (Bourgault et al., 2015; Giusti et al., 2017; Jacobs et al., 2020; Martin et al., 2012; Ollevier et al., 2019; Saral et al., 2016) and recommended by international guidelines (Thieme et al., 2017). Nonetheless, this intervention approach is in its infancy in the Spanish public health sector.

Since 2016, accredited units specializing in Central Sensitivity Syndromes have provided multidisciplinary healthcare to FMS patients in Catalonia's primary care centres and hospitals (Departament de Salut, Generalitat de Catalunya, 2017). As Stein and Miclescu (2013) explain, primary care is an appropriate setting for delivering treatment on chronic pain and supporting patients and their families with health education and coping skills.

To the best of our knowledge, qualitative research about the benefits of multidisciplinary treatments remains scarce (Bourgault et al., 2015; Miranda et al., 2016; Oliveira et al., 2019; Susmita Kashikar-Zuck et al., 2016). However, through a mixed-methods design, Bourgault et al. (2015) have evidenced that qualitative research is suitable for detecting patients' global impression of change regarding pain management, functionality, and QOL.

According to the Medical Research Council in Implementation Science (NIH, 2018), communication with stakeholder groups is a valuable resource for assessing quality, acceptability, feasibility, and the contents of healthcare interventions. In addition, understanding participants' treatment lived experience and its impact on daily life helps adapt the implemented practices to their true health needs and priorities (McMahon et al., 2012; Sim & Madden, 2008). Furthermore, focus group discussions (FGDs) are among the most popular data collection methods implemented in qualitative research (Gill et al., 2008) based on interpersonal interaction dynamics to extract information about the participants' experiences and beliefs on a specific topic.

This study aims to assess patients' experiences and appraisals about a complex intervention programme for FMS in primary care centres belonging to the Gerència Territorial Terres de L'Ebre of the Institut Català de la Salut, Spain. Precisely, this study intends to detect the improvable aspects of this programme, its barriers and facilitators, the adequacy of its elements (timeframe, setting, materials, group-based approach, among others), the quality of the therapeutic components, the relevance of the thematic content, its benefits on symptom control, and its impact on QOL in the short and long-term. The results are expected to tailor the intervention according to the patients' actual health needs and available resources to strengthen the programme benefits and implementation. Additionally, this study may support and extend the results of a randomized clinical trial (RCT) linked to this project (ClinicalTrials.gov: NCT04049006) (Caballol Angelats et al., 2019). Finally, this study will allow the intervention programme's standardization to be adjusted and replicable in other healthcare contexts and promote adherence.

2 Materials and methods

2.1 Design

Qualitative interpretative research was conducted following a hermeneutic phenomenological perspective (Dibley et al., 2020; Wilson, 2000). This design approach helps detect and interpret participants' common meanings engaging what, why, and how questions in the intersubjective setting (Charmaz, 2008; Laverty, 2003; Tindall, 2009; Villegas, 1992).

2.2 Multicomponent intervention programme

The MCI implemented consists, in addition to the UCC, in a 12-week/2-hour session group-based programme combining: health education -including an introduction to multicomponent therapy, neurophysiology and pharmacology of pain, techniques of postural hygiene, nutrition, insomnia management, memory, and sexuality; physical exercise -focus on breathing and relaxation, stretching, strength/joint, and coordination exercises; and cognitive-behavioural therapy (CBT) -based on pain and attention management, learning to manage emotions, strategies for coping with difficulty, and pleasurable activities planning. It is delivered by a general practitioner, a physiotherapist, a psychologist, and each health centre's head nurse.

This MCI programme aims to promote patients' literacy and skills development for FMS management, enhance their physical status and reduce their emotional distress in order to overcome psychological difficulties. Further details about the thematic contents of each session and the research specifications were published in the study protocols of the RCT study and the qualitative research (Arfuch et al., 2020; Caballol Angelats et al., 2019).

2.3 Participants

All participants were recruited from the 11 primary care centres in the Gerència Territorial Terres de l'Ebre.

Purposive heterogenous sampling was implemented to reach maximum discursive variability considering gender, age, birth country, educational level, occupational situation, working status, and geographical area. According to the RCT data collection schedule, this sampling strategy divided the sample into two groups to assess the perception of benefits in the short and medium/long-term. As a result, the first FGD (FGD1) was performed in February 2020, including patients with ≥6 and 12 months of follow-up post-intervention. The second one (FGD2) was conducted in July 2020, including patients up to <6 months of follow-up.

The inclusion criteria involved a clinical diagnosis of FMS (International Classification of Diseases-10 codes: M79.0, M79.7), over 18-year-old, language skills in Catalan or Spanish, a phone number, a minimum of 75% attendance at the MCI programme (equal to or more than 9 out of 12 sessions), voluntary participation in the study and signed informed consent. On the other hand, the exclusion criteria included: active psychotic episode, intellectual impairment, severe depression and or personality disorder, auto/hyper-aggressive behaviour, psychoactive substances administration, not having met the minimum attendance, not signing the informed consent.

The recruitment was conducted three weeks in advance and via phone calls to those patients who met the inclusion criteria. They were provided with key information about the study goals and the date and place where the FGD would be carried out. In order to prevent absenteeism, two telephone contacts were made as reminders a week before the FGD date and the previous day.

As Figure 1 shows, from the 88 subjects (85 women/3 men) that participated in the MCI during the planned periods (FGD1 = 57; FGD2 = 31), 40 (39 women/1 man) were excluded for not meeting the inclusion criteria of 75% attendance. Consequently, 48 subjects (46 women/2 men) were included in the recruitment process, from which 24 were excluded, leaving 24 possible participants in the first lists. Finally, 19 informants participated in the FGDs (FGD1 = 12; FGD2 = 7) and were included in the thematic analysis. In addition, two members of this final sample were included as extra informants in the last call, although they had 66.7% of attendance in case of no-shows.

The study sample includes 63.2% of participants with a follow-up >6 months and 36.8% with <6 months. The sample comprises women as the only two men who met the inclusion criteria did not accept participating in the FGDs due to the COVID-19 outbreak. Furthermore, the participants belonged to 7 of the 11 primary care centres involved in the study. The attendance criterion was fulfilled with a total mean of 10.3 sessions attended (SD 1.2), representing a mean of 85.5% of participation and no substantial differences between focus groups. Table I shows a description of the study sample.

Table I. Study sample.

Among the most remarkable characteristics of the sample, the informants' mean age was 61.8 years, being the second FGD more mixed-age than the first one. FMS evolution was estimated based on the diagnostic year showing a mean of 7.9 years (SD 5.5), with approximately 2 points of difference between groups. Furthermore, 94.7% of the sample were born in Spain, and the most frequent marital status was married (68.4%) in both FGDs. Regarding the educational

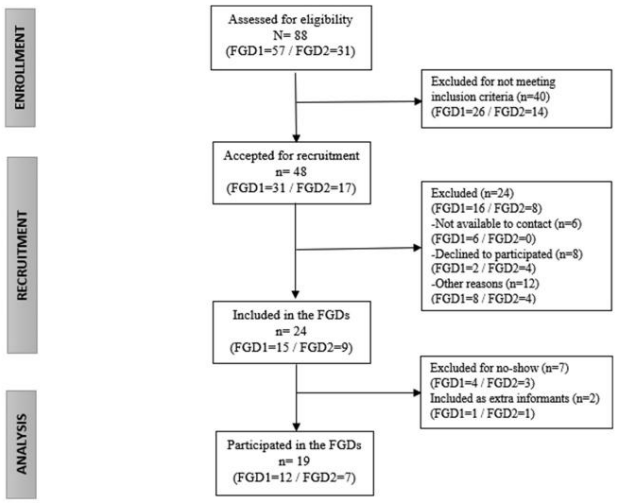

Figure 1. FGDs flow chart.

level, 73.7% of the total sample had no studies or just a complete primary education. In reference to the occupational situation, 36.8% of the sample were employed while 47.4% were unemployed, disabled, or retired; and only 15.8% were homemakers. However, 50% of the informants in FGD1 were employed, whereas in FGD2, it represented 14.3% as 57.1% of the sample were retired.

2.4 Data collection

2.4.1 Focus group discussions

Two FGDs with 19 patients (FGD1 = 12; FGD2 = 7) who received the MCI were performed in February and July 2020, respectively, to assess the programme's socially constructed meaning using an interview guide. The meetings were conducted in the same room and primary care centre. They were audio-recorded, with prior signed informed consent, and the verbatims were systematically transcribed, guaranteeing informants' anonymity.

The FGDs lasted 90 min each, and they were conducted by the first author of this article (PhD candidate), together with a co-moderator (PhD) and an observer (PhD) who performed field notes. Both moderators have education and training in psychotherapy and researching and are experienced with group techniques, while the observer belongs to the biomedical field. Participants had neither previous knowledge nor contact with the qualitative research team before the FGDs, and they were informed about professionals' backgrounds at the beginning of the sessions. Moreover, the FGDs were attended by three members of the research team and the recruited informers.

2.4.2 Interview guide

The semi-structured interview guide (Supplementary material 1) included open-ended and follow-up questions covering the following topics: patients' experiences during the MCI programme and their effectiveness overall perception, the adequacy of the frame elements (timeframe, setting, professionals, beneficiaries, group-based intervention approach) and contents, improvable aspects, barriers and facilitators on the intervention implementation, and the benefits on patients' QOL in daily life. The interview guide was not pilot-tested with FMS patients but reviewed exhaustively by the research team.

2.5 Ethical considerations

Helsinki/Tokyo Declaration was followed for the study design being 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). Participants received oral and writing information, guaranteeing data protection and anonymity before signing the informed consent sheet.

2.6 Data analysis

A thematic analysis (Braun & Clarke, 2006) of the participants' accounts was carried out to detect outstanding topics through the interpretative methodology. The text corpus and the observer's field notes were read several times and interpreted by the three qualitative research team members, including preliminary analytical intuitions, a coding process, and

Table I. Study sample.

	Total sample	FGD1 (> 6 months follow-up)	FGD2 (< 6 months follow-up)
	N = 19	*n = 12*	*n = 7*
	Mean (SD) min-max		
Age	61.8 (8.4) 46–79	59.4 (5.2) 53–71	65.8 (11.5) 46–79
Diagnostic evolution	7.9 (5.5) 1–19	7.3 (5.3) 2–16	9.1 (6.2) 1–19
Participation in the MI	10.3 (1.2) 8–12	10.4 (1.2) 8–12	10 (1.2) 8–11
	N(%)		
Country of birth			
• Spain	18 (94.7)	12 (100)	6 (85.7)
• Other	1 (5.3)	0	1 (14.3)
Marital status			
• divorced	3 (15.8)	2 (16.7)	1 (14.3)
• married	13 (68.4)	9 (75)	4 (57.1)
• single	1 (5.3)	0	1 (14.3)
• widow	2 (10.5)	1 (8.3)	1 (14.3)
Occupational situation			
• employed	7 (36.8)	6 (50)	1 (14.3)
• unemployed	1 (5.3)	1 (8.3)	0
• disabled	2 (10.5)	2 (16.7)	0
• homemakers	3 (15.8)	1 (8.3)	2 (28.6)
• retired	6 (31.6)	2 (16.7)	4 (57.1)
Educational level			
• primary	12 (63.2)	8 (66.7)	4 (57.1)
• secondary	4 (21.1)	4 (33.3)	0
• post-secondary	1 (5.3)	0	1 (14.3)
• without studies	2 (10.5)	0	2 (28.6)
Work status			
• hight professionals	1 (5.3)	0	1 (14.3)
• intermediate professionals	2 (10.5)	2 (16.7)	0
• skilled white-collar workers	6 (31.6)	6 (50)	0
• skilled manual workers	0	0	0
• manual labourers	10 (52.6)	4 (33.3)	6 (85.7)
SD = standard deviation			

the data organization into categories. Saturation of the data was assumed once no more codes could be captured from the data and no more meaningful insights were deduced from them according to the study goals and after an interactive and reflective process of analysis.

Subsequently, the analysts' triangulation was performed to detect the essential attributes of the narratives, compare perspectives, and reach an agreement on the most prominent domains and emerging themes of the FGDs. Discrepancies were resolved through consensus after reviewing transcripts. As a result, the selected themes were identified and clustered, and an explanatory framework was drafted.

No specific qualitative analyst software was implemented to carry out the coding. Finally, no informers' feedback was requested for the analysis process.

2.7 Rigour

In attendance of the key component of data trustworthiness (Korstjens & Moser, 2018), this study presents two analysts' triangulations with three research team members compiling credibility. Nevertheless, transcriptions were not returned to participants for comment and correction but double-checked by the research team.

Moreover, purposive sampling has been conducted, including thick descriptions with individual and contextual factors, in order to obtain maximum discursive variability and FMS patient representation for outcome transferability. Even though no external audit trail has been performed to ensure dependability, the research path was documented and described throughout the study section. For instance, the same interview guide was implemented in both FGDs, and three different analysts' codings were contrasted during triangulation to guarantee the study's consistency. Additionally, verbatims were transcribed by an external specialist and reviewed by the research team.

Furthermore, confirmability has been achieved by using literal quotations and including researchers' backgrounds. Finally, preliminary analytical intuitions focused on reflexivity during the thematic analysis to detect possible sources of the investigator's bias.

3 Findings

The thematic analysis results were systematically organized in five domains according to the interview guide with the view of focusing on the purpose of this study and including one central theme that emerged from the answers reported in the FGDs. Additionally, representative quotations are cited to support the interpretation of the corpus text. For this purpose, quotations were translated from Catalan and Spanish to English. Unfortunately, due to some of the participants refused to be filmed, no video-recorded was carried out. Consequently, it was not possible to identify the informers during the transcriptions so that they are presented by FGD instead.

3.1 Domain 1: user satisfaction

Theme 1: "A positive but improvable experience".

The MCI was unanimously embraced by users from both FGDs, describing it as an enriching and positive experience in terms of acceptability. The programme was acknowledged for its educational and health benefits as well as for its positive group cohesion effect.

"I have learned a lot from this programme. I have been with FMS for 19 years now, but I have learned many things about physical activity, eating, about … about many, many things […] Really good; excellent. I feel, let's see … a little relieved. Anybody can stop your pain but provides you psychological relief. As it is said that this syndrome is just in our heads. Let's see … when you know that people are feeling worse than you … you know? Be aware of it relieves you. […] From my point of view, it encourages you to live because as the lady said: the family does not understand fibromyalgia, and we are not understood either. The person who has it does understand though. We support each other." (FGD2)

"I wanted to say that, for me, this whole experience has been incredibly positive, especially emotionally." (FGD2)

Participants´ acceptance is strongly related to their feeling of being acknowledged, understood, comforted, and accompanied, especially by peers:

"Discovering that you are not alone." (FGD1)

"To have someone who is going through the same as you, who understands you completely." (FGD2)

The identification process involved, given by the group cohesion effect, confirmed their illness, validating them as legitimate patients from a legitimate health condition. Thus, FMS legitimacy, not only as a diagnostic category but as a frequent and genuine affliction, represents one of the most critical informants' concerns:

"How can I demonstrate that I have this pain? […] I cannot prove it scientifically." (FGD2)

"I think you made an excellent programme. It reinforced something very important, which is accepting and assuming the diseases […]. I have learned more from my colleagues than from the doctor. Why? Because each experience is unique, and each case is singular." (FGD2)

The group involves a task, a purpose, and a common objective, finding its participants in an environment of unity and representativeness. Social interaction shapes subjectivity in multiple directions and, as it is expressed in the first quote, "*it encourages you to live*". Therefore, group cohesion is presented as vital, it represents life drive, and therefore, it embodies well-being and health.

"When the course was over, we used to meet once a week to practice what we had learnt and to spend some time together." (FGD2)

Overall, informers reported being satisfied with the professionals' performance. However, participants from the second FGD questioned communication skills, specifically when practising physical activity.

"They worked with goodwill; I can tell. The problem was that they insisted too much on 'walk, walk, walk'. But what if I do not like so much this type of work out and I prefer something else? I think they do not really understand our limits […]. I think they did not adjust their methods to our condition. However, it was not deliberately, I believe […]." (FGD2)

"We would rather be motivated more softly." (FGD2)

"We are very susceptible. Generally, nobody listens to you, nobody understands you, and on top of that, professionals put pressure on you. Consequently, you end up in a terrible mood. Truly. We are highly emotionally sensitive people, easily overwhelmed. You do what you can, but If you add a burden to this sensitivity, the body just cannot handle it." (FGD2)

The proposed MCI was also considered feasible to be incorporated into usual clinical care, replicable in other health contexts, and recommended to other patients with FMS by the informers.

"Would be useful to get prompt access to therapy service and receive psychological support more frequently." (FGD1)

"The programme has gone very well, but it should not end here … it should be a continuum, […] we should have regular psychological help." (FGD2)

3.2 Domain 2: users' overall perception of MCI effectiveness

Theme 2: "Health improvements and suffering relief".

Regarding the perceived health benefits, informers from both FGDs agreed in the positive impact of the MCI on their QOL. Nevertheless, they do not report significant changes in physical symptoms such as pain. On the other hand, they explained that the MCI allowed them to improve their lifestyles by incorporating healthy habits and routines, reducing the pharmacological intake, developing a positive attitude towards pain, and enriching psychological and social well-being.

"I do think that we made progress with our quality of life because we had the opportunity to relate to others with the same problem and who understood our suffering. […]. Nevertheless, it is not so simple as it looks. Even though you can 'look better' for the rest of the world, any extra physical effort could leave you motionless for days." (FGD2)

"We were taught about the different symptoms, the pain, the consequences of medication … but we need to be aware of what we are going through, how we feel, and what our limits are. […]. If we know our needs and limits in-depth, we can avoid complaining and self-compassion. […] Doing so, I have managed to lower the medication by half being proactive and energetic, even not feeling well." (FGD1)

"I am in pain from the moment I get up. I know that the pain is not going to disappear, but I try to avoid it somehow. So, I keep taking my medication, and I try

to take short breaks and rest if I feel tired. I also practice physical activity regularly. I started swimming, and I go to the sauna and the jacuzzi. Honestly, I am doing very well now. I try to do it every day for at least one hour." (FGD1)

Additionally, participants considered the MCI as an eye-opening experience given the alternative non-pharmacological treatment strategy offered.

"Participating has helped me out to enhance as I had the chance to get what I needed. And then, when it finished, I knew what another kind of healthcare I had to look for. In other words, this programme opened new doors for me." (FGD1)

This experience's benefits have proved to go beyond the symptomatic relief of FMS, offering patients a new perspective on the health-disease process. The informers emphasized the acquisition of self-understanding, self-control, and self-management of the syndrome.

"In my case, I have noticed self-help improvement, learn how to help myself […] I have managed to get to know my problem so deeply that now I can say to FMS: "I am the boss, not you". Do I still have pain? Absolutely […] But even so, I have managed to reduce my medication which means a better health status. […] First me, then me, and always me. Here is my conclusion." (FGD1)

"You cannot get rid of the pain, but you can learn how to control it." (FGD2)

Patients realized that FMS's psychological implications do not make it less real or tangible in their daily suffering physically, emotionally, and socially. Indeed, informers accepted that psychological well-being is essential to symptom management, as experienced during the intervention programme.

"The doctors told me that I had nothing. So, what can you do with that answer? Even though all your body hurts, you do not know where to go … I was told it was all psychological. But no matter how psychological it can be, it hurts me … " (FGD2)

"I have been thinking about all the medication that I am taking, and I would like to cut it all down as I found that this condition is more about your emotions … I have experienced that when I have problems, or I feel upset, I feel physically worse […] So, I believe that treating our psychological needs can actually help us more than any medication." (FGD1)

In resonance with the mentioned benefits, this intervention programme has contributed to awakening participants about gender disparities in health and the socially constructed roles of men and women.

"I firmly believe that as women, we have much more burden than men to cope with all kinds of situations in life. […] It is evident for me that women make much more effort in daily life than men." (FGD1)

"Currently, women relate more and more to each other. And from these exchanges, you can conclude that we are the real family pillar [.]. I spent my whole life taking care of others […]. So then you understand that we carry a burden that is very difficult to deal with. I am not surprised what is happening to us considering the accumulated stress in our bodies." (FGD1)

"The problem of our generation is that we were taught to shut up. Around my 40ish, a woman told me once: 'you were born in the time of the mutes'. I was astonished. Then she asked me: 'Have you ever answered your parents unproperly?' 'No, and I am also very cautious with my children', I said. 'Now you see that you belong to the voiceless times?', she replied. […] But when you get to a certain age, your temper comes out like a boiling pot, and no one will ever be able to stop it. Once it arises, no one can do anything about it anymore." (FGD2)

3.3 Domain 3: users' opinions about the MCI format and framework

Theme 3: "Correct but limited".

Informers from both FGDs claimed that the programme timeframe was not enough to cover in-depth all its contents and offer them time to work on their suffering.

"It was insufficient … Not for professionals' quality. […]. Each participant has her/his needs, and there was not enough time to dedicate to everyone. That is why it was not enough." (FGD1)

"The problem was the lack of time to delve a little deeper into the different topics. Moreover, because each person had things to say and issues to share, and there was not enough time for everybody." (FGD1)

"I believe that a little more quantity would guarantee more quality. Extending the timetable will provide better quality over time." (FGD2)

Regarding the group approach, informers showed acceptance, acknowledging its benefits but also remarking its drawbacks.

"In my opinion, the group approach has been very helpful. We have been incredibly brave dealing with this condition every day, this backpack that … and we needed to learn to get rid of things that we carry inside the backpack. It was very important and beneficial as we could identify ourselves with our colleagues' suffering so that I no longer felt alone again." (FGD2)

"The problem with large groups is that … if all the members of the group talk, then you are suddenly run out of time." (FGD2)

"But the good thing with large groups is that you can find plenty of different scenarios. Some people have fibromyalgia terribly, and some others manage it better. Some people already accepted this condition, and

some others are still in process. Therefore, you can learn about each experience and keep what better suits you." (FGD2)

"In my case, I have many health issues. Therefore, listening to my partners' problems make it worse for me. […] Sometimes, the group could make me feel overwhelmed due to the emotional burden it entails." (FGD1)

Additionally, participants proposed including the family and general practitioners in the sessions in order to inform them about the characteristics of this condition, the related suffering, and patients' real health needs.

