Development of responder criteria for multicomponent non-pharmacological treatment in fibromyalgia

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ABSTRACT

Objective. *There is a need to identify individual treatment success in patients with fibromyalgia (FM) who received non-pharmacological treatment. The present study described responder criteria for multicomponent non-pharmacological treatment in FM, and estimated and compared their sensitivity and specificity.*

Methods. *Candidate responder sets were 1) identified in literature; and 2) formulated by expert group consensus. All candidate responder sets were tested in a cohort of 129 patients with FM receiving multicomponent non-pharmacological treatment. We used two gold standards (both therapist's and patient's perspective), assessed at six months after the start of treatment.*

Results. *Seven responder sets were defined (three identified in literature and four formulated by expert group consensus), and comprised combinations of domains of 1) pain; 2) fatigue; 3) patient global assessment (PGA); 4) illness perceptions; 5) limitations in activities of daily living (ADL); and 6) sleep. The sensitivity and specificity of literature-based responder sets (n=3) ranged between 17%–99% and 15%-95% respectively, whereas the expert-based responder sets (n=4) performed slightly better with regard to sensitivity (range 41%–81%) and specificity (range 50%–96%). Of the literature-based responder sets the OMERACT-OARSI responder set with patient's gold standard performed best (sensitivity 63%, specificity 75% and ROC area = 0.69). Overall, the expert-based responder set comprising the domains illness perceptions and limitations in ADL with patient's gold standard performed best (sensitivity 47%, specificity 96% and ROC area = 0.71).*

Conclusion. *We defined sets of responder criteria for multicomponent non-pharmacological treatment in fibromyalgia. Further research should focus on the validation of those sets with acceptable performance.*

Introduction

Fibromyalgia (FM) is a chronic, musculoskeletal illness of largely unknown aetiology. Key symptoms of FM are widespread pain, sleep problems or unrefreshing sleep, physical exhaustion and cognitive difficulties (1). Although several criteria have been developed to characterise and define FM, diagnosing patients with FM is still a challenging process, as no objective gold standard exists (2, 3). Updated treatment strategies for FM recommend that management of FM should focus first on non-pharmacological modalities, such as aerobic and strengthening exercise, cognitive behavioural therapies (CBT) and multicomponent therapies. Further (pharmacological) therapies should be considered according to patients' needs (4).

Given the chronic nature of FM, patients are forced to deal with their illness and handle its consequences. Non-pharmacological interventions focus on this process of adaptation and coping with FM in daily life. Exercise for example, has beneficial effects on physical capacity and FM symptoms (5), whereas cognitive behavioural therapies can improve coping with pain, and reduce depressed mood and health care seeking behaviour (6). Despite these positive treatment effects it needs to be recognised that FM is a heterogeneous illness implicating that FM symptoms, severity and effectiveness of treatment vary largely between patients. Therefore, in clinical practice it is very important to also assess the effectiveness of treatment for individual patients in order to tailor further treatment.

Responder criteria can assess the effectiveness of treatment and define clinically meaningful change in health

outcomes on patient level. Responder criteria are based on relevant outcome domains for the concerning illness. For rheumatoid arthritis (RA) and osteoarthritis (OA) for instance, responder criteria have been formulated and validated for pharmacological interventions focusing mostly on the outcome domains of pain, physical characteristics and patient's or physician's global assessment (7-11). For pharmacological interventions in FM, core sets of outcome domains have been formulated and tested (12). Two responder sets were identified as most sensitive in identifying response to pharmacological treatment in patients with FM; the first responder set comprised the outcome domains of pain, physical function, sleep or fatigue; the second responder set comprised the former outcome domains and the additional domains of depression, anxiety or cognition (12). Currently, no specific responder criteria for non-pharmacological treatment in rheumatic diseases, including FM, exist.

To our knowledge, only one study examined the validity of the OARSI responder sets for non-pharmacological care (13). The validity of these OARSI responder sets was demonstrated in OA patients receiving manual therapy and exercise therapy. Although these promising results, it is questionable whether responder sets developed for pharmacological interventions are suitable for non-pharmacological treatment. Other outcome domains, such as cognitions and limitations in activities of daily living (ADL), could be more important than pain or physical characteristics in non-pharmacological care, in particular for patients with FM. Furthermore, no study has systematically and comprehensively examined a range of existing criteria sets for their sensitivity and specificity in non-pharmacological care in FM.

In this study newly formulated and existing responder criteria sets will be tested for their applicability in an evidence based multicomponent non-pharmacological treatment for FM, comprising (graded) exercise and tailored CBT. The overall goal of this treatment was to learn to cope with and diminish the consequences of FM in daily life and increasing or regulating the level of daily activities, which reflects different physical and psychological outcome domains. The aim of this exploratory study is to define responder criteria for multicomponent non-pharmacological treatment in FM; and to estimate and compare their sensitivity and specificity.

