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# Accepted Manuscript

Cost-utility of Group Acceptance and Commitment Therapy for Fibromyalgia versus recommended drugs: An economic analysis alongside a 6-month randomised controlled trial conducted in Spain (EFFIGACT study)

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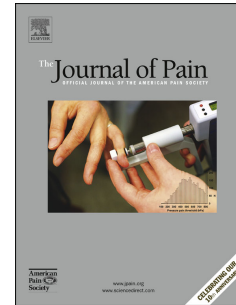
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**Cost-utility of Group Acceptance and Commitment Therapy for Fibromyalgia  
versus recommended drugs: An economic analysis alongside a 6-month  
randomised controlled trial conducted in Spain (EFFIGACT study)**

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**Abstract**

The aim of this study was to analyse the cost-utility of a group-based form of Acceptance and Commitment Therapy (GACT) in patients with fibromyalgia (FM) compared to patients receiving recommended pharmacological treatment (RPT) or on a waiting list (WL). The data were derived from a previously published study, an RCT that focused on clinical outcomes. Health economic outcomes included health-related quality of life and healthcare use at baseline and at 6-month follow-up using the EuroQol (EQ-5D-3L) and the Client Service Receipt Inventory (CSRI), respectively. Analyses included Quality-Adjusted Life Years (QALYs), direct and indirect cost differences, and incremental cost-effectiveness ratios (ICERs). A total of 156 FM patients were randomized (51 GACT, 52 RPT, 53 WL). GACT was related to significantly less direct costs over the 6 month study period compared to both control arms (GACT €824.2 ± 1,062.7 vs. RPT €1,730.7 ± 1,656.8 vs WL €2,462.7 ± 2,822.0). Lower direct costs for GACT in comparison to RPT were due to lower costs from primary care visits and FM-related medications. The ICERs were dominant in the completers' analysis and remained robust in the sensitivity analyses. In conclusion, ACT appears to be a cost-effective treatment in comparison to RPT in patients with FM.

Trial number: ISRCTN96465010 (<http://www.isrctn.com/ISRCTN96465010>)

**Perspective:** Decision-makers have to prioritise their budget on the treatment option that is the most cost-effective for the management of a specific patient group. From both government and healthcare perspective, this study shows that a group-based form of Acceptance and Commitment Therapy is more cost-effective than pharmacological treatment in management of fibromyalgia.

**Keywords:** Fibromyalgia; Acceptance and Commitment Therapy; Cost-utility; Cost-effectiveness; Quality-adjusted life years.

## Introduction

Since the seminal work of Hayes, Strosahl, and Wilson,<sup>12</sup> there has been burgeoning interest in Acceptance and Commitment Therapy (ACT). This therapy includes a wide variety of methods that foster *psychological flexibility*, generally including exposure-based techniques, metaphors, mindfulness, and more conventional behavioral activation or skills training.<sup>12,23,25,31</sup>

A-Tjak and colleagues meta-analysed 39 studies and indicated that ACT outperforms control conditions (Hedges'  $g = 0.57$ ) in the global analysis of primary clinical outcome measures across pooled time points and types of disorders.<sup>2</sup> ACT was also superior to control conditions on secondary outcome measures (Hedges'  $g = 0.30$ ). The Öst's meta-analysis yielded a global Hedges's  $g$  of 0.42 at post-treatment.<sup>26</sup> The effect sizes for comparisons with waiting list, placebo, and TAU were moderate and significantly heterogeneous, whereas the effect size for the comparison with different types of cognitive-behavioural treatments did not reach the limit for a small effect size.

One of the areas where ACT has been widely applied is in multiple problems entailed in chronic pain disorders.<sup>24,34,37</sup> Veehof et al<sup>37</sup> carried out a meta-analysis of 28 studies to assess the effectiveness of acceptance and mindfulness-based treatments for chronic pain patients. In comparison with waiting list or usual care, small effects were found for pain intensity, depression, disability, and quality of life in favour of these treatments. A moderate effect was found for anxiety and pain interference. At follow-up, the effects on depression and quality of life increased and became moderate and the effect on pain interference increased and became large. ACT interventions reported a statistically significant higher mean effect on depression and anxiety than mindfulness-

based interventions. The differences between acceptance- and mindfulness-based interventions with CBT were not significant.