"I do not know how this could be managed to inform family members about our suffering and what we are going through. Maybe they should be invited to a session […]. We need them to be aware of the consequences of this condition and our daily fight to cope with it." (FGD1)

"I think that a family member should attend the meetings, and especially those who are incredulous so that they comprehend why it hurts so much even when you do nothing. They usually say: 'If you are doing nothing, you should not feel pain.' And it makes sense that they cannot find it a logic, but sometimes it can be tough for us to explain it adequately." (FGD2)

"To include general practitioners into the sessions to make them comprehend the problem of their patients […]. I was diagnosed recently, but I have been twelve years with this pain visiting several doctors without an accurate response. That is not normal." (FGD2)

3.4 Domain 4: users' opinions about the MCI thematic content

Theme 4: "Relevant topics but psychological support should be reinforced".

Towards health education, sexuality was mentioned as a relevant theme briefly explained during the intervention programme. Informers from the first FGD showed concern about coping with FMS in their sexual life and communication with their sexual partners. Indeed, the interpretative analysis revealed participants´ veiled worry about the side effects of medication on sexual libido.

"When we talked about sexuality, it was all speedy, inhibited and shyly. We could not speak freely about it. For example, in my case, my husband does not understand that I do not feel like having sex lately […]. But I am the one who has the problem, it's me … I just can't because I am over medicated, I am nervous, I cannot stand to be touched … and he cannot comprehend me. We are in serious trouble. I think these issues should be addressed properly in the programme, among other things. Sexuality was a subject that we saw very quickly, very quickly, very quickly, as well as the medication matter […]." (FGD1)

"When you do not know how to explain to him why you feel bad … sexually. But we should make this clear to the people we live with. Sometimes, it is not because we do not want to; it is just because we cannot. And this is something very complicated to be understood and be explained." (FGD1)

Accordingly, there is a scope for further clarification about pharmacological treatment. Informers expressed doubts and confusion regarding its efficacy, specificity, side effects, and administration. Furthermore, a trend towards self-medication and self-administer treatment without professional guidance was observed. Besides, participants expressed disbelief about the effectiveness of the pharmacological approach.

"The presentation of this issue was very light and superficial, and we ended up with a ton of doubts." (FGD2)

"We lack information about medication because they just talked about it in general during the course, and then a little bit about anxiolytics and antidepressant." (FGD1)

"I have been taking pills for almost 19 years, and now I am developing a drug allergy. I honestly I feel worse and worse. I wish there were something more natural." (FGD2)

Participants from the first FGD also suggested improving memory and nutrition sessions since they found them shallow.

"Another topic that has not been properly discussed during the programme is memory." (FGD1)

"In my opinion nutrition is essential, but unfortunately, we did not get any special diet or food guidelines from this course." (FGD1)

As mentioned throughout the results, informers emphasized that the psychological component is crucial when living with FMS and demanded regular access to this type of treatment as part of the UCC. Overall, participants highlighted the coping skills acquired during the programme. Nevertheless, they expressed the need for including a therapy group with a psychodynamic approach to work on their emotional issues and psychological suffering in addition to cognitive-behavioural techniques. The interpretative analysis showed that they also need to be heard and express their feelings and concerns in a therapeutic context and not exclusively educational. According to their experiences, the intervention programme did not provide the appropriate framework for it.

"About the psychology sessions, it would be helpful if you could organize groups of 10–12 people, once a month, and led by a psychologist to work out on mental health issues instead of just give us some guidelines." (FGD1)

Finally, informers showed resistance to the methodology implemented as it has been stated above regarding physical activity. Even though some participants reported they had incorporated exercise in their routines after the programme, others admitted that it was impossible for them due to the pain and physical limitations.

> "Well, the physio recommended us several exercises and stretches, but the thing is … you try to walk and then you cannot move for two days. Even when you try with water gym because … but then I am two or three days that I am motionless." (FGD1)

> "Let's see, they gave us guidelines, and I do some exercises at home. Well, I do the exercises, and I do not do them … Even if I am tired or for whatever reason, I try to do it anyway. […] And every ten days or so, I also take a physiotherapy session, which is truly helpful." (FGD1)

3.5 Domain 5: additional users' improvement proposals

Theme 5: "Supporting material reorganization, social backing and prevention strategies".

Regarding the supporting materials, informers proposed delivering it in dossier format instead of giving single sheets at the beginning of the programme, to avoid losing relevant information and not attending a session.

> "Today I give you this sheet; tomorrow I will give you that one; the day after tomorrow, this other one and so on. Suddenly you realized that you had missed a paper someday or you had lost it somewhere.[…] I think they should organize it better, at least delivering this material all together by areas such as the gymnastic guideline, the psychological guideline, etc. […] Otherwise, we had to ask our colleagues for the missing sheets." (FGD2)

Another emerging theme was the need for social support, in terms of access for a financial benefit specifically due to fibromyalgia diagnosis, for those unable to continue working actively or require early retirement.

> "For example, I would like that if you could support with Fibromyalgia literacy to members of the medical board. Many people suffering from this disease do not get any social benefit from it. In my case, I do not have a pension, but I heard about people who do. But just a few. The majority of us do not have access to it." (FGD2)

Finally, it was suggested to include prevention strategies to avoid health status deterioration and personal autonomy loss in the long term.

> "I am very concerned about the future. […] I would like to be more autonomous as I get old, but of course, I don't want that … I don't want to depend on anyone as much as possible. But about this point, I do think that the programme could work on preventing deterioration. Trying to 'anticipate' what awaits us and work out on acceptance […]" (FGD1)

4 Discussion

This study presents patients' accounts about an MCI programme for FMS conducted in Catalonia´s primary care settings. Based on this valuable information, adjustments were identified to adapt the intervention and increase its benefits. The results suggest that the informants' expectations have been fulfilled thanks to the proposed multidisciplinary and comprehensive treatment approach, allowing them to bond with people under the same health condition. Consistently with another study, the FGDs revealed patients' dissatisfaction with the UCC and the need for more effective and less harmful alternative strategies (Briones-Vozmediano et al., 2013).

Even though FMS diagnosis may first concede hope to patients, it becomes an empty promise, as Boulton (2019) describes, since neither provides a final solution nor social legitimacy. Given the lack of a diagnostic test, peers' pain becomes a relief working as a mirror, reflecting belonging and support, and representing living proof of FMS authenticity. The more a peer suffers, the more FMS is proved, as said in the first informant's quote. The group re-signifies the individual suffering transforming it into a meaningful and valuable experience. Indeed, the group myth arises as an account for what cannot be medically explained. It is a narrative construction that gives meaning to an inexplicable phenomenon closing a knowledge gap, raising a structure, and defining the group's history and path's edges. In other words, the group effect consists of finding something familiar from something unknown, conferring a relieving and comforting explanation that is better than none (Nietzsche, 2003). Therefore, the satisfaction to the proposed MCI seems to lay in the symbolic efficacy (Levi-Strauss, 1978) of a socially constructed and shared myth about FMS. Our results are in general agreement with Oliveira et al. (2019), on the repercussions of interdisciplinary intervention for FMS women, about the group's positive influence on changing health habits and behaviours and its psychological support benefits. Furthermore, another study suggests that offering patients with alternative narratives could benefit their self-perception and lifestyle change (Hyland et al., 2016). Consequently, our results confirm that the group cohesion represented, in most cases, a facilitator to the MCI implementation, which should be considered for future treatment designs.

While expecting an improvement in symptomatology, the MCI proved to cover a wide range of health needs beyond physical indicators, as Bourgault et al. (2015) observed. Accordingly, participants adopted a

new active role in their illness experience that increased autonomy and empowerment. In addition, recognizing FMS frequency between peers played a key role in patients accepting this disorder, prioritizing and addressing their health needs. Hence, this initial insight entailed the first step in their health processes. This finding mirrors a recent study (Tangen et al., 2020), concluding that pain acceptance is associated with better functionality and fewer FMS symptoms.

On the other hand, physical activity benefits for this specific MCI depend partially on participants' will in exercising afterwards what they have learned during the programme. Should not implement participants self-management recommendations as part of their lifestyle could become a barrier to educational programmes. Thus, informants might not have perceived any significant symptomatic change, particularly pain reduction, as they have probably not practised enough post-intervention. Some of the possible reasons could have been accessibility, lack of social support, activity-induced pain, lack of motivation, among others. However, our results are supported by Merriwether et al. (2018), who observed that lifestyle physical activity is positively associated with function and fatigue but not pain.

Nevertheless, considering FMS patients' tendency to emotional lability and low pain tolerance threshold, it seems necessary to promote their enthusiasm and commitment through reviewed tailored tactics respecting their pace and encouraging physical work. A previous study (Larsson et al., 2020) reported that adjusting exercises and the pace, avoiding overload, offering enjoyable activities, and creating the right conditions were crucial factors when promoting physical activity. Future adjustments to the proposed MCI should therefore consider incorporating a person-centred rehabilitation approach and adding extra physical training sessions to ensure a minimum of continued and supervised exercise.

Overall, our results provide compelling qualitative evidence for educational programmes oriented to acquiring multiple skills to cope with FMS. The presented MCI has not been designed to replace the UCC but to reinforce it providing patients with a more holistic approach, including multidisciplinary and non-pharmacological methodologies. Participants reported having been taught several thematic contents and strategies to reduce FMS impact on their QOL. Nevertheless, an expressive psychotherapy approach has been suggested to help patients face psychological suffering and prevent voiceless, especially considering the total pain experience registered, which involves physical, spiritual, psychological, and social suffering (Williams & Craig, 2016). For instance, Lumley et al. () designed emotional awareness and expression therapy, showing promising results compared to CBT.

Informants described FMS pain as disruptive, unpredictable, and ungovernable, interfering with daily life and interpersonal relationships. These findings extend those of Ashe et al. (2017), confirming FMS's biopsychosocial impact. Pain suffering entails a subjective experience but subjectivizing insofar as it challenges all the individual's spheres. Total pain copes with the body as a whole where, according to informants' words, "everything hurts" without boundaries or gradient. As a result, they feel frustrated when distinguishing FMS symptoms from other comorbidities. This feeling of hopelessness could be accountable, among other aspects, for patients' seeking disability health insurance, which excludes them from the social production system.

However, a health programme should encourage patients to rejoin the social dynamics and perform active roles. From this perspective, including relatives in the programme could promote healthier family relationships based on comprehension and destigmatization. Alameda Cuesta et al. (2021) explain that the ultimate aim of healthcare for FMS patients should be to decrease vulnerability and exclusion. A family approach would also allow implementing a gender perspective working on gender roles in the family group. Additionally, inviting reliable sexual partners into the programme could help patients cope with sexual dysfunction (Granero-Molina et al., 2018). According to the evidence, one of the side effects of antidepressants, commonly prescribed for FMS, is serotonin overproduction associated with libido inhibition (Lorenz et al., 2019). Consequently, sexual climax could be seriously disturbed, which could frustrate pleasure and compromise couples' sexual life and relationships (Matarín Jiménez et al., 2017; Romero-Alcalá et al., 2019).

The present study contributes to detecting barriers and facilitators for implementing an MCI according to participants' appraisals. Even though this programme must be tailored based on detected weaknesses in format and content, it offers a promising approach to be incorporated in the UCC.

4.1 Limitations

In reference to the methodological limitations, these study results are not generalizable, although the intervention programme can be considered a model experience replicable in other contexts. Attending the nature of self-reported data, group effect, memory, selection, or attribution biases could have affected the results.

In addition to the method shortcomings, any preliminary qualitative implementation study was not

conducted for the proposed MCI. Moreover, the FGDs sample only included those who consented to participate in the qualitative study and had a high assistance record; therefore, overestimation bias could have been possible. Besides, the sample has no male representation due to women's FMS hight-prevalence, and since the only two possible men candidates did not accept participating in the qualitative study. Therefore, they were no focus groups according to sex.

Furthermore, the sample includes patients from only 7 of the 11 primary care centres of the region as the MCI groups performed in the rest of the centres did not meet the time inclusion criteria (a maximum of 12 months of follow-up). Additionally, participants were Spanish and except only for one informant. Even though two informants did not fulfil the attendance inclusion criteria (presenting only 66.7%), they were recruited to join in the FGDs to compensate for possible no-shows and guaranteeing sample variability. Finally, FGDs differ in the number of participants due to the eligible sample availability by follow-up criteria and the COVID-19 outbreak, which impacted the recruitment process of the second FGD.

Regarding the data collection, no video recording was performed, and, consequently, the quotations could not be presented identified by the informer but by FGD. Lastly, no external expert was included in the analytics triangulation processes since discrepancies were solved by consensus.

4.2 Strengths

Among the strengths, this study has been drafted based on the literature and according to the consolidated criteria for reporting qualitative research (COREQ) (Tong et al., 2007) and the standards for reporting qualitative research (SRQR) (O'Brien et al., 2014). Implementation research guidelines have also been considered (Brownson et al., 2012; Proctor et al., 2009). Moreover, the recruitment strategy and the sample description were performed according to high-research standards to enrich variability and avoid biases. For the analysis process, two analytics triangulations were conducted involving three experienced investigators. Methodologically, based on critical thinking, a hermeneutic interpretative analysis was implemented to assess the narratives in-depth. Finally, this study's results provide a depth comprehension of patients' live experience with FMS treatment, strengthening primary care professionals' understanding and daily practice.

5 Conclusion

In summary, no significant contradictions were observed between the study groups in the thematic analysis results. Both FGDs expressed a positive experience with the MCI programme, mainly related to the group cohesion effect. The global perception of effectiveness indicates no substantial differences between short- and long-term health benefits. Informants perceived an improvement in their QOL and highlighted the benefits of emotional, psychological, and social levels over the physical-symptomatic control. Additionally, other health benefits were registered, such as reducing the medication, acquiring a healthier lifestyle, awareness of their health needs and self-care, autonomy, and gender awareness. Therefore, the MCI fulfilled users' overall expectations about results and procedure.

In closing, the informants accepted and valued the MCI due to its holistic perspective, safety, health benefits, and FMS legitimacy promotion. Although identified adjustments should be performed to cover patients' real health needs, the proposed programme accomplished its main goal according to participants' appraisals requesting its continuation as part of the UCC.

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Clinical Trial registration number

This qualitative study is linked to the clinical trial number: NCT04049006 (ClinicalTrials.gov)

Disclosure statement

No potential conflict of interest was reported by the author (s).

Author contributions

VMA, AB, CAM, RCA and **AQG** designed the study. **VMA** carried out the sample recruitment, was the interviewer in

the FGDs, performed the thematic analysis, and wrote the manuscript's draft versions, which all the other authors reviewed. **AB** was the co-moderator in the first FGD, and **AQG** was the observer in both groups. **VMA, AB** and **AQG** conducted the triangulation analysis processes together. **RCA, NCQ, GGS, MCS, IFA, AQG, AB, CAM**, and **VMA** are involved in developing the general project and the RCT study to which this qualitative study is related.

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5.3. Study II

Title

Patients' Lived Experience in a Multicomponent Intervention for Fibromyalgia Syndrome in Primary Care: A Qualitative Interview Study

Reference

Arfuch, V. M., Caballol Angelats, R., Aguilar Martín, C., Gonçalves, A. Q., Carrasco-Querol, N., González Serra, G., Sancho Sol, M. C., Fusté Anguera, I., Friberg, E., & Berenguera, A. (2022). Patients' Lived Experience in a Multicomponent Intervention for Fibromyalgia Syndrome in Primary Care: A Qualitative Interview Study. International journal of environmental research and public health, 19(20), 13322. https://doi.org/10.3390/ijerph192013322

Summary

Introduction: This study explores, through qualitative methodology, the lived experiences of patients with Fibromyalgia (FMS) who attended a multicomponent intervention (MCI) programme in primary care settings from *Gerència Territorial Terres de L'Ebre* in south Catalonia, Spain. This study aims to understand patients' subjective insights, perceived benefits and drawbacks from the MCI. Furthermore, it is focused on exploring the impact on participants' psychological, physical and social aspects, lifestyle changes and personal growth. The MCI covered a 12-session programme which combined health education, physical activity and cognitive-behavioural therapy.

Methods: 10 in-depth individual interviews were conducted in July 2020 with patient-participants who attended a minimum of 75% of the MCI programme within the previous 12 months. A semi-structured discussion schedule with open-ended questions guided the encounters, which were audio-recorded. Verbatim transcriptions were analysed through thematic analysis from a hermeneutic phenomenological approach. Two analyst triangulations and an external audit were conducted to guarantee the study's trustworthiness.

Results: Four main themes emerged from the analysis: *'Legitimizing fibromyalgia through the MCI'*, *'The MCI as a socialising experience'*, *'Learning how to live with FMS through the MCI'*, *'Room for improving the MCI'*. Informers remarked on the FMS validation outcome from this experience and emphasised the role of professionals and peer participants in proving FMS as a genuine health condition. On this account, experiencing social support was inferred as the trigger for engaging in empowering health processes and developing new strategies and attitudes to cope with FMS.

Conclusion: This group-based complex intervention for FMS prompted multiple benefits to patient-participants beyond measurable health outcomes. In a scenario of medical discrepancies, illness experiences become a valuable source of information to understand the impact of healthcare services, adapt interventions, and boost their benefits to promote patients' satisfaction, adherence, quality of life and well-being.

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Article

Patients' Lived Experience in a Multicomponent Intervention for Fibromyalgia Syndrome in Primary Care: A Qualitative Interview Study

Victoria Mailen Arfuch [1,2,3,*], Rosa Caballol Angelats [4,5], Carina Aguilar Martín [1,6], Alessandra Queiroga Gonçalves [1,7], Noèlia Carrasco-Querol [1], Gemma González Serra [8], Maria Cinta Sancho Sol [5,9], Immaculada Fusté Anguera [4,5], Emilie Friberg [3] and Anna Berenguera [2,10,11]

[1] Unitat de Suport a la Recerca Terres de l'Ebre, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol I Gurina (IDIAPJGol), 20 Cristòfol Colom Avenue, 43500 Tortosa, Spain
[2] Department of Pediatrics, Obstetrics and Gynecology and Preventive Medicine and Public Health, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain
[3] Division of Insurance Medicine, Department of Clinical Neuroscience, Karolinska Institutet, 3 Berzelius väg Street, 6 Floor, 171 77 Stockholm, Sweden
[4] Centre d'Atenció Primària (CAP) El Temple, Gerència Territorial de Terres de l'Ebre, Institut Català de la Salut (ICS), Plaça Carrilet sn., 43500 Tortosa, Spain
[5] Unitat d'Expertesa en Sindromes de Sensibilització Central Terres de l'Ebre, Gerència Territorial de Terres de l'Ebre, Institut Català de la Salut (ICS), 20 Cristòfol Colom Avenue, 43500 Tortosa, Spain
[6] Unitat d'Avaluació, Direcció d'Atenció Primària Terres de l'Ebre, Gerència Territorial de Terres de l'Ebre, Institut Català de la Salut (ICS), 20 Cristòfol Colom Avenue, 43500 Tortosa, Spain
[7] Unitat Docent de Medicina de Família i Comunitària Tortosa-Terres de L'Ebre, Institut Català de la Salut (ICS), 44-58 Esplanetes Street, 43500 Tortosa, Spain
[8] Servei de Rehabilitació i Medicina Física, Hospital de Tortosa Verge de la Cinta, Gerència Territorial de Terres de l'Ebre, Institut Català de la Salut (ICS), 44-58 Esplanetes Street, 43500 Tortosa, Spain
[9] Centre de Salut Mental d'Adults (CSMA) de Fundació Pere Mata Terres de l'Ebre, 50 Rambla de Pompeu Fabra, 43500 Tortosa, Spain
[10] Central Research Unit, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol I Gurina (IDIAPJGol), 08007 Barcelona, Spain
[11] Department of Nursing, Universitat de Girona, Plaça de Sant Domènec, 3, 17004 Girona, Spain
* Correspondence: varfuch@idiapjgol.info; Tel.: +46-070-569-73-45

Abstract: Fibromyalgia syndrome (FMS) disrupts patients' biopsychosocial spheres. A multicomponent intervention (MCI) program, which combined health education, cognitive behavioral therapy, and physical activity, was conducted in South Catalonia's primary care centers with the aim of improving symptom self-management and quality of life. A qualitative interview study was carried out to understand patients' lived experiences during the intervention program. Sampled purposively, 10 patients were interviewed via phone calls and face-to-face. The encounters were audio-recorded, verbatim transcribed, and analyzed through thematic analysis. As a result, four themes emerged: legitimizing fibromyalgia through the MCI, the MCI as a socializing experience, learning how to live with FMS through the MCI, and room for improving the MCI. Participants agreed on the program being an insightful experience that promoted illness knowledge and acceptance and that improved their coping skills and symptom self-management. The inclusion of additional psychological guidance, expressive psychological group therapy, and providing relatives with information were proposed for enhancing the program. Our findings have contributed to gaining insight into the subjective impact of the MCI and identifying new therapeutic targets to tailor the program to patients' needs, which will hopefully increase its effectiveness and improve their quality of life.

Keywords: fibromyalgia syndrome; primary care; multicomponent intervention; qualitative research; interview study; thematic analysis

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1. Introduction

Fibromyalgia syndrome (FMS) is a chronic condition that impacts patients in multiple directions. It compromises their personal, social, working performance, and quality of life (QOL) and potentially leads to mental health problems and disability [1,2]. Its complexity is given by the similarity of its symptoms with other diagnoses, the variability of the clinical picture, the associated comorbidities, and its patients' profiles [3]. FMS is mainly characterized by widespread musculoskeletal pain and fatigue, yet its etiopathogenesis and gold standard treatment options are under-researched and carry ethical and scientific controversies [4].

The burden on society seems undeniable in terms of healthcare services and productivity losses [5]. Being classified as a central sensitivity syndrome [6,7], FMS is the most frequent among rheumatic diseases, with a worldwide prevalence of 2.7% and a prevalence of 2.4% in Spain [8,9]. FMS is more common among women, as well as among those over 50 years of age; with low levels of education; with low socioeconomic statuses; living in rural areas; and possibly, who are overweight [10]. Even though the reported sex difference is still not medically understood, studies propose a diagnosis criterion bias [11–13]. In line with this, Valls [14] suggests a gender bias in searching for a differential diagnosis, while Martínez-Lavín [15] proposes a different approach considering fibromyalgia as a sex-dimorphic neuropathic pain syndrome frequently observed in women. Additionally, the literature also stresses the resemblance of FMS with perimenopause and menopause symptoms and its potential link with a hormone deficit-related disorder [16,17].

Existing research indicates that poor perception of illness, including perceiving a fluctuating and unpredictable illness course and a low emotional representation of FMS, which means not connecting emotionally with one's health condition, is associated with higher medical costs [18]. Therefore, healthcare approaches may benefit from including patients' subjective experiences of living with and being treated for FMS.

In the literature on FMS illness experience, the most prevalent themes include the inauthenticity of the syndrome and the uncertainty about its prognosis, identity and family disruptions, distress, social stigma, pain management, illness acceptance, and alternative healthcare approaches [19–24].

