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Economic evaluation of the FIBROWALK multicomponent intervention in online and outdoor formats for fibromyalgia (The On&Out Study)

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Abstract:	<p>Fibromyalgia (FM) is a chronic condition with substantial healthcare and societal costs. Although multicomponent interventions are widely available, evidence of their economic impact remains scarce. This study evaluated the cost-utility and cost-effectiveness of the FIBROWALK intervention in online (FIBRO-On) and outdoor (FIBRO-Out) formats, compared to treatment as usual (TAU), for individuals with FM. An economic evaluation (n = 225) was conducted over six months from government (total costs) and healthcare (direct costs) perspectives. The follow-up assessment was conducted six months after baseline, which corresponds to three months after the end of the 12-week intervention. Direct and indirect costs were collected through the Client Service Receipt Inventory. Cost-utility was assessed with Quality Adjusted Life Years (QALYs) and cost-effectiveness with the Revised Fibromyalgia Impact Questionnaire (FIQR). FIBRO-On was superior to TAU in reducing specialized healthcare costs (Cohen's d = 0.71), improving perceived health (d = 0.50), and reducing FM severity (d = 0.56). Compared to FIBRO-Out, FIBRO-On also reduced healthcare costs and improved both QALYs and FIQR scores. In contrast, FIBRO-Out led to significantly higher costs than TAU and showed no significant benefit in QALYs or FIQR scores. Across intention-to-treat, complete case, and per-protocol analyses, FIBRO-On was also the more favorable intervention, particularly in comparison to FIBRO-Out. These findings suggest that FIBRO-On may be a cost-effective intervention for managing FM compared to TAU or FIBRO-Out. Furthermore, they underscore the potential benefits of exploring digital interventions such as FIBRO-On to improve accessibility and promote efficient use of healthcare resources to manage FM.</p>

Highlights

- Multicomponent therapies are considered the gold standard for FM but lack economic evaluations.
- FIBROWALK can be administered online (FIBRO-On) and in outdoor (FIBRO-Out) formats.
- FIBRO-On was found to be a cost-effective alternative compared to TAU and FIBRO-Out.
- FIBRO-Out shows promise but requires refinement to optimize economic and clinical outcomes.

Economic evaluation of the FIBROWALK multicomponent intervention in online and outdoor formats for fibromyalgia (The On&Out Study)

Short-running title: Economic evaluation of a multicomponent intervention

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Conflict of interest statement

The authors have no conflict of interest to declare.

Abstract

Fibromyalgia (FM) is a chronic condition with substantial healthcare and societal costs. Although multicomponent interventions are widely available, evidence of their economic impact remains scarce. This study evaluated the cost-utility and cost-effectiveness of the FIBROWALK intervention in online (FIBRO-On) and outdoor (FIBRO-Out) formats, compared to treatment as usual (TAU), for individuals with FM. An economic evaluation ($n = 225$) was conducted over six months from government (total costs) and healthcare (direct costs) perspectives. The follow-up assessment was conducted six months after baseline, which corresponds to three months after the end of the 12-week intervention. Direct and indirect costs were collected through the Client Service Receipt Inventory. Cost-utility was assessed with Quality Adjusted Life Years (QALYs) and cost-effectiveness with the Revised Fibromyalgia Impact Questionnaire (FIQR). FIBRO-On was superior to TAU in reducing specialized healthcare costs (Cohen's $d = 0.71$), improving perceived health ($d = 0.50$), and reducing FM severity ($d = 0.56$). Compared to FIBRO-Out, FIBRO-On also reduced healthcare costs and improved both QALYs and FIQR scores. In contrast, FIBRO-Out led to significantly higher costs than TAU and showed no significant benefit in QALYs or FIQR scores. Across intention-to-treat, complete case, and per-protocol analyses, FIBRO-On was also the more favorable intervention, particularly in comparison to FIBRO-Out. These findings suggest that FIBRO-On may be a cost-effective intervention for managing FM compared to TAU or FIBRO-Out. Furthermore, they underscore the potential benefits of exploring digital interventions such as FIBRO-On to improve accessibility and promote efficient use of healthcare resources to manage FM.

Trial number: NCT05377567

Perspective: Economic evaluations of interventions for fibromyalgia are crucial to guide healthcare decisions and optimize resource allocation. This study shows that the multicomponent FIBROWALK intervention in its online format (FIBRO-On) offers good value for money compared to TAU or the outdoor format (FIBRO-Out), based on cost-utility and cost-effectiveness analyses performed from a government and healthcare perspective.

Keywords: Fibromyalgia; Multicomponent intervention; FIBROWALK; Cost-utility; Cost-effectiveness

1. Introduction

Fibromyalgia (FM) is characterized by chronic musculoskeletal pain, fatigue, and a wide range of additional symptoms, such as cognitive impairment, stiffness, and sleep disturbances.^{1–3} FM affects millions of individuals worldwide and is strongly associated with significant psychological distress due to its complexity,^{4,5} which impacts multiple aspects of an individual's life, including physical, emotional, and social well-being.^{6,7} It is estimated that approximately 2.7% of the global population is affected by FM, with a notably higher prevalence among women aged 40 to 50.^{8,9}

The elevated healthcare and socioeconomic burden of FM poses a major concern for the medical community and society, driven by increased healthcare demands and financial barriers to providing/accessing quality care.^{10–13} To address this issue, non-pharmacological treatments are commonly implemented in real-world clinical practice, aiming to enhance quality of life, reduce psychological symptoms, and mitigate pain interference.^{13,14} Strong evidence supports the effectiveness of such multicomponent therapies that integrate education, psychological support, and physical exercise in managing FM.^{6,15–17} Accordingly, these multicomponent approaches are widely recognized as the gold standard for FM treatment.^{9,18}

Over the past decade, research has also increasingly assessed the cost-utility and cost-effectiveness of non-pharmacological treatment for FM to identify those that provide the best value for money. A recent meta-analysis highlights the importance of non-pharmacological treatments, including physical exercise, cognitive-behavioral therapy (CBT), and educational interventions, in managing FM.¹⁹ Specifically, this meta-analysis estimated that these treatments may reduce healthcare costs by approximately \$2,087 over six months, highlighting that non-pharmacological interventions would be both effective and cost-effective in individuals with FM.¹⁹

The multicomponent FIBROWALK program administered in the Spanish public health system adopts an integrative approach to managing FM symptoms by combining therapeutic physical exercise, pain science education (PSE), CBT, and mindfulness training within a unified, coordinated treatment protocol.^{20,21} Although this structured program of therapeutic strategies was initially designed for implementation in a hospital (indoor) setting specializing in central sensitivity syndromes, it has since been adapted for application in outdoor and online environments.^{20–23} In this regard, the COVID-19 pandemic prompted the adoption of alternatives to face-to-face therapy. Evidence demonstrated the efficacy of online interventions such as FIBROWALK²² and nature-based therapies^{24,25} for chronic pain, including FM.

To date, the cost-utility and cost-effectiveness of the FIBROWALK program remain unexplored, representing a critical gap that must be addressed to facilitate its consolidation and integration into healthcare systems. This study aims to provide an economic evaluation from both government (defined as total costs, including both direct costs and indirect costs, such as productivity losses) and healthcare (defined as direct costs related to primary healthcare services, specialized healthcare services, medical tests, and pain-related medications) perspectives of the FIBROWALK multicomponent intervention delivered through face-to-face outdoor (FIBRO-Out) or online (FIBRO-On) formats added to treatment as usual (TAU), compared to TAU alone.

2. Method

2.1. Design

This research was based on data from the On&Out study. Full details of the randomized control trial (RCT) protocol (registration number: NCT05377567) can be found elsewhere²³. In brief, the study was a six-month, parallel-group RCT in which outcome assessors and the statistician conducting the analyses were blinded to group

allocation. Participants were randomly allocated to one of three arms (1:1:1 ratio) using a computer-generated randomization list: FIBRO-On (online) + TAU (hereafter referred to as FIBRO-On), FIBRO-Out (outdoor) + TAU (hereafter referred to as FIBRO-Out), and TAU alone. Data for economic evaluation were collected at two time points: baseline and follow-up (six months after baseline).

The On&Out project was designed to evaluate multiple aspects of the intervention, including clinical effectiveness, economic impact, and biomarker-based mechanisms. Given the complexity of these objectives, each component has been analyzed separately to ensure a rigorous and in-depth examination. This article focuses on the cost-utility and cost-effectiveness of the interventions, assessing both healthcare and societal costs over a six-month follow-up period. A separate publication has already reported the biomarker-based mechanistic findings of the trial.²⁶

This research was approved by the Ethics Committee of the Vall d'Hebron Barcelona Hospital (PR(AG)120/2018) and conducted following the 1964 Declaration of Helsinki. All participants provided written informed consent, and no financial incentives were offered for their participation. Patients or members of the public were not involved in the design, conduct, or reporting of this study. However, patient and public involvement is planned for the dissemination of the main results to ensure that the findings are communicated in an accessible and meaningful manner.

2.2. Participants

A total of 225 participants diagnosed with FM were recruited from the Unit for Central Sensitivity Syndromes at Vall d'Hebron Barcelona Hospital (Spain) between September 2022 and February 2023. The inclusion criteria were: (1) being aged between 18 and 65 years old; (2) receiving a prior diagnosis of FM by a medical doctor and being classified as having FM according to the American College of Rheumatology

(2010/2011);²⁷ and (3) having proficiency in Spanish. The exclusion criteria included: (1) being diagnosed with severe mental disorder (e.g., schizophrenia); (2) having current or scheduled treatments that could interrupt study follow-up; (3) receiving psychological treatment currently or within the last year; and (4) being unable to attend weekly sessions. As shown in Figure 1, participants were randomly assigned to FIBRO-On ($n = 75$), FIBRO-Out ($n = 75$), and TAU ($n = 75$).

Insert Figure 1

2.3. Procedure

Participants who met the eligibility criteria completed an online assessment with the support of two research assistants. The assessments included a battery of self-reported measures to assess sociodemographic (gender, age, marital status, living arrangement, educational level, and employment status) and clinical information (body mass index [BMI], date of FM diagnosis, comorbidity with other diagnosed medical/psychiatric conditions, disability litigation, degree of disability, and medication). For cost-utility and cost-effectiveness analyses, health-related quality of life, FM severity, and cost-related outcomes (use of healthcare services, medication, and sick leaves) were assessed. Both outcome assessment and data analysis were conducted blind to the condition (i.e., incorporating both blinded outcome assessment and a blinded data analyst), ensuring unbiased evaluation and interpretation.

Baseline assessments were conducted immediately before the start of the intervention, marking the point of initiation for the six-month evaluation period. Follow-up assessments took place six months after baseline, which represents approximately three months post-treatment, given that the intervention lasted 12 weeks. The evaluation thus covered a temporal window extending from six months prior to the start of the intervention to six months after its initiation, capturing both pre-treatment and post-

treatment costs and outcomes. Randomization of participants into study arms was performed by a research technician who was not involved in the research, following the completion of baseline assessments.

2.4. Interventions

2.4.1. *FIBRO-On and FIBRO-Out*

The FIBROWALK program combines PSE, CBT, physical exercise, and mindfulness training, supported by motivational interviewing and the fear-avoidance model.²⁸ The program was delivered in two formats: online (FIBRO-On) and outdoor (FIBRO-Out). Participants in the FIBRO-On format accessed 12 weekly 60-minute video sessions, delivered flexibly via email. Adherence was monitored through brief post-session questionnaires assessing video completion and comprehension. While participants could contact the therapist via email if needed, no therapist-initiated contact occurred. Participants who were unable to watch the video during the scheduled week could voluntarily request an extension of 1 to 2 weeks to complete the tasks. These requests were participant-initiated and did not involve follow-up or monitoring by therapists. Most interactions addressed minor technical issues (e.g., video access), not therapeutic support. Contact frequency was not systematically recorded.