Economic evaluations describe the costs and effects of alternative treatments and are a useful tool for public health decision making.<sup>35</sup> Policy-makers are faced with limited economic resources and therefore, they routinely have to prioritize available treatments or choose among different alternatives. Cost-effectiveness analyses allow cost comparisons of different interventions in relation to the health improvement that is gained from each one. Here the decision about whether to provide a specific treatment depends not only on the levels of demonstrated effectiveness, but also on the magnitude of the incremental costs required to obtain each additional unit of benefit. The small-medium positive effects of ACT for different physical and psychiatric conditions are a compelling reason to test also its cost-effectiveness. To date, there are only two previous economic evaluations of ACT in the chronic pain field.<sup>10</sup> A web-delivered 10-week ACT program significantly reduced medication consumption, direct non-medical costs, work cutback, and need of domestic help.<sup>18</sup> Kemani et al<sup>15</sup> demonstrated that ACT is cost-effective for patients with chronic pain compared to applied relaxation at post-treatment and 3-month follow-up. Recently, the effectiveness of group ACT (GACT) was compared to recommended pharmacotherapy (RPT: pregabalin + duloxetine) for patients with fibromyalgia (FM).<sup>21</sup> The 6-month follow-up analysis indicated that when compared to RPT (active control arm that is not equivalent to the GACT arm in treatment exposure), the participants in GACT reported less functional impairment ( $d= 1.43$ ), pain catastrophising ( $d= 0.69$ ), pain ( $d= 0.47$ ), anxiety ( $d= 0.39$ ), and depression ( $d= 0.37$ ) as well as greater pain acceptance ( $d= 1.01$ ) and health-related quality of life (HRQoL;  $d= 0.66$ ) following treatment.

In the current study, we further analyse the results of Luciano et al's RCT<sup>21</sup> by comparing, for the first time, the 6-month healthcare and societal costs as well as the 6-month cost-utility of GACT, RPT, and waiting list (WL; passive control arm) in terms of gains in Quality-Adjusted Life Years (QALYs) and increases in HRQoL in patients with FM.

## **Methods**

### *Design*

A detailed description of the EFFIGACT protocol and the effectiveness findings appear elsewhere.<sup>21</sup> Briefly, a 6-month RCT was carried out with a random allocation of the participants into three conditions (using a computer-generated randomization list): GACT (n= 51), RPT (n= 52), or WL (n= 53). Randomisation was stratified by the presence/absence of comorbid major depression. The patients were randomized in blocks; the size of the blocks was randomly selected as comprising either 3 or 6 patients.

A research assistant, who was not otherwise involved in the study, generated the allocation sequence. The sequence was concealed until interventions were assigned. The patients agreed to participate before random allocation and without knowing which treatment they would receive. The patients in the intervention arms (GACT and RPT) were informed that two treatments would be compared: one treatment based on psychotherapy and the other on pharmacotherapy. Patients participating in the WL arm were offered their preferred treatment after completion of the RCT.

Signed informed consent was obtained from all participants before initiating the study. The patients were provided with a general overview of the study and informed that they could withdraw at any time, with the guarantee that they would continue to

receive the treatment considered most appropriate by their general practitioner. The study followed Helsinki Convention norms and subsequent updates and the Study Protocol was approved through the Ethical Review Board of the regional health authority, Aragon, Spain (Act 07/2011).

Regarding the context where the RCT was carried out, it is important to mention that Aragon is one of the 17 regions or autonomous communities of Spain. As a consequence of a devolution process that started in 1981, the autonomous communities have full governance of health and social care. Unlike other countries such as US, health care is publicly financed, with universal coverage. The Aragon Health Care System covers all of the region's territory (the region of Aragon has more than 1,200,000 inhabitants). Social care is also covered for people with a functional dependency due to severe disability.

#### *Participants*

FM patients were recruited from 24 primary healthcare centres in Zaragoza, Spain. The patients considered for inclusion were adults aged 18–65 years who could speak and read Spanish fluently and who fulfilled the American College of Rheumatology (ACR) 1990 criteria<sup>39</sup> for FM at screening, with no pharmacological treatment (or agreed to discontinue use to participate in the study) and no psychological treatment during the previous year. The patients considered for exclusion were those with severe Axis I psychiatric disorders (dementia, schizophrenia, paranoid disorder, alcohol and/or drug use disorders), severe somatic disorders which, from the clinician's point of view, prevented patients from carrying out a psychological assessment or participating in other treatment or research procedures. All the patients included in the study had been diagnosed with FM by a rheumatologist working for the Spanish

National Health Service. General practitioners (GPs) selected FM patients fulfilling the inclusion criteria until the required sample number was achieved, without a quota of patients assigned for each centre. The GPs assessed the depression of the patients for the subsequent stratification of the sample. After referral, a research assistant assessed patients for eligibility. Diagnostic confirmation of major depression was carried out by research assistants (highly-trained clinical psychologists) using the MINI Neuropsychiatric Interview. Informational brochures, briefly describing the two interventions as alternative treatments potentially capable of enhancing the wellbeing of FM patients, were provided. The study was conducted from September 2011 to June 2012.

The participants were interviewed at baseline, post-treatment, and at 3- and 6-month follow-up. The study personnel who conducted the interviews and assessed the outcomes were blinded to treatment allocation. Due to the characteristics of the RCT, the patients were not blinded to the treatment allocation.