Methods

Design

In this exploratory study we followed a three-step approach, integrating evidence from literature and face validity of an expert panel, to develop responder criteria for multicomponent non-pharmacological treatment for fibromyalgia. Subsequently these responder criteria were collated to responder sets and tested against two gold standards, for their sensitivity and specificity in a sample of patients with fibromyalgia.

Patients

Data for this observational pre-post study was obtained between March 2012 and February 2014, and came from two samples of patients enrolled in a multicomponent non-pharmacological treatment for fibromyalgia 'Fibromyalgie in Actie" (FIA), after being classified as having FM by certified rheumatologists. Study location was the Sint Maartenskliniek rheumatology outpatients clinic, located in Nijmegen and Woerden, the Netherlands. Sample one (FIA8; moderate FM complaints) and sample two (FIA16; more severe FM complaints) comprised of patients attending respectively 8 and 16 sessions during a 8-week period. Allocation to the FIA8 or FIA16 was based on patients' intake score of the Hospital Anxiety and Depression Scale (HADS) (14) (HADS total score ≥15 points is indicative for FIA 16).

Further eligibility criterion for study participation was provision of informed consent. Before the start of the treatment programme, no differences in gender, age and body mass index (BMI) were found between both samples. Therefore, data from both samples was collated to examine the sensitivity and specificity of responder sets. The Institutional Review Board of the Radboud University Medical Centre, Nijmegen concluded that the Medical Research Involving Human Subjects Act did not apply to this study (protocol number: 2009/166).

Procedure data collection

Questionnaires were sent by mail or e-mail to all patients before, and at six months after the start of the multicomponent non-pharmacological treatment programme. Furthermore, questionnaires were sent by e-mail to the health professionals at six months after the start of treatment, and they were asked to complete these questionnaires after a consult by phone with the patient.

Patient Reported Outcome Measures (PROMS)

Measures were sought that were able to evaluate the most important symptoms and/or relevant outcome dimensions in fibromyalgia before and after multicomponent non-pharmacological treatment. Patients filled out a set of questionnaires comprising the following outcome dimensions: 1) pain; measured with the Visual Analogue Scale (VAS), ranging from 0 'no pain' to 100 'unbearable pain', 2) fatigue; measured with item 16 of the Fibromyalgia Impact Questionnaire (FIQ) (15), ranging from 0 'no tiredness' to 10 'very tired', 3) sleep; measured with item 17 of the FIQ, ranging from 0 'awoke well rested' to 10 'awoke very tired', 4) patient's global assessment (PGA); measured with the question: "If you consider all ways in which your rheumatic disease influences your life, how are you doing at this moment?" (VAS), ranging from 0 'miserable' to 100 'excellent', 5) illness perceptions; measured with the Brief Illness Perception Questionnaire (B-IPQ) (16), total ranging score from 0 to 80; consisting of 8 items each with a numerical rating scale from 0 to 10, (a higher score reflecting a threatening view of the illness), and 6) functional status, *i.e.* limitations in activities of daily living (ADL); measured with the Patient Specifieke Klachten (PSK) (17), ranging from 0 'no problems' to 100 'impossible'. As allocation to treatment was based on patient's mood (HADS-

score), this measure was not included in the outcome measures. The previously mentioned six PROMS were used in the development of the responder sets (paragraph 2.6), and the responder sets were subsequently compared to gold standards for treatment effect in FM (paragraph 2.5), in order to obtain their sensitivity and specificity.

Definition of gold standard

As a gold standard for treatment effect in FM is lacking, two questions, one from patient's perspective and one from health professional's perspective, were used as gold standard in this study. For the first gold standard patients' perspective on health status change six months after start of treatment was taken. Patients answered the question "To what extent is your daily functioning improved from the start of the treatment programme?" Rating was done using a seven point Likert scale: "worse than ever", "much deteriorated", "somewhat deteriorated", "no improvement", "somewhat improved", "much improved" and "very much improved". Patients were defined as responder, if according to the patient, daily functioning was "much improved" or "very much improved". For the second gold standard health professional's judgement about patient's goal attainment six months after the start of treatment was taken. General goals for both multicomponent non-pharmacological treatment programmes ("FIA") were: 1) To gain knowledge and insight in FM and personal perpetuating factors of FM, 2) To integrate a healthy movement pattern in daily life (avoid being overactive or underactive), 3) To move from pain contingent activity towards goal contingent activity, and 4) To increase the level of activities in daily life. Health professionals answered the question: "To what extent was treatment goal (*i.e.* 1 through 4) reached by the patient?" Rating was done using a five point Likert scale: "not at all", "to some extent", "to moderate extent", "to a large extent" and "completely". Patients were defined as responder, if according to the health professional, treatment goals were reached at least on average "to moderate extent".