The FIBRO-Out format consisted of 12 outdoor sessions held at the “Parc del Cargol” (location: 41.43028486467208, 2.13941336194866).²⁰ Both formats were facilitated by trained therapists and emphasized participant engagement and adaptability to participant needs.²⁹ The program was implemented in groups of 18–20 participants in the FIBRO-Out arm. In contrast, the FIBRO-On arm was delivered individually and self-administered, with an equivalent number of participants enrolled concurrently as part of the parallel-group design, although no group sessions were held for the online

intervention. A more detailed description of the program's content is available elsewhere.²³

FIBRO-On and FIBRO-Out participants continued receiving their TAU throughout the study. For ease of reading, the terms 'FIBRO-On' and 'FIBRO-Out' are used throughout the manuscript to refer to the intervention arms that received the online or outdoor FIBROWALK formats, respectively, in addition to TAU. Accordingly, all comparisons involving FIBRO-On or FIBRO-Out should be interpreted as reflecting the effects and costs of these interventions when added to TAU.

2.4.2. TAU

In the Spanish public healthcare system, TAU for FM includes medication prescriptions and general recommendations for aerobic activity, tailored to the symptomatology profile of each individual and adapted to the individual's limitations. For ethical reasons, individuals assigned to the TAU arm were offered the option to join either the FIBRO-On or FIBRO-Out program after the trial concluded, based on their preferences.

2.5. Study measures

2.5.1 Sociodemographic and clinical characteristics

A self-report questionnaire was used to obtain information about the participant's sociodemographic (gender, age, marital status, living arrangement, educational level, and employment status) and clinical characteristics (BMI, date of FM diagnosis, comorbidity with other diagnosed medical/psychiatric conditions, disability litigation, degree of disability, and medication). This questionnaire was administered at baseline.

2.5.2. EuroQol 5-Dimension 5-Level Health Questionnaire (EQ-5D-5L)

The *EuroQol 5-Dimension 5-Level Health Questionnaire (EQ-5D-5L)* was used to assess health-related quality of life.^{30,31} It consists of two sections: the first evaluates

five domains (mobility, self-care, regular activities, pain/discomfort, and anxiety/depression) on a scale from 1 (*no problems*) to 5 (*extreme problems*), with higher scores indicating greater individual difficulties. This assessment identifies one of 3,125 possible health states, each of which is linked to distinct utility scores obtained from the EQ-5D model (i.e., EQ-5D utility scores). These scores, ranging from negative (*worse than death*) to 1 (*perfect health*), are then used to calculate Quality Adjusted Life Years (QALYs) and are based on Spanish tariffs for this study. The second section includes a visual analog scale (EQ-VAS), where participants rate their overall health from 0 (*worst imaginable health*) to 100 (*best imaginable health*), with a higher score indicating greater perceived health. The EQ-5D-5L was administered at baseline and six-month follow-up assessments.

2.5.3. Revised Fibromyalgia Impact Questionnaire (FIQR)

The *Revised Fibromyalgia Impact Questionnaire* (FIQR) is a gold-standard measure for assessing overall FM severity, including functional impairment, symptom severity, and perceived global impact over the past week.^{32,33} It consists of 21 items grouped into three dimensions: physical dysfunction (9 items), the perceived global impact (2 items), and symptom severity (10 items). Each item is rated on an 11-point numerical scale from 0 (*no problem*) to 10 (*no difficulty*). The total score of FIQR ranges from 0 to 100, with higher scores indicating greater severity. The Spanish version of the FIQR demonstrates excellent internal consistency (Cronbach's alpha [α] = .91 to .95).³² The FIQR was administered at baseline and the six-month follow-up.

2.5.4. Client Service Receipt Inventory (CSRI)

The *Client Service Receipt Inventory* (CSRI) was used to collect retrospective data on medication and healthcare service use.³⁴ Information on fibromyalgia-related medications (non-opioid analgesics, opioids, anti-inflammatories, anticonvulsants,

muscle relaxants, anxiolytics, sleep medicines, and antidepressants) was gathered, documenting the medication name, dosage, total prescription days, and daily dose consumed. Additionally, data were collected on total visits to accident and emergency departments, days of hospital admission, diagnostic tests performed, and visits to healthcare professionals (general practitioners, nurses, social workers, psychologists, psychiatrists, group therapists, and others), specifying whether the public or private sector provided services. The CSRI was administered at baseline and the six-month follow-up, referring to the previous six months.

2.6. Statistical analyses

The analyses were computed with STATA (v17) and SPSS (v29). The economic evaluation followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines³⁵ and complied with the Good Research Practices for Cost-Effectiveness Analysis Alongside Clinical Trials.³⁶

2.6.1. Costing procedure

Costs were estimated from both the healthcare (direct costs) and the government perspective (total costs), using the previous six months as the time frame for each economic evaluation (baseline and follow-up) in this RCT.

Direct costs were calculated by adding the costs of primary healthcare services, specialized healthcare services, medical tests, and pain-related medications. Unit cost data for healthcare services and medical tests were sourced from the ECONOS healthcare cost database (<https://econos.org/>). The total intervention costs for FIBRO-Out accounted for the price per participant and group session, based on the healthcare professional's fees, with attendance recorded by the therapists. The cost of treatment sessions and resources was consistent across all sessions and groups. As in similar studies,^{37–39} intervention costs were adjusted based on the number of sessions attended. The costs

associated with delivering the FIBRO-On intervention, such as hosting expenses, were negligible, as the videos were hosted on a free-of-charge YouTube channel. Development costs for the intervention and research-specific expenses were excluded from the analysis, as these are non-recurring costs that would not be incurred again if the intervention were implemented in other settings. Therapist support associated with the FIBRO-On intervention was not included in the costing analysis, as it was estimated to involve minimal time (e.g., less than 30 minutes per week in total across more than 100 users), was unscheduled, primarily technical in nature, and not systematically recorded or attributable to study participants. Likewise, TAU was present equally across all three study arms and, therefore, its implementation cost was considered equivalent and set to zero in all groups. Medication costs were calculated using the Vademecum International 2023, by multiplying the price per milligram by the total daily dose and the number of treatment days, with value-added tax included.

Indirect costs, representing lost productivity due to absenteeism, were calculated using the human capital approach. The minimum daily wage in Spain for 2023 was multiplied by the number of sick leave days reported by each participant in the CSRI. Total costs were then determined by summing direct and indirect costs. As shown in Table 1, unit costs are reported in euros (€) based on 2023 prices.

Insert Table 1

2.6.2. Descriptive and between-group analyses

Descriptive analyses were conducted for continuous variables (means and standard deviations) and categorical variables (frequencies and percentages). No significant baseline differences were detected across treatment arms in sociodemographic or clinical variables; therefore, covariates were not included in the analyses. A linear mixed model (LMM) with restricted maximum likelihood regression was used to assess

intervention effects on costs and outcomes, accounting for within-individual correlations. The LMM included a random intercept, adjusted for baseline scores, time, and the “group $\times$ time” interaction. Regression coefficients (β) and 95% confidence intervals (*CI*) were calculated for group comparisons (FIBRO-On vs TAU, FIBRO-Out vs TAU, and FIBRO-On vs FIBRO-Out) at the six-month follow-up. Effect sizes (Cohen's *d*) were categorized as very small (0.10), small (0.20), medium (0.50), large (0.80), very large (1.20), and huge (2.00).⁴⁰ Statistical significance was set at $p < 0.05$.

2.6.3. Cost-utility and cost-effectiveness analyses

Cost-utility and cost-effectiveness analyses assess the relationship between resources used (costs) and health outcomes (effects or benefits).³⁷ Specifically, cost-utility focuses on costs relative to effects, typically measured in QALYs, while cost-effectiveness examines costs relative to clinical benefits, measured by a primary clinical outcome (in this study, FIQR). These complementary approaches are widely used in public health decision-making.^{37,41} In the cost-utility analyses, the utility was assessed based on the mean change in mean QALY scores, with higher scores indicating a more beneficial intervention. In the cost-effectiveness, effectiveness was assessed based on mean changes in FIQR scores, with lower scores reflecting a more beneficial intervention. The incremental cost-utility ratio (ICUR) and incremental cost-effectiveness ratio (ICER) were calculated as the ratios between incremental costs and incremental effects, measured by QALYs and FIQR, respectively.⁴²

To improve clinical interpretability of the cost-effectiveness results, an additional sensitivity analysis was conducted using a responder-based definition of effectiveness. In this analysis, the minimal clinically important difference (MCID) was defined as a 20% improvement from the baseline FIQR score, a threshold selected to reflect a meaningful change in this specific patient-reported outcome. A binary outcome variable was created,

coded as 1 if the participant achieved at least a 20% reduction from their baseline score, and 0 otherwise. The proportion of responders in each group was then used as a measure of effectiveness to calculate new ICERs, reflecting the cost per additional responder. In the present work, this responder-based analysis is presented as a complementary sensitivity analysis.

In health economic evaluation, dominance describes a scenario in which an intervention is both more effective and less costly than the alternative. In this study, four potential scenarios were considered: (1) the tested intervention is more effective/useful and less expensive; (2) the tested intervention is more effective/useful but more expensive; (3) the tested intervention is less effective/useful and less expensive; and (4) the tested intervention is less effective/useful and more expensive.

The first scenario indicates dominance, where the tested intervention is both more effective and less costly than the alternative, making it the preferred option irrespective of cost-effectiveness thresholds. Conversely, the fourth scenario represents a dominated situation, where the intervention is less effective and more costly, and thus unequivocally not cost-effective. The second and third scenarios require further interpretation based on the ICUR or ICER concerning established cost-effectiveness thresholds. Specifically, the second scenario (more effective but more expensive) can be considered cost-effective if the ICUR remains below the acceptable threshold. Similarly, the third scenario (less effective but less expensive) may be acceptable if the savings justify the reduction in effectiveness. In Spain, the commonly accepted cost-utility threshold is €25,000 per QALY gained, which serves as a benchmark for determining whether the additional cost of an intervention is justified by its health benefits.^{37,44}

Incremental costs and effects were analyzed using Zellner's seemingly unrelated regression models.⁴⁵ This model includes both costs and outcomes (QALYs or FIQR) as

dependent variables in separate equations, based on study arms (FIBRO-On, FIBRO-Out, or TAU). Both the cost and outcome equations in the SUR model were adjusted for baseline values (i.e., baseline costs and baseline QALYs or FIQR), ensuring that estimated group differences reflect change over time rather than unadjusted post-treatment values. Incremental cost and incremental effect estimates were derived using 1,000 bootstrap replicates to address potential skewness.

Cost-utility and cost-effectiveness were evaluated using one main analysis (intention-to-treat, ITT) and two sensitivity analyses (complete case analysis, CCA; and per-protocol analysis, PPA). In the ITT, missing data at the follow-up were imputed using multiple imputations with chained equations,⁴⁶ assuming data were missing at random. Finally, CCA included only participants with complete data at baseline and follow-up, while PPA included those who completed at least 9 out of 12 sessions.

3. Results

3.1. Sample characteristics

The participants were predominantly middle-aged married women who had completed at least primary or secondary studies. They mostly lived with their partner and were in paid employment. The most common comorbidities were anxiety, depression, chronic fatigue syndrome, and osteoarthritis. On average, they had received an FM diagnosis for over 10 years, and most were taking antidepressants, anti-inflammatories, and non-opioid analgesics. Table 2 provides an overview of the baseline demographics and clinical characteristics for each study arm.