### *Interventions*

**GACT.** This intervention was based on a published guide adapted to FM patients.<sup>38</sup> The structured intervention comprised eight 2.5-hour sessions (1 session/week) with groups ranging from 10 to 15 patients. All group sessions included a 15-minute break to mitigate fatigue. The sessions covered specific exercises and topics within the context of ACT practice and training, including various types of formal mindfulness practice. Upon enrolment, the participants were asked to commit to daily homework assignments of 15–30 min. The therapist was an experienced clinical psychologist trained in ACT and group management, with clinical experience treating FM patients. All sessions were video recorded and two research assistants randomly

reviewed two sessions in each group of ACT to confirm that the GACT followed the treatment manual. We decided to test the effectiveness and cost-utility of ACT as a stand-alone intervention. Thus, co-medication was not allowed in the GACT arm. Only occasional analgesics were permitted, but no anticonvulsants, opioids, antidepressants, or anxiolytics.

**RPT.** On the basis of US Food and Drug Administration (FDA) recommendations and the Spanish Consensus for the Treatment of Fibromyalgia, treatment with pregabalin (300-600 mg/day) was administered to FM patients by their GP.<sup>1</sup> In addition, those patients that fulfilled the criteria for major depression also received duloxetine (60-120 mg/day). Doses for each medication were administered within the recommended range according to efficacy and adverse effects. Other complementary pharmacological treatments, such as analgesics, benzodiazepines, hypnotics, etc., were also provided according to clinical guidelines. All participating GPs were provided with the Consensus, and a 2-hour information session was performed for the treatment of FM patients. One of the authors (JGC), with experience in treating FM patients, reviewed the medical records to confirm that the treatment was administered according to the aforementioned clinical guidelines, and the GPs were informed when any deviation was observed.

**WL.** Participants randomised to this condition were able to receive usual care and were offered their preferred intervention (GACT or RPT) at the conclusion of the RCT.

Figure 1 shows the flow of participants through the economic evaluation, and Table 1 displays the baseline sociodemographic and clinical characteristics of the participants by treatment group. A total of 39 participants (25%) had comorbid major

depression according to the MINI. There were no statistically significant differences between the three study arms in any sociodemographic or clinical variable at baseline.

Insert Figure 1

Insert Table 1

### *Study measures*

*Sociodemographic-clinical questionnaire.* The following information was collected: gender, age, ethnic group, marital status, living arrangements, education level, employment status, and annual income. In addition, relevant clinical variables, such as family and personal medical history, years elapsed since the first diagnosis of FM, and comorbid conditions were also assessed.

The *Mini-International Neuropsychiatric Interview* (M.I.N.I v5.0) is a brief and sound structured diagnostic interview.<sup>32</sup> The M.I.N.I. comprises 130 items and screens sixteen Axis I DSM-IV disorders and one personality disorder. The M.I.N.I is organized in diagnostic modules. For most modules, 2-4 screening questions are used to rule out the diagnosis when responded negatively. Positive responses to screening questions are explored by further investigation of other diagnostic criteria. We specifically assessed the presence of severe Axis I psychiatric disorders (dementia, schizophrenia, paranoid disorder, alcohol and/or substance use disorders).

### *Outcome measures*

The *EuroQoL questionnaire* (EQ-5D-3L)<sup>4</sup> is a widely used HRQoL instrument with a non-disease specific classification system that consists of two parts: A five-domain descriptive system assessing level of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with each domain being described at three levels: 'no problems' (level 1), 'some problems' (level 2), and 'extreme problems'

(level 3). The time frame is the day of response. Combinations of these categories define a total of 243 unique health states. Part 2 records the current subject's health on a Visual Analogue Scale (VAS); it consists of a visual scale graded from 0 to 100 where the respondent can self-report their current health status, with 100 being the best imaginable health level.

The *Client Service Receipt Inventory – Spanish version (CSRI)*.<sup>36</sup> The version of the CSRI used in this study was designed to collect retrospective data upon medication and service receipt. *Medication use*: a profile of the patient's use of some prescribed medications (analgesics, short- and long-acting opioids, anticonvulsants, antidepressants etc.) was requested, including the name of the drug, the prescriber, the dosage level, the total number prescription days for the drug, the daily dosage consumed, the reasons for changing the drug (when applicable), and adherence. *Service receipt*: the main categories were: emergency services (total visits), general medical inpatient hospital admissions (total days), and outpatient health care services (total visits to GP, nurse, social worker, psychologist, and other community health care professionals). Each service was recorded as being provided by the public or by the private sector. Patients were also asked about the type and number of diagnostic tests administered. The CSRI was administered on two occasions with equal timeframes: at baseline and at a 6-month follow-up; at both occasions, the previous 6 months were reviewed.

#### *Statistical analyses*

The economic evaluation of this RCT was performed according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement<sup>14</sup> and following the Good Research Practices for Cost-Effectiveness Analysis Alongside

Clinical Trials [ISPOR RCT-CEA Task Force report].<sup>28</sup> All statistical analyses were performed using STATA v13.0.