While there has been a great deal of research on FMS patients' illness narratives, to the best of our knowledge, very few studies have been designed to assess FMS interventions implementing the qualitative methodology [25,26]. Relevant but limited, the evaluation of intervention programs and healthcare technologies is commonly based on quantitative techniques to measure their effectiveness on health status, symptomatology, and functionality but not on patients' accounts about their perception of change and benefits. Exploring patients' subjective treatment experiences will provide novel insights into patients' health needs and a broader understanding of the barriers and facilitators of a new healthcare strategy to be tailored according to these results [21–27]. Furthermore, this approach is in correspondence with the mix-method strategy recommended by the Medical Research Council guidance when evaluating complex interventions [28].

According to international guidelines and reviews, multicomponent interventions (MCI) based on physical activity, cognitive behavioral therapy (CBT), health education, and pharmacotherapy are beneficial to addressing FMS [4,29,30]. Additionally, published evidence suggests a promising future for this multimodal therapeutic approach [25,26,31–35].

Initiatives for delivering interdisciplinary healthcare in Catalonia's primary care sector (Spain) have been operating since 2016 [36]. Currently, an ongoing MCI project is being run by the Central Sensitivity Syndromes Unit in the Gerència Territorial Terres de L'Ebre (GTTE) of the Institut Català de la Salut (ICS) [37]. This MCI program seeks to strengthen routine practice by providing non-pharmacological resources for symptomatic control and biopsychosocial suffering relief including health education, physical activity, and CBT. Nevertheless, MCI programs are still in their onset in the Spanish public health system and elsewhere globally, so there is scope for further research.

Our study aims to understand the structure and meanings of patients' lived experiences during the proposed MCI program and to explore its subjective insight. Specifically, this study plans to identify informers' overall perception of benefits from the MCI; to detect the extent to which the informers implement the coping strategies delivered during the program in their daily lives; and to explore to what degree this experience may have influenced informers' psychological, physical, and social spheres and contributed to personal growth. Additionally, we aim to detect improvement aspects of the program according to participants' views.

The results will be helpful to adapt the intervention according to patients' appraisals in order to reinforce its benefits. Furthermore, this study is expected to complement the quantitative results of the randomized controlled trial (RCT) linked to this MCI (ClinicalTrials.gov: NCT04049006) [37] and the recently published findings of a focus group study conducted on the same project [38].

2. Materials and Methods

2.1. Design

The design of this work involves a qualitative interview study through thematic analysis [39].

2.2. Multicomponent Intervention Program and Setting

The MCI program includes a 12-week/2-h session group-based interdisciplinary program in addition to the usual clinical care (UCC). The latest is delivered cost-free by the public health system and is generally based on the screening of a general practitioner, the delivery of general information about the syndrome and coping strategies, and the prescription of symptom-control medication. Nonetheless, there is a health care gap in the provision of additional therapies that could complement the pharmacological treatment for FMS management. For this reason, the proposed program combines health education, physical exercise and CBT. It covers topics such as the neurophysiology and pharmacology of pain, postural hygiene, nutrition, insomnia management, memory, sexuality, breathing and relaxation techniques, stretching, coordination exercises and pain, attention, and emotional management. Participants were encouraged to practice what they learned during the sessions, such as walking for 6 to 20 min, at home. However, private practice was not formally registered. The healthcare team comprised female staff including a general practitioner, a physiotherapist, a psychologist, and each health center's head nurse who delivered the sessions in the primary care centers. Further details of the intervention program can be found in the study protocols [37,40] and Appendix B.

2.3. Population and Recruitment

The study sample includes 5 out of 11 primary care centers from the GTTE, south Catalonia, Spain. The MCI groups included in the sample consisted of between 9 and 18 participants. The informers were recruited through purposive heterogeneous sampling to achieve maximum discursive variability based on sociodemographic features (health center, age, sex, birth country, educational level, occupational situation, occupational class, and working status) obtained from the regional digital medical history system for primary care (eCAP).

All participants of the MCI program had a clinical diagnosis of FMS (International Classification of Diseases-10 codes: M79.0, M79.7), were adults, had oral and writing skills in Spanish and/or Catalan, and had a phone contact number. Additionally, the inclusion criteria to participate in this qualitative study involved a minimum of 75% session attendance to the program (equal to or more than 9 out of 12 sessions), up to 12 months since receiving the MCI to avoid memory bias, voluntary participation in the study, and written informed consent. Accordingly, the recruitment process and the sample reached were impacted by informers' availability within the study, as described in Figure 1.

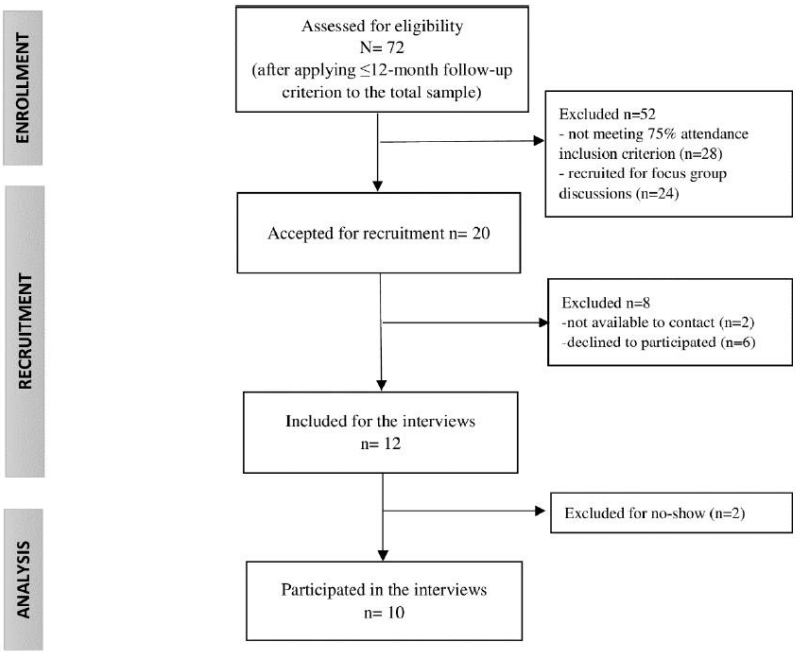

Figure 1. Study sample flow chart.

The recruitment was carried out via phone calls in June 2020, one week earlier than the interview. In order to prevent absenteeism, a reminder text message was delivered the previous day of the meeting. In addition, participants were provided with relevant information about the study's aim, the interview, and the data protection protocol.

2.4. Data Collection

A total of 10 in-depth interviews were conducted to explore patients' experiences during the MCI program with a mean duration of 30 min

The interviews were scheduled according to participants' availability. Four of them were conducted face-to-face in the same primary care center (*CAP Baix Ebre de Tortosa*) and six were conducted over telephone due to the COVID-19 pandemic recommendations. The first author (V.M.A.) was the sole interviewer and had no previous contact with the informers before the recruitment process. Only interviewer and interviewee were present during the discussion. The interviewer has an academic background in clinical psychotherapy (BMT) and public health (MPH), with previous experience in qualitative methods, and is currently working towards a PhD in biomedical research.

The interviews were audio-recorded, with prior signed informed consent. A semi-structured discussion schedule including open-ended and follow-up questions (Appendix A) was used, covering the following topics: introduction about the study aims and the interviewer, informer's overall opinion about the MCI, perceived benefits, implementation of coping strategies in daily life, psychological and emotional perceived changes, social feedback, improvable aspects of the program, and additional comments and suggestions. Interview techniques such as summarizing and clarification were implemented when necessary to facilitate the data collection process during the interviews. Additionally, field notes were made during the meetings by the interviewer that were considered during the data analysis. This discussion schedule was created specifically for this study based on

the literature review and previous professional experiences of the research team. Even though it was not previously pilot-tested, it was exhaustively reviewed by the qualitative research team. Additionally, transcripts were not returned to participants for comment and/or correction.

The most illustrative quotations were translated from Catalan and Spanish to English to support our interpretations in the result section.

2.5. Data Analysis

A thematic analysis was performed on the informants' accounts. The hermeneutic phenomenology tenants underlined the analytical process, providing a circular and non-linear interpretative approach which is particularly suitable when exploring subjective lived experiences and including researchers' preunderstanding [41,42]. Operationally, recordings were transcribed verbatim and carefully read. The researchers' role was explored for assuring reflexivity and considering possible bias. In this regard, no potential influences were found, and a critical thinking position was adopted to approach the material.

Firstly, preliminary analytical intuitions were registered after a thoughtful reading of the material. Secondly, the text corpus of one of the interviews was analyzed by V.M.A. using NVIVO12 [43] software in order to detect, code, and categorize the most outstanding units of meaning. Consecutively, an analysts' triangulation process with two research team members (V.M.A. and A.B.) and one external auditor was performed to spot the essential attributes of the patient's answers, to exchange primary intuitions, and to reach an agreement on the most relevant emerging themes of the interview.

Subsequently, the rest of the analyses of the interviews were conducted based on the previous results and cross-analyzed and compared. After that, a second triangulation with the same researchers was carried out to review and discuss the emerging themes and to address discrepancies through consensus.

Data saturation was assumed once no more themes were captured from the data or more insights were interpreted based on the study objectives. Additionally, the results were double-checked by an external collaborator researcher to guarantee the rigor of the analysis.

3. Results

The study sample consists of 10 women, all born in Spain, with a mean age of 58.5 years (min 45, max 73) and a mean of 11 years with a diagnosis of FMS (min 2, max 30). In terms of its impact, the scores obtained at baseline from the Revised Fibromyalgia Impact Questionnaire (FIQR) [44] and the Pain Visual Analogue Scale (PVAS) [45] suggest that the sample was from moderate to severely affected. More details of the sample features are shown in Table 1.

As a result of the thematic analysis, four themes were identified from the data, as shown in Figure 2.

3.1. Theme 1: Legitimizing Fibromyalgia through the MCI

3.1.1. Perceiving Fibromyalgia as a Real Health Condition

According to our informers, the MCI legitimized FMS by validating patients´ illness accounts. Patients reported a sense of being cared about given the provided health education, psychological guidance, professional support, and continuous follow-up. As detected, the invalidation process linked to FMS diagnosis is experienced by patients both physically, due to the lack of medical evidence, and socially, due to the lack of social acknowledgement as a real health issue.

Table 1. Sample description.

ID	Interview Type	Health Area *	Age (Years)	Civil Status	Occupational Situation	Educational Level	Occupational Class **	Years Since Diagnosis	Months after MCI	Session Attendance (%)	FIQR	PVAS
P1	face-to-face	1	46	married	working	secondary	IVa	7	12	83%	47.33	8
P2	phone	2	73	married	retired	university	I	9	5	100%	65	10
P3	phone	3	59	divorced	working	primary	IVb	2	12	92%	88.67	8
P4	face-to-face	1	51	married	unemployed	primary	IVb	13	12	75%	78.17	8
P5	phone	1	54	divorced	disabled	secondary	IVa	11	6	83%	96.33	8
P6	phone	2	45	married	unemployed	secondary	II	2	5	75%	42.17	7
P7	phone	1	71	married	retired	secondary	IVb	30	6	75%	81.17	8
P8	face-to-face	1	65	married	working	primary	IVa	12	6	92%	64.67	8
P9	phone	4	63	married	retired	primary	IVb	22	12	83%	93.17	6
P10	face-to-face	1	58	married	retired	primary	IVb	2	6	75%	69.33	5

MCI = Multicomponent intervention; FIQR = Revised Fibromyalgia Impact Questionnaire; PVAS = Pain Visual Analogue Scale. * Health area: 1 = Tortosa; 2 = La Rápita; 3 = Flix; 4 = Aldea. ** Occupational class: I (professionals); II (intermediate occupations); IVa (skilled manual workers); IVb (other manual workers).

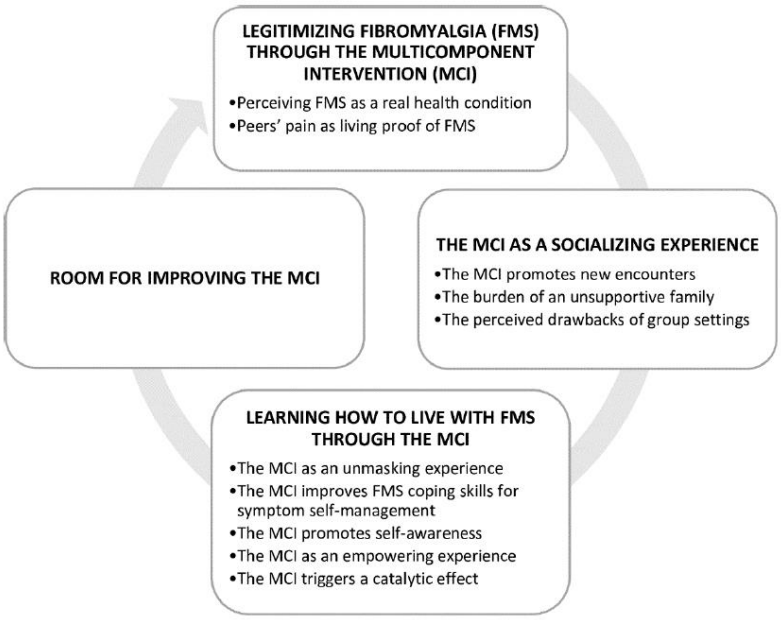

Figure 2. Themes and categories figure.

In this regard, informers described hopelessness when their proprioceptive experience is overlooked by the biomedical field and the social network. Further discernment revealed how patients could have undergone emotional dejection, confusion, and doubts regarding their suffering, which led to a nihilistic attitude towards themselves and the healthcare services. While existing treatment strategies are essentially based on pharmacological symptom control and lifestyle changes, patients may not be willing to make any effort if they do not perceive their condition as a real and frequent health problem that requires

being addressed to improve functionality and QOL and to prevent future complications. As the following quotes show, interviewees suggested that the proposed MCI contributed to providing clinical value to FMS and its patients, which encouraged them to adopt an active role in their health process:

> "The program represents the tranquility of having a point of reference. I used to think it was just my imagination or that I was a complaining person. However, it turns out that it is much more complex than that." (P5)

> "This experience helped me to show all those people who did not believe me that I was not lying." (P9)

3.1.2. Peers' Pain as Living Proof of FMS

While there is no medical evidence for supporting FMS, it has been detected that peers' illness experiences provide living testimony to support this health condition. Hence, the significant other seems to play a key role in making sense of one's health experience and promoting the sense of belonging to a group. Indeed, this biomedical identification process may have facilitated FMS legitimization in the explored sample. We discovered throughout the informers' accounts that when the different spheres of signification or influence in which they live (social network, legal system, academia, religion, and the media) fail to provide meaning to their health experience, social identity groups offer a socially constructed answer and a sense of being understood. The quote below explains how the patient emotionally struggles when her health experience conflicts with the social and medical perception of FMS, and how the MCI program contributed to it be apprehensible in a context of social validation:

> "As this disease is not evident externally, only the person who has it can understand it. It affects you to the point that you cannot move, you do not want to talk, you do not even want to think. It has killed me, indeed. It is very frustrating as it is not reflected anywhere, neither in an analysis, resonance, or image. However, discussing with people who are going through the same thing, make you feel not so weird and shamed. Because this disease is incomprehensible. The program has helped me understand that I am not the only person who is going through it." (P3)

3.2. Theme 2: The MCI as a Socialising Experience

3.2.1. The MCI Promotes New Encounters

Our interviewees acknowledged the benefits of the group setting leading to new encounters, identification processes, and social networks. Isolation was reported as one of the main consequences of FMS. As informed, patients tend to avoid social contact in order to save explanations on their health progression, changes in their physical performance, and feelings of shame and guilt. The group modality of the MCI offered them the opportunity to create new social networking with people diagnosed alike and who were facing similar challenges. In this regard, finding support from peers emerged as a psychological facilitator for the informers. One of the major strengths of the program transcended the sessions' setting:

> "A very warm bond was born between the participants of the program. Having the opportunity to talk, exchange experiences, and obtain new information blessed me with relief." (P6)

> "We have made very good friendships with people who suffer the same condition, and we are very fond of each other. We have had phone calls; we have met; we encourage one another daily. We know that we are there for each other and that we are not alone. Finally, someone understands and cares about us." (P9)

Additionally, the program has contributed beyond the intra-group relationships. The group effect was found to benefit patients' self-confidence in social contexts as well as their social initiative. Analytically, as peers become significant others, patients' self-worth grows and their social performance anxiety and low social perception decrease. Consequently,

informers recovered the strength to re-connect with their social environment, which no longer seemed as frightening as before:

> "Socially, this experience (the MCI program) has also been beneficial since I no longer feel that I need to justify myself when I cannot do something. Now I relate with others differently because I feel more secure about my illness." (P5)

> "The program has also helped us to be more sociable in general." (P6)

> "Before the intervention, I was closed in on myself. There was a time when I practically did not relate to anyone." (P9)

3.2.2. The Burden of an Unsupportive Family

Informers reported being poorly supported by family members, particularly by male partners. Patients revealed how their closest discredited FMS. Their need for regular breaks, rescheduling home and work routines, reducing and adapting physical activities, and avoiding intimacy, among others, were frequently taken with hesitancy and intolerance. Informers described this situation as their biggest burden and requested professional help to address it. As portrayed, experiencing one's health needs being neglected entails a de-subjectivizing process, which impacts both the patient's well-being and the relationship involved.

Reflecting on these findings, the group effect could have found its ground in the limited family support, whereas peers fill the gap in social understanding. Moreover, given the high prevalence of FMS among women, patients might find more frequent empathy among female peers, a pattern that could have been reinforced by the fact that the MCI program was delivered entirely by female staff.

The following quotes illustrate how FMS challenges the popular beliefs about health and disease within the household context and confronts patients with their partners' denial:

> "The only problem I have is that my partner does not understand it . . . Let's see He does understand it, but sometimes he tells me "Well, that's nothing." He does not quite assimilate it yet." (P4)

> "I have had a horrible time with this disease because nobody understood me, nobody knew what it was. My husband, for instance, is a person who has never understood it and does not want to; he does not want to believe that I am sick. Since he has cancer, my pain is irrelevant compared to his. And he cannot accept that I am not who I was anymore." (P9)

3.2.3. The Perceived Drawbacks of Group Settings

On the other hand, the group setting was also found to be a barrier to personal change. One of the participants who hid behind the group as a shield and due to feeling overwhelmed by other members' experiences disclosed:

> "In the groups, for example, I always take the role of the funny guy. It is my shield. I am not that expressive. However, this experience was helpful to find out that there are many people in worse conditions than me. In this sense, I realized that I am not handling it as bad as I thought. Anyway, there were too many people in the group; too many problems to share; too many mouths to talk; too many thoughts to be said. It is complicated." (P1)

Likewise, social comparison processes were detected throughout the informers' narratives, with a downward contrast. Informers reported gaining perspectives on their health situations in light of hearing about peers in a worse condition. In this line, a feeling of pity towards those peers emerged from their narratives, which helps them to cope with moments of discomfort:

> "My mood has improved since I had the opportunity to interact with people who experience the same condition as me or even more seriously. I feel sorry for them." (P4)

> "Many times, you feel bad, but maybe next to you there is another person who is feeling worse than you. And then you think: 'well, maybe my situation is not so terrible'. And this strengthens you and gives you a little more encouragement." (P8)

3.3. Theme 3: Learning How to Live with FMS through the MCI

3.3.1. The MCI as an Unmasking Experience

Participants' accounts indicated that the MCI facilitated an unmasking and unveiling of their suffering for both themselves and others, a bridge between appearance and reality, and the promotion of understanding and self-acceptance. FMS is an invisible condition that confronts patients' illness experiences against its social perception. However, supporting FMS legitimacy encouraged patients to open up about their vulnerability, limits, health needs, and emotions. As inferred, learning how to live with FMS includes accepting the condition and facing it beyond social roles and expectations:

> "'Have they called you again?' He asked, surprised. Since I have to act as Mrs. Strength, it looks like I am not that wounded. Right? But what the program does is show my suffering face. To give it a face [. . .]. It is useful to make the rest of the world realize that something is happening to you. Now I can prove that something else is going on here. From my viewpoint, the experience of the program has been very positive." (P1)

> "For many years I had had a terrible time with this disease. I did not talk to people. I used to not say what hurt me because everyone could be in pain except me. So, I learned not to say anything. But then, being surrounded by people in the same situation, opened the doors to a world where there were people like me." (P9)

3.3.2. The MCI Improves FMS Coping Skills for Symptom Self-Management

Informers revealed having developed new coping skills and a healthier attitude toward FMS, which help them to overcome symptoms, stigma, and uncertainty about the prognosis. Patients gaining insight into their health processes were highlighted as part of the educational benefits of the MCI. In this vein, learning about FMS and coping techniques was highly regarded for symptom self-management. Reflectively, even though widespread pain seems to be still a challenge, adopting new perspectives in FMS may have moved patients beyond the persistent symptomatology and toward acceptance and change. Informers remarked having reduced medication intake; controlled emotional distress; implemented new coping strategies such as physical activity, nutrition, relaxation, and anxiety-control techniques; and adapted their daily activities and exercises to their capabilities. Furthermore, informers stressed the importance of daily exercising; maintaining a routine; following psychological and physical guidelines; or simply but not less important, giving patients something to engage in:

> "If I was able to quit the anxiolytics and reduce the panic attacks, it means that the program works." (P4)

> "I was diagnosed when I was thirty years old, and I practically had to give up my entire life. I lost many friends along the way, and it has been very hard. In the program, I learned how to live with Fibromyalgia. Even though I still have pain, I don't break down or cry like I used to anymore." (P9)

> "I notice that even though the exercises we learned with the physiotherapist are quite simple, they make a difference if practicing regularly [. . .]. In this sense, it has been very helpful to have received guidance to know what is particularly useful for us. The nutritional session was also interesting. I have noticed that when eating healthy, I have less muscular pain. Designing a schedule with the psychologist was also very helpful in my view since it encouraged me to keep going and have better track of my progress." (P5)

3.3.3. The MCI Promotes Self-Awareness

The MCI successfully promoted participants' self-awareness, allowing them to acknowledge their physical and psychological needs. As understood, gaining insights into their health condition could have helped the participants to assess their symptoms and possibilities more accurately, to avoid under or overestimating their ailment, and to prioritize themselves. The following quote depicts to what extent FMS patients can experience bodily dissociation as a mechanism to cope with physical pain:

> "The program promotes awakening consciousness. For instance, I was not aware that I had so little resistance training capacity [. . .]. Or sometimes, I did not even notice the tachycardias. I have also noticed that my sight is getting worse. Now I understand that I need more time for myself. I remember once when I went for a nail job, and the manicurist did not stop hitting my hands. I was not understanding why he was doing that until I realized that he just wanted me to relax my hands. I was completely unaware of the amount of tension in my hands." (P1)

> "Thanks to the program, I have incorporated self-awareness. Particularly, I have learned to focus on positive aspects. It has been a valuable experience to me." (P2)

Furthermore, reflecting on the informers' narratives revealed an improvement in their subjective embodiment, which entails connecting their symptoms to their emotional status. Approaching FMS as a complex chronic condition emerged as a key to symptom self-management. In this regard, the proposed MCI aims to address patients suffering holistically including physical, psychological, and social well-being. The metaphor of the fish chasing its tail described in the quote below illustrates the complexity that FMS patients face daily:

> "It is the story of the fish chasing its tail. Although we have learned physical techniques, our pain is also related to our emotions. Because in the end, the body retains everything. It is mainly Psychological. In my case, I have an unsolved (psychological) knot. But it refuses to be solved, and I can prove it with my weight raise." (P1)

3.3.4. The MCI as an Empowering Experience

Informers' accounts revealed that the intervention program helped them to increase their autonomy by promoting physical and psychological independence. As experienced by the participants, FMS limits their basic daily activities regarding going out or commuting due to fear of physical impediments and social judgment. Recovering the strength and the courage to face daily life has been interpreted as a valuable experience:

> "The MCI encouraged me to be more independent. Before participating in the program, I could not go out alone since I was afraid of falling due to vertigo. I used to panic outdoors. But during the program, I discovered that I was not afraid of falling but of what people could think when they saw me walking with instability. I was ashamed of myself and felt limited. Now, I go everywhere by myself; I no longer care what others think or say." (P4)

> "I live 12 km from the town where the program took place, and instead of asking my husband to drive me, I preferred to take the bus by myself. Despite my limitations, I used to get on and off the bus following the professionals' advice about being proactive and increasing physical activity." (P7)

3.3.5. The MCI Triggers a Catalytic Effect

FMS was described as a life disruptor that leads to patients abandoning their life projects and losing enthusiasm. In this regard, the MCI program proved to provide patients with a sense of purpose and motivation to carry out new plans. Informers shared their experiences on taking new courses, keeping busy, and exercising daily:

> "I was feeling overwhelmed because I could not do anything. But one day the psychologist asked me what I would like to do. And I explained to her that I have always liked languages, but life circumstances had not been in my favor. Anyway, she encouraged me to try it out. Now I study English at a local academy, and I am doing great." (P4)

> "The professionals encouraged us to keep our minds occupied with other things. For instance, I have signed up for an online course. Being partially disabled and not working, I have more free time to do other things." (P5)

3.4. Theme 4. Room for Improving the MCI

Informers expressed satisfaction with the experience of the program as a whole and willingness to recommend it. However, they suggested some key points for improvement including more psychological guidance, expressive group therapy, and inviting family members to the sessions to help them to understand the diagnosis and its consequences:

> "I would have needed more psychological guidance and strategies. Especially to improve attention and relaxation. For instance, I practise creative meditation through drawing and music in my spare time. It would be interesting to include something like this in the program [. . .]. Besides, some people also needed to talk about family and personal problems because they probably have no other place to do so." (P1)

> "The staff insisted that the program was not a psychotherapy group. That was crystal clear. But it would have been nice to have a little space for sharing worries in life. They cut us short in this sense." (P2)

> "The professionals had so little time that they had to explain everything very quickly, and there was no time for letting us express a little more about how we felt about the topic that was being discussed." (P3)

> "I need someone to explain to my husband, to make him understand what I have because he doesn't. That's why it would help if at least one day we could invite our couples to the session. I would sign up right away for that because this is my biggest burden. I would add a bit of therapy so that people could express themselves. what I missed is exactly this, to be able to talk a little more between us." (P4)

4. Discussion

In this qualitative study, four themes emerged when analyzing FMS patients' experiences during the MCI program: legitimizing fibromyalgia through the MCI, the MCI as a socializing experience, learning how to live with FMS through the MCI, and room for improving the MCI. Overall, the MCI program was valued unanimously as a positive and insightful experience that should continue as part of the UCC. Another common denominator was the benefits of the social encounter with people with the same diagnosis who could truly understand their suffering without judging them.

4.1. The Contributions of Social Support in Legitimizing FMS

Our results provide insights into the role of social support in legitimizing FMS. As Cooper S. and Gilvert L. [46] have disclosed, family, partners, and peers can contribute to accepting the diagnosis, coping with its symptoms and demands, and seeking professional healthcare. In line with this, a meta-synthesis of qualitative studies emphasized the importance of legitimacy in the subjective experience of FMS [21]. Informers reported that only people who suffer from FMS understand it, remarking on the general lack of comprehension of relatives and healthcare professionals. A recent study about the experience of healthcare services for FMS in Sweden indicated that more than half of the sample felt misunderstood by the personnel and were missing an adequate treatment strategy [47].

Our informers showed a tendency to compare themselves with their peers. According to Festinger's social comparison theory (SC) [48], humans have the drive to compare

themselves with others in two different directions: upward and downward by identification or contrast. The former is when people look for similarities with others above them regarding social status or abilities to feel part of that exclusive group (upward identification). On the contrary, they can also find differences with the elite (upward contrast). The latter happens when people compare themselves with others in a worse condition. If they keep their distance from this group, they feel less frustrated with their own (downward contrast). Alternatively, they can highlight the resemblances (downward identification). SC is ubiquitous when there is uncertainty and an information gap and is especially frequent among chronic illnesses [49]. Patients look for answers by mirroring people with the same health condition.

Notably, our informers tended to make a downward contrast with their peers, which helped them to relativize their health condition in contrast to others perceived as equals (since they have the same diagnosis) but worse off and, consequently, allegedly different. Even though this phenomenon could temporarily improve self-esteem, it may redefine patients' perception of well-being and promote remaining in conformity not visualizing their health needs. Hence, if SC is not skillfully monitored by healthcare professionals, the group effect could be iatrogenic. As a double-sided coin, group interventions can bring social support and belonging, facilitating patients' health processes, but could also be used as a way to resist change by externalizing one's health needs to others. Accordingly, the evidence shows that frequent SC can trigger destructive emotions and behaviors [50]. Furthermore, stress appraisal, including intolerance of uncertainty, has been proven as a predictor of SC [49,51]. In order to prevent it, Cabrera-Perona [52] suggests promoting upward identification in SC for intervention programs for chronic pain and fibromyalgia patients due to its self-improvement effect. Therefore, we encourage healthcare providers to approach SC in group settings as a target intervention for FMS patients and not just a feature of human social life.

4.2. Monitoring Group-Based Interventions for FMS

The proposed MCI proved to be a socializing experience for its participants. Nevertheless, preventing the drawbacks of a group setting is particularly important considering the high prevalence of alexithymia among FMS patients, which is characterized by difficulty in recognizing and expressing feelings, and it is correlated to psychological distress [53,54]. Contrary to our expectations, some informers referred to struggling when communicating emotions and profound thoughts in front of a group even though they reported significant benefits from this setting. Including emotional awareness and expression psychotherapy [55] in the MCI program in addition to CBT could possibly address this concern as well as cover the improvement aspects proposed by the informers, which coincide with our previous study with focus group discussions [38].

4.3. Learning How to Live with FMS: Overcoming Health-Related Guilt

According to our results, health-related guilt emerged among the FMS patients' accounts and lack of illness legitimacy was indicated as the reason behind it. Sebic et al. [56] found through a systematic review that health-related guilt is a frequent psychological factor in chronic illness associated with more pain, functional impairment, and poor psychological performance. Furthermore, studies corroborate that FMS patients present low levels of forgiveness, both in relation to themselves and to others [57,58]. Forgiveness has been shown to positively impact health and well-being by decreasing stress, improving lifestyle, and encouraging social support [58]. The work of Vallejo et al. [58] demonstrates that high self-forgiveness is related to high levels of active coping and acceptance. Our findings are consistent with previous results suggesting that learning how to live with FMS entails overcoming illness-related guilt and embracing self-forgiveness, which should be included as a psychosocial coping strategy for symptom self-management and well-being promotion [57].

4.4. Understanding Health-Related Guilt in FMS from a Gender Perspective

From a gender perspective, guilt is women's historically inherited burden related to the patriarchal social order [59]. Guilt can be described as the mechanism of gender submission by which we learn to fulfil gender role stereotypes. Indeed, the published evidence indicates that guilt is more frequent and intense in women [60,61]. Research on gender inequalities in health [62] has provided examples of how women's health has been misunderstood, misdiagnosed, and mistreated by following a biased-men-centered concept of health and well-being in medical practice and healthcare services access [63]. Generally, women are taken less seriously regarding pain, and their accounts are described as "emotional" or "psychological" [64]. A fact that our informers described when being diminished by their social network or partner. Accordingly, Samulowitz et al. [12] have identified gender bias in pharmacological pain treatment. Likewise, Valls [14,65] claims that the differential diagnosis of chronic pain and its gender understanding remains unsolved.

On the other hand, this sex bias may also affect men by being underdiagnosed which delays assessing the peculiarities of FMS in this population and its best treatment approach [13,66]. Studies on men's illness experience with FMS have found some differences with women's symptomatology [66–68]. For instance, Miró and colleagues [66] found that emotional distress and sleep disorders affect cognitive functions differently between sex. Consequently, therapies for reducing emotional distress seem to be more effective in improving attentional function in women than men. Hence, future research should also focus on the latter sex group in order to specifically tailor interventions to their health needs. On this matter, Werner et al. [69] propose that patients' illness narratives can be lived out in a "storied form" to overcome stereotyped classifications of gender and illness.

The gender bias in medicine and its gap in comprehensively addressing women's health needs triggers further consequences. For instance, Shahvisi [70] demonstrated that patriarchal medicine contributes to women's over-representation within alternative treatments limited in scientific evidence. Note that our informers reported complementary therapeutic strategies to be included in the MCI program. Furthermore, patriarchal medicine is linked to sickness absence and delays in returning to work (RTW), which is a serious concern given FMS patients' high risk of work absence due to sickness [70], employment impact, and resource consumption [5,71,72]. Women who have reported experiencing negative encounters with healthcare professionals, including teams such as indifference, disrespect, unbelief, and incomprehension, have shown high sick-leave rates and low RTW rates compared to men [73]. Moreover, in agreement with the conclusion of a recent review by Ben-Yosef M. et al. [74] "*patients must be encouraged to continue working*", since evidence suggests that FMS patients who do not leave their jobs show a promising prognosis. In addition, a recent review proposes that healthcare providers support employers with guidance about workplace accommodation [75].

In light of the evidence, healthcare professionals and intervention programs should contemplate patients' subjective reports about their illness experiences and circumstances from a psychological and gender approach [64,76]. In this line, the proposed MCI program could address the gender differences in FMS as part of its content considering that it is targeted to both sex groups.

4.5. Learning How to Live with FMS: A Mind–Body Approach

The literature recommends that working on a positive body image can improve pain perception [77–79]. Indeed, Martinez et al. [80] have found a disturbing embodiment in FMS characterized by poor body awareness. According to our informers' narratives, the proposed MCI program has helped awaken body needs and sensitivity beyond the pain. Furthermore, Valenzuela-Moguillansky [81] has advanced the hypothesis that disruptions in body awareness led to a paradoxical experience for FMS patients that, while in pain, they cannot actually feel it. An explanation that matches informant P1's account about not feeling the tension in her hands while receiving a manicure. In order to address these issues, Markey et al. [82] propose that pain acceptance is a key predictor of body image constructs.

Thus, healthcare interventions for FMS ought to focus on developing illness coping skills and not just reducing pain levels. Accordingly, a multidisciplinary intervention such as the one assessed would be aimed to regain mobility, sensitivity, and emotional connection with one's own body in order to re-inhabit it and to overcome the unresponsiveness produced by the experience of pain.

4.6. The Multicomponent Intervention Approach in FMS

The proposed MCI program is in line with the latest trend of multidisciplinary approaches for FMS treatment combining pharmacological and non-pharmacological strategies [30]. Even though there is no cure for this condition to date, multicomponent services have been demonstrated to improve patients' quality of life [83,84]. In this regard, a similar experience conducted in the Royal London Hospital showed that all health outcomes assessed improved significantly at both 6- and 9-month post-MCI-intervention with overall positive feedback from the patients in terms of illness self-management [26]. In accordance with our results, the authors highlighted that, ultimately, the intervention helped patients to learn to deal with FMS. Even though many other therapeutic strategies have been revised including pilates, yoga, mindfulness, walking programs, water exercises, and multimedia techniques, among others, a new systematic review suggests that the most effective treatments are those that incorporate health education and complete physical activity (including aerobic and relaxation exercises) [83]. In addition, the psychological component is also indicated as a key factor in supporting patients' mental health and developing coping skills, which coincide with our findings.

4.7. Strengths and Limitations

Our study follows the consolidated criteria for reporting qualitative research (COREQ) [85] in order to achieve scientific rigor. The sample recruitment was systematically and purposively conducted to guarantee variability and to avoid selection bias. Furthermore, two analytics triangulations were performed during the analysis process involving two experienced members of the qualitative research team and one external auditor.

Methodologically, the reported findings result from a non-linear interpretation process that intends to summarize the "essence" of the informers' accounts by means of themes that recover the embodied lived experiences in their narratives. In this regard, themes within the context of hermeneutic phenomenology attempt to overcome a superficial description of patterns in the text, which is particularly suitable for modest samples.

Notwithstanding the sample size, efforts were made to obtain quality data and to analyze it with reflexivity and rigor. As a result, this study pretends to understand the impact and benefits of an MCI program on patients' subjectivity from a critical thinking perspective.

Regarding the limitations, and since the interviewee sample only included those with high assistance records and willingness to participate in the study, the results could have overestimated the benefits of the program. However, the interview schedule included questions concerning improvement aspects for the MCI and interpretations were focused on the unveiled effects of the program.

Moreover, the sample did not include men as the only two possible candidates did not agree to be interviewed. Women's FMS high prevalence contributed to a limited number of men within the MCI program. Moreover, the data collection process was conducted during the COVID-19 pandemic, which could have affected participation. Future projects should make efforts to recruit this population group. Additionally, the informers included belonged to only 5 out of 11 primary care centers of the health region owing to inclusion criteria requirements and sample availability. Nevertheless, since the MCI was performed the same in every center, we do not consider that this aspect could have impacted the results significantly.

Regarding the data collection, due to the COVID-19 outbreak telephonic interviews had to be conducted in some cases. Therefore, the interviewer–interviewee relationship could have been more impersonal than face-to-face interviews since it was the first contact between

the informant and the researcher. However, the interviewer provided relevant information about her background to the participants and encouraged a natural and fluent conversation, including follow-up questions and promoting meaningful exchanges, in order to reduce this potential limitation.

In addition, even though the results were not delivered to the informers for review and feedback, an outside research group was consulted for further validation.

Lastly, our findings may not be generalizable beyond the study sample. Nevertheless, the MCI program could be tailored and assessed in other contexts.

5. Conclusions

Our study has contributed to gaining novel insight into FMS patients' lived experiences during an MCI in primary care. Informers agreed on the program as a revealing, insightful, and motivating experience that has facilitated illness knowledge and acceptance and improved their coping skills and self-management in daily life. Furthermore, peer support was emphasized as a key benefit, beyond clinical outcomes, due to the sense of comprehension, bonding, and encouragement that remains active post-intervention as a positive social network. Gender awareness and empowerment have also been observed as remarkable results. In this regard, including gender diversity within the staff might help patients to deliver information to their partners. Moreover, complex psychological mechanisms were identified intra-group level, which the professionals should skillfully monitor and intervene. In addition, the inclusion of expressive psychological group therapy and inviting relatives to the sessions were claimed as improvement aspects of the program. Nonetheless, our findings warrant further discussion. Finally, these results will allow for adjusting the program to patients' health needs to broaden its benefits and to support the UCC.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and 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 April 2018 (codes P17/069 and P18/068). Participants were guaranteed data anonymity both by oral and written information, and written signed informed consent was required to participate in the study.

Informed Consent Statement: Written informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Due to ethical restrictions, supporting data cannot be made openly available. Participants of this study did not agree for their data to be shared publicly since it may contain potentially identifying or sensitive patient information. Nonetheless, specific data analysis results, such as a section of the audit trail, could be shared by the corresponding author, V.M.A., upon reasonable request and are subjected to a non-disclosure agreement.

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Appendix A

Discussion Schedule

1. What is your general opinion about the fibromyalgia program in which you participated? How would you describe the experience?
2. Could you mention any benefit you may have perceived from the program if any?
3. Have you implemented any of the techniques and learnings performed during the sessions in your daily life? Which ones? How often?
4. Do you think that this experience has helped you to relate differently to your body? How so?
5. How do you feel emotionally after participating in this program? Could you describe it (a bit more)?
6. To what extent the intervention has improved your fibromyalgia coping strategies? How so?
7. To what extent has this healthcare experience developed your social skills? How so?
8. What kind of feedback have you received from people close to you who have experienced your process before and after the intervention?
9. What would you change or improve in the program?
10. Why would you recommend this intervention program to other patients with a diagnosis of fibromyalgia if so?
11. Would you like to comment on something else or address any other issue that has not been discussed?

Appendix B

Table A1. Multicomponent intervention description.

Sessions	Health Education Component	Physical Component	Psychological Component: Cognitive Behavioral Therapy (CBT)
1	Introduction to Multicomponent Therapy (30 min)	6 min walking test (45 min)	Cognitive-behavioral strategies (45 min)
2	Neurophysiology and Pharmacology of Pain (1 h)		Breathing and Relaxation (1 h)
3		Breathing and Relaxation (1 h)	Management of Attention (1 h)
4	Techniques of Postural Hygiene (1 h)	Stretching exercises (1 h)	
5	Nutrition (1 h)	Breathing and Relaxation (1 h)	
6	Management of Insomnia (1 h)	Joint exercises/games (1 h)	
7	Memory (1 h)	Stretching/joint exercises (1 h)	
8	Sexuality (1 h)	Postural hygiene/stretching (1 h)	
9		Strength/joint exercises (1 h)	Activities and Mood (1 h)
10		Coordination exercises (1 h)	Planning pleasant activities (1 h)
11		Breathing and Relaxation (1 h)	Management of Difficulties (1 h)
12		6 min walking test (1 h)	Identification of Objectives (1 h)
Total time	6.5 h	10.75 h	6.75 h

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5.4. Study Protocol for Study III

Title: 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 randomised control trial

Reference: Arfuch, V. M., Aguilar Martín, C., Berenguera, A., Caballol Angelats, R., Carrasco-Querol, N., González Serra, G., Sancho Sol, M. C., Fusté Anguera, I., Fernández Sáez, J., Gonçalves, A. Q., & Casajuana, M. (2021). 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 randomised control trial. BMJ open, 11(2), e043562. https://doi.org/10.1136/bmjopen-2020-043562

Summary

Introduction: This study protocol presents the design of a health economic evaluation conducted alongside a 12-month pragmatic randomised controlled trial (PRCT) to compare a novel multicomponent intervention (MCI) programme with the usual clinical care (UCC) for fibromyalgia syndrome (FMS). This programme covered a 12-session programme which combined health education, physical activity and cognitive-behavioural therapy and was delivered in primary care centres from *Gerència Territorial Terres de L'Ebre*, in south Catalonia, Spain.

Methods: A cost-utility analysis was planned to be performed from a societal perspective, a human-capital approach and a one-year time horizon. Data collection was expected to be carried out from April 2017 to March 2021. A sample of 260 individuals (130 per study arm intervention/control) was calculated to attain statistical power. The study outcomes would include quality of life (using the SF-36v2 questionnaire) for the estimation of quality adjusted life years (QALYs), cost estimations (including direct healthcare costs and indirect non-medical costs), and cost-utility ratios (ICUR). Direct healthcare costs would cover primary care services (GP and nurse visits), referrals, hospitalisations, emergency visits, diagnostic tests, prescribed drugs, and the MCI cost. Indirect costs would be represented by productivity losses (sick leave days). Finally, a deterministic sensitivity analysis was proposed on the variation of items with the highest weight in the cost composition.

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 randomised control trial

Victoria Mailen Arfuch ,[1,2] Carina Aguilar Martín,[1,3] Anna Berenguera ,[4,2] Rosa Caballol Angelats,[5,6] Noèlia Carrasco-Querol,[1] Gemma González Serra,[1,6] Maria Cinta Sancho Sol,[1,6] Immaculada Fusté Anguera,[5,6] José Fernández Sáez,[1] Alessandra Queiroga Gonçalves,[1,7] Marc Casajuana[4]

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For numbered affiliations see end of article.

Correspondence to
Mr Marc Casajuana;
mcasajuana@idiapjgol.org

ABSTRACT

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 programme and UCC of patients with FMS who attend primary healthcare centres of the Gerència Territorial Terres de L'Ebre region of Catalonia, Spain. This article is linked to the pre-results of a randomised control trial study on the implementation of this intervention programme (ClinicalTrials.gov: NCT04049006).

Method and analysis A cost–utility analysis 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 April 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.

Trial registration number: NCT04049006; Pre-results.

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 fibromyalgia syndrome.
- 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 randomised control trial; it includes a broad perspective from society, and a 1-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 characterised 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 €7900 (direct €910, indirect €6990) for France, €7256 (direct €1765, indirect €5491) for Germany and €7814 (direct €5241, indirect €2573) 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, 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 hospitalisations) and non-healthcare resource utilisation (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 €5010 for patients with FMS, being €614 (12.3%) for direct costs and €4394 (87.7%) for indirect costs.[10]

In line with these findings, another cross-sectional study conducted in Spain, based on face-to-face patient interviews, encountered a mean total cost per patient per year of €9982, comprising €3245.8 (32.5%) of direct healthcare costs and €6736.2 (67.5%) of indirect costs attributable to productivity losses.[11] This study also showed that: (1) non-pharmacological therapies accounted for the highest costs of direct healthcare resources, involving three times more than the cost of drug treatments; (2) there was a significant direct association between disease severity and total costs; and (3) patients with a permanent working disability made the most extensive use of resources.[11] However, these findings were collated over a decade ago, and are in need of updating with reference to the Spanish public health system.