Insert Table 2

3.2. Participants' flow and study compliance

From the 298 potential screened participants, 225 met the inclusion criteria and were randomized into three study arms, with 75 participants per arm (see Figure 1). For

the six-month follow-up, the attrition rates were 16% ($n = 12$), 20% ($n = 15$), and 1.3% ($n = 1$) for FIBRO-On, FIBRO-Out, and TAU arms, respectively. The average attendance was significantly higher for FIBRO-On sessions compared to FIBRO-Out ($M = 10.6$ vs. 8.8 , $p = 0.001$).

3.3. Costs and outcomes

Table 3 presents descriptive statistics and between-group differences in costs and outcomes (FIBRO-On, FIBRO-Out, and TAU) based on the ITT approach. Adjusted for baseline and time comparisons at follow-up indicated significant differences, as reflected in the reported effect sizes (d), t-statistics (p), and unstandardized coefficients (B , 95% CI).

As TAU costs were common across all groups and excluded from the analysis, only the additional intervention costs were considered. The FIBRO-On arm incurred no additional per-participant cost, as therapist involvement was minimal and not systematically recorded. The FIBRO-Out arm incurred an average intervention cost of 109.46 euros ($SD = 37.99$) per participant. Complementary data on unadjusted pre–follow-up differences in disaggregated costs and outcomes (completer sample) are provided in Supplementary Table 1.

Insert Table 3

3.3.1. Costs

All reported between-group differences in costs and outcomes reflect adjusted change over time, as derived from models that account for baseline values. FIBRO-On yielded a significantly greater reduction in specialized healthcare services costs compared to TAU ($\beta = 411.69$, $p = 0.003$) and FIBRO-Out ($\beta = -377.64$, $p = 0.006$) at six-month follow-up. Specifically, FIBRO-On demonstrated an average reduction of €73 in total costs for specialized healthcare services. As shown in Table 3, no significant differences

were observed between the three study arms regarding the costs of primary care services, medical tests, pain-related medications, direct costs, indirect costs, and total costs.

3.3.2. Outcomes

FIBRO-On obtained significant improvements in EQ-VAS ($\beta = -0.69$, $p = 0.031$) and FIQR ($\beta = -6.02$, $p = 0.013$) scores compared to TAU at the six-month follow-up, although no significant changes were observed in EQ-5D utility scores. As observed in Table 3, no significant differences were found in any outcome when comparing FIBRO-Out with TAU or FIBRO-On with FIBRO-Out.

3.4. Cost-utility and cost-effectiveness analyses

The comparison between the three study arms is displayed in Table 4, from a government perspective (total costs), and in Table 5, from a public healthcare perspective (direct costs). Both tables include results based on ITT, as well as CCA and PPA sensitivity analyses.

Insert Tables 4 and 5

Additionally, Figure 2 shows the degree of uncertainty around the differences in costs and QALY scores (cost-utility), while Figure 3 presents the differences in costs and FIQR scores (cost-effectiveness), both from the government cost and public healthcare perspectives according to the main analysis (ITT). Supplementary Figures 1 to 4 provide these differences in cost and QALY/FIQR scores based on the sensitivity analyses (CCA and PPA).

Insert Figures 2 and 3

3.4.1. FIBRO-On vs TAU

In the main analysis (ITT), a slight increase in FIBRO-On total costs was observed (around $\Delta = \text{€}123$) and a reduction of direct costs (around $\Delta = \text{€}-37$), although neither difference was significant. While a slight incremental effect was observed in FIBRO-On

compared to TAU regarding QALY scores ($\Delta = 0.02$), it was non-significant from either perspective. However, from both the government and healthcare perspectives, FIBRO-On showed larger decreases in FIQR scores compared to TAU ($\Delta = -6.24$).

Regarding the cost-utility analysis based on QALYs, FIBRO-On was not dominant from the government perspective, as it was more effective but also associated with higher costs compared to TAU. However, since the ICUR was €6,919/QALY, which is significantly below the Spanish threshold of €25,000/QALY, the intervention can be considered cost-effective. Conversely, from the healthcare perspective, FIBRO-On was dominant, as it was both less costly and slightly more effective in improving health-related quality of life compared to TAU.

In terms of cost-effectiveness based on FIQR scores, FIBRO-On was not dominant from a government perspective, as it was associated with higher costs per point of improvement compared to TAU, resulting in an ICER of 19 (cost per point improvement in FIQR). When examining the MCID-adjusted ICER, the resulting value was 855, suggesting a potentially acceptable level of investment for a public payer, despite the absence of an established threshold for this outcome. However, from a direct healthcare perspective, FIBRO-On was considered dominant, as it was both less costly and more effective in reducing FIQR scores compared to TAU.

The sensitivity analyses (CCA and PPA) were in line with those observed in the main ITT analysis from both perspectives. Furthermore, the PPA analysis demonstrated a further significant incremental effect on QALY scores ($\Delta = 0.02$), underscoring FIBRO-On's beneficial impact, particularly in individuals who completed at least 9 out of 12 sessions.

3.4.2. FIBRO-Out vs TAU

In the main analysis (ITT), FIBRO-Out did not show a significant increase in total costs (approximately €336), although a significant rise in direct costs was observed (€553). Regarding effects, no incremental improvement in QALY scores was detected compared to TAU; in fact, a slight decrease favoring TAU was noted ($\Delta = -0.01$) from both perspectives. However, a significant improvement in FIQR scores was identified for FIBRO-Out compared to TAU ($\Delta = -4.35$), consistent across both the government and healthcare perspectives.

Regarding cost-utility based on QALYs, FIBRO-Out was dominated by TAU from both perspectives, as TAU was less costly and slightly more effective in enhancing health-related quality of life.

For cost-effectiveness based on FIQR scores, FIBRO-Out was not dominant from either the government (ICER = 77) or healthcare perspectives (ICER = 127), as it was more effective, but also incurred higher costs compared to TAU. The corresponding MCID-adjusted ICERs of 2,978 and 4,876 indicate a relatively low cost per clinically meaningful change in FIQR, which may be considered acceptable from a public payer perspective.

Similar patterns were observed in the sensitivity analyses (CCA and PPA) from both perspectives. However, unlike the main analysis (ITT), no significant differences in FIQR score reduction were detected in the PPA and CCA analyses from either perspective.

3.4.3. FIBRO-Out vs FIBRO-On

In the main analysis (ITT), no significant difference in total costs was observed between FIBRO-Out and FIBRO-On (€212 vs. €213). However, from a direct cost perspective, FIBRO-Out was significantly more costly (€591). Regarding effects,

FIBRO-On demonstrated a slight advantage over FIBRO-Out in both QALY scores ($\Delta = -0.02$) and FIQR scores ($\Delta = 1.89$), but these differences were not statistically significant from either perspective.

Regarding cost-utility based on QALYs, FIBRO-On was dominant from both the government perspective (ICUR = -11,368) and the healthcare perspective (ICUR < -25,000), as it was less costly and more effective than FIBRO-Out. Although neither treatment corresponds to standard care, this result suggests that FIBRO-On represents a more cost-efficient innovative option compared to FIBRO-Out.

For cost-effectiveness based on FIQR, FIBRO-On was consistently more dominant than FIBRO-Out from both government and healthcare perspectives, as it was both more effective and less costly.

Similar patterns were observed in the sensitivity analyses (CCA and PPA) from both perspectives. However, unlike the main analysis (ITT), significant improvements in QALY scores ($\Delta = -0.02$) were observed in the PPA analysis from the government perspective, as well as in both the PPA and CCA analyses ($\Delta = -0.02$) from the healthcare perspective.

4. Discussion

This study is the first to evaluate the cost-utility and cost-effectiveness of multicomponent interventions delivered in face-to-face outdoor (FIBRO-Out) and online (FIBRO-On) formats compared to TAU in managing FM. The findings demonstrated significant clinical improvements and economic advantages for FIBRO-On from both the government and public healthcare perspectives, supporting its integration into standard care protocols.^{47,48}

From the government perspective, FIBRO-On achieved an ICUR below the commonly accepted cost-effectiveness threshold in Spain, indicating that it is a cost-

effective intervention compared to TAU. From the healthcare perspective, FIBRO-On was found to be dominant, as it was both more effective and less costly than TAU. These findings underscore FIBRO-On's potential to deliver superior health outcomes, consistently providing greater improvements in QALYs and FIQR scores than TAU, while optimizing resource allocation within the healthcare system. They also align with prior research demonstrating the cost-effectiveness of digital health interventions for FM⁴⁹ and other musculoskeletal disorders⁵⁰ and are consistent with evidence supporting the comparable effectiveness of online and in-person therapies.⁵¹

Furthermore, the findings from this study provide additional evidence supporting the cost-effectiveness of multicomponent interventions for FM. Similarly, a recent study conducted in a primary care setting in Spain demonstrated the cost-effectiveness of a comparable 12-week multidisciplinary intervention, delivered in person and including a nurse, with a one-year follow-up period.⁵² The present study extends this growing body of evidence by providing cost-effectiveness data for a fully online intervention, FIBRO-On. This highlights the unique strengths of FIBRO-On, which offers enhanced accessibility, scalability, and feasibility compared to traditional in-person formats.

In contrast, FIBRO-Out, while incorporating nature-based interventions with potential therapeutic benefits,^{21,53} and a face-to-face format known to enhance social interaction and peer support,²⁰ did not demonstrate cost-effectiveness or cost-utility compared to either TAU or FIBRO-On. In this regard, the higher costs associated with delivering outdoor sessions, combined with limited QALY improvements, likely contributed to the lack of cost-effectiveness observed.^{20,41} While a significant reduction in FIQR was observed in the ITT analysis, this was not replicated in the PPA or CCA analyses.

Unlike the only previously published study evaluating the short-term effectiveness of FIBRO-Out,²⁴ in which the program's creator was the sole therapist delivering the intervention, the present study involved multiple therapists to enhance external validity and assess feasibility in real-world settings.⁵⁴ While this approach improved generalizability, it may have also reduced clinical effectiveness and health-related quality of life improvements, as interventions delivered by their developers often achieve better outcomes. Logistical challenges, including weather dependency, transportation burdens, and the physical effort required to attend sessions,^{20,41} may also have limited the overall effectiveness of the intervention. Furthermore, year-round scheduling of FIBRO-Out sessions may have further impacted clinical outcomes, with participants exposed to extreme temperatures affecting session quality and adherence, particularly given FM individuals' sensitivity to temperature changes.⁵⁵ This factor may also explain differences compared to the study by Arfuch et al.,⁵² which evaluated an indoor multi-component program. Future research should include qualitative methods to explore individual experiences, identify barriers/facilitators, and optimize outcomes.

4.1. Implications, opportunities, and recommendations

The online version of the multicomponent FIBROWALK intervention offers significant opportunities for advancing FM care. In this regard, the high scalability of FIBRO-On minimizes infrastructure requirements, making it accessible in underserved or resource-limited settings, which could be particularly valuable for low- and middle-income countries, addressing disparities and promoting equitable FM care. By eliminating logistical barriers such as travel and geographic limitations, FIBRO-On is also especially suitable for individuals with mobility challenges or those residing in rural areas.^{20,41} Furthermore, its asynchronous design allows participants to engage at their own pace, improving adherence and enabling flexible integration into their daily lives.⁴⁷

While these findings showed favorable trends in cost-effectiveness, particularly for FIBRO-On, the magnitude of cost reductions was more modest than the ~\$2,000 reported in a previous meta-analysis of non-pharmacological interventions.¹⁹ This discrepancy may be due to methodological differences—such as the baseline-adjusted analyses versus post-treatment comparisons—as well as to the higher clinical complexity of the present sample and the relatively short follow-up period. Furthermore, despite the promise of the online version of the program, its implementation presents several challenges. FIBRO-On's dependence on digital tools could also exclude individuals with limited access to technology or insufficient digital literacy, posing a barrier to equitable delivery.⁵⁶ Addressing digital literacy through targeted training programs and simplified user interfaces could reduce these barriers, ensuring that vulnerable populations are not excluded. Incorporating peer-support networks or community-based digital education could further enhance accessibility and engagement. Strategies such as providing technical support and improving access to digital resources are essential to overcome these limitations and expand the intervention's reach.