*Description of the costing procedure.* Costs were estimated from the healthcare and government perspectives during the 6 months of follow-up. Our government perspective included direct healthcare costs borne by the regional government at the different public health providers plus costs related to sick leave (lost productivity) borne by the Spanish government. Our healthcare perspective approaches only direct healthcare costs. Direct health care costs were calculated by adding the costs derived from medication consumption, medical tests, use of health-related services, and cost of the staff running the GACT intervention. The cost of medication was calculated by determining the price per milligram according to the Vademecum International (Red Book; edition 2014) and included the value-added tax. The total costs of medications were calculated by multiplying the price per milligram by the daily dosage used (in milligrams) and the number of days that the treatment was received. The main source of the unit cost data for medical tests and health services use was the SOIKOS database of health care costs.<sup>5</sup> The SOIKOS database contains information about Spanish healthcare service costs and was derived by systematic reviews of the literature; it consists of approximately 18,000 entries. The calculation of the total cost of the GACT intervention was based on the price per participant per group session of a clinical psychologist, established by the Official College of Psychologists of Spain. We obtained GACT data from therapist records. The cost of GACT session resources was assumed to be consistent across all sessions and groups, but the number of patients attending those sessions was not, therefore, actual GACT costs were dependent on the number of sessions attended by each participant. Indirect costs: Lost productivity was

calculated using the human capital approach, which involves multiplying the minimum daily wage in Spain for 2014 by the number of days of sick leave, as reported by each patient. Finally, total costs were calculated by adding the direct and indirect costs. Unit costs are expressed in Euros (€) based on 2014 prices. For the purpose of ICER/ICUR comparisons between countries, local currency can be converted into international dollars (Int\$) using purchasing power parity (PPP) exchange rates with 2014 as reference year (Indicators available at <http://www.oecd.org/std/prices-ppp>). PPP indicators are calculated by comparing the cost of living, domestic goods and services in countries across the world. An international dollar has the same purchasing power that the United States dollar has in the United States. PPP index in 2014: €1 = Int\$0.7. Table 2 shows the unit costs of healthcare resources. The time horizon was less than a year; therefore, it was not necessary to apply a discount factor to the costs.

Insert Table 2

*Utility scores.* They are obtained from the EQ-5D classification system and are used to rate patients' HRQoL on a scale from 0 (as bad as death) to 1 (perfect health). Negative values are possible and indicate a health state that is "worse than death". They reflect how the general population values the health status described by the subject, which is preferred for economic evaluations from a broad perspective. The first value set for the EQ-5D-3L health states was obtained from the general UK population, but country-specific EQ-5D-3L value sets were subsequently developed using a similar protocol. In our case, QALYs were calculated on the basis of these scores using the Spanish tariffs of EQ-5D-3L.<sup>3</sup> QALYs are an effort to take into account measures of both mortality and morbidity generated by healthcare interventions.<sup>35</sup> A QALY places a weight on time in different health states. Thus, a year of perfect health is worth 1 and a

year of less than perfect health is worth less than 1. QALYs provide a common metric to assess the extent of the benefits gained from different treatments in terms of HRQoL and survival for the patient. Along with EQ-5D utility scores, scores recorded on the EQ VAS were also used as an outcome for the analysis.

*Cost-utility analyses.* Cost-utility was explored through the calculation of incremental cost-effectiveness ratios (ICER), defined as the ratio between incremental costs and incremental effects measured on QALYs or EQ VAS points.<sup>29</sup> We use the term “incremental” because costs and benefits of the tested treatment are relative to a valued alternative treatment. There were four potential results from each intervention group comparison:

- (i) The intervention costs less and is more effective (has better outcomes) than the alternative, in which case the decision-maker would be likely to be attracted to the intervention;
- (ii) The intervention costs more and is less effective than the alternative, in which case it would be unlikely that the decision-maker considers the intervention;
- (iii) The intervention costs less but is less effective than the alternative; and
- (iv) The intervention costs more and is more effective than the alternative.

Results (i) and (ii) are scenarios that exhibit strong dominance, and the decision of whether or not to adopt the new intervention is typically straightforward. For results (iii) and (iv) however, the decision will depend on the value attached to differences in outcome. In these circumstances the approach would first be to calculate the ICER:

$$\text{ICER} = \Delta C / \Delta E$$

Where  $\Delta C$  denotes the difference in mean cost between the interventions being compared and  $\Delta E$  denotes the corresponding difference in the outcome.