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

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

This study aims to perform a CUA on an MI consisting of health education, physical activity, and cognitive-behavioural therapy, for patients with FMS compared with their treatment under usual clinical care (UCC),[33] provided within the 11 primary care centres of the Gerència Territorial Terres de L'Ebre of the Institut Català de la Salut, Spain. The results of this economic assessment are expected to support the evidence of the randomised clinical trial (RCT) related to this project[34] (ClinicalTrials.gov: NCT04049006).[35] It is hoped that this new proposed intervention will reinforce the UCC, enhance patients' QOL, and promote the efficient allocation of health and social resources.

METHOD

Design

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

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

The human capital approach has been judged the most suitable method for this study due to the limitations of

the data source, given that only full sick days, prescribed by the general practitioner (GP), and the period with a medical disability can be extracted from the computerised medical history programme (eCAP).

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

Study population

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

Patient and public involvement

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

Outcomes measures and data collection

Health outcomes

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

Cost outcomes

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

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 hospitalisations. Costs will be calculated based on unit service prices, which will be obtained from the DOGC. Additionally, drug prices will be obtained from the Council of Pharmaceutical Colleges of Catalonia.

Indirect non-medical costs include temporary and permanent disability. As stated in the Spanish General Law of Social Security (Law 20/2014; Royal Legislative Decree 8/2015),[42] the term 'temporary disability' refers to sick leave days due to short-term common or professional illness, whereas 'permanent disability' refers to the impossibility of working due to the permanent and total or partial loss of working capacity in the long-term. In the former case, a GP determines whether a patient is unable to work in the short term. In the latter case, a medical board conducts an in-depth assessment of the medical background, including the physical and mental condition of the person, in order to determine whether a permanent disability should be declared. These measurements will be estimated from the number of full sick leave days and the months spent with a disability, respectively.

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

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

Data collection is expected to be completed by April 2021.

Sample size

In order to detect a score difference of at least five 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 α error of 0.05, a β 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 V.25 and Stata V.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% CIs will be calculated for all parameter estimates.

Table 1 Cost outcome measurements and data collection

Cost outcomes				
Cost outcome	**Cost outcome description**	**Data source**	**Cost data source**	**Cost calculation**
Direct healthcare costs				
Primary care visits	► General practitioner ► Nurse ► Physiotherapist ► Psychologists	eCAP	DOGC	Number of visits×price
Professional referral visits	► Traumatology ► Psychiatry ► Rehabilitation ► Other specialities	eCAP	DOGC	Number of visits×price
Clinical tests	► Blood test ► Diagnostic imaging techniques ► Other tests	eCAP	DOGC	Test performed x price
Pharmacological prescriptions	► Muscle relaxants -Analgesics ► Corticoids ► Antidepressants ► Anxiolytics ► Antiseizure -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 hospitalisation days×price
Indirect non-medical costs				
Temporary disability (TD)		eCAP	NS	Number of full sick leave days×salary
Permanent disability (PD)		eCAP	NSI	Number of months with PD×salary

DOGC, Diario Oficial de la Generalitat de Catalunya; eCAP, computerised medical history programme; NSI, Spanish National Statistics Institute.

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

Sensitivity analysis

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

DISCUSSION

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

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

More accurate methods, such as the friction cost approach, have been acknowledged as being effective for estimating productivity costs. However, the human capital approach has been considered the most suitable for this study, given the data available. However, a sensitivity analysis will be performed to assess alternative cost scenarios that take into account the limitations of this methodological approach. It will include different direct healthcare

costs and, if necessary, the weighted price of the social cost, considering that the salary rate will be an overall annual average estimate without distinction between the type of activity or the working schedule.

Additionally, another economic concern involves the costs of the diagnostic process since it is purely clinical.[45] Before FMS is diagnosed, other possible diseases must be ruled out with objective tests and by a variety of medical specialists. This process is often long and exhausting for patients, frustrating for doctors, and expensive from the perspective of the health system.[46] Furthermore, the presence of comorbidities can hinder and delay the diagnosis, as well as complicating the choice of a treatment strategy.[47] Hence, the study sample could show differences in the use of resources between patients depending on the year of diagnosis and the medical records. However, it is expected that the randomised allocation will balance these differences between the study arms.

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

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

Evidence of efficiency is essential for decision-making in order to allow budgets to be prioritised for those treatment options that prove to be cost-efficient and to fulfil patients' health needs. Economic evaluation is key to overcoming the obstacles arising from the uncertainty about the real costs and the sustainability of particular interventions.[54] The CUA is a popular measurement tool that combines quantity data and QOL, based on the opinions of the healthcare users, associated with a monetary cost. It involves a participatory and economic evidence-based decision-making strategy that considers stakeholders' preferences.[55] However, this methodology is controversial,[56] the main points of contention being: (1) the lack of transparency about data collection and analysis regarding the measurement of the value that society assigns to a state of health; (2) that the gain in health depends on the severity of the condition, so the value is affected by patients' perception of their pain and health status; (3) the limited value of this measurement tool for long-term diseases such as FMS, where disability accumulates over time since it assumes that the utility of a health state is independent of the time the patient has experienced it, and the influence of previous and subsequent health conditions.[24] Although all these factors pose methodological challenges, CUA is still a valid and effective strategy for carrying out health economic evaluations and collaborating with decision-makers in choosing between intervention alternatives.[24]

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

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

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

Finally, this study could be affected by sample loss to follow-up given the 1-year time horizon. This methodological characteristic is also a strength of the study since it will allow long-term changes to be assessed. In order to minimise the number of participants abandoning the study, reminders of upcoming interviews will be sent, and different data collection methods, such as telephone calls and online survey platforms, may even be used.

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

ETHICS AND DISSEMINATION

This study was designed in accordance with the Helsinki/Tokyo Declaration. It was approved by the Clinical Research Ethics Committee of the Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), on 25 April 2018 (code P18/068). Information is delivered to participants orally

and in writing before their necessary informed consent is obtained. This project respects the data protection laws guaranteeing participant anonymity. Dissemination strategy includes publications in scientific journals and through presentations in the local and national media and at academic conferences.

Author affiliations
[1]Unitat de Suport a la Recerca Terres de l'Ebre, IDIAP Jordi Gol, Barcelona, Catalunya, Spain
[2]Department of Pediatrics, Obstetrics and Gynecology, and Preventive Medicine, Universitat Autonoma de Barcelona, Barcelona, Catalunya, Spain
[3]Unitat d'Avaluació, Direcció d'Atenció Primària Terres de l'Ebre, Institut Català de la Salut, Tortosa, Catalunya, Spain
[4]Central Research Unit, IDIAP Jordi Gol, Barcelona, Catalunya, Spain
[5]Equip d'Atenció Primària Tortosa Est, Institut Català de la Salut, Tortosa, Catalonia, Spain
[6]Unitat d'Expertesa en Síndromes de Sensibilització Central Terres de l'Ebre, Institut Català de la Salut, Tortosa, Catalonia, Spain
[7]Unitat Docent de Medicina de Família i Comunitària Tortosa-Terres de L'Ebre, Institut Català de la Salut, Tortosa, Catalonia, Spain

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Twitter Anna Berenguera @ABerenguera

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ORCID iDs
Victoria Mailen Arfuch http://orcid.org/0000-0001-5935-6907
Anna Berenguera http://orcid.org/0000-0002-0889-2002

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6. Discussion

6.1. Main findings

This doctoral thesis encompasses a mixed-method assessment of a novel MCI for patients with FMS in south Catalonia, Spain. Consistently with complex intervention research, two qualitative studies and a health economic evaluation were conducted to support and broaden the results on the effectiveness of this programme.

Based on qualitative methodology, a focus group and an interview study were carried out to explore the design, benefits, barriers, facilitators, and subjective impact of the MCI from patients' perspectives. Overall, the results revealed informers' acceptability with this therapeutic initiative and greater satisfaction compared to the UCC. In both studies, informers were positive about recommending this programme to other patients with FMS and supported its continuation as part of the routine practice.

As examined in ***Study I***, the intervention's format and content were positively valued. Nonetheless, suggestions for improvement were disclosed. Concerning the design, the sessions' length was considered insufficient for addressing patients' health needs, particularly for sharing their personal illness experiences and adjusting the activities to their individual needs. In addition, the group session modality was found to play a crucial role in therapeutic adherence and perceived benefits. However, group dynamics may also become a barrier if not skilfully monitored. Regarding the setting, PCCs were considered appropriate spaces for delivering the MCI. In times when online health services are increasing in popularity, and considering that FMS limits patients' functionality and social life, informers highlighted the gain in autonomy and self-confidence when commuting to the health centre by themselves and appreciated face-to-face encounters.

Concerning the content of the MCI, a summary of the suggestions received regarding each component is presented as follows:

- **Health education:** deepening the information on FMS cognitive impact, nutrition in pain management, strategies to prevent autonomy loss, pharmacological treatment, and sexuality. In addition, a family approach was suggested to provide relevant information to family members in order to promote FMS literacy and comprehension, endorse its legitimacy and prevent stigmatisation.
- **Physical activity:** providing a person-centred approach to tailored physical exercise to

individuals' capacity and promoting home workouts.

- **Psychological approach (CBT):** expanding the psychoeducational goals by including expressive group therapy where patients could find a safe space to share and discuss emotional needs and illness experiences.

Participants disclaimed several benefits from the MCI beyond the targeted health outcomes. The conducted qualitative studies facilitated identifying the impact of the MCI on multiple patients' spheres in addition to FMS symptomology. As a complex syndrome, its repercussions affect patients' lives broadly, including work life, family dynamics, social interactions, functionality, self-esteem and acceptance, and, ultimately, their quality of life. Although widespread pain is central in defining and diagnosing this condition, the gathered evidence shows that patients might perceive an improvement in their quality of life even when not reporting significant pain relief. In other words, the presented MCI programme appears to have supported patients in coping with the illness experience and total pain [185]. In a scenario of medical uncertainty, where the origin of FMS-related pain remains unclear, new multidisciplinary programmes that mainly focus on reducing pain levels may fail in this attempt. Instead, therapeutic approaches for FMS should not underestimate the importance of the illness experience and patients' feedback on quality of life and well-being.

Study II broadens these findings by exploring patients' subjective impact and providing insights into the underpinning mechanisms of the MCI. One of the most alleged benefits of the programme was supporting FMS legitimisation and acceptance. In this regard, professionals' validation and peers' illness accounts were reported as crucial to acknowledge FMS as a real health condition. As inferred, this healthcare and social support triggered an empowering and catalytic effect that boosted patients' proactivity, understanding of FMS, and coping skills. The MCI experience seems to have contributed to building resilience in patients with FMS.

Furthermore, the group of peers was regarded as a facilitator in both qualitative studies. From an interpretative angle, peers' illness accounts provide a living testimony that validates and re-signifies the individual illness experience in a context of scientific discrepancies and poor public acknowledgement of FMS. In this line, the symbolic efficacy of social encounters could have facilitated patients' FMS understanding, self-confidence and concept, lifestyle and health behavioural changes. Under the same clinical label, this polysymptomatic condition arises in multiple ways, which might obscure biomedical identification processes. Nonetheless, the *Study*

II findings show that socially constructed narratives confer comfort, relief, and a sense of belonging in peer group contexts.

In ***Study III***, the MCI programme proved its cost-utility for society compared to the UCC by increasing patients' QALYs below the Spanish willingness to pay. Even though participants' quality of life improved significantly in the intervention group, no significant differences between the study arms were observed regarding direct and indirect costs. However, post-intervention data collection was conducted after the first wave of the COVID-19 pandemic for almost half of the study sample, which could have negatively impacted the use of health services and sick leave days. In addition, the sample presented comorbidities that could have also been responsible for the cost invariance. Furthermore, these results are similar to the findings in *Studies I* and *II,* as informers disclaimed an overall improvement in quality of life and well-being but with limited physical benefits, which could be reflected in a non-significant change in health resource utilisation.

Moreover, results from *Study III* were confirmed when variating large cost components according to the regional health expenditure 2021. In addition, potential cost-savings were observed when filtering session attendance to a minimum of 66% (8 out of 12 sessions). This result suggests that the MCI schedule plays a role in its societal benefits. As found in the performed qualitative studies, the intervention programme entails a process of encounters, reflections, and insights that go beyond the technical knowledge and skills provided. Nevertheless, public healthcare resources are scarce, and it is essential to prove the possible benefits of not condensing complex interventions into short GP visits and a brochure.

6.2. The results in light of the literature

The presented findings align with the literature on multidisciplinary approaches for FMS, which have shown acceptability and promising results in improving patients' quality of life [112,124]. Methodological gaps have been observed, as most studies principally focus on studying the effectiveness of the interventions in improving primary health outcomes. Yet, few studies have performed nested qualitative and health economic evaluations to broaden assessments on efficacy.

Qualitative studies were initially focused on patients' illness experiences with FMS. In this regard, informers' accounts seem not to have substantially changed despite the efforts to broaden the therapeutic approach in recent years. As found in this doctoral thesis, patients still fight for credibility and legitimacy in the medical and social domains, as highlighted by a meta-synthesis of qualitative studies published over ten years ago [186].

The presented results resemble those of the PASSAGE study, a Canadian experience of a multicomponent interdisciplinary group intervention for self-management of FMS with a mixed-method approach from 2015 [187]. This programme showed to have improved FMS symptoms and gained patients' acceptance. The qualitative results stressed the role of the intervention facilitators in promoting participants' feelings of care, understanding and self-esteem. Furthermore, group cohesion was observed as a motor for sharing illness experiences and finding social support and motivation. Lastly, the authors detected that the programme's benefits were beyond expectations by increasing participants' empowerment when learning self-management strategies in the context of clinical and social comprehension and empathy.

Another recently reported initiative on a MCI, conducted in London and evaluated through mixed methodology, found that the programme significantly improved scores for all the health outcome measures (perceived health, anxiety, pain catastrophising, and self-efficacy). In addition, patient-participants highlighted gaining knowledge in how to deal with FMS [188]. Furthermore, the group setting was considered beneficial for receiving unprejudiced validation of their health condition, support for sharing illness accounts, and hints for self-management. Remarkably, patients' willingness to change was identified as the motor for the programme's success. Hence, the literature shows that promoting therapeutic engagement and motivation are key factors when delivering health intervention programmes.

Moreover, a previous qualitative study conducted in Catalonia, Spain, found positive effects on the physical and mental health and well-being of women with FMS who participated in a peer social support network [189]. According to the authors' findings, the informers benefited from this experience by developing illness acceptance, finding relevant information, breaking stigma, receiving emotional support, feeling understood and gaining self-satisfaction.

Likewise, another FMS treatment initiative in Catalonia, which involved a group-based body awareness therapy, found similar benefits from group experiences, suggesting the synergic effect of interpersonal encounters and cohesion [190]. Their findings remark on the role of trust, confidence, motivation, altruism and mutual learning in creating movement awareness.

The scientific evidence on health economic evaluations for assessing FMS non-pharmacological interventions is also scarce [191–198]. The findings of this thesis align with those conducted in Spanish territory, showing increasing-cost outcomes below the willingness to pay for gaining one QALY or even dominance. However, technical differences have been observed as none exclusively compares a MCI with the UCC within the public health system but rather with single interventions such as psychoeducational programmes, mindfulness, or group-based support therapy.

Methodologically, CUA is the most widely used health economic evaluation among published studies on FMS. In addition, the ICURs are the most frequently reported outcome. Even though some scholars may support introducing new methods such as the net benefit [199,200], ICURs are still an in-force and reliable tool in this field, particularly when only two health technologies are being compared.

Furthermore, using QALYs presents some advantages, such as including stakeholders' preferences, covering a broad perspective beyond traditional health outcomes, allowing comparisons between interventions that lead to different health benefits, and supporting resource allocation. Nevertheless, this method may also face some controversies around the self-reported nature of health-related quality of life data and the societal value attached to different health statuses. In the presented CUA, the obtained QALYs were closer to 0 (death) than to 1 (excellent health). This phenomenon has been reported by Abellán Perpiñán [173], who explained that the Spanish utility metrics have a substantially inferior lower limit than the ones from the United Kingdom. Hence, the extrapolation of results across territories should be

done and interpreted cautiously. Despite the efforts in defining and standardising the concepts of health, quality of life and well-being, cultural values influence our measurements.

In light of the literature, this doctoral thesis contributes to closing the knowledge gap in assessing a MCI programme for patients with FMS in Spain from a qualitative and health economic perspective.

6.3. Strengths and Limitations

6.3.1. Strengths

By following complex intervention research, this doctoral thesis provides a comprehensive and mixed-method evaluation of a novel and multidisciplinary healthcare programme for patients with FMS within Catalonian's public health system. Furthermore, the assessment of the MCI has followed the high-research standards of PRCTs, which delivers controlled-biased knowledge on how a new health technology works in a real-world scenario.

Using the qualitative methodology and collecting both group and individual data, this work has incorporated patients' voices and perspectives to tailor the MCI programme to their health needs and enhance its benefits. In addition, an interpretative methodological approach has been adopted to gain a deep understanding of the therapeutic experience. In addition, systematic analyst triangulations were performed by an experienced qualitative research team to guarantee trustworthiness.

Furthermore, considering the Spanish willingness to pay, the societal cost of gaining QALYs has been evaluated. Given the impact of FMS on patients' biopsychosocial spheres, assessing changes in patients' quality of life and other health outcomes is crucial to fully capture an intervention programme's potential benefits and, ultimately, its value. CUA is a well-known and solid scientific method for this purpose. In addition, registered data from the medical record system has been used for cost estimations, providing a more accurate representation of healthcare services utilisation.

Moreover, the study processes were led by consolidated criteria guidelines for reporting research, including the COREQ [134], SRQR [135], and CHEERS [162].

Lastly, it is worth pointing out that this doctoral thesis and the research project were conducted during the COVID-19 pandemic. Thus, several obstacles had to be overcome to conclude the research schedule and aims and, most importantly, fulfil our commitment to patients.

6.3.2. Limitations

In terms of limitations, the findings of this doctoral thesis should not be generalised beyond the Catalonian framework, first, due to the subjective nature of patients' accounts and the limited sample. Secondly, utility values, services, costs and effectiveness thresholds vary across territories. Nevertheless, the results could be used as an experience to adapt the MCI

programme to other populations and healthcare contexts or to guide the development of new therapeutic strategies. Noteworthy, generalisation in healthcare services is being contested by the realist evaluation approach, whose main questions are *"What works, for whom, in what respects, to what extent, in what contexts, and how?"* [201–203]. In this framework, the contextual feature gains protagonism over standardising interventions across populations. The realist perspective is particularly suitable for complex health conditions in which the general common denominator is the heterogeneity of patients' clinical profiles and health needs. Hence, instead of focusing on generalisation as an ultimate goal in research, the realistic approach proposes understanding the mechanisms behind the achieved outcomes and the role of the context.

Regarding the study population, although the MCI was offered to both sexes, few males participated in the programme. Hence, the findings have a limited representation of this sex group. Among the reasons, it is partially related to the fact that FMS is most prevalent in females. Therefore, there is no information about how to adapt the MCI to males, as only females participated in the qualitative studies in this doctoral thesis. Further research should explore men's perspectives on this programme to promote enrolment and therapeutic adherence and enhance its health benefits.

On the one hand, the number of informers in the qualitative studies was restricted by the programme schedule, the time inclusion criteria, and the fact that data collection took place after the first wave of the COVID-19 pandemic. As preventing memory bias was prioritised, only those patients with less than 12 months post-intervention and 75% of session attendance were considered for recruitment. However, theoretical variability was taken into consideration for contributing to data quality and saturation.

On the other hand, the final sample size attained in the CUA was according to estimations and analogous to the PRCT sample, which minimises the shortcomings of a "piggyback study". In addition, the study groups were reasonably homogenous, which evidences the effect of randomisation. Thanks to the reached simple size, a complete case analysis was feasible. This strategy included those participants with complete follow-up pre- and 12-month post-intervention. In addition, participants were included regardless of their level of attendance to the programme; thus, different levels of therapeutic adherence were included in the analysis with the same weight, representing a real-world scenario.

Concerning the data collection, the discussion schedules used for the qualitative studies were not previously pilot-tested with participants of the MCI programme due to the limited available sample. However, the qualitative research team reviewed and tested the questions beforehand. In addition, the FGDs and interviews were flexible to facilitate the conversation flow and encourage informers' disclosures. Also, the thesis's author conducted all the FGDs and interviews, which enabled the consistency of the data collection process.

Data included in the CUA might face the limitations of the self-reported nature of the SF-36v2 questionnaire and the fact that costs were estimated based on available data in the eCAP. Concerning the former, other instruments, such as the EuroQol [204], are popular tools for conducting CUA studies and are frequently compared in the literature. However, the SF-36v2 is still considered a valuable and informative clinical tool for assessing HQOL, especially considering the pragmatic feature of the RCT from this project. About the latter, not all types of direct or indirect costs were possible to include, such as over-the-counter drugs, out-of-pocket health services purchases, informal care, non-health costs such as administrative and commuting costs, or disability pension. Therefore, the societal benefits should be interpreted in light of the limitations of the available data. Yet, this potential underestimation of costs could have been outweighed by the fact that resource utilisation was not solely linked to FMS, which could have overestimated its real burden. In point of fact, the most accurate way to account for costs would be using actual health and social expenditures. However, there were barriers to accessing this information; thus, estimations were made based on resource utilisation, official prices, and average wages. Still, direct medical costs covered a wide range of healthcare services across primary care and hospital settings, and productivity losses were estimated from the total number of sick leave days, regardless of the payer. Additionally, the SA included adjusting major cost components (GP and nursing) based on the health expenditure 2021.

Another possible intrinsic limitation of the CUA methodology is the human capital approach, as it does not account for work replacement. However, the literature is debated in this regard. Even if any overestimation of the societal losses were incurred, it probably offset the productivity losses not captured from those in the sample who were not active in the labour force, such as pensioners and homemakers.

Finally, the two-way deterministic SA conducted for the CUA may present a non-conservative strategy when excluding those 20 individuals with less than 66% of session attendance (8 out of

12 sessions). However, this methodological decision was intended to assess the benefits of the MCI programme schedule with a reasonable therapeutic adherence expectation. Hence, its interpretation shows the potential benefits of following the therapeutic design. In times of limited resources within the public health administration and the dominance of the biomedical paradigm, the evidence must demonstrate the benefits of complex interventions when addressing complex health conditions.

6.4. Implications and future research

Findings from this doctoral thesis are expected to provide evidence to adjust a novel MCI programme for patients with FMS to reinforce the routine practice in Catalonian primary care settings. By broadening the results on efficacy, qualitative and health economic evaluations are aimed to shed light on implementation and resource allocation evidence for healthcare providers and decision-makers.

As a non-pharmacological intervention programme, the proposed MCI is expected to contribute to patients acquiring essential information about FMS, its therapeutic approach and impact, and developing coping skills for disease self-management. Ultimately, introducing this programme is expected to improve patients' quality of life and reduce resource utilisation, which are essentially public health goals.