Given the current findings on cost-utility and cost-effectiveness, the implementation of FIBRO-Out does not appear justified. Rather, its integration into blended or hybrid delivery models may offer a more viable and scalable solution that might be tested in subsequent trials. By integrating the accessibility and flexibility of FIBRO-On with the social and experiential benefits of FIBRO-Out, such models could mitigate practical barriers while enhancing engagement and reducing intervention costs. Additionally, personalized approaches may further enhance these interventions, as individual characteristics—such as mental health comorbidities, physical activity levels, and perceived social support—are likely to influence both clinical outcomes²⁰ and so cost-effectiveness. Identifying these predictors could enable clinicians to tailor

interventions to individual needs, maximizing clinical effectiveness, cost-effectiveness, and participant satisfaction while improving accessibility and scalability.

4.2. Limitations and strengths

The findings should be interpreted considering some limitations. The six-month follow-up (i.e., three months post-treatment) restricts insights into the long-term sustainability of FIBRO-On and FIBRO-Out outcomes. Extending the follow-up to at least 12 months from post-treatment would provide more robust evidence of enduring benefits and allow for better detection of potential economic savings, particularly in terms of productivity losses. Future studies should consider a 12-month post-treatment follow-up to better assess long-term sustainability, which extends beyond the current 6-month post-baseline period. The study's regional focus in Barcelona, Catalonia, may limit its generalizability to healthcare systems with different resources or economic structures. Future studies should also account for cultural and sociodemographic differences that may influence the feasibility and acceptance of FIBRO-On and FIBRO-Out. Adapting these interventions to diverse healthcare settings, including those in low-resource environments or with different cultural attitudes toward digital health, could expand their applicability and relevance globally.

Productivity loss due to presenteeism was recorded during the RCT but was excluded from this analysis, given the inherent difficulties in accurately capturing reduced workplace productivity through self-reported measures. Although self-reported data have been shown in some studies to be as valid as information collected from public registries in health and economic evaluations, verifying these results against public registries would enhance their reliability.^{49,57} However, such verification was not feasible due to restricted access to this information. Additionally, direct non-health costs—such as out-of-pocket expenses, costs for paid and unpaid assistance, travel expenses, and the use of non-

prescription medications or alternative treatments—were not included in this study. The potential cost associated with therapist involvement in the digital intervention was not included in the analysis, as it was estimated to be minimal, sporadic, and not systematically documented. Support was primarily technical and not therapeutic in nature. Even though the expected impact on total costs is negligible, future trials should ensure that even minimal auxiliary resource use is systematically recorded to enhance the precision and reproducibility of economic evaluations. The use of self-reported data for healthcare utilization and productivity losses, while common in economic evaluations, could introduce recall bias, potentially affecting the validity of the results.

Lastly, although in the setting the intervention incurred negligible incremental operational costs—since hosting was free of charge, staff time was absorbed within usual care, and the online program was self-administered—it is important to acknowledge that future implementations in different healthcare systems may require investment in staff training, user support, and communication infrastructure. These considerations could affect cost-effectiveness estimates. However, once initial investments are made, marginal costs per additional participant are expected to be very low, as the same infrastructure can support delivery to large numbers of patients.

Despite these limitations, the study offers significant strengths. It is one of the few to comprehensively compare two multicomponent FM interventions against TAU, providing valuable evidence for their integration into clinical practice. The inclusion of both online and outdoor formats expands the applicability of the findings, offering adaptable solutions for diverse participant needs and logistical challenges. The use of ITT, CCA, and PPA analyses strengthens the reliability of the results, while the integration of economic and clinical outcomes, such as QALYs and FIQR, provides a multidimensional perspective on the interventions' impacts. Furthermore, treatment arms showed low

attrition (between 1.3% and 20%), minimizing attrition bias and ensuring more reliable cost and outcome estimates for the cost-effectiveness analysis.

5. Conclusions

This study demonstrates that FIBRO-On is a cost-effective and cost-utility-supported alternative to TAU and FIBRO-Out for managing FM. The fully online format of the multicomponent FIBROWALK intervention enhances accessibility to evidence-based care, addressing common mobility and logistical barriers while remaining within acceptable cost-effectiveness thresholds. In contrast, the lack of cost-effectiveness and cost-utility observed for FIBRO-Out suggests that its implementation as an add-on intervention should not be prioritized. Instead, future efforts might focus on developing hybrid formats that incorporate FIBRO-Out elements in a flexible and tailored manner, while building on existing standardized training protocols and enhancing implementation strategies as the program continues to scale. Future studies should evaluate these interventions over longer follow-up periods, incorporate qualitative assessments, and identify individual-specific factors that predict better outcomes to further enhance their effectiveness and reach.

Disclosures

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Author contributions

Conceptualization, M.S. and A.F.-S.; Methodology, W.A., M.S., J.P.S.-M, J.V.L., and A.F.-S.; Resources, M.S. and A.F.-S; Writing — original draft preparation, W.A., M.S., J.P.S.-M, and A.F.-S.; Writing — review and editing, W.A., M.S., J.P.S.-M, E.R.-C., A.P.-A., S.F., B.R., F.D.A., M.A., E.C., X.B., J.V.L., and A.F.-S.; Visualization, W.A., M.S., J.P.S.-M., and A.F.-S.; Supervision, M.S., J.V.L., and A.F.-S.; Project administration, M.S. and A.F.-S.; Funding administration, A.F.-S. All authors have read and agreed to the published version of the manuscript.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Figure 1. Flowchart of the On & Out cost-utility and cost-effectiveness substudy.

Figure 2. Cost-utility plane of 1000 bootstrap replicated incremental cost-utility from the government perspective (total costs; upper figure) and healthcare perspective (direct costs; lower figure) in the ITT sample: Fibro-Out vs. TAU (green color); Fibro-On vs. TAU (blue color); and Fibro-Out vs. Fibro-On (red color).

Figure 3. Cost-effectiveness plane of 1000 bootstrap replicated incremental cost-effectiveness from the government perspective (total costs; upper figure) and healthcare perspective (direct costs; lower figure) in the ITT sample: Fibro-Out vs. TAU (green color); Fibro-On vs. TAU (blue color); and Fibro-Out vs. Fibro-On (red color).

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Figure 1. Flowchart of the On & Out cost-utility and cost-effectiveness substudy.

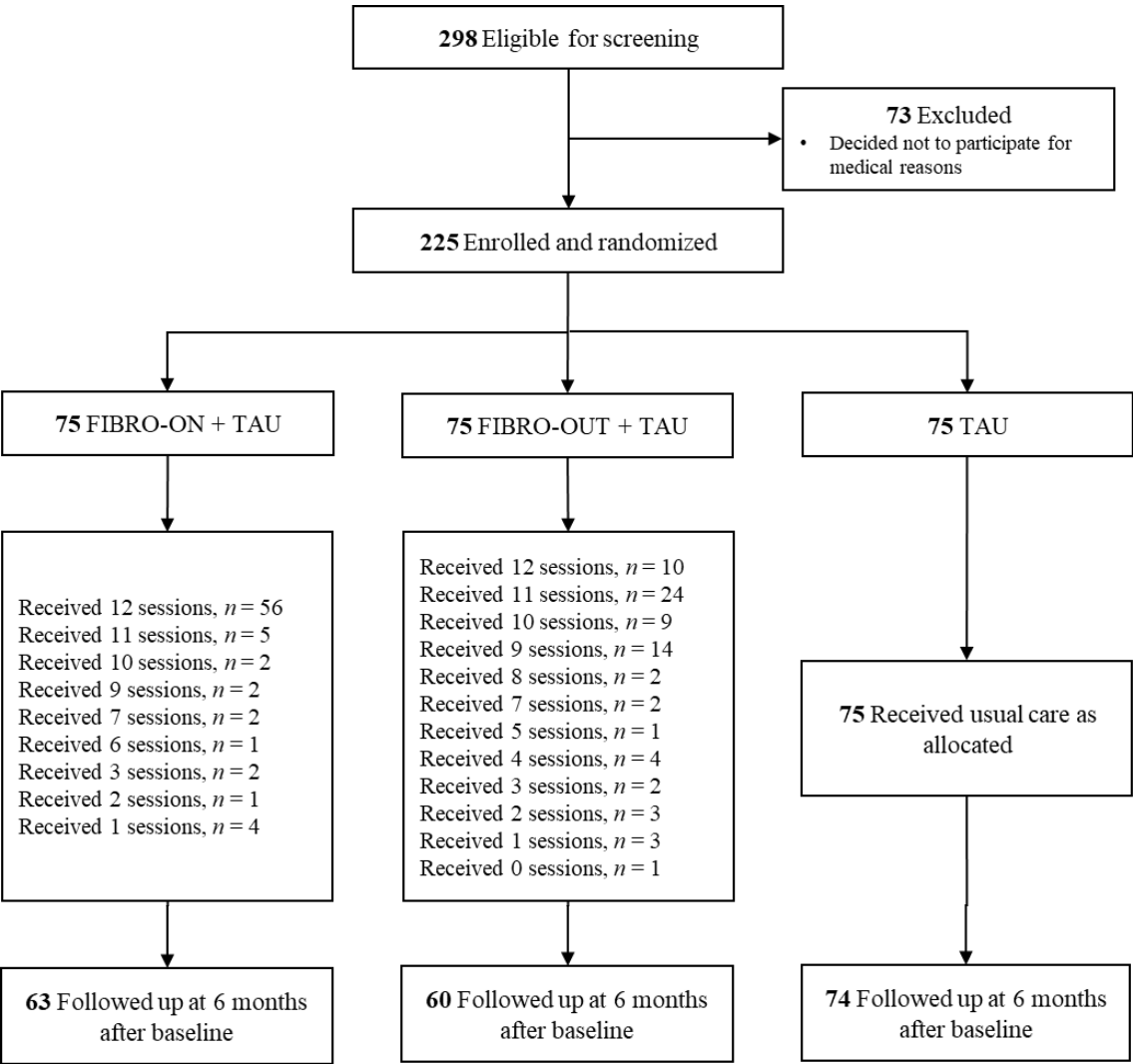


Figure 2. Cost-utility plane of 1000 bootstrap replicated incremental cost-utility from the government perspective (total costs; upper figure) and healthcare perspective (direct costs; lower figure) in the ITT sample: Fibro-Out vs. TAU (green color); Fibro-On vs. TAU (blue color); and Fibro-Out vs. Fibro-On (red color).