Incremental costs and incremental effects were estimated with Zellner's seemingly unrelated regression (SUR) models using Stata's `sureg` command.<sup>8</sup> Cost and outcome measures were therefore included in a bivariate system that implemented a regression of costs and QALYs (or EQ VAS) on treatment allocations, i.e., whether they were assigned to GACT, RPT, or WL. The regressions controlled also for the following variables at baseline: age, gender, marital status, education level, living arrangement, employment status, minimum wage, duration of the illness since the first diagnosis, baseline costs and baseline outcome, depending on the equation considered. Estimates were run using 1000 bootstrap replications to address a possible skewness in the distribution of the dependent variables.<sup>6</sup>

First, we did a complete case analysis without the 20 FM patients who were lost at 6-month follow-up. Second, the cost-utility analysis was repeated following an intention-to-treat (ITT) approach (1st sensitivity analysis). The way in which missing data are handled is of crucial importance when assessing the results of economic evaluations. For the 6-month follow-up evaluation, a small number of missing values (12.8%) were imputed. We assumed data to be missing at random (MAR). Multiple imputation methods according to the chained equations approach were used to impute missing values for the EQ-5D-3L domains and for the costs of the non-responders at 6 months.<sup>30</sup> The imputation model, run on ten imputed datasets, included important sociodemographic and prognostic variables associated with the outcome variables and dropouts. Finally, we also performed a per protocol analysis (PPA; 2nd sensitivity analysis) in which the FM patients who did not attend the eight GACT sessions were excluded.

## Results

Table 3 contains the descriptive statistics of costs and outcomes at baseline and at 6-month follow-up, split by the three arms of the RCT, along with the adjusted and un-adjusted  $p$  values.

Insert Table 3

#### *Baseline costs*

Omnibus comparisons indicated that none of the apparent costs discrepancies between treatment arms reached statistical significance at baseline. Only differences in direct costs were marginally significant (adjusted  $p$  value = 0.08). Looking at the aggregates, it appears that RPT was the most expensive group at baseline in terms of direct costs (including only healthcare services), with an average cost of about €2700, higher than its counterparts GACT (around €1900) and WL (around €1500).

#### *Follow-up costs*

Looking at six-month follow-up costs, we could see that direct costs were higher for the WL group (around €2500) than for the RPT (€700) and for the GACT groups (€800). Posthoc pairwise comparisons were statistically significant (all adjusted  $p < 0.05$ ) with the exception of the comparison RPT vs WL that was marginally significant (adjusted  $p = 0.06$ ). Such higher costs observed in the WL group appeared to be mainly driven by specialised health care services. In this specific cost, the difference between GACT and RPT did not reach statistical significance (adjusted  $p = 0.07$ ). RPT and WL costs related to medication were unsurprisingly significantly higher when compared to GACT, but the specific comparison RPT against WL was not statistically significant. This result is obviously attributed to the nature of the GACT intervention that required individuals from this group to discontinue the use of most medications. Finally, while the mean cost of primary care visits slightly diminished at 6 months post baseline in the

control conditions, the use related to patients from the GACT group diminished to approximately €80. All between-group differences here were found to be statistically significant both with the un-adjusted and adjusted  $p$  values.

Focusing on indirect costs, participants from the WL group obtained significantly higher indirect costs than the GACT and RPT groups. The difference between the two active interventions was not significant (adjusted  $p$  value = 0.14). In a similar manner, in terms of total costs the WL group demonstrated the highest costs at greater than €4100, much more than the RPT group (almost €2700) and the GACT group (almost €2300). There were no significant differences in total costs between the active interventions (adjusted  $p$  value = 0.16).

#### *Baseline quality of life outcomes*

Outcomes at baseline were very similar between the three groups, ranging between 0.54 and 0.58 for the EQ-5D utility score and between 48 and 51 for the EQ VAS. The pairwise tests did not indicate any significant difference.

#### *Follow-up quality of life outcomes*

At this time-point the between-group differences were overall significant ( $p < 0.05$ ). EQ-5D for the GACT group was on average 0.80 while for RPT it was 0.75 and for WL it was 0.57. With the exception of the comparison GACT vs RPT, the other between-group differences were statistically significant. Average EQ VAS for GACT was 63, while for RPT it was 54 and for WL it was 51. With the exception of the comparison RPT vs WL, the other between-group differences were statistically significant. At the follow-up we were also able to compute QALYs based on the EQ-5D utility score. We did not find significant differences in QALYs between the active interventions (GACT and RPT), but the differences with the WL condition reached

statistical significance in both comparisons (GACT vs WL and RPT vs WL). Such QALYs based on the EQ-5D are one of the two outcomes that were used in the subsequent cost-effectiveness analyses.

*Cost-utility analysis from the government's perspective*

As shown in Table 4, GACT was found to be strictly dominant when compared to WL, that is, both the incremental cost (in €) and the incremental effects or benefits (in QALYs and EQ VAS points) were found to be statistically significant for the outcomes considered. In particular, the GACT intervention reduced costs of an average between €1800 and €2000 when compared against WL, depending on sample considered (Completers, ITT or PPA). The highest reduction was observed in the Completers' sample, whilst the lowest reduction has been shown within the ITT sample. For all the three samples, incremental effect on QALYs was found to be around 0.05. However, looking at the other outcome, EQ VAS, the highest incremental effect was observed in the PPA sample, with an average incremental effect of around 16, while in the ITT and in the Completers' sample the same effect was around 11 points.