Multicomponent interventions for FMS are in their onset in the Spanish context and worldwide. Even though there is some consensus about the biopsychosocial and educational approach that these programmes should adopt to mitigate the impact of this condition, further development and research are needed to provide the best care possible.

Furthermore, patients with FMS may present other concomitant health conditions that complicate their clinical picture and intensify their health needs. Therefore, interventions could increase their benefits if tailored according to patients' functionality and quality of life impact by adapting physical activities, psychosocial support and literacy. In addition, these therapeutic initiatives should also be explored in-depth in males to elucidate their particular health mechanisms and perspectives.

As suggested by the results, future research lines could explore the potential benefits of delivering FMS literacy and promoting work adaptations to patients' family networks and work environments.

Moreover, an implementation evaluation should be conducted in a real-world scenario to assess whether the MCI programme activities, schedule, and resources are implemented and used as intended. Furthermore, a process evaluation should include healthcare staff and researchers' perspectives.

From a health economic perspective, CUAs could be enhanced in accuracy by expanding data access to registered health and social insurance expenditures and adding information on other

non-registered medical and non-medical costs.

In addition, to adjust the MCI to other health territories within the region and even at a national level, new multicentred PRCT should be carried out, including a larger and more representative sample, to validate the results of these findings and increase its impact on the public health system.

7. Conclusions

In closing, the assessed MCI programme was accepted and positively valued by its patient-participants, who found it beneficial for enhancing their quality of life and well-being. Further benefits were disclosed beyond mitigating FMS symptoms, including accepting this condition, developing empowerment and coping skills for illness self-management, leading to lifestyle changes, gaining personal insights and self-confidence, and triggering body and gender awareness. The analyses revealed that these outcomes were triggered not only by the programme's content but by the social support received from the healthcare staff and the peer group. This network was found to be of relevance for legitimising FMS as a genuine health condition and engaging patients in the MCI and their health processes. The interpretative analyses revealed that peers played the role of 'significant other' by providing new meaning to the illness experience and bridging between the scientific knowledge gap, the limited social acknowledgement, and FMS-related symptoms and impact.

As suggested by the results, there is room for improving the MCI design to guarantee meeting individual health needs, physically and psychologically, in therapeutic group settings.

The health economic evaluation confirmed the reported benefits in quality of life. The results from the CUA suggest that the gain in QALYs offset the financial consequences of carrying out this programme in the Spanish public health system.

Overall, this doctoral thesis provides evidence to strengthen primary care practices for FMS by implementing a MCI programme as part of the health services portfolio in the territory.

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Annexe

Supplementary materials

S.1. Study I

Focus Group Discussions Interview guide [130]:

1. Greetings and presentation of the research team.
2. General information on the focus group discussion (FGD).
3. Explanation of the ethical and confidentiality aspects.
4. Explanation of the FGD dynamics.
5. Individual presentation of the informants.
6. FGD questions:
    1) What do you think as a whole about the group programme for Fibromyalgia?
    2) To what extent have you found it helpful?
    3) What have you liked the most about the programme?
    4) What have you liked the least?
    5) What aspects of the programme do you think could be improved?
    6) How have you felt participating in a group programme compared to the individual clinical care you usually receive?
    7) Regarding the programme´s setting features, what do you think of the place and timeframe of the programme?
    8) To what extent has this programme helped you to improve symptoms management? For example, have you noticed any enhancement in your Fibromyalgia?
    9) To what extent have you noticed any improvement in other aspects of your daily life after participating in the programme?
    10) How would you describe the professionals' performances during the programme?
    11) Would you like this programme to be included as part of the usual treatment in primary care centres? Why/Why not?
    12) Would you recommend this intervention programme to other Fibromyalgia patients? Why?/ Why not?
    13) Would you like to comment on something else?

7. Ending of the FGD:
    - Summary of the informants 'contributions.
    - Acknowledgement and thanks.

S.2. Study II

Discussion schedule in Individual interviews [131]:

1. What is your general opinion about the fibromyalgia programme in which you participated? How would you describe the experience?
2. Could you mention any benefit you may have perceived from the programme if any?
3. Have you implemented any of the techniques and learnings performed during the sessions in your daily life? Which ones? How often?
4. Do you think that this experience has helped you to relate differently to your body? How so?
5. How do you feel emotionally after participating in this programme? Could you describe it (a bit more)?
6. To what extent the intervention has improved your fibromyalgia coping strategies? How so?
7. To what extent has this healthcare experience developed your social skills? How so?
8. What kind of feedback have you received from people close to you who have experienced your process before and after the intervention?
9. What would you change or improve in the programme?
10. Why would you recommend this intervention programme to other patients with a diagnosis of fibromyalgia if so?
11. Would you like to comment on something else or address any other issue that has not been discussed?

Pending publications

Study III

Title

Cost-utility analysis of a multicomponent intervention for fibromyalgia syndrome versus usual clinical practice in primary care: a 12-month pragmatic randomised controlled trial in Spain

Information

This manuscript is currently under peer-review process in an International Journal. Do not cite or share this work.

Summary

Introduction: A health economic evaluation was performed alongside a pragmatic randomised controlled trial (PRCT) to compare a novel multicomponent intervention (MCI) programme with the usual clinical care (UCC) for fibromyalgia syndrome (FMS). The MCI covered a 12-session programme which combined health education, physical activity and cognitive-behavioural therapy and was conducted in primary care settings from *Gerència Territorial Terres de L'Ebre* in south Catalonia, Spain.

Methods: A cost-utility analysis was conducted from a societal perspective, a human-capital approach and a one-year time horizon. Data collection lasted from April 2017 to March 2021. Direct medical costs, productivity losses and quality-adjusted life years (QALYs) were used to estimate crude and adjusted incremental utility ratios (ICUs). Direct medical costs covered healthcare services in primary care, specialised medical care, diagnostic imaging techniques, and prescribed drugs. Productivity losses were estimated based on registered sick leave days and regional average wages. QALYs were derived from mapping scores from the SF-36vs questionnaire into SF-6Dv2 metrics. In addition, one and two-way deterministic sensitivity analyses were performed to assess the robustness of the initial findings by correcting large cost components with actual health expenditure, and secondly, subtracting those individuals with less than 66% of participation.

Results: 297 subjects were included in the final complete case analysis (161 in the intervention group and 136 in the control group). The resulting crude and adjusted ICURs proved a significant improvement in QALYs with a cost-increasing outcome that fell below the Spanish willingness to pay (€1,780.75 gained and ICUR of €851.67 per QALY, respectively). These findings were supported by the sensitivity analyses showing potential for cost-savings.

Conclusion: The assessed MCI shows cost-utility for society in terms of direct and indirect costs and health benefits. These findings provide evidence that supports MCI programme in the regional health services portfolio with the aim of improving patients' quality of life and reducing the economic burden on society.

ORIGINAL RESEARCH - *Do not cite or share this work* **-**

Cost-utility analysis of a multicomponent intervention for fibromyalgia syndrome versus usual clinical practice in primary care: a 12-month pragmatic randomised controlled trial in Spain

Short Title: An economic evaluation of a non-pharmacological programme for fibromyalgia syndrome

Author Names: Victoria Mailen Arfuch, MPH[1,2,3*], Carina Aguilar Martín, MD, PhD[1,4], Anna Berenguera, PhD[2,5,6], Rosa Caballol Angelats, MD[7,8], Alessandra Queiroga Gonçalves, PhD[1,9], Noèlia Carrasco-Querol, PhD[1], Gemma González Serra, BS[10], Maria Cinta Sancho Sol, BS[8,11], Immaculada Fusté Anguera, RN[7,8], Emilie Friberg, PhD[3], Emma Pettersson, MS[3] and Marc Casajuana, MS[2,5]

Affiliations:

[1]Unitat de Suport a la Recerca Terres de l'Ebre, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol I Gurina (IDIAPJGol), Tortosa, Spain

[2]Department of Pediatrics, Obstetrics and Gynecology, and Preventive Medicine, Universitat Autònoma de Barcelona, Bellaterra, Spain

[3]Division of Insurance Medicine, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

[4]Unitat d'Avaluació, Direcció d'Atenció Primària Terres de l'Ebre, Gerència Territorial de Terres de l'Ebre, Institut Català de la Salut (ICS), Tortosa, Spain

[5]Unitat Central de Recerca, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain

[6]Department of Nursing, Universitat de Girona, Plaça de Sant Domènec, Girona, Spain

[7]Centre d'Atenció Primària (CAP) El Temple, Gerència Territorial de Terres de l'Ebre, Institut Català de la Salut (ICS), Tortosa, Spain

[8]Unitat d'Expertesa en Sindromes de Sensibilització Central Terres de l'Ebre, Gerència Territorial de Terres de l'Ebre, Institut Català de la Salut (ICS), Tortosa, Spain

[9]Unitat Docent de Medicina de Família i Comunitària Tortosa-Terres de L'Ebre, Institut Català de la Salut (ICS), Tortosa, Spain

[10]Servei de Rehabilitació i Medicina Física, Hospital de Tortosa Verge de la Cinta, Gerència Territorial de Terres de l'Ebre, Institut Català de la Salut (ICS), Tortosa, Spain

[11]Centre de Salut Mental d'Adults (CSMA) de Fundació Pere Mata Terres de l'Ebre, Tortosa, Spain

***Correspondence author**

Abstract

Objective: To perform an economic evaluation on a multicomponent intervention programme for patients with fibromyalgia syndrome compared to the usual clinical practice in primary care.

Design: A cost-utility analysis was conducted alongside a pragmatic randomised controlled trial* from a societal perspective, a human capital approach, and a one-year time horizon.

Subjects/Patients: Patients diagnosed with fibromyalgia syndrome from the public health system in south Catalonia, Spain.

Methods: Crude and adjusted incremental cost-utility ratios were estimated to compare the treatment strategies based on cost estimations (direct medical costs and productivity losses) and quality-adjusted life years. One-way and two-way deterministic sensitivity analyses were performed.

Results: The final analysed sample comprised 297 individuals, 161 in the intervention group and 136 controls. A crude incremental cost-utility ratio of €1,780.75 and an adjusted ratio of €851.67 were obtained, indicating that the programme significantly improved patients' quality of life with a cost-increasing outcome that fell below the cost-effectiveness threshold. The sensitivity analysis reinforced these findings when variating large cost components and showed dominance when increasing session attendance.

Conclusion: The proposed programme proved its cost-utility for society, which suggests this new intervention could support the standard practice for fibromyalgia in the regional primary care service.

*ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/record/NCT04049006

Key words: Cost-utility analysis, fibromyalgia syndrome, health economic evaluation, multicomponent intervention, primary care

Lay Abstract

Following the gold standard trial design for evaluating healthcare technologies, a health economic evaluation was conducted on a new multidisciplinary intervention programme for patients with fibromyalgia syndrome in Catalonia primary care centres. Estimations of direct healthcare and social costs were assessed jointly with the effect on the quality of life to compare the new intervention with the usual clinical care. Results showed that the programme proved its cost-utility for society as patients' perceived health improvements outweighed the cost increase according to the maximum price accepted for an extra unit of quality of life in Spain. These findings were verified when cost estimations were corrected with the actual health expenditure. In addition, the intervention implementation scheme demonstrated having cost-saving potential when increasing participants' session attendance to at least 66%. Therefore, patients and society could benefit from this new therapeutic strategy for fibromyalgia if adopted by the regional services portfolio.

Introduction

Fibromyalgia syndrome (FMS) is one of the most frequent pain disorders among rheumatic illnesses (1), particularly in women (2). Its prevalence has been estimated between 0.2% and 6.6% globally (3) and 2.45% in the Spanish population (4). In addition, Ursini et al. (5) have found FMS as a new facet of the post-COVID-19 syndrome spectrum, given the similarity of their clinical picture, which alerts the public about its growing trend.

FMS is currently classified as a central sensitivity syndrome (6,7) and characterised by widespread musculoskeletal pain and fatigue as core clinical diagnostic criteria (8) owing to the lack of biomarkers and specific medical tests. While its etiopathogenesis remains unclear and controversial (9), FMS entails a high cost for society (10–15), estimated at €12,993 million annually in Spain in 2017 (15). Its chronic and disabling nature significantly impacts patients' quality of life (QOL) and functionality, leading to high productivity losses (16). Yet, there is no gold standard treatment for this condition. International guidelines suggest a multidisciplinary approach (17–19) based on promising research experiences. Yet, the evidence is still limited (20).

Economic evaluations in health management are gaining importance in decision-making. A recently published systematic review on economic evaluations for non-pharmacological treatment strategies for FMS highlighted the need for similar studies alongside randomised controlled trials (RCTs) (21). Cost-utility analysis (CUA) provides a valuable tool for assessing cost and patients' QOL and comparing them with other health technologies for resource allocation (22). Previous studies on CUA and non-pharmacological treatment approaches for FMS conducted in Spain (23–28) have found favourable results supporting these new strategies from a health-economic standpoint. However, there is scope for further research in this field.

Alongside a pragmatic RCT, this study aims to conduct a health economic evaluation to assess the cost-utility of a novel multicomponent intervention (MCI) programme for patients with FMS compared to the usual clinical care (UCC) in primary care settings in south Catalonia, Spain. The study results are expected to provide helpful evidence for decision-makers in healthcare management.

Methods

Design

A CUA was conducted alongside a pragmatic RCT (29) (ClinicalTrials.gov: NCT04049006) on the effectiveness of a MCI programme for patients with FMS compared to the UCC. This type of economic evaluation is particularly suitable considering the decremental effect of FMS on patients' QOL. Likewise, the study adopted a societal perspective (30), meaning that all registered available costs incurred by the patient, the healthcare funder, and society were considered. In addition, this study covered a one-year time horizon in light of the reported large impact of FMS on productivity losses and QOL.

Moreover, the human capital approach (31), which assumes workers value their earnings, was implemented due to data availability in the digital medical history programme (eCAP), where only full sick leave days prescribed by the general practitioner (GP) are recorded. Finally, this study was designed following the CONSORT guidelines for pragmatic trials (32), the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (33) and the UK Medical Research Council guidance for complex interventions (34).

Setting

The UCC for FMS in the Spanish National Health Service system consists of cost-free medical services, including diagnosis, treatment and pharmacological guidance with co-payment (35) for medicines (36). The Gerència Territorial Terres de L'Ebre (GTTE) of the Institut Català de la Salut (ICS) follows the Catalonian's medical practice guidelines for treating FMS within the Central Sensitivity Syndromes Specialized Units located in primary care centres and hospitals where multidisciplinary health care has been targeted as the gold standard treatment strategy since 2016 (37).

The proposed MCI was developed according to this framework and consists, in addition to the UCC, of a total 24-hour group programme (2-hour week) integrating health education sessions, physical activity and cognitive behavioural therapy (CBT) delivered by a nurse and a GP, a physiotherapist and psychologist respectively. Content details of the programme can be found in the study protocol (29). This intervention aimed to strengthen the routine practice by providing non-pharmacological strategies for symptomatic control to improve patients' QOL and reduce FMS biopsychosocial impact.

Study population

Patients with an active FMS diagnosis (International Classification of Diseases-10 codes: M79.0, M79.7) (38) within the GTTE health region were shortlisted from the eCAP system and recruited telephonically to participate in the study. Furthermore, the included individuals were all adults (over 18 years) with Catalan or Spanish language skills, a phone number, and no record of a psychotic episode, intellectual impairment, severe depression and personality disorder, auto/hyperaggressive behaviour, and psychoactive substances consumption as noteworthy comorbidities. Informed written consent was required for participation in the study, and anonymous data management was ensured for data analysis and publication.

Individual-based random allocation to intervention and control (waiting list) groups was conducted by stratifying primary care centres due to the sociodemographic variety throughout the territory. Randomised lists were created by the Efron procedure (39) in advance and delivered to the researchers before patients' visits for baseline data collection. Both researchers and patients were kept blind during the first encounter and until the next contact call, when patients were informed if they were recruited for the intervention or control group. Intervention groups included 8 to 15 participants. Patients in the control group were offered to receive the MCI after their follow-up period in addition to the UCC.

Data collection and data sources

The MCI programme has been conducted since April 2017 through a multi-stage strategy, including five waves until January 2020, when the sample size for the RCT study was achieved (Supplementary material Table S1). The study follow-up finished in March 2021. This implementation scheme was based on the availability of patients with FMS willing to participate in the study and personnel in the different primary care centres. Due to the COVID-19 outbreak, online data collection surveys and phone calls were implemented in addition to face-to-face interviews. The collected data were registered into a software application for FMS within the ICS health digital system.

Sociodemographic and clinical variables

Sociodemographic and clinical variables were extracted from the eCAP system at baseline.

Health outcomes

Based on the results obtained from the SF-36v2 questionnaire (40) (Optum, Inc., license number QM048943), quality-adjusted life years (QALYs) were calculated using the SF-6Dv2 (41) instrument weighted for the Spanish population (42) (QualityMetric, non-commercial license, order 240835D). Health-related QOL measurements were collected at baseline, immediately post-intervention, and 6 and 12 months after the programme ended. However, only pre- and 12-month post-intervention data were included in this study sample.

Cost outcomes

Cost outcomes and data sources are detailed in Supplementary material Table S2. Medical expenditure (direct costs) and productivity losses (indirect costs) were collected during the 12 months before and after the administration of the MCI programme. Costs were estimated in euros (€), corresponding to current prices in 2021, according to official Spanish service prices (43).

The estimation of medical expenditure included healthcare services in primary care and the regional Hospital de Tortosa Verge de la Cinta, whose costs were obtained by multiplying the number of services delivered per unit cost (Supplementary material Table S2). Only prescribed drugs (all types), partially publicly financed, were included in pharmaceutical expenditure. Costs were calculated by multiplying the prescribed number of administration days with its correspondence cost of treatment per day (CTD) linked to the drug national code and according to the official final consumer prices in September 2021 (44). All prices included tax, considering the societal perspective of the study.

Furthermore, full sick leave days prescribed by the GP were endorsed as productivity losses. Indirect costs were estimated by multiplying the number of days by the total daily average wages before tax for 2021 in Catalonia, obtained from the Spanish National Statistics Institute (NSI) (45). As an indicator of the weighted price for the social costs, it included regular and extra payments, part-time and full-time working schedules, and all activity sectors (industry, construction, and all services except housework). According to the Spanish General Law of Social Security (Law 20/2014; Royal Legislative Decree 8/2015) (46), sick leave days conceptually and operationally refer to "temporary disability" which entails absenteeism from work due to short-term common or work-related illness, based on a GP's criteria. Even though the temporary disability is payable between the National Social Security System, the Social Security Mutual Society Partner and the employers (47),

depending on the number of sick leave days, we have considered the same price weight for all days due to the societal perspective of the study.

Lastly, the MCI cost per participant was estimated based on the actual professionals' services expenditure and the hours dedicated to the programme. As the staff's payment was based on working hours regardless of the number of participants, a mean of 10 patients per group was adopted to estimate the individual cost of the intervention (Supplementary material Table S2).

Statistical analysis

Given the pragmatic nature of the study, the attained sample size and the moderate dropout level (25%), the analysis included complete cases in the follow-up. Hence, only those individuals who answered the pre-post intervention questionaries and whose data for estimating costs was available in the eCAP system were included in the analysed sample. Therefore, non-included cases encompassed those individuals who either dropped out from the MCI or were lost during the study follow-up. This analytical strategy intended to capture real-world data, including individuals who attended the MCI regardless of the number of sessions attended. Accordingly, the study randomisation was preserved, different therapeutic adherences were included, and the sample size was carefully monitored to ensure the study rigour.

Using R Studio software (48), a description of the sample was carried out by including a bivariate analysis of the sociodemographic and clinical variables and independence tests (T-test, Pearson's chi-squared test, and Fisher's exact test) to assess the homogeneity of the sample at baseline. Furthermore, QALYs and costs per major component were statistically described for the pre-and post-intervention study periods, including means, percentile bootstrap confidence intervals, absolute mean differences and p-values. T-test, Wilcoxon signed-rank and rank-sum tests were applied to compare the study groups' paired and independent mean differences.

Thirdly, the incremental cost-utility ratio (ICUR) was calculated based on crude and adjusted Seemingly unrelated regression (SUR) models (49) (systemfit R package), which estimate a set of equations for costs and QALYs jointly, assuming the correlation of the error terms. This statistical method has been implemented in previous CUA studies (26). Furthermore, bootstrap intervals were estimated for the difference in incremental costs and

QALYs between the study groups in order to accommodate for the skewed distribution of these variables.

The ICUR results from the quotient between the differences in the total mean costs and the QALYs between the MIC programme and the UCC adjusted by the pre-intervention values. The result is interpreted according to the cost-effectiveness plane, where four decision scenarios are possible across the quadrants. In two of them, the ICUR presents less room for doubts as the incremental cost-effect of the new intervention is either dominated (quadrant II: north-west) by the standard practice, for proving to be more costly and less effective, or dominant (quadrant IV: south-east) concerning the latest for reducing costs and improving health. In the remaining quadrants, the interpretation relies on the threshold that the founder is willing to pay for a QALY gained since either the new intervention is more costly but more effective (quadrant I: north-east) or cost-saving but less effective compared to its alternative (quadrant III: south-west). In this regard, it is recommended that everything that falls below the threshold should be accepted and rejected otherwise (50).

Finally, one-way and two-way deterministic sensitivity analyses (SA) were conducted to evaluate the robustness of the results (51,52). The SA criteria entailed primary care cost variations (GP and nursing) based on the regional weighted health expenditure from 2021 (Supplementary material Table S3), provided by the Catalonian Primary Care Services Information System (SISAP), and the exclusion from the sample of those participants with a session attendance <66% (with a minimum participation of 8 out of 12 sessions). The latter was intended to assess the implementation scheme of the MCI programme.

Results

A total of 297 individuals were included in the analysis, 161 and 136 in the intervention and control groups, respectively, which meets the estimated sample size for this study (260 individuals, 130 per study arm) [53]. As expected for pragmatic RCTs, missing data entailed 25% of the initial randomised sample (n=396), including those who dropped out of the study before or during the programme course (8.8 %) and those who were lost during the follow-up (17.7%). (See Fig. 1). Overall, these non-included individuals showed a fairly similar sociodemographic and clinical profile compared to the included cases (Supplementary materials Table S4).

Table 1 displays the distribution of the sociodemographic and clinical characteristics of the total sample and according to study groups at baseline, which proved to be comparatively homogeneous. Notably, the sample is composed principally of women with a low education level on the whole. Statistical differences among the study groups showed that more participants in the MCI programme reported not having achieved basic schooling. Regarding work-life, approximately 47% of the sample were out of the labour force, 35% were employed, and 10% were unemployed at the beginning of the programme. Moreover, 63% of the participants were manual workers.