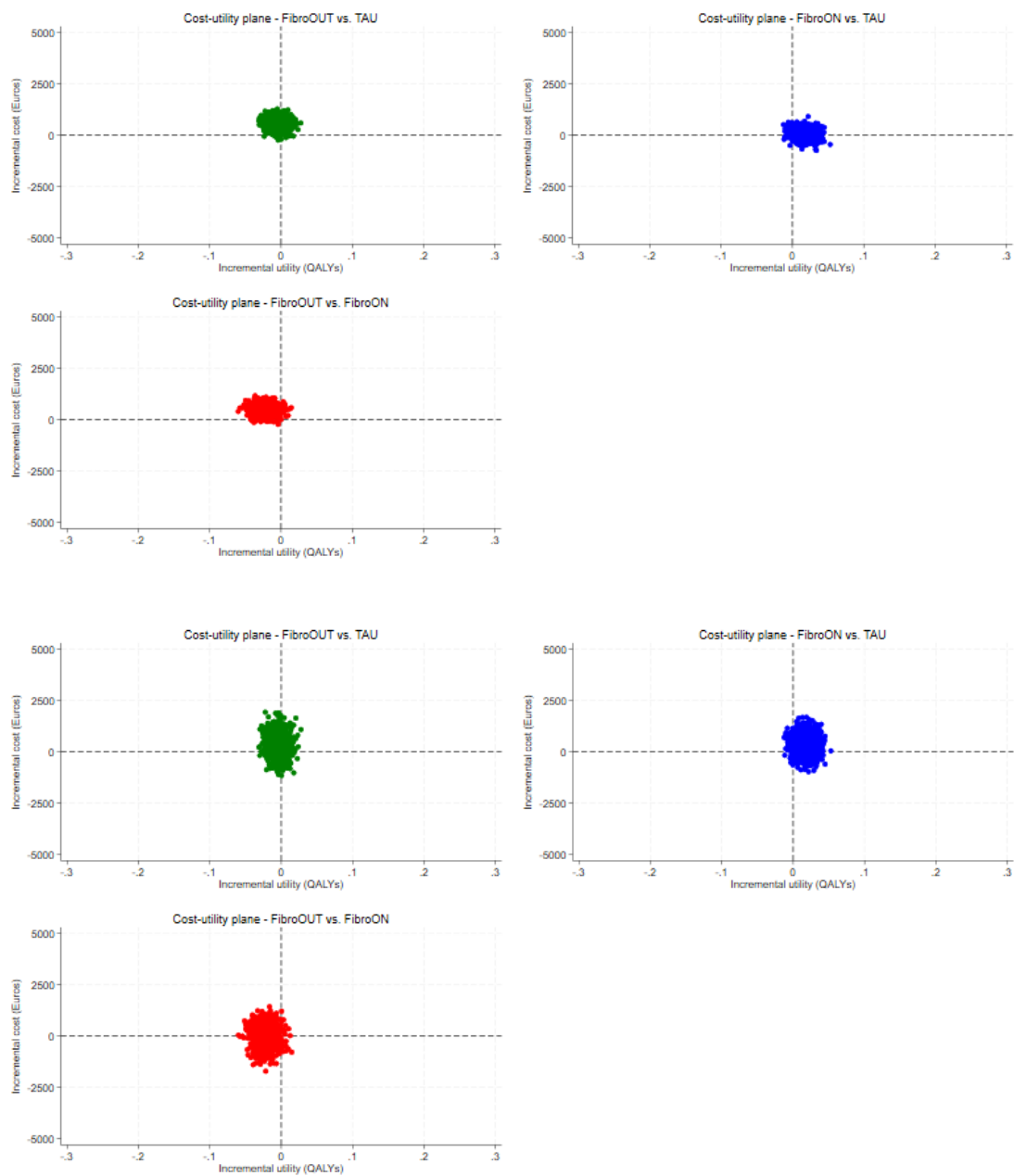


Figure 3. Cost-effectiveness plane of 1000 bootstrap replicated incremental cost-effectiveness from the government perspective (total costs; upper figure) and healthcare perspective (direct costs; lower figure) in the ITT sample: Fibro-Out vs. TAU (green color); Fibro-On vs. TAU (blue color); and Fibro-Out vs. Fibro-On (red color).

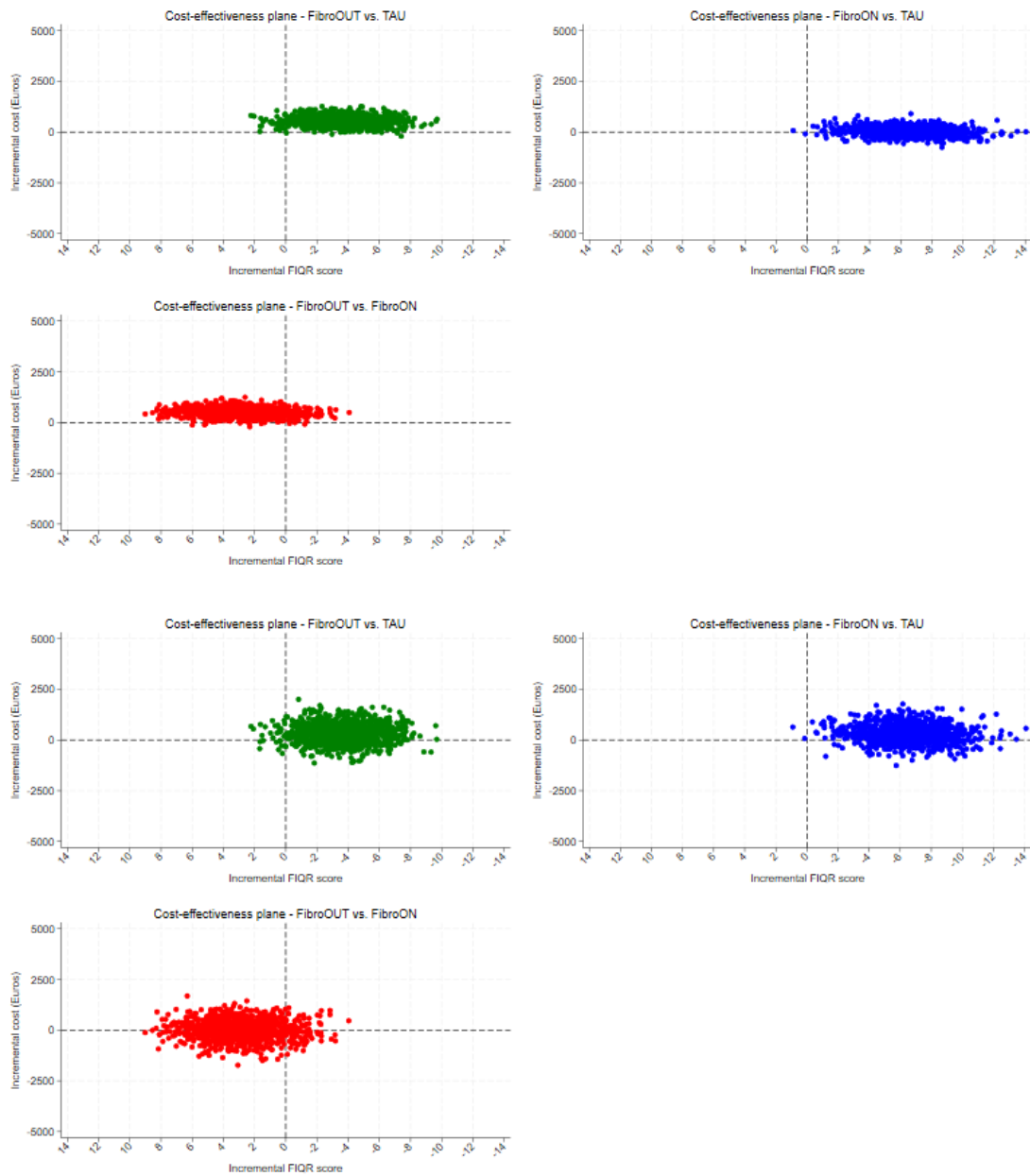


Table 1. Unit costs used in the calculations of direct and indirect costs (Financial Year 2023; values in €)

Service (unit)	Cost (€)
Healthcare (direct costs)	
General practitioner (per appointment)	44
Nurse/psychiatric nurse (per appointment)	41
Social worker (per appointment)	43
Clinical Psychologist (per appointment)	54
Psychiatrist (per appointment)	54
Other medical specialists (per appointment)	52
Accident and emergency in hospital (per attendance)	118
Hospital stay (per night)	133
Diagnostic tests (range)	7-543
Pharmacological treatment (per daily dose) *	Various
FIBRO-On and FIBRO-Out (per participant per group session)	0 -114
Productivity loss (indirect costs)	
Absenteeism from work (minimum daily wage)	36

Note. The unit costs were applied to each resource used to calculate the total cost of the resources used by each participant. All unit costs were for the year 2023. *The cost of prescribed medications was calculated by determining the price per milligram according to the Vademecum International (Red Book; edition 2023) and included the value-added tax.

Table 2. Baseline characteristics of participants by treatment arm

	FIBRO-On (n = 75)	FIBRO-Out (n = 75)	TAU (n = 75)
Gender, n females (%)	75 (100)	72 (96)	73 (97.3)
Age, mean (SD)	52.6 (9.7)	54.5 (10.1)	55.7 (9.1)
BMI, mean (SD)	28.1 (6.1)	27.5 (5.7)	29.1 (5.9)
Years diagnosis, mean (SD)	13.9 (9.7)	11.7 (9.1)	16.9 (10.9)
Marital status, n (%)			
Single	8 (10.7)	12 (16)	8 (10.7)
Married/with a partner	50 (66.7)	44 (58.7)	48 (64)
Separated/divorced	14 (18.7)	11 (14.7)	16 (21.3)
Widowed	3 (4)	8 (10.7)	3 (4)
Living arrangement, n (%)			
Living alone	7 (9.3)	10 (13.3)	13 (17.3)
Living with a partner	68 (90.7)	65 (86.7)	62 (82.7)
Education level, n (%)			
Illiterate	-	2 (2.7)	2 (2.7)
Not graduate from primary school	7 (9.3)	4 (5.3)	7 (9.3)
Primary school	18 (24)	20 (26.7)	22 (29.3)
Secondary school	31 (41.3)	31 (41.3)	32 (42.7)
University	15 (20)	17 (22.7)	11 (14.7)
Others	4 (5.3)	1 (1.3)	1 (1.3)
Employment status, n (%)			
Homemaker	6 (8)	4 (5.3)	7 (9.3)
Paid employment	22 (29.3)	15 (20)	19 (25.3)
Paid employment but in sick leave	15 (20)	21 (28)	13 (17.3)
Unemployed with subsidy	3 (4)	6 (8)	5 (6.7)
Unemployed without subsidy	6 (8)	6 (8)	4 (5.3)
Retired/pensioner	5 (6.7)	7 (9.3)	12 (16)
Temporal disability	5 (6.7)	4 (5.3)	4 (5.3)
Others	13 (17.3)	12 (16)	11 (14.7)
Comorbid conditions			
Chronic fatigue syndrome, n (%)	43 (57.3)	43 (57.3)	46 (61.3)
Rheumatoid arthritis, n (%)	9 (12)	9 (12)	11 (14.7)
Multiple chemical sensitivity, n (%)	9 (12)	10 (13.3)	9 (12)
Cancer, n (%)	1 (1.3)	1 (1.3)	2 (2.7)
Depression, n (%)	46 (61.3)	53 (70.7)	55 (73.3)
Anxiety, n (%)	52 (69.3)	53 (70.7)	55 (73.3)
Irritable bowel syndrome, n (%)	20 (26.7)	15 (20)	28 (37.3)
Osteoarthritis, n (%)	39 (52)	43 (57.3)	51 (68)
Disability litigation, n (%)	19 (25.3)	26 (34.7)	19 (25.3)
Degree of disability, n (%)			
No	36 (48)	33 (44)	26 (34.7)
Less than 33%	1 (1.3)	1 (1.3)	2 (2.7)
Between 33-66%	24 (32)	34 (45.3)	29 (38.7)
More than 66%	3 (4)	6 (8)	15 (20)
Others	3 (4)	1 (1.3)	3 (4)
Medication, n (%)	71 (94.7)	72 (96)	70 (93.3)
Antidepressants, n (%)	53 (70.7)	60 (80)	63 (84)
Anxiolytics, n (%)	31 (41.3)	29 (38.7)	21 (28)
Sleep medications, n (%)	29 (38.7)	30 (40)	21 (28)
Anticonvulsants, n (%)	17 (22.7)	20 (26.7)	19 (25.3)
Muscle relaxants, n (%)	41 (54.7)	41 (54.7)	43 (57.3)
Anti-inflammatories, n (%)	65 (86.7)	57 (76)	49 (65.3)
Non-opioid analgesics, n (%)	67 (89.3)	67 (89.3)	65 (86.7)
Opioids, n (%)	18 (24)	21 (28)	20 (26.7)

Note. TAU = Treatment as Usual; FIBRO-On = online; FIBRO-Out = outdoor; BMI = Body Mass Index.