When looking at the RPT intervention compared to WL, the incremental cost was negative and significant, averaging between €-400 and €-1600, depending on the sample considered. While the incremental cost was less than the one found in the GACT vs. WL comparison, the incremental effect was found to be similar in terms of QALYs, ranging around 0.04 for all the samples considered. While the RPT intervention remains competitive with GACT in terms of incremental costs (slightly higher) and incremental effects (slightly lower) when looking at quality of life based on EQ-5D, the situation looks different when considering EQ VAS as the main outcome, as it shows an

incremental effect between 3 and 4 points. This incremental effect is only significantly different from zero in the Completers' sample.

The lower part of Table 4 aims to compare the two interventions that have shown potential of cost-effectiveness, GACT vs. RPT. The average incremental cost for this comparison was around €-400, with GACT demonstrating lower cost than RPT, although such difference was not found to be significant in any of the three samples considered. The incremental effect for QALYs was found to be around 0.01, although it was significant only in the ITT sample. On the other hand, when looking at the EQ VAS outcome, the incremental effect was found to be significant in each comparison, with an average around 8 points in the Completers' and in the ITT samples, and a peak in the PPA sample, where the incremental effect of 13 points was observed.

Insert Table 4

#### *Cost-utility analysis from the healthcare perspective*

As shown in Table 5, results were very similar to those found in the government scenario, while incremental costs varied, given the different cost aggregated used for this part of the analysis. In particular, the incremental cost observed in the comparison between GACT and WL was included in a range between around €-1600 and €-1800. Incremental costs observed when comparing RPT and WL were around €-800 but were not found to be significantly different from zero at 95% confidence level. Finally, the incremental cost of the comparison between GACT and RPT was found to be around €-900 and significantly different from zero in all the samples considered.

In general, the healthcare scenario was more favourable for GACT than the government scenario, as incremental costs were negative and significant both for the comparison against WL and for the comparison against RPT. Symmetrically, the

healthcare scenario was penalising for the RPT when compared with GACT and when compared with WL. In the latter case, although the incremental cost remained negative, it was not significantly different from zero.

Insert Table 5

## Discussion

A group-based form of ACT as standalone intervention in comparison to recommended pharmacological treatment was related to better quality of life as well as less direct health care costs in people with FM. This significant decrease of direct costs was mainly due to a significant reduction in the costs related to medications and by significant savings in primary healthcare costs during the follow-up period. From the health care and government perspectives, all ICERs were dominant for GACT independent of the approach (completers, ITT or per protocol). Although our results should be viewed in a context of some design weaknesses and need cross-cultural validation, adopting any European or North-American investment ceiling (e.g., Spain= €25,000/QALY; Netherlands= €30,000/QALY; UK= £30,00/QALY; USA = \$60,000/QALY), GACT seems cost-effective for FM treatment compared to recommended medications and WL. In turn, recommended drugs for FM were cost-effective in comparison with the WL condition taking both perspectives and all type of analyses into account.

Despite the fact that regression models were bootstrapped with 1000 replications in order to address skewness within the data, the results reported here should be interpreted with caution given that the sample size in each study arm did not allow a robust estimation of costs, and confidence intervals were large in most cases. It is also important to point out that the only source of direct costs consisted of health care costs.

Direct non-healthcare costs including out of pocket expenses, costs of paid and unpaid help, travel expenses, and over-the-counter pharmacological use (eg. anti-constipation, vitamins, etc.) were not estimated. The intangible costs associated with patient suffering naturally were not included in the study either. In addition, due to potential reporting bias, we cannot dismiss the possibility that patients from the GACT condition concealed the use of medications, for example the use of opioids or anxiolytics as rescue medication. In contrast, participants in the RPT can claim to have taken their prescribed medication, when this is not the case. Regretfully, we do not know the extent of this contamination risk. Furthermore, the adherence to medication in the RPT arm was not measured with a reliable standardized instrument (e.g. The Morisky Medication Adherence Scale) or by other methods (e.g. pill counts), leaving no way to analyse the potential relationship between medication adherence, HRQoL, and costs. An important limitation is the six-month duration of the RCT. Possible long-term effects could not be assessed in this work. In contrast, we want to highlight that Hann & McCracken<sup>10</sup> recently judged the present RCT as having low risk of bias in relation to selection, detection, attrition and reporting. More recently, the study quality was assessed as high (7 of 8 quality criteria were met) using an adapted Jadad.<sup>37</sup>