Clinically, the variable "total symptoms" summarises both physical and psychological common symptoms associated to FMS. On average, individuals were experiencing six different types of symptoms at baseline, including attention and memory disturbances, restless sleep, paraesthesia, low back pain and fatigue, among the most frequently reported. Regarding anxiety and depression, the results from the administrated Hospital Anxiety and Depression Scale (HADS) (54,55) show that approximately 48% of the sample had the highest anxiety and depression levels. Additionally, as the mean score from the Revised Fibromyalgia Impact Questionnaire (FIQR) (56,57) was close to 70 (out of 100), it suggests that this condition severely afflicted the participants. Comorbidities were explored in the eCAP following the literature (58), which indicates a list of potential diagnoses that share similar symptomatology with FMS, especially in women (Supplementary material Table S5). The presence of comorbidities was found in over 60% of the total sample, and it showed statistical differences between the study groups as controls had more registered simultaneous medical conditions.

Lastly, the programme achieved a high level of participation with an average session attendance of over 80% and only 12.4% of the sample with less than eight sessions (<66%) listed.

Costs and health outcomes for the pre- and post-intervention periods according to study groups are described in Table 2. Primary care and prescribed drug components contributed the most to direct costs at baseline, accounting for more than 86% in the intervention group and 67% in the controls. Nonetheless, these values remained relatively constant for the MCI participants in the post-intervention period, whereas they increased by 28% for the controls, particularly in primary care services. Moreover, specialised medical care and diagnostic imaging tests had the lowest contributions to direct costs (approximately 10% and 3%,

respectively). They did not show significant differences between the study groups, either pre- or post-intervention. Even though the results were not statistically significant, direct costs showed a growing trend in the intervention group while they decreased in the controls. The post-intervention comparison of direct costs between the study groups indicated potential cost-saving in favour of the programme, non-significant nonetheless.

Not surprisingly, indirect costs represented more than 50% of the total costs. In the pre-post intervention comparison, a decreasing shift was found in the costs of productivity losses in both groups separately. However, no statistical differences arose between the study groups.

Overall, total costs decreased for both study groups post-intervention, yet not significantly. The differences between treatments were not substantial either.

Regarding the gain of QALYs, a significant improvement was detected in the intervention group and compared to the standard practice post-intervention.

Table 3 presents the mean differences in the total costs and the QALYs, pre- and post-intervention, for each study group and the incremental outcome between them with the respective estimated ICURs. The crude model showed an incremental cost between the study groups of €213.69 and an incremental effect of 0.12 QALYs per year, resulting in an ICUR of €1,780.75 per QALY gained. Nonetheless, this estimation decreases when being adjusted by sociodemographic and clinical variables, resulting in an incremental cost of €102.20 but with the same incremental effect and an ICUR of €851.67 per QALY gained. In both cases, ICUR is situated in the first quadrant of the cost-effectiveness plane, which means that the MCI programme raises the cost of treating patients with FMS but with a significant health improvement. Despite the cost-increasing result, the confidence intervals showed no significant differences, and the ICUR falls way below the cost-effectiveness threshold, as Fig. 2 displays. According to the literature, the cost-effectiveness threshold has been estimated between €22,000 and €25,000 for the Spanish National Health System (NHS) [59], even though it could also rise to €30,000.

The one-way deterministic SA included variations in primary care costs, specifically on GP and nurse services, due to its large contributions to total costs. The results in Table 4 support the robustness of the study findings with a crude ICUR of €1,665.27 per QALY gained and an adjusted ICUR of €644.39. These new results reduced the previous estimations and were also below the cost-effectiveness threshold.

As expected, the outcomes of the two-way deterministic SA (Table 4), revealed a dominant scenario for the MCI programme when not accounting for the 12.4% of participants with <66% of session attendance. Excluding those 20 individuals from the intervention group resulted in a new crude ICUR of €-668.21 per QALY gained, which entails cost savings and health enhancement. Furthermore, the adjusted model of the incremental costs and effect differences triggered €2,141.31 of savings per QALY gained, which confirmed and increased the programme's dominance.

Discussion

This study presents a trial-based CUA conducted on a multidisciplinary intervention for patients with FMS in Spain, which proved cost-effective compared to the usual practice. The results showed that the proposed programme improves patients' QALYs significantly compared to the control group, and its incremental costs do not exceed the cost-effectiveness threshold with the potential for cost-savings when administrated at least 66%.

The incremental cost-effectiveness ratio (ICER) is the most popular tool for reporting CUAs. Notably, alternatives are gaining relevance in the economic evaluation scene. Paulden M. (60,61) claims it may be time to replace the ICER for measurements such as the net benefit. The author advocates for its simplicity in calculating and interpreting the cost-effectiveness of each healthcare strategy individually and the probabilistic assessment of the uncertainty of the results in contrast to the pairwise ICER. Nonetheless, these methodological advantages are particularly gainful when comparing more than two alternatives, which is not the case in this study. Additionally, the use of the ICER is still in force in Spain and is supported by international guidelines (62,63).

The singularity of the CUA is the use of the QALYs. This metric allows incorporating patients' self-reported health perception into consideration when evaluating the benefits of a new medical intervention, and it allows comparisons between strategies with different health outcomes. In agreement with the literature, the estimated QALYs showed a decreased lower threshold limit compared to the results we would have obtained if using the utility model for the United Kingdom (UK). As reported by Abellán Perpiñán J.M. (42), the Spanish utility model produces considerably smaller metrics compared to the British one, which explains the modest margin found in this study between 0.18 to 0.35. However, the MCI yielded statistically significant improvements in QALYs compared to the control group, which provides evidence in its favour.

Contrary to expectations, no statistically significant differences in direct and indirect costs were observed between the study groups. These findings are less surprising if we consider that waves 4 and 5 of the programme, representing 44.2% of the sample, had their post-intervention data collected throughout 2020 and the beginning of 2021 during the most challenging times of the COVID-19 pandemic. According to the results of an ad hoc survey administered to these subgroups in June and July 2020 (data not published), we observed that 48% of the respondents (44% in the intervention group and 56% in the controls) reported an adverse effect on the FMS symptoms after the first wave of the pandemic. Therefore, it is highly likely that both costs and health outcomes could have been negatively impacted by this critical event in both study groups. Studies have described severe consequences for patients with FMS associated with the pandemic measurements, including sleep disturbances, poor QOL, pain increase, and psychological distress, particularly in those countries with strict and long periods of lockdowns, such as Italy, France or Spain (64–66). A scoping review conducted in Spain has evidenced the impact on chronic pain patients' physical and mental health and stressed the need for data on medical consultations and the development of preventive protocols (67). We would encourage researchers to examine this phenomenon for the Spanish FMS community in terms of the use of health services and medication consumption, among other relevant factors. In any case, the proposed MCI programme has proved cost-effective beyond the potential repercussions of the COVID-19 pandemic. In addition, future research could explore other potential influential factors in resource utilisation among patients with FMS, including (but not exclusively) chronic use of medication and associated comorbidities.

Our results are consistent with previous studies from the last ten years showing a dominant pattern of non-pharmacological intervention strategies for FMS compared to the usual clinical practice in Spain (23–28). The findings would suggest that patients with FMS and society will benefit from incorporating new holistic approaches such as, but not limited to, health education, CBT, Mindfulness, relaxation techniques, and physical rehabilitation. D'Amico et al. (28) recently conducted a pilot RCT in the Spanish healthcare system to compare attachment-based compassion therapy with relaxation. Their results have shown promise for the future psychotherapy approaches in treating FMS, highlighting the potential gains for the public sector. As far as we can claim, the present study broadens these findings to society as a whole.

Lastly, the presented SA supports the robustness of the study results. It particularly demonstrates the benefits of implementing the MCI programme in a real cost scenario and the relevance and benefits of covering the programme session scheme as planned. As discovered through qualitative research within this project, the programme's success relies not only on implementing intervention techniques but also on the process and group effect it triggers (68). Finding that increasing patient participation leads to better outcomes could be taken as an incentive for supporting complex interventions and preventing them from being shortened in length and professionals involved in contexts of limited resources. Moreover, considering the challenges of therapeutic adherence in pain rehabilitation and its potential influence on cost-effectiveness, efforts should be made to promote higher patient participation and engagement. Furthermore, a follow-up post-MCI could benefit the implementation of the programme learnings to trigger lifestyle changes.

Strengths and limitations

This study is novel in conducting a four-year pragmatic trial-based CUA in the Spanish public healthcare sector on a MCI programme for patients with FMS and achieving the described sample size. Multiple challenges were overcome during this process, including the multicentre strategy throughout the healthcare region, personnel training, patient follow-up monitoring, and the COVID-19 outbreak.

Regarding the study design, economic evaluations conducted alongside RCTs are described in the literature as piggyback evaluations (69), which carry several potential drawbacks. One of them is the sample size estimation, as it generally responds to an outcome variable that does not meet the needs of a health economic study. Nonetheless, in this case, the sample size of the linked RCT was estimated based on the expected differences between the study groups from the SF-36v2 questionnaire. Accordingly, 260 subjects (130 per study arm) were estimated to detect a difference of at least 5 points, assuming an α error of 0.05, a β error of 0.05 (bilateral contrast), and a 20% dropout rate. As this study reached the calculated sample, a complete case analysis strategy was implemented. In addition, as the number of non-included individuals was according to expectations and showed a fairly similar sociodemographic and clinical profile compared to the rest of the sample, nothing indicates that having used a different analytical approach, by imputing missing data from these cases, would have led to significantly different results Even though complete case

analysis faces a potential loss of valuable data, it also preserves real-world information through a simple and robust method.

Concerning the cost outcomes used for this study, none of the direct medical cost components could be specifically identified for the diagnosis and attention of FMS, which could have led to an overestimation of the real costs. Nevertheless, given the societal perspective of the study, this obstacle may have been offset by the lack of data about over-the-counter drugs and out-of-pocket health services consumption, especially for rehabilitation and psychological help. Given the non-inclusion of information on non-health costs (such as administrative costs, training, waiting time, and travelling, among others) or care-given costs, the study findings should not be over-interpreted in terms of societal benefits. However, the primary care cost variations included in the SA were weighted according to the regional health expenditure from 2021, including additional operating expenses. Future research will have to address these estimates in more detail.

Performing a SA by excluding individuals with <66% session attendance pursued implementation assessment purposes. Given the limited resources of the public health system, health programmes may tend to be reduced and simplified to meet other priorities. Even though not all patients would reach this level of participation in the MCI in practice, this methodological decision on the SA only excluded a small portion of the sample (12.4%) and entailed a standard therapeutic adherence expectation.

Likewise, the human capital approach may tend to overestimate productivity losses since work replacement is not considered as in another method like the friction cost approach. Yet, this methodological limitation could have been outweighed by the 47% of the sample who were out of the labour force (pensioners and homemakers) whose loss of contribution to society could not be captured. In addition, productivity losses were only accountable for the registered sick leave days in the eCAP system, and unfortunately, no data was available regarding disability pension (DP). However, patients with FMS are rarely granted DP in Spain unless diagnosed with another more severe disabling disease.

Finally, the study findings are not generalisable beyond the assessed regional population, even though the proposed MCI may serve as an example to adapt the programme to other national or international contexts.

Conclusion

The study findings proved the MCI to be cost-effective compared to the usual clinical practice for patients with FMS. The incremental costs did not exceed the cost-effectiveness threshold compared to the control group, and it was accompanied by a significant improvement in QALYs, particularly when patients received at least 66% of the intervention scheme. Overall, the results support strengthening the standard practice for FMS with the proposed MCI programme in regional primary care settings. These findings provide decision-makers with evidence to improve the treatment strategies for FMS in the public healthcare system and its efficiency.

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Conflict of interest declaration

The authors have no conflicts of interest to declare.

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Contributors:

Victoria Mailen Arfuch, Karolinska Institutet, IDIAP Jordi Gol Institutet, Universitat Autònoma de Barcelona
Conceptualisation, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – Original Draft, Writing – Review & Editing, Visualisation, Funding acquisition.

Carina Aguilar Martín, IDIAP Jordi Gol Institutet, Institut Català de la Salut
Conceptualisation, Methodology, Resources, Writing – Review & Editing, Supervision, Project administration, Funding acquisition.

Anna Berenguera, IDIAP Jordi Gol Institutet, Universitat Autònoma de Barcelona, Universitat de Girona
Conceptualisation, Methodology, Resources, Writing – Review & Editing, Supervision, Project administration, Funding acquisition.

Rosa Caballol Angelats, Institut Català de la Salut
Conceptualisation, Investigation, Resources, Writing – Review & Editing, Supervision, Project administration, Funding acquisition.

Alessandra Queiroga Gonçalves, IDIAP Jordi Gol Institutet, Institut Català de la Salut
Conceptualisation, Writing – Review & Editing, Project administration, Funding acquisition.

Noèlia Carrasco-Querol, IDIAP Jordi Gol Institutet
Investigation, Writing – Review & Editing, Project administration.

Gemma González Serra, Institut Català de la Salut
Investigation, Resources, Writing – Review & Editing, Funding acquisition.

Maria Cinta Sancho Sol, Institut Català de la Salut, Fundació Pere Mata Terres de l'Ebre
Investigation, Resources, Writing – Review & Editing, Funding acquisition.

Immaculada Fusté Anguera, Institut Català de la Salut
Investigation, Resources, Writing – Review & Editing.

Emilie Friberg, Karolinska Institutet
Resources, Writing – Review & Editing, Supervision.

Emma Pettersson, Karolinska Institutet
Software, Formal analysis, Writing – Review & Editing.

Marc Casajuana, IDIAP Jordi Gol Institutet, Universitat Autònoma de Barcelona
Methodology, Validation, Formal analysis, Data curation, Writing – Review & Editing.

Ethical Clearance

The study was conducted in accordance with the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of the IDIAPJGol Institute (codes P17/069 and P18/068 on 25 April 2018). Written informed consent has been obtained from the patients to use their anonym information for research and publication.

Trial details

ClinicalTrials.gov: NCT04049006, Registered 7 August 2019 - Retrospectively registered, https://clinicaltrials.gov/ct2/show/record/NCT04049006

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Tables and Figures

Table I. Distribution of the sociodemographic and clinical characteristics of the sample

		Total	Intervention	Control	
		N=297	n=161	n=136	*p-value*
Sociodemographic characteristics					
Sex	*Female*	288 (97%)	157 (98%)	131 (96%)	0.7367
	Male	9 (3%)	4 (2%)	5 (4%)	
Age	Mean (sd.)	58.18 (10.5)	57.25 (10.15)	59.29 (10.84)	0.0957
	Median (min-max)	58 (25-83)	58 (33-79)	59 (25-83)	
Birth country	*Spain*	290 (98%)	159 (99%)	131 (96%)	0.253
	Other	7 (2%)	2 (1%)	5 (4%)	
Education	*None*	52 (18%)	36 (22%)	16 (12%)	0.0025**
	Primary	137 (46%)	71 (44%)	66 (49%)	
	Secondary	63 (21%)	34 (21%)	29 (21%)	
	Tertiary	20(7%)	4 (2%)	16 (12%)	
	Missing	25 (8%)	16 (10%)	9 (7%)	
Marital status	*Married*	208 (70%)	119 (74%)	89 (65%)	0.1
	Divorced	35 (12%)	16 (10%)	19 (14%)	
	Single	13 (4%)	6 (4%)	7 (5%)	
	Widow/er	17 (6%)	5 (3%)	12 (9%)	
	Missing	24 (8%)	15 (9%)	9 (7%)	
Living alone		25 (8%)	6 (4%)	19 (14%)	0.0026**
Living with partner		209 (70%)	117 (73%)	92 (67%)	0.3733
Living with partner & children		71 (24%)	37 (23%)	34 (25%)	0.685
Living with partner, children & parents		3 (1%)	2 (1%)	1 (1%)	1
Living with others		11 (4%)	4 (3%)	7 (5%)	0.3558
Working condition	Employed	105 (35%)	59 (37%)	46 (34%)	0.2448
	Unemployed	29 (10%)	13 (8%)	16 (12%)	
	Retired	70 (24%)	3 (20%)	38 (28%)	
	Disabled	23 (8%)	16 (10%)	7 (5%)	
	Homemaker	46 (15%)	26 (16%)	20 (15%)	
	Missing	24 (8%)	15 (9%)	9 (7%)	
Occupational class	I: Professionals	23 (8%)	7 (4%)	16 (12%)	0.1509
	II: Intermediate occupations	21 (7%)	12 (7%)	9 (7%)	
	III: Skilled non-manual workers	36 (12%)	21 (13%)	15 (11%)	
	IVa: Skilled manual workers	33 (11%)	21 (13%)	12 (9%)	
	IVb: Other manual workers	153 (52%)	82 (51%)	71 (52%)	
	Missing	31 (10%)	18 (11%)	13 (10%)	
Clinical characteristics					
Years since FMS diagnosis	Mean (sd.)	7.05 (6)	6.83 (6.15)	7.30 (5.83)	0.5026
	Median (min-max)	6 (0-39)	6 (0-39)	6 (0-25)	
Having a family history of FMS		84 (28%)	46 (29%)	38 (28%)	1
Physical trigger factor		58 (19%)	32 (20%)	26 (19%)	0.8844
Psychological trigger factor		83 (28%)	43 (27%)	40 (29%)	0.6068
Physical activity as trigger factor		75 (25%)	37 (23%)	38 (28%)	0.35
Stress as trigger factor		140 (47%)	75 (47%)	65 (48%)	0.9072
Total symptoms	Mean (sd.)	5.95 (2.80)	5.74 (2.84)	6.21 (2.74)	0.1526
	Median (min-max)	6 (0-12)	6 (0-12)	7 (0-12)	
HADS scale	≤14	51 (17%)	22 (14%)	29 (21%)	0.1486
	>14≤22	102 (34%)	54 (33%)	48 (35%)	
	>22≤42	141 (48%)	83 (52%)	58 (43%)	
	Missing	3 (1%)	2 (1%)	1 (1%)	
FIQR total score	Mean (sd.)	66.16 (18.67)	65.08 (19.47)	67.44 (17.67)	0.2796
	Median (min-max)	68.25 (0-97.5)	67.83 (0-96.33)	69.09 (0-97.5)	
Comorbidities	Yes	183 (62%)	90 (56%)	93 (68%)	0.0313*
	No	114 (38%)	71 (44%)	43 (32%)	

Attendance to MCI programme	Mean (sd.)	N/A	9.7 (2.32)	N/A	N/A
	Median (min-max)	N/A	10 (1-12)	N/A	
	Missing	N/A	5	N/A	

FMS: fibromyalgia syndrome; HADS: Hospital Anxiety and Depression Scale; FIQR: Revised Fibromyalgia Impact Questionnaire; MCI: multicomponent intervention; N/A: not applicable

Note: Categorical variables are presented with n (%).

*sig.≤0,05 **sig.≤0,01 ***sig.≤0,001

Table II. Descriptive statistics of costs (per major components) and health outcomes by study groups

		Intervention **Mean** [Bootstrap 95% CI]	Control **Mean** [Bootstrap 95% CI]	Difference Absolute mean diff. [Bootstrap 95% CI]	independent t p-value
Cost outcomes					
Primary care	pre-intv.	**967.18** [856.96 ; 1,083]	**1,075.13** [895.65 ; 1,338.5]	-107.95 [-389.34 ; 111.94]	0.6244
	post-intv.	↑ **1,030.78** [912.27 ; 1,155.78]	↑ **1,181.04** [1045.49 ; 1327.3]	-150.26 [-343.67 ; 37.35]	0.1124
	paired p-value	*0.4683*	*0.02813**		
***Specialised** medical care (Hospital)*	pre-intv.	**220.73** [167.19 ; 279.75]	**264.78** [194.36 ; 340.9]	-44.05 [-137.16 ; 47.42]	0.7217
	post-intv.	↑ **222.07** [163.82 ; 288.2]	↓ **262.28** [187.46 ; 342.07]	-40.21 [-141.78 ; 60.89]	0.674
	paired p-value	*0.6658*	*0.3446*		
Diagnostic imaging tests	pre-intv.	**74.24** [54.77 ; 95.68]	**60.13** [45.77 ; 75.27]	14.11 [-10.47 ; 39.31]	0.4791
	post-intv.	↓ **66.56** [47.53 ; 87.69]	↑ **66.08** [47.47 ; 87.2]	0.49 [-27.79 ; 29.24]	0.7444
	paired p-value	*0.1235*	*0.9511*		
Prescribed drugs	pre-intv.	**882.38** [734.25 ; 1,050.04]	**1,066.96** [866.91 ; 1,291.35]	-184.59 [-458.17 ; 76.37]	0.1297
	post-intv.	↑ **959.34** [760.9 ; 1,192.68]	↓ **917.68** [778.11 ; 1,069.75]	41.66 [-213.72 ; 326.36]	0.2425
	paired p-value	*0.8128*	*0.05914*		
Direct costs	pre-intv.	**2,144.53** [1,897.13 ; 2,404.08]	**2,467.01** [2,131.04 ; 2,851.41]	-322.48 [-787.96 ; 103.11]	0.2794
	post-intv.	↑ **2,278.75** [1,971.05 ; 2,611.04]	↓ **2,427.07** [2,163.17 ; 2,699.01]	-148.33 [-556.52 ; 276.39]	0.1211
	paired p-value	*0.4189*	*0.5754*		
Indirect costs	pre-intv.	**3,290.95** [2,166.04 ; 4,557.69]	**3,176.46** [1,964.77 ; 4,495.37]	114.49 [-1,605.04 ; 1,865.02]	0.9412
	post-intv.	↓ **2,206.50** [1,321.36 ; 3,202.14]	↓ **2,112.47** [1,175.21 ; 3,214.24]	94.02 [-1,288.54 ; 1,469.76]	0.5942
	paired p-value	*0.1041*	*0.03381**		
TOTAL COSTS	pre-intv.	**5,435.48** [4,241.9 ; 6,714.72]	**5,643.47** [4,291.46 ; 7,116.44]	-207.99 [-2,120.25 ; 1,670.63]	0.5593
	post-intv.	↓ **4,545.24** [3,568.23 ; 5,630.57]	↓ **4,539.54** [3,499.36 ; 5,734.02]	5.7 [-1,503.05 ; 1,552.76]	0.6011
	paired p-value	*0.8263*	*0.2599*		
Health outcome					
QALYs	pre-intv.	**0.22** [0.18 ; 0.25]	**0.21** [0.17 ; 0.25]	0.01 [-0.04 ; 0.06]	0.7706
	post-intv.	↑ **0.31** [0.27 ; 0.35]	↓ **0.19** [0.14 ; 0.23]	0.13 [0.07 ; 0.18]	0,0264*
	paired p-value	*0.00000263***	*0.3467*		

diff: differences; intv.: intervention; QALYs: quality-adjusted life years; *paired p value*: intra-group mean comparison; *independent p value*: inter-group mean comparison.