Table 3. Descriptive Statistics and Between-group Analysis for costs (total and disaggregated in components) and outcomes (ITT approach)

	FIBRO-On <i>M (SD)</i>	FIBRO-Out <i>M (SD)</i>	TAU <i>M (SD)</i>	FIBRO-On vs TAU			FIBRO-Out vs TAU			FIBRO-On vs FIBRO-Out		
				<i>d</i>	<i>t (p)</i>	<i>B (95% CI)</i>	<i>d</i>	<i>t (p)</i>	<i>B (95% CI)</i>	<i>d</i>	<i>t (p)</i>	<i>B (95% CI)</i>
Costs												
Primary healthcare services *												
Baseline	361.72 (421.54)	322.88 (339.79)	411.45 (524.75)	0.48	1.78 (.077)	110.57 (-12.03 to 233.17)	0.35	1.30 (.195)	80.67 (-41.53 to 202.88)	0.13	-0.47 (.636)	-29.89 (-154.20 to 94.42)
Follow-up	328.69 (373.78)	311.29 (219.25)	296.88 (342.43)									
Specialized healthcare services *												
Baseline	598.40 (760.15)	689.01 (830.94)	487.76 (723.01)	0.71	3.07 (.003)	411.69 (146.53 to 676.84)	0.06	0.25 (.799)	34.04 (-229.39 to 297.48)	0.65	-2.77 (.006)	-377.64 (-647.15 to -108.13)
Follow-up	525.32 (645.34)	903.69 (965.77)	489.91 (825.46)									
Medical tests *												
Baseline	797.82 (1108.61)	829.07 (947.20)	736.68 (836.17)	0.22	0.97 (.335)	121.13 (-125.96 to 368.21)	0.07	-0.33 (.774)	-40.77 (-286.66 to 205.12)	0.30	-1.27 (.207)	-161.90 (-413.93 to 90.13)
Follow-up	605.01 (718.49)	767.66 (810.21)	644.25 (779.94)									
Pain-related medications *												
Baseline	401.14 (761.84)	324.92 (494.48)	502.75 (1184.88)	0.01	0.06 (.952)	5.22 (-167.44 to 177.89)	0.03	0.20 (.840)	17.39 (-153.04 to 187.82)	0.02	-0.13 (.893)	12.16 (-165.64 to 189.96)
Follow-up	356.37 (833.22)	307.80 (561.31)	390.86 (928.72)									
Intervention costs	0	109.46 (37.99)	0	-	-	-	-	-	-	-	-	-
Direct costs *												
Baseline	2159.10 (2083.76)	2165.90 (1820.12)	2130.24 (2039.26)	0.41	1.80 (.076)	549.03 (-58.63 to 1156.69)	0.01	-0.02 (.983)	-6.53 (-608.73 to 595.66)	0.41	-555.56 (.078)	-555.56 (-1174.15 to 63.02)
Follow-up	1815.40 (1762.96)	2371.07 (2002.91)	1821.92 (1850.91)									
Indirect costs *												
Baseline	2023.68 (2810.60)	2560.80 (3016.26)	1233.60 (2483.43)	0.34	1.45 (.149)	667.46 (-240.84 to 1575.76)	0.26	1.12 (.266)	508.91 (-390.22 to 1408.06)	0.08	-0.34 (.734)	-158.54 (-1078.32 to 761.23)
Follow-up	2109.71 (2914.13)	2271.54 (2892.26)	1594.21 (2624.89)									

Total costs *												
Baseline	4182.78 (3651.47)	4726.70 (3893.22)	3292.95 (3707.45)									
Follow-up	3863.79 (3765.54)	4532.95 (3613.50)	3416.14 (3201.28)	0.44	1.92 (.057)	1111.04 (-32.12 to 2254.19)	0.18	0.77 (.442)	440.83 (-688.28 to 1569.94)	0.26	-1.14 (.254)	-670.21 (-1826.50 to 486.08)
Outcomes												
EQ-5D utility (0-1) *												
Baseline	0.28 (0.28)	0.28 (0.24)	0.29 (0.24)									
Follow-up	0.35 (0.29)	0.28 (0.24)	0.28 (0.26)	0.01	-0.09 (.928)	-0.01 (-0.09 to 0.08)	0.41	1.50 (.137)	0.06 (-0.02 to 0.15)	0.41	1.55 (.123)	0.07 (-0.02 to - 0.16)
EQ-VAS (0-100) *												
Baseline	78.89 (16.24)	80.71 (14.23)	77.32 (18.06)									
Follow-up	68.98 (22.01)	73.83 (16.85)	75.44 (19.27)	0.50	-2.16 (.031)	-0.69 (-1.32 to - 0.06)	0.29	-1.16 (.248)	-0.37 (-1.00 to 0.26)	0.23	0.97 (.332)	0.32 (-0.33 to 0.96)
FIQR (0-100) *												
Baseline	73.08 (15.91)	74.14 (15.10)	70.59 (16.13)									
Follow-up	64.97 (19.17)	67.84 (15.94)	69.54 (16.87)	0.56	-2.49 (.013)	-6.02 (-10.78 to - 1.27)	0.40	-1.76 (0.079)	-4.29 (-9.08 to 0.50)	0.16	0.70 (0.486)	1.73 (-3.15 to 6.62)

Note. TAU = treatment-as-usual; FIBRO-On = online; FIBRO-Out = outdoor; FIQR = Fibromyalgia Impact Questionnaire; VAS = Visual-Analogue Scale of Perceived Pain; EQ-5D = EuroQol five-dimensional classification; EQ-VAS = visual analog scale. *B*, regression coefficients; CI, confidence interval; *d*, Cohen's *d* as an effect size measure; ITT, intention-to-treat. Means (*M*) and standard deviations (*SD*) are unadjusted. Effect sizes (Cohen's *d*), *t*-values (with *p*-values), and unstandardized regression coefficients (*B*) with 95% confidence intervals (CI) are derived from linear mixed models (LMMs) comparing groups at follow-up, adjusted for baseline values and time. These estimates reflect adjusted between-group differences. Intervention costs are only shown for descriptive and transparency purposes. They were computed as part of the direct costs in the analysis. * Indicates that the baseline level of the variable was a significant covariate in the model.

Table 4. Incremental cost, effect, and cost-utility ratios from the government perspective (total costs)

	Incremental cost	Incremental effect	Dominant treatment	ICUR/ICER	MCID-adjusted ICER
	<i>M</i> (95% Bootstrap CI)	<i>M</i> (95% Bootstrap CI)			
Main analysis (ITT)					
FIBRO-On vs TAU (<i>n</i> = 150)					
QALY (0-1)	123.01 (-856.02 to 1102.04)	0.02 (-0.01 to 0.04)	None †	6,919	-
FIQR (0-100)	123.94 (-849.43 to 1097.31)	-6.24 (-10.84 to -1.64)	None †	19	855
FIBRO-Out vs TAU (<i>n</i> = 150)					
QALY (0-1)	335.76 (-669.72 to 1341.25)	-0.01 (-0.02 to 0.02)	TAU *	< -25,000	-
FIQR (0-100)	337.26 (-648.08 to 1322.61)	-4.35 (-8.64 to -0.06)	None †	77	2,978
FIBRO-Out vs FIBRO-On (<i>n</i> = 150)					
QALY (0-1)	212.75 (-876.22 to 1301.73)	-0.02 (-0.04 to 0.01)	FIBRO-On ***	-11,368	-
FIQR (0-100)	213.32 (-883.90 to 1310.55)	1.89 (-3.57 to 7.35)	FIBRO-On ***	-113	-6,799
Sensitive analysis (CCA)					
FIBRO-On vs TAU (<i>n</i> = 134)					
QALY (0-1)	70.53 (-854.70 to 918.12)	0.02 (-0.01 to 0.04)	None †	3,212	-
FIQR (0-100)	169.94 (-727.04 to 1157.43)	-5.62 (-10.33 to -1.18)	None †	30	1,422
FIBRO-Out vs TAU (<i>n</i> = 137)					
QALY (0-1)	323.73 (-761.22 to 1279.38)	-0.01 (-0.02 to 0.02)	TAU *	< -25,000	-
FIQR (0-100)	381.44 (-705.24 to 1442.23)	-3.50 (-8.02 to 0.72)	None †	109	3,718
FIBRO-Out vs FIBRO-On (<i>n</i> = 123)					
QALY (0-1)	253.20 (-815.53 to 1305.09)	-0.02 (-0.04 to 0.01)	FIBRO-On ***	-11,585	-
FIQR (0-100)	211.49 (-859.79 to 1380.60)	2.12 (-2.71 to 6.95)	FIBRO-On ***	-99	-12,545
Sensitive analysis (PPA)					
FIBRO-On vs TAU (<i>n</i> = 128)					
QALY (0-1)	75.86 (-839.22 to 1015.44)	0.02 (0.01 to 0.05)	None †	3,269	-
FIQR (0-100)	119.82 (-799.45 to 1039.05)	-5.79 (-10.13 to -1.45)	None †	20	908
FIBRO-Out vs TAU (<i>n</i> = 130)					
QALY (0-1)	453.39 (-642.17 to 1632.58)	-0.01(-0.02 to 0.02)	TAU *	< -25,000	-
FIQR (0-100)	462.10 (-603.30 to 1711.25)	-3.51 (-7.73 to 0.61)	None †	131	4,210
FIBRO-Out vs FIBRO-On (<i>n</i> = 122)					
QALY (0-1)	377.53 (-750.02 to 1571.75)	-0.02 (-0.04 to -0.01)	FIBRO-On ***	-16,200	-
FIQR (0-100)	342.28 (-877.98 to 1616.51)	2.28 (-2.85 to 6.92)	FIBRO-On ***	-149	-15,904

Note: Significant values ($p < 0.05$) are shown in bold. CCA = complete case analysis; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; MCID = minimal clinically important difference; ITT = intention-to-treat; PPA = per-protocol analysis. CCA ($N = 197$), ITT ($N = 225$), and PPA ($N = 185$). In terms of interpretation, an increase in the QALY score (positive values) and a decrease in the FIQR score (negative values) means that the intervention is beneficial. The sign of the ICER has been inverted since the result is positive when the change is negative.

*TAU costs less and is more effective or useful than FIBRO-Out or FIBRO-On.

**FIBRO-Out or FIBRO-On costs less and is more effective or useful than TAU.

***FIBRO-On costs less and is more effective or useful than FIBRO-Out.

†TAU costs less than FIBRO-Out or FIBRO-On, but FIBRO-Out or FIBRO-On is more effective or useful than TAU.

Table 5. Incremental cost, effect, and cost-utility ratios from the healthcare perspective (direct costs).