This economic analysis was not the primary concern when the original RCT was designed. As a result there were design elements included that are not ideal for the current study. Specifically, one of the essential outcomes (direct costs) may be biased in favor of the GACT condition. This is because all participants in this condition were required to discontinue medication. In turn this design element could have directly resulted in decreased costs (not just in medication but also in medical visits) separate from effects of GACT itself. In light of a potential effect in the cost data from this

design element, the significant decrease in some costs associated with GACT should be interpreted with caution. Thus, it would have been preferable to have included a RPT *plus* GACT condition to determine the additive benefits of GACT over recommended medications. A related limitation is that our study design does not allow us to discern the relative contribution of the ACT methods versus the stopping of medication consumption – these are confounded here. In the Spanish healthcare system at least, the present RCT may not represent how ACT would be administered in the public clinical practice. If expanded in the public health sector, ACT would become a recommended add-on rather than alternative treatment to recommended medications. Again, we sincerely think that there is value in examining the cost-effectiveness of adding ACT to routine care as actually delivered, whether this includes RPT or not, for patients with FM. This will inform whether the addition of ACT is efficient. Moreover, an additive design (ACT *plus* RPT) may produce better clinical outcomes, at least among those FM patients not yet ready to discontinue RPT. We also want to point out that there were baseline imbalances in depression diagnosis and educational level between conditions. Even though these did not emerge as statistically significant, some impact on the cost-effectiveness results cannot be ruled out. While the trial was randomized and stratification was employed, precisely equal groups were not produced, by chance. This is not unusual but also not desirable. On the positive side can confirm that no detectible baseline imbalance in important clinical measures occurred (data available from the authors on request and published elsewhere<sup>21</sup>).

There is considerable evidence regarding the effectiveness of ACT,<sup>9,13,37,40</sup> but to our knowledge, the present work is the second published cost-effectiveness study for ACT in patients with chronic longstanding pain.<sup>15,18</sup> Although some studies that are in

progress include cost-effectiveness evaluations of ACT for chronic pain patients, we can state that economic evaluations are a neglected topic in this field. Currently, Hayes and colleagues<sup>11</sup> are examining the effectiveness and cost-effectiveness of an internet-delivered ACT treatment programme among chronic pain patients compared to waiting list as control condition. We hope that more ACT studies in the future will focus on efficiency besides effectiveness. To date, second-generation cognitive behavioural therapies have provided relatively robust evidence for their cost-effectiveness in the management of chronic pain. Lamb et al<sup>17</sup> conducted a large, pragmatic, multicentre, RCT that recruited participants from 56 general practices in seven regions across England. Patients in the intervention group attended the Back Skills Training (BeST) programme, which comprised an individual assessment plus six sessions of group CBT. Compared with the advice alone condition, the intervention was associated with significant benefits in nearly all outcomes at one-year follow-up. The probability of the CBT being cost effective reached 90% at about £3000 and remained at that level or higher above that threshold. More recently, one Dutch study<sup>7</sup> evaluated the effects of a CBT Internet-based intervention with e-mail therapist contact for patients with non-specific chronic pain complaints in comparison with the effects of a face-to-face CBT group intervention. Participants in both the Internet course and the face to face group showed significant improvement on pain catastrophizing, but at follow-up this improvement was significantly larger in the Internet course than in the face to face group. The cost-effectiveness analysis indicated that when 1 additional point improvement was gained on the Pain Catastrophizing Scale, an amount of €40 was saved. Future studies should address the cost-effectiveness of ACT for chronic pain patients compared to classical treatment options, such as CBT<sup>19</sup> or psycho-education<sup>22</sup>.

In our case, prescribing the FDA recommended drugs demonstrated lower total costs and higher QALYs from the government's perspective than waiting list. Cost-effectiveness studies of FM pharmacotherapy are beginning to appear in the literature,<sup>33</sup> particularly focused on pregabalin and duloxetine.<sup>16,27</sup> A recent network meta-analysis and cost-effectiveness analysis of new generation antidepressants indicated that duloxetine was the least well tolerated drug analysed,<sup>16</sup> while Parker and colleagues<sup>27</sup> concluded that more studies with favourable results are needed before pregabalin can be considered a cost-effective treatment option. Only 39 patients (25% of our sample) presented comorbid major depression, so we were underpowered to perform a cost-effectiveness analysis considering this subgroup of patients. It has been reported that there are subgroups of FM patients with different level of impairment, quality of life, and associated health care costs.<sup>20</sup> In the field of personalized medicine, the prescription of treatments depending on the profile of the FM patient, may be a relevant strategy for increasing effectiveness and, eventually, cost-effectiveness of available therapeutic approaches for the syndrome.

To sum up, this RCT represents the first computation of ICERs for group ACT in Spanish patients with FM. Our study shows that treating patients with FM with ACT in a group format resulted in significant quality of life benefits and it appears cost-effective compared to recommended pharmacotherapy. Therefore, group ACT might be considered not only an effective but also a cost-effective option in the management of patients with FM in public healthcare settings. However, due to the relatively small sample size in each study arm and other methodological shortcomings mentioned above, results based on the present RCT must be considered preliminary until more economic evaluations alongside well-designed RCTs are conducted. Our findings are

limited to patients with FM in Spain, so more empirical evidence is needed from RCTs carried out in other countries and sociocultural contexts before concluding that ACT is a cost-effective treatment for FM compared to usual care and recommended medications.