Note: The bootstrap confidence intervals were computed using 10,000 bootstrap replications. All costs are presented in euros (€) according to 2021 prices.

**sig.≤0,05* ***sig.≤0,01* ***sig.≤0,001

Table III. Incremental costs and effects pre-post intervention by study group

	Cost difference pre-post intervention Mean [Bootstrap 95% CI]	**Effect difference pre-post intervention** Mean [Bootstrap 95% CI]
Intervention	-890.24 [-2,098.77 ; 242.55]	0.09 [0.06 ; 0.14]
Control	-1103.93 [-2,203.64 ; -58.29]	-0.02 [-0.06 ; 0.02]
	Δ Incremental total costs Mean [Bootstrap 95% CI]	**Δ Incremental effect** Mean [Bootstrap 95% CI]
Intervention vs. Control (crude model)	213.69 [-1,394.94 ; 1,822.32]	0.12 [0.06 ; 0.18]
ICUR (€/QALY)	1,780.75 **(quadrant I)**	
Intervention vs. Control (adjusted model)	102.20 [-1,460.92 ; 1,630.59]	0.12 [0.06 ; 0,18]
Adjusted ICUR[1] (€/QALY)	851.67 **(quadrant I)**	

ICUR: incremental cost-utility ratio; **QALY:** quality-adjusted life year
[1]ICUR adjusted by the following covariates: age, education level, living alone, years since diagnosis, reported symptoms, having a family history of fibromyalgia, presence of comorbidities, HADS (Hospital Anxiety and Depression Scale) and FIQR (Revised Fibromyalgia Impact Questionnaire) total scores.
Note: The bootstrap confidence intervals were computed using 10,000 bootstrap replications.

Table IV. One-way and two-way deterministic sensitivity analyses

	Cost difference pre-post intervention Mean [Bootstrap 95% CI]		**Effect difference pre-post intervention** Mean [Bootstrap 95% CI]	
	One-way SA	Two-way SA	One-way SA	Two-way SA
Intervention	-880.03 [-2,099.84 ; 267.46]	-1,165.75 [-2,095.64 ; 254.57]	0.10 [0.06 ; 0.14]	0.11 [0.06 ; 0.14]
Control	-1,078.19 [-2,191.61 ; -28.35]	-1,078.19 [-2,398.75 ; 32.49]	-0.02 [-0.06 ; 0.02]	-0.02 [-0.07 ; 0.03]
	Δ Incremental total costs Mean [Bootstrap 95% CI]		**Δ Incremental effect** Mean [Bootstrap 95% CI]	
	One-way SA	Two-way SA	One-way SA	Two-way SA
Intervention vs. Control (crude model)	198.159 [-1,435.98 ; 1,786.77]	-87.55 [-1,445.32 ; 1,954.16]	0.12 [0.06 ; 0.17]	0.13 [0.06 ; 0.18]
ICUR (€/QALY)	**1,665.27 (quadrant I)**	**-668.21 (MCI Dominant)**		
Intervention vs. Control (adjusted model)	77.41 [-1,490.07 ; 1,614.95]	-272.29 [-1,546.14 ; 1,651.31]	0.12 [0.06 ; 0.18]	0.13 [0.05 ; 0.18]
Adjusted ICUR[1] (€/QALY)	**644.39 (quadrant I)**	**-2,141.31 (MCI Dominant)**		

ICUR: incremental cost-utility ratio; **QALY:** quality-adjusted life year
[1]ICUR adjusted by the following covariates: age, education level, living alone, years since diagnostic, reported symptoms, having a family history of fibromyalgia, presence of comorbidities, HADS (Hospital Anxiety and Depression Scale) and FIQR (Revised Fibromyalgia Impact Questionnaire) total scores.
Note: The bootstrap confidence intervals were computed using 10,000 bootstrap replications.

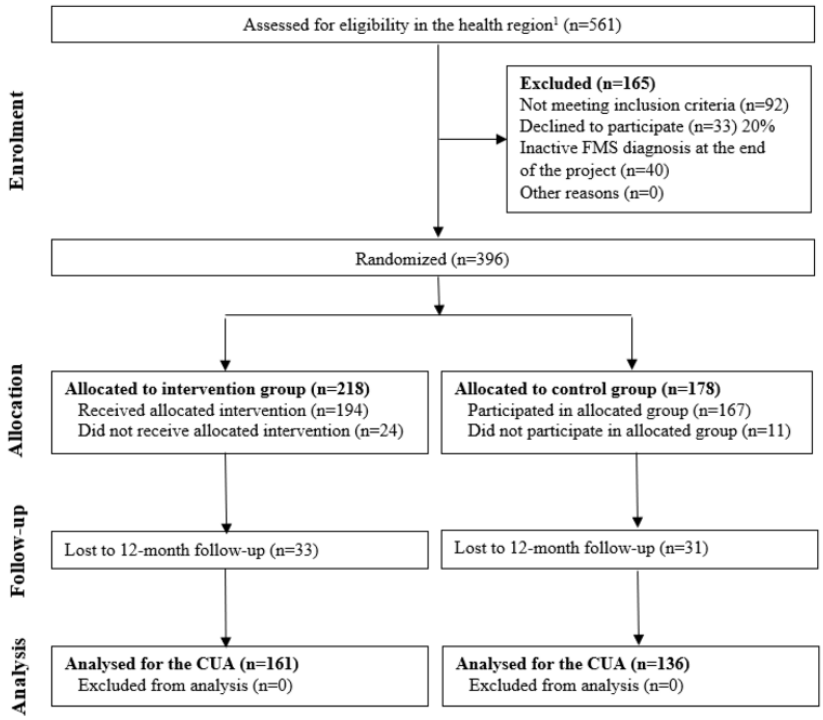

Fig. 1. Sample flow diagram
(CUA: cost-utility analysis)
[1]Patients with an active fibromyalgia syndrome diagnosis in their digital medical record system (eCAP) in Gerencia Territorial Terrres de L'Ebre, Catalonia, Spain.

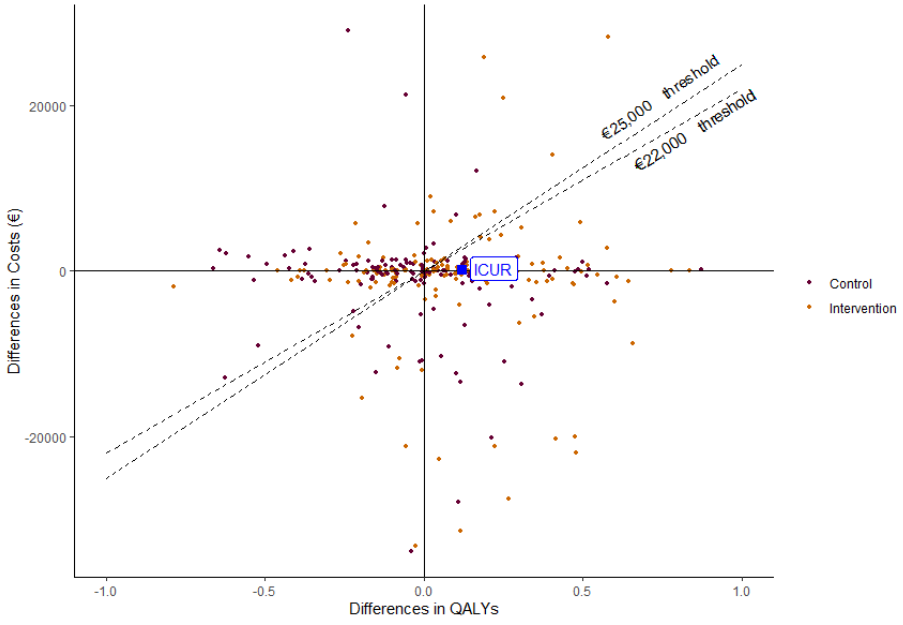

Fig. 2. Cost and effect differences by study group and cost-utility ratio (ICUR)
Note: The incremental cost-utility ratio (ICUR) in fig. 2 corresponds to the adjusted model €851,67/QALY from Table 3.

Supplementary material

Cost-utility analysis of a multicomponent intervention for fibromyalgia syndrome versus usual clinical practice in primary care: a 12-month pragmatic randomised controlled trial in Spain

Table S1. MCI programme implementation scheme

Basic Health Areas in Terres de L'Ebre region		Wave 1 April-June 2017	Wave 2 September 2017-February 2018	Wave 3 April-December 2018	Wave 4 April-June 2019	Wave 5 October 2019-February 2020
PCC1	AMPOSTA and ST BÀRBARA		x	x		
PCC2	DELTEBRE		x			
PCC3	FLIX	x			x	
PCC4	ALDEA and AMPOLLA	x		x	x	
PCC5	AMETLLA	x		x		
PCC6	MORA	x		x		
PCC7	LA RÀPITA and ALCANAR	x	x	x		x
PCC8	TERRA ALTA	x		x	x	
PCC9	TORTOSA east		x	x	x	x
PCC10	TORTOSA west		x	x	x	x
PCC11	ULLDECONA and LA SÉNIA					
	Sample included (n, %)	70 (23.6%)	53 (17.9%)	43 (14.5%)	53 (17.9%)	78 (26.3%)

MCI: multicomponent intervention; PCC: primary care centre

Table S2. Costing matrix for direct healthcare services and indirect costs

	TYPE OF SERVICE	UNIT COST (euros)	SOURCE
Direct Costs	Visits at the healthcare centre		
Primary care	General practitioner, no urgent	50	Departament de salut (2020). Order SLT/71/2020, June 2. Diari Oficial de la Generalitat de Catalunya, number 8153 June 12, 2020
	Nurse, no urgent	35	
	Rehabilitation	30	
	Physiotherapist, low complexity	118	
	Basic blood tests	55	
	Emergency, without stay	105	
Specialised medical care (Hospital)	Traumatology	171/80	
	Psychiatry	171	Departament de salut (2020). Order SLT/63/2020, March 8. Diari Oficial de la Generalitat de Catalunya, number 8134 May 15, 2020.
	Rehabilitation, B level	128.36	Departament de salut (2021). Order SLT/82/2021, April 19. Diari Oficial de la Generalitat de Catalunya, number 8392, April 22, 2021.
	Emergency, no urgent and without stay	130	Departament de salut (2020). Order SLT/71/2020, June 2. Diari Oficial de la Generalitat de Catalunya, number 8153 June 12, 2020
	Other practices, external referrals	171/80	Departament de salut (2020). Order SLT/71/2020, June 2. Diari Oficial de la Generalitat de Catalunya, number 8153 June 12, 2020
	Hospital discharge	905.52	Departament de salut (2020). Order SLT/91/2020, June 17. Diari Oficial de la Generalitat de Catalunya, número 8159 June 22, 2020.
Diagnostic imaging techniques	Identified prices in the sample according to consumption	9.7 to 220*	Departament de salut (2020). Order SLT/71/2020, June 2. Diari Oficial de la Generalitat de Catalunya, number 8153 June 12, 2020 Departament de salut (2012) Order SLT/42/2012, February 24. Diari Oficial de la Generalitat de Catalunya, number 6079 March 2 2012.
Pharmacological treatment	All kinds of prescribed drugs. Cost of treatment per day (CTD)	Various	Spanish Health Ministry. Specific formal consultation.
Indirect Costs			
Productivity loss	Absenteeism from work due to sick leave days. Cost per day based on the average labour salary for the third trimester of 2021.	91.7	Spanish National Statistics Institute (INE)
MCI programme**	Per participant per group programme	60	

CTD: Cost per treatment per day; MCI: multicomponent intervention.

Notes:

* When prices were missing from the 2020 price list, data was collected from 2012. In these cases, prices were updated according to the calculation of variations in the consumer price index, which registered an upward variation of 7.3% until June 2020. (Spanish National Institute of Statistics, INE https://www.ine.es/varipc/)

** The MCI cost per participant was estimated based on the actual professionals' services expenditure and the hours dedicated to the programme, given a mean of 10 patients per group. Costs per professional were GP, 43,90 euros/hour; Nurse, 26,36 euros/hour; Physiotherapist, 22,50 euros/hour; Psychologist, 23,7 euros/hour.

Table S3. Costing matrix for weighted direct primary healthcare services included in the sensitivity analysis

	TYPE OF SERVICE	UNIT COST (euros)	SOURCE
Direct Costs	Visits at the healthcare centre		
Primary care	General practitioner	78.64	Catalonian Primary Care Services Information System (SISAP). Requested in July 2022.
	Nurse	55.08	

Table S4. Distribution of the sociodemographic and clinical characteristics of the non-included individuals

	Intervention					**Control**				
	Included (n = 161)	**Dropouts** (n = 24)	*p-value*	**Follow-up losses** (n = 35)	*p-value*	**Included** (n = 136)	**Dropouts** (n = 11)	*p-value*	**Follow-up losses** (n = 29)	*p-value*
Sociodemographic characteristics										
Sex			1		1			1		0.588
female	157 (98%)	24 (100%)		34 (97%)		131 (96%)	11 (100%)		29 (100%)	
male	4 (2.5%)	0 (0%)		1 (2.9%)		5 (3.7%)	0 (0%)		0 (0%)	
Age	58 (50, 65)	61 (57, 66)	0.077	60 (53, 66)	0.462	59 (52, 68)	51 (44, 62)	0.085	56 (51, 64)	0.473
Birth country			0***		0***			0.117		0***
Spain	159 (99%)	18 (75%)		25 (71%)		131 (96%)	10 (91%)		19 (66%)	
Other	2 (1.2%)	1 (4.2%)		0 (0%)		5 (3.7%)	0 (0%)		1 (3.4%)	
Missing	0 (0%)	5 (21%)		10 (29%)		0 (0%)	1 (9.1%)		9 (31%)	
Education			0.06		0.744			0.559		0.292
None	36 (22%)	8 (33%)		9 (26%)		16 (12%)	1 (9.1%)		7 (24%)	
Primary	71 (44%)	9 (38%)		13 (37%)		66 (49%)	8 (73%)		12 (41%)	
Secondary	34 (21%)	1 (4.2%)		7 (20%)		29 (21%)	1 (9.1%)		6 (21%)	
Tertiary	4 (2.5%)	0 (0%)		2 (5.7%)		16 (12%)	0 (0%)		1 (3.4%)	
Missing	16 (9.9%)	6 (25%)		4 (11%)		9 (6.6%)	1 (9.1%)		3 (10%)	
Marital status			0.665		0.952			0.456		0.663
Married	119 (74%)	17 (71%)		25 (71%)		89 (65%)	9 (82%)		23 (79%)	
Divorced	16 (9.9%)	2 (8.3%)		5 (14%)		19 (14%)	0 (0%)		2 (6.9%)	
Single	6 (3.7%)	0 (0%)		1 (2.9%)		7 (5.1%)	1 (9.1%)		0 (0%)	
Widow/er	5 (3.1%)	1 (4.2%)		1 (2.9%)		12 (8.8%)	0 (0%)		2 (6.9%)	
Missing	15 (9.3%)	4 (17%)		3 (8.6%)		9 (6.6%)	1 (9.1%)		2 (6.9%)	
Living alone	6 (3.7%)	1 (4.2%)	1	2 (5.7%)	0.635	19 (14%)	0 (0%)	0.36	0 (0%)	0.027*
Living with partner	117 (73%)	11 (46%)	0.008**	23 (66%)	0.409	92 (68%)	8 (73%)	1	21 (72%)	0.616
Living with partner & children	37 (23%)	5 (21%)	0.815	6 (17%)	0.449	34 (25%)	3 (27%)	1	4 (14%)	0.193

Living with partner, children & parents	2 (1.2%)	0 (0%)	1	0 (0%)	1	1 (0.7%)	0 (0%)	1	0 (0%)	1
Living with others	4 (2.5%)	2 (8.3%)	0.175	4 (11%)	0.035*	7 (5.1%)	1 (9.1%)	0.472	2 (6.9%)	0.659
Working condition			0.157		0.054			0.029*		0.785
Employed	59 (37%)	5 (21%)		15 (43%)		46 (34%)	3 (27%)		9 (31%)	
Unemployed	13 (8.1%)	1 (4.2%)		3 (8.6%)		16 (12%)	2 (18%)		3 (10%)	
Retired	32 (20%)	3 (13%)		6 (17%)		38 (28%)	0 (0%)		6 (21%)	
Disabled	16 (9.9%)	3 (13%)		7 (20%)		7 (5.1%)	3 (27%)		3 (10%)	
Homemaker	26 (16%)	6 (25%)		0 (0%)		20 (15%)	2 (18%)		6 (21%)	
Missing	15 (9.3%)	6 (25%)		4 (11%)		9 (6.6%)	1 (9.1%)		2 (6.9%)	
Occupational class			0.117		0.797			0.41		0.347
I: Professionals	7 (4.3%)	0 (0%)		2 (5.7%)		16 (12%)	0 (0%)		0 (0%)	
II: Intermediate occupations	12 (7.5%)	0 (0%)		2 (5.7%)		9 (6.6%)	1 (9.1%)		2 (6.9%)	
III: Skilled non-manual workers	21 (13%)	3 (13%)		6 (17%)		15 (11%)	1 (9.1%)		3 (10%)	
IVa: Skilled manual workers	21 (13%)	2 (8.3%)		6 (17%)		12 (8.8%)	0 (0%)		3 (10%)	
IVb: Other manual workers	82 (51%)	11 (46%)		14 (40%)		71 (52%)	6 (55%)		16 (55%)	
Missing	18 (11%)	8 (33%)		5 (14%)		13 (9.6%)	3 (27%)		5 (17%)	
Clinical characteristics										
Years since FMS diagnosis	6.0 (1.0, 11.0)	9.0 (4.5, 12.0)	0.252	7.0 (2.0, 11.0)	0.682	6.0 (2.0, 11.0)	7.0 (2.0, 12.0)	0.965	8.0 (2.0, 11.0)	0.605
Having a family history of FMS	46 (29%)	8 (33%)	0.632	11 (31%)	0.736	38 (28%)	3 (27%)	1	5 (17%)	0.233
Physical trigger factor	32 (20%)	5 (21%)	1	5 (14%)	0.444	26 (19%)	1 (9.1%)	0.69	1 (3.4%)	0.05*
Psychological trigger factor	43 (27%)	7 (29%)	0.8	7 (20%)	0.409	40 (29%)	2 (18%)	0.729	7 (24%)	0.568
Physical activity as trigger factor	37 (23%)	4 (17%)	0.487	5 (14%)	0.256	38 (28%)	2 (18%)	0.728	6 (21%)	0.423
Stress as trigger factor	75 (47%)	7 (29%)	0.109	12 (34%)	0.184	65 (48%)	3 (27%)	0.189	3 (10%)	0***
Total symptoms	6.0 (4.0, 8.0)	4.0 (2.0, 7.3)	0.039*	6.00 (4.0, 8.0)	0.878	7.00 (4.0, 8.0)	4.00 (3.5, 7.0)	0.21	4.00 (2.0, 5.0)	0***
HADS scale			0.762		0.955			0.008**		0.813
(0,14]	22 (14%)	4 (17%)		4 (11%)		29 (21%)	0 (0%)		5 (17%)	
(14,22]	54 (34%)	6 (25%)		13 (37%)		48 (35%)	1 (9.1%)		9 (31%)	
(22,42]	83 (52%)	14 (58%)		18 (51%)		58 (43%)	9 (82%)		15 (52%)	
Missing	2 (1.2%)	0 (0%)		0 (0%)		1 (0.7%)	1 (9.1%)		0 (0%)	
FIQR total score	68 (53, 81)	72 (67, 83)	0.134	70 (46, 80)	0.966	69 (56, 82)	71 (50, 84)	0.828	68 (47, 83)	0.535
Missing	1	0		0		0	0		0	
Presence of comorbidities	90 (56%)	11 (46%)	0.355	24 (69%)	0.168	93 (68%)	9 (82%)	0.504	12 (41%)	0.006**

HADS: Hospital Anxiety and Depression Scale; FIQR: Revised Fibromyalgia Impact Questionnaire. *sig.≤0,05 **sig.≤0,01 ***sig.≤0,001

Note: (i) Numerical continuous variables are presented with a Median (IQR); Categorical variables are presented with n (%)

(ii) P-values were estimated to explore statistical differences between non-included cases and the included ones by using Fisher's exact test, Wilcoxon rank sum test, or Pearson's Chi-squared test

Table S5. List of explored comorbidities at baseline	
Diagnostic	**CI-10 code**
Other mental disorders due to known physiological conditions	F06
Persistent mood [affective] disorders	F34
Other anxiety disorders	F41
Anxiety disorder, unspecified	F41.9
Specific personality disorders	F60
Borderline personality disorder	F60.3
Bipolar disorder	F31
Osteoporosis without current pathological fracture	M81
Other specified disorders of bone density and structure	M85.8
Other anaemias	D64
Type 2 diabetes mellitus	E11
Lupus erythematosus	L93
Vitamin D deficiency, unspecified	E55.9
Other and unspecified osteoarthritis	M19
Rheumatoid arthritis, unspecified	M06.9
Unspecified osteoarthritis, unspecified site	M19.90
Polymyalgia rheumatica	M35.3
Myopia	H52.1
Chronic fatigue, unspecified	R53.82
Other types of fatigue	R53.83
Other cervical displacement	M50.2
Pain and other conditions associated with female genital organs and menstrual cycle	N94
Absent, scanty and rare menstruation	N91
Endometriosis	N80
Noninflammatory disorders of the ovary, fallopian tube and broad ligament	N83
Pelvic and perineal pain	R10.2

CERTIFICADO DE DIRECCIÓN DE TESIS DOCTORAL

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Título de la tesis:

Cost-utility and qualitative aspects on the implementation of a complex intervention for fibromyalgia syndrome: a pragmatic randomised controlled trial in primary care

(Español) Coste-utilidad y aspectos cualitativos sobre la implementación de una intervención compleja para el tratamiento de la fibromialgia: un ensayo pragmático controlado aleatorizado en la atención primaria

Doctoranda: Victoria Mailen Arfuch Prezioso

Directora: Anna Berenguera

BERENGUERA OSSO, ANNA (AUTENTICACIÓN)

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Co-directora: Carina Aguilar Martín

AGUILAR MARTIN CARINA PILAR - 25144642F

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