	Incremental cost	Incremental effect	Dominant treatment	ICUR/ICER	MCID-adjusted ICER
	<i>M</i> (95% Bootstrap CI)	<i>M</i> (95% Bootstrap CI)			
Main analysis (ITT)					
FIBRO-On vs TAU (<i>n</i> = 150)					
QALY (0-1)	-37.81 (-501.69 to 426.06)	0.02 (-0.01 to 0.04)	FIBRO-On **	-2,127	-
FIQR (0-100)	-37.70 (-506.09 to 430.69)	-6.24 (-10.84 to -1.64)	FIBRO-On **	-6	-262
FIBRO-Out vs TAU (<i>n</i> = 150)					
QALY (0-1)	553.43 (64.52 to 1042.34)	-0.01 (-0.02 to 0.02)	TAU *	< -25,000	-
FIQR (0-100)	553.57 (73.60 to 1033.54)	-4.35 (-8.65 to -0.06)	None †	127	4,876
FIBRO-Out vs FIBRO-On (<i>n</i> = 150)					
QALY (0-1)	591.24 (115.64 to 1066.85)	-0.02 (-0.04 to 0.01)	FIBRO-On ***	< -25,000	-
FIQR (0-100)	591.27 (118.36 to 1064.18)	1.89 (-3.57 to 7.35)	FIBRO-On ***	-313	-18,957
Sensitive analysis (CCA)					
FIBRO-On vs TAU (<i>n</i> = 134)					
QALY (0-1)	-23.24 (-458.49 to 440.73)	0.02 (-0.01 to 0.04)	FIBRO-On **	-1076	-
FIQR (0-100)	-4.39 (-432.76 to 398.85)	-5.62 (-10.31 to -1.18)	FIBRO-On **	-1	-40
FIBRO-Out vs TAU (<i>n</i> = 137)					
QALY (0-1)	548.71 (90.21 to 1025.32)	-0.01 (-0.02 to 0.17)	TAU *	< -25,000	-
FIQR (0-100)	566.80 (109.88 to 1055.44)	-3.50 (-8.05 to 0.64)	None †	161	5,505
FIBRO-Out vs FIBRO-On (<i>n</i> = 123)					
QALY (0-1)	571.95 (124.23 to 1002.57)	-0.02 (-0.04 to -0.01)	FIBRO-On ***	-23,934	-
FIQR (0-100)	571.19 (135.18 to 1025.70)	2.12 (-2.69 to 6.93)	FIBRO-On ***	-269	-34,840
Sensitive analysis (PPA)					
FIBRO-On vs TAU (<i>n</i> = 128)					
QALY (0-1)	-66.74 (-537.53 to 368.42)	0.02 (0.01 to 0.05)	FIBRO-On **	-2876	-
FIQR (0-100)	-48.01 (-484.43 to 380.68)	-5.79 (-9.78 to -1.43)	FIBRO-On **	-8	-368
FIBRO-Out vs TAU (<i>n</i> = 130)					
QALY (0-1)	661.59 (171.47 to 1215.25)	-0.01(-0.02 to 0.02)	TAU *	< -25,000	-
FIQR (0-100)	661.66 (187.44 to 1186.18)	-3.51 (-7.79 to 0.60)	None †	188	6,065
FIBRO-Out vs FIBRO-On (<i>n</i> = 122)					
QALY (0-1)	728.34 (254.01 to 1245.49)	-0.02 (-0.04 to -0.01)	FIBRO-On ***	< -25,000	-
FIQR (0-100)	709.67 (225.27 to 1245.14)	2.28 (-2.96 to 6.85)	FIBRO-On ***	-310	-33,561

Note: Significant values ($p < 0.05$) are shown in bold. CCA = complete case analysis; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; MCID = minimal clinically important difference; ITT = intention-to-treat; PPA = per-protocol analysis. CCA ($N = 197$), ITT ($N = 225$), and PPA ($N = 185$). In terms of interpretation, an increase in the QALY score (positive values) and a decrease in the FIQR score (negative values) means that the intervention is beneficial. The sign of the ICER has been inverted since the result is positive when the change is negative.

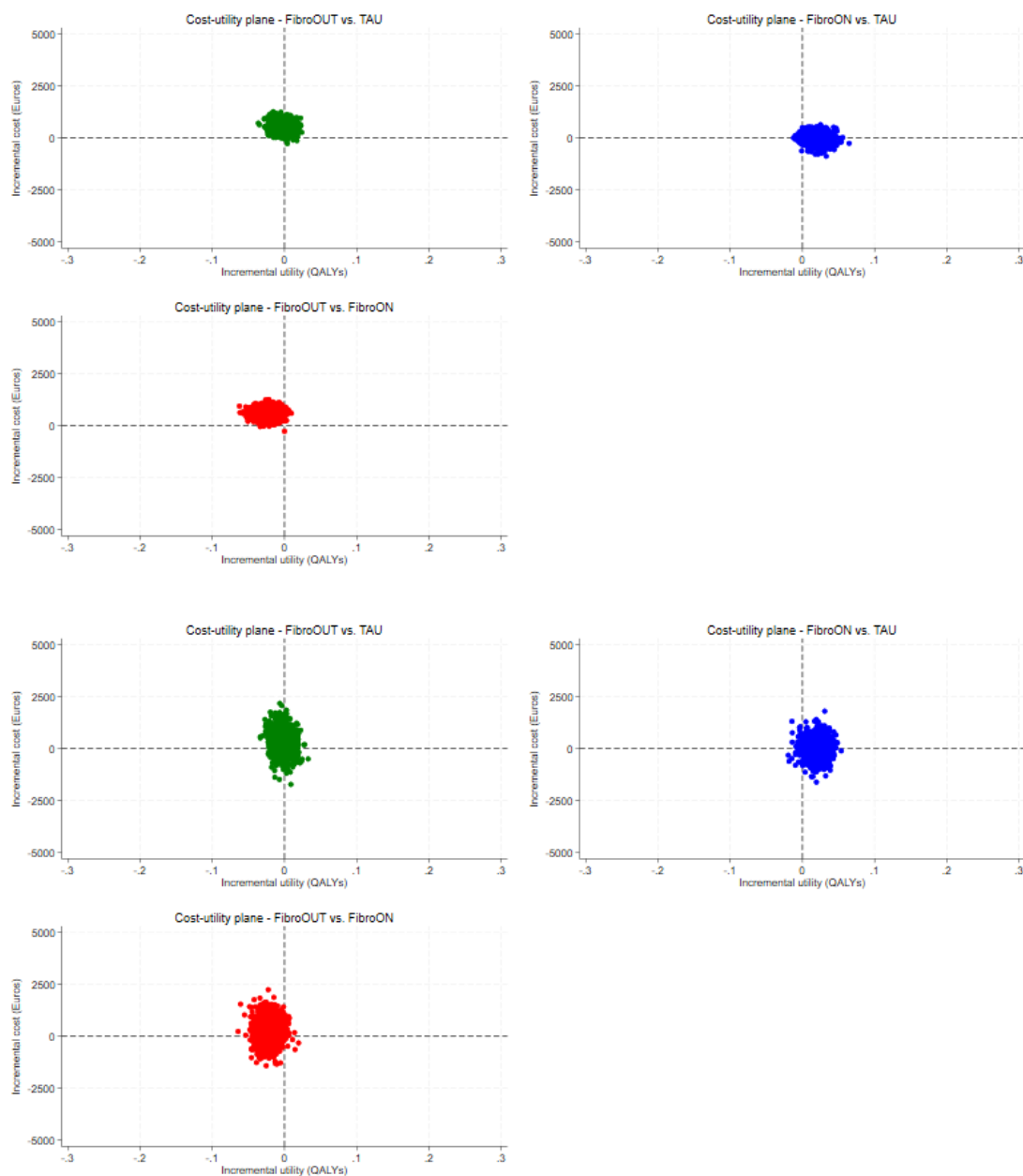
* TAU costs less and is more effective or useful than FIBRO-Out or FIBRO-On.

** FIBRO-Out or FIBRO-On costs less and is more effective or useful than TAU.

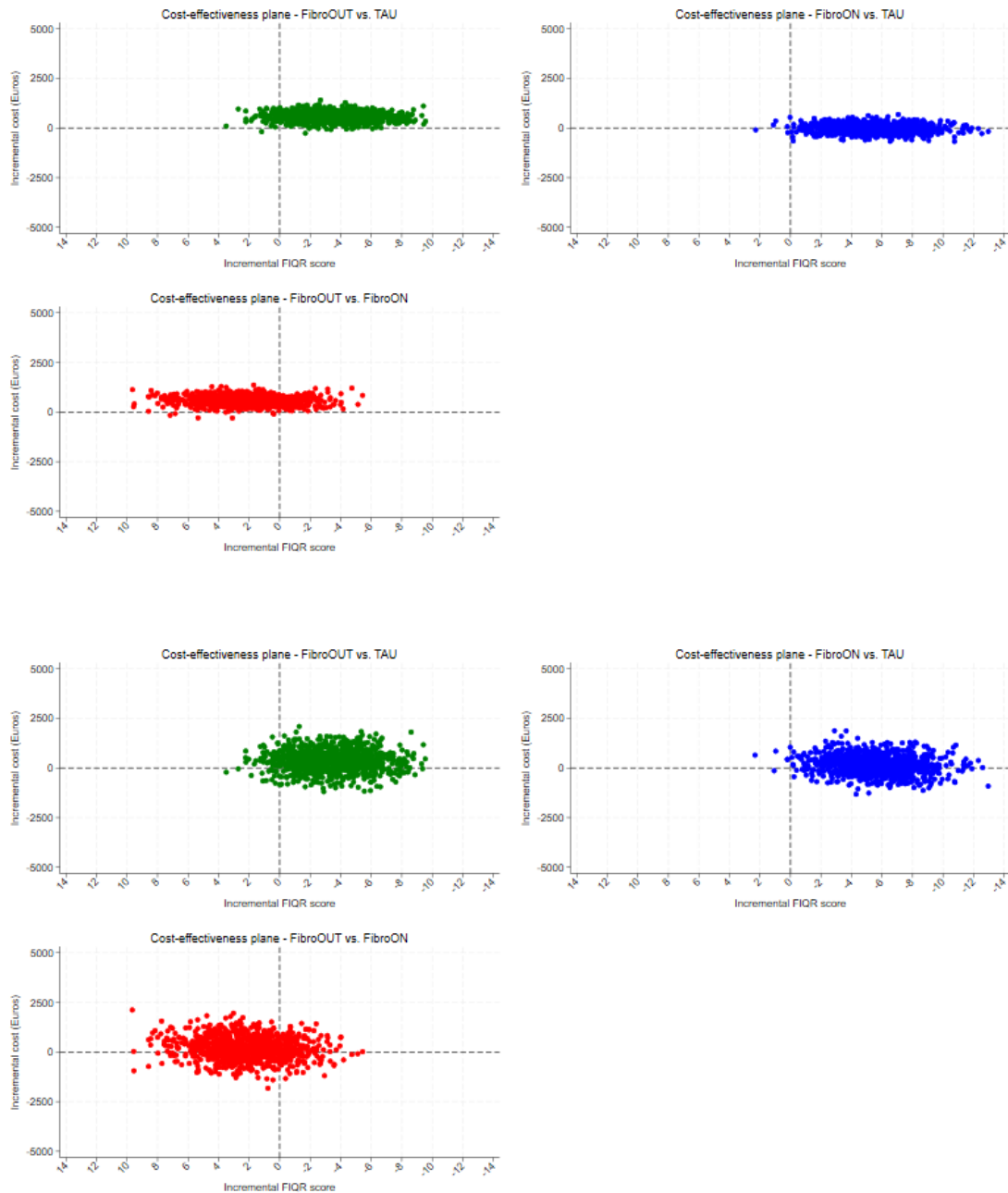
*** FIBRO-On costs less and is more effective or useful than FIBRO-Out.

† TAU costs less than FIBRO-Out or FIBRO-On, but FIBRO-Out or FIBRO-On is more effective or useful than TAU.