ACCEPTED MANUSCRIPT

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**Figure legends**

**Figure 1.** Flowchart of participants in the economic evaluation

**Table legends**

**Table 1.** Baseline socio-demographic and clinical characteristics of FM patients by treatment group.

**Table 2.** Unit costs used in the calculations of direct and indirect costs (financial year 2014; values in €)

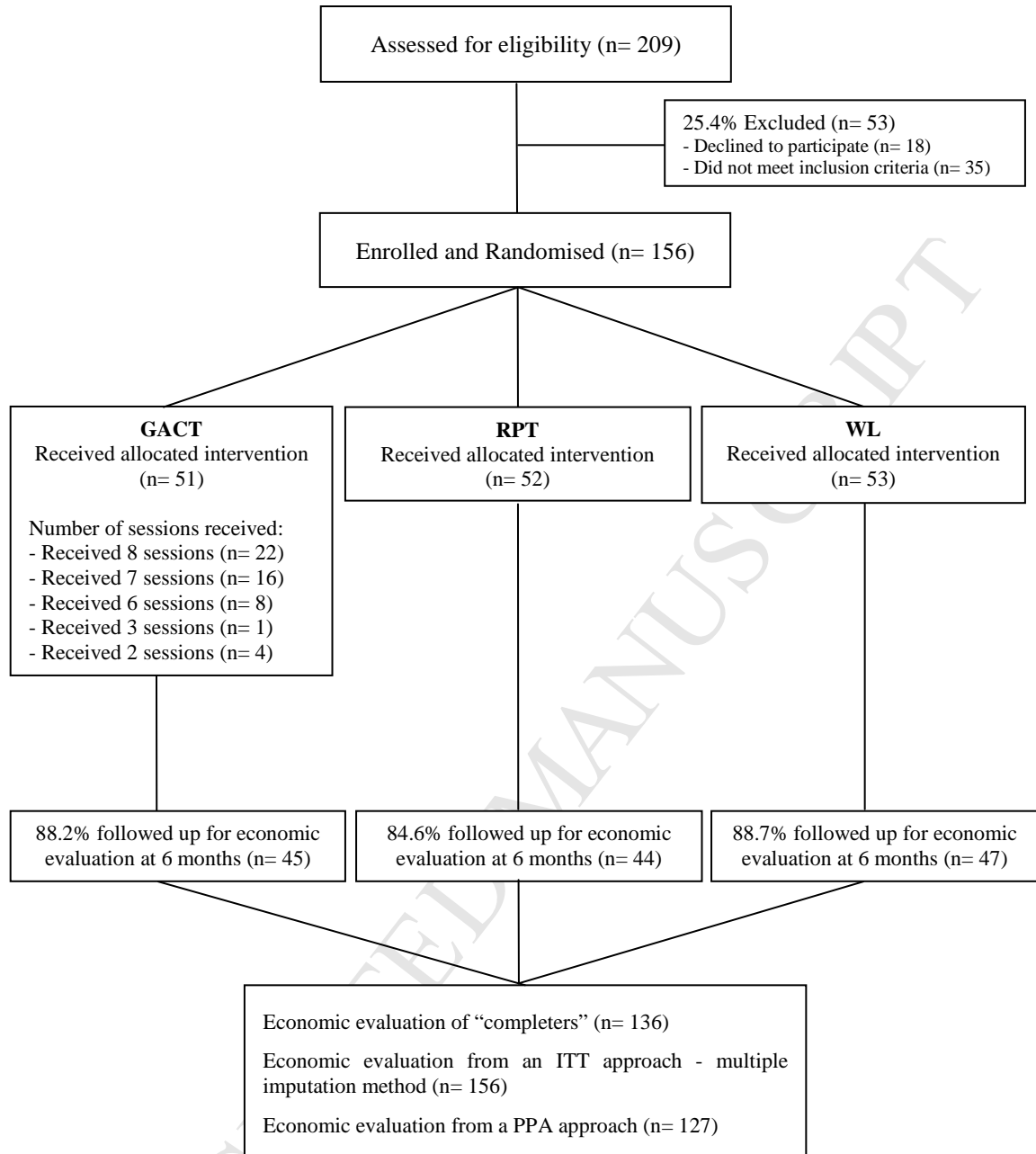
**Table 3.** Summary statistics of the costs (total and disaggregated in components) and outcomes by treatment group.

**Table 4.** Incremental cost, effect, and cost-effectiveness ratios from the government's perspective.

**Table 5.** Incremental cost, effect, and cost-effectiveness ratios from the healthcare perspective.

**Supplementary Table 1.** Incremental cost, effect, and cost-effectiveness ratios from the government's perspective (without covariates).

**Supplementary Table 2.** Incremental cost, effect, and cost-effectiveness ratios from the healthcare perspective (without covariates).



**Highlights**

- Economic evaluations of psychological therapies are scant in the chronic pain field.
- First cost-utility report of Acceptance & Commitment Therapy (ACT) in fibromyalgia.
- ACT was less costly and more effective than recommended pharmacological treatment.
- The inclusion of lost productivity costs slightly reduced the cost-utility of ACT.