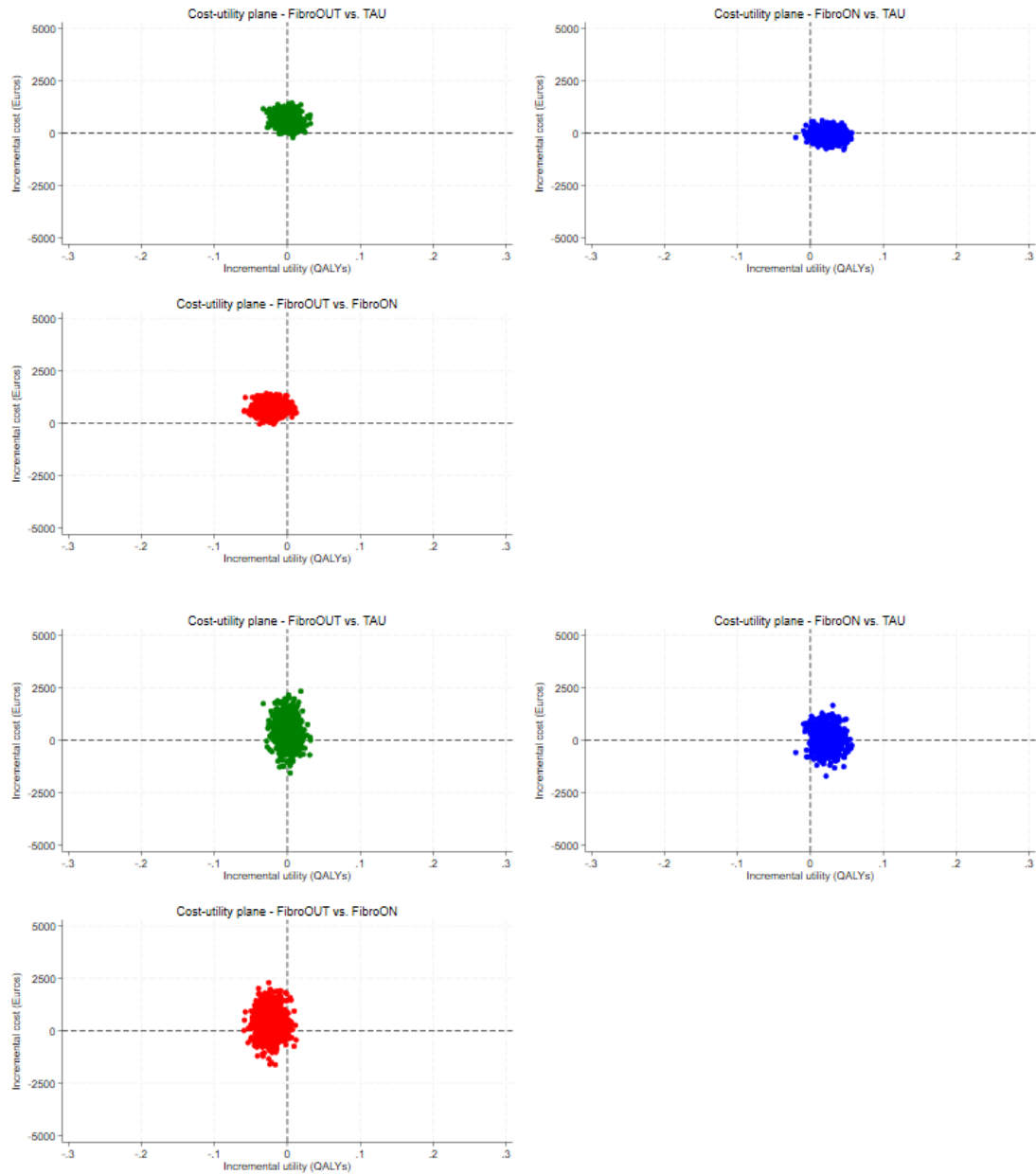
Supplementary Figure 1. Cost-utility plane of 1000 bootstrap replicated incremental cost-utility from the government perspective (total costs; upper figure) and healthcare perspective (direct costs; lower figure) in the CCA sample: Fibro-Out vs. TAU (green color); Fibro-On vs. TAU (blue color); and Fibro-Out vs. Fibro-On (red color).



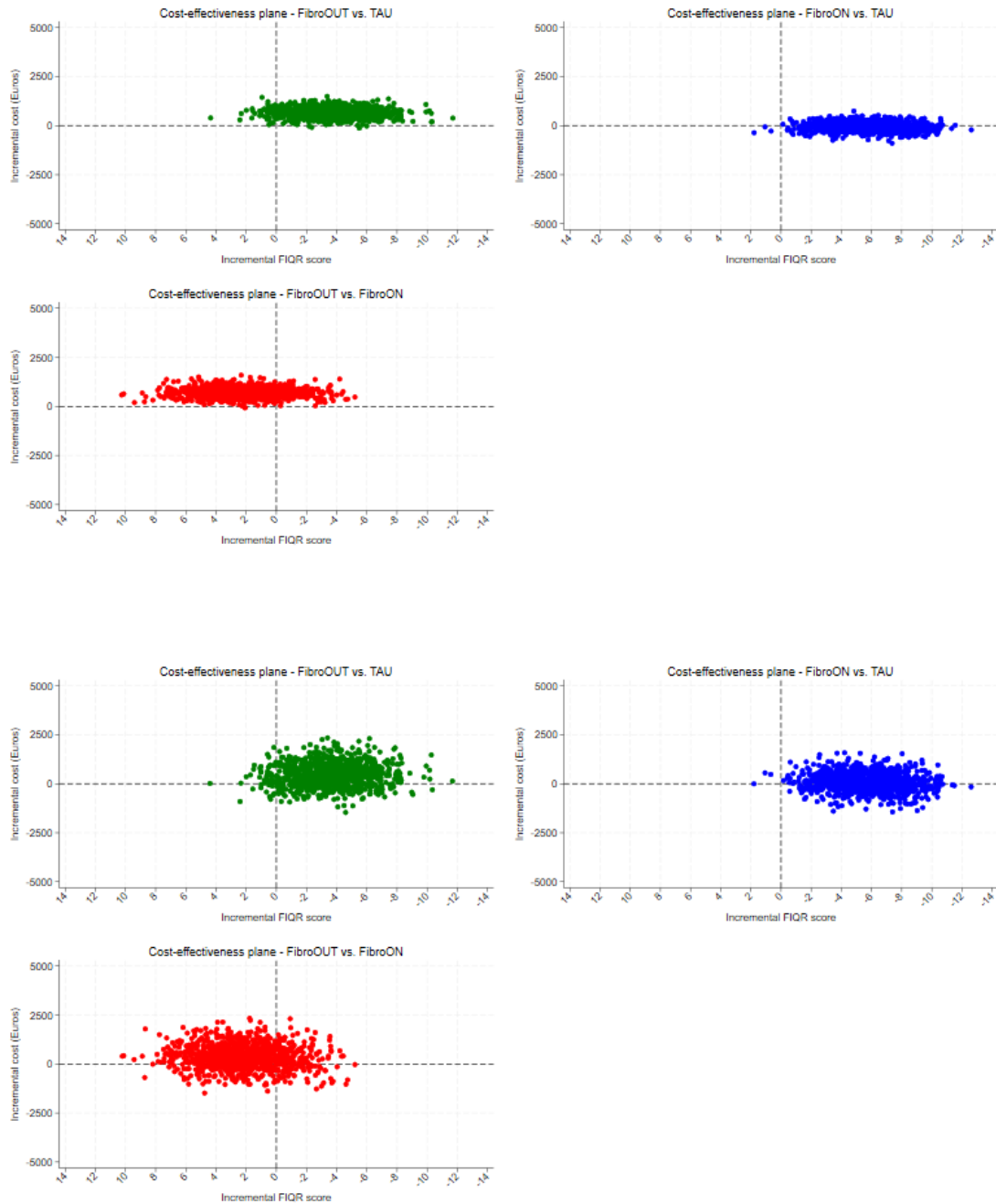
Supplementary Figure 2. Cost-effectiveness plane of 1000 bootstrap replicated incremental cost-effectiveness from the government perspective (total costs; upper figure) and healthcare perspective (direct costs; lower figure) in the CCA sample: Fibro-Out vs. TAU (green color); Fibro-On vs. TAU (blue color); and Fibro-Out vs. Fibro-On (red color).



Supplementary Figure 3. Cost-utility plane of 1000 bootstrap replicated incremental cost-utility from the government perspective (total costs; upper figure) and healthcare perspective (direct costs; lower figure) in the PPA sample: Fibro-Out vs. TAU (green color); Fibro-On vs. TAU (blue color); and Fibro-Out vs. Fibro-On (red color).

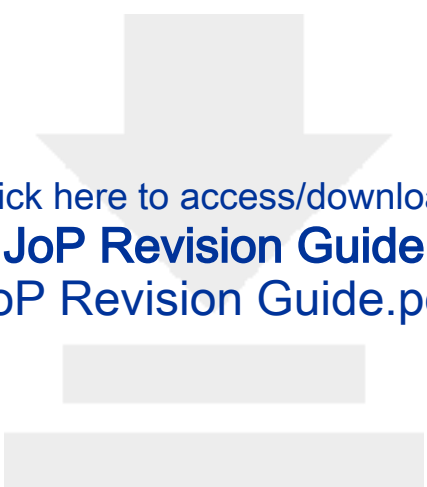


Supplementary Figure 4. Cost-effectiveness plane of 1000 bootstrap replicated incremental cost-effectiveness from the government perspective (total costs; upper figure) and healthcare perspective (direct costs; lower figure) in the PPA sample: Fibro-Out vs. TAU (green color); Fibro-On vs. TAU (blue color); and Fibro-Out vs. Fibro-On (red color).



Supplementary Table 1. Mean (unadjusted) pre-follow-up differences of the costs (total and disaggregated in components) and outcomes according to treatment arm (completer sample)

	FIBRO-On <i>M (SD)</i>		FIBRO-Out <i>M (SD)</i>		TAU <i>M (SD)</i>	
	Mean	SD	Mean	SD	Mean	SD
Costs						
Primary healthcare services	-38.32	353.28	-2.78	285.15	-118.40	478.38
Specialized healthcare services	-53.61	574.53	232.04	770.82	-4.074	855.15
Medical tests	-224.89	1267.90	-72.022	943.50	-102.38	692.34
Pain-related medications	-42.71	280.85	-14.80	301.50	-117.93	760.48
Direct costs	-359.53	1550.94	222.35	1418.40	-328.77	1679.21
Indirect costs	256.00	2253.61	-652.13	3589.76	343.95	2615.97
Total costs	-142.91	3052.11	-369.36	4045.87	108.65	3126.14
Outcomes						
EQ-5D utility (0-1)	0.07	0.27	-0.02	0.23	-0.001	0.21
EQ-VAS (0-100)	-0.92	1.92	-0.55	1.70	-0.23	1.84
FIQR (0-100)	-7.16	13.66	-5.14	13.22	-1.15	14.06



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CHEERS 2022 Checklist

Topic	No.	Item	Location where item is reported
Title			
	1	Identify the study as an economic evaluation and specify the interventions being compared.	Page 1
Abstract			
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Page 4
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Pages 6 and 7
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Pages 13 and 14
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Pages 8 and 15
Setting and location	6	Provide relevant contextual information that may influence findings.	Pages 7-9
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Page 9
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Pages 11 and 12
Time horizon	9	State the time horizon for the study and why appropriate.	Pages 7-11
Discount rate	10	Report the discount rate(s) and reason chosen.	Pages 13 and 14
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Pages 10 and 11
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Pages 10 and 11
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Pages 11 and 12
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Pages 13 and 14

Topic	No.	Item	Location where item is reported
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Pages 13 and 14
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	NA
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Pages 11-14
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Pages 11-14
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Pages 11-14
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Pages 11-14
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Pages 8 and 9
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Pages 15-19
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Pages 16-19
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Pages 16-19
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Pages 16-19
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Pages 19-25
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Page 1

Topic	No.	Item	Location where item is reported
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Page 1

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