Table I. Characteristics of study sample and PROMS pre-treatment and follow-up (six months after start of treatment).

	Pre-treatment	Follow-up
Study sample (n=129)		
Female; n (%)	121 (94%)	
Age, years; mean (SD)	44 (11)	
Body mass index, kg/m^2; mean (SD)	27.7 (5.2)	
PROMS*±		
Pain, VAS (0-100); mean (SD)	63.3 (19.7)	50.5 (23.4)
Limitations in activities of daily living, PSK; mean (SD)	69.4 (12.8)	51.8 (20.9)
Patient's global assessment, VAS (0-100); mean (SD)	44.0 (22.6)	54.4 (21.6)
Illness perceptions, IPQ (0-80); mean (SD)	49.2 (9.3)	40.0 (11.1)
Fatigue, FIQ (0-10); mean (SD)	7.9 (1.6)	6.7 (2.4)
Sleep, FIQ (0-10); mean (SD)	8.1 (1.7)	7.0 (2.4)

*High scores on pain, limitations in activities of daily living, illness perceptions, fatigue and sleep reflect poor outcomes on these health domains. High scores on patient's global assessment reflect good outcomes on this heath domain.
± All measurements are significantly different between pre-treatment and follow-up (p<0.01).

Development of candidate responder sets

A three-step approach, derived from previous work (18), was used to define candidate responder sets for successful multicomponent non-pharmacological treatment. An expert panel (n=7) was formed, consisting of a physical therapist, an occupational therapist, a social worker, a rheumatologist and three researchers. Step one was a literature search conducted by one researcher (V.V.). In step two, members of the expert panel independently evaluated and ranked existing responder sets and the magnitude of change scores. In step three a face-to-face meeting with the expert panel was conducted to discuss previous steps and reach consensus about candidate responder sets.

• *Step one: Literature review*

Existing responder sets for (pharmacological) treatment of rheumatic diseases until 2016 were collected through a literature search in PubMed using the terms: "responder" or "core set", and "fibromyalgia" or "osteoarthritis" or "rheumatoid arthritis". Additional references were identified from references found in the articles of the original search.

• *Step two: Ranking responder sets and outcome domains, and defining change scores*

Members of the expert panel systematically reviewed the existing responder sets from literature, by indicating the importance (from 1 = "most important" to 3 = "least important") of each set for use in non-pharmacological treatment. Outcome domains extracted from all responder sets were scored on importance (from 1 = "most important" to 3 = "least important") for non-pharmacological treatment. Additional relevant outcome domains could be formulated and scored as well. Furthermore, members of the expert panel were asked to indicate whether absolute and/or relative change would be used to measure improvement in outcome domains. Furthermore, this step comprised formulation of the absolute number and/or percentage of change in the relevant outcome domains. Existing change scores from responder sets in literature were used as a guide in the formulation of change scores for multicomponent non-pharmacological treatment in FM.

• *Step three: Consensus expert panel*

Data from step one and step two was collected by one researcher (V.V.), and the expert panel received this data at the start of the face-to-face meeting. The goal was to reach consensus about appropriate candidate responder sets for multicomponent non-pharmacological treatment in FM. For both responder sets from literature, and newly defined responder sets, consensus was reached by discussion and democratic decision-making.

Statistical analyses

Of the initial 173 participants in the study, 29 participants were lacking pre-treatment PROMS measurement and/or gold standard measurement from the health professional, and were therefore excluded from the analyses (17%). Of the remaining 144 participants, 15 participants were lost to follow-up (*i.e.* response rate of 90% at six months after the start of treatment). No significant differences in variables measured pre-treatment were found, between participants with and without follow-up ($p \geq 0.05$). Complete cases analyses were conducted for 129 patients. Further missing data of PROMS ranged between 0 and 3%, and missing data of gold standards was 5% for the health professionals, and 1% for the patients.

Descriptive statistics (mean and SD), where appropriate, were computed pre- and post-treatment. Scores on the FIQ and B-IPQ were converted to range from 0 to 100, hereby equalising the scoring range of all outcome measure before entering the responder set.

Crosstabs were calculated for sensitivity, specificity and ROC area of the responder sets against the gold standard of both health professional and patient. A figure was designed, integrating all responder sets' ROC area in one figure for optimal visual comparison of differences between the responder sets. For this study, an acceptable ROC area was defined as 0.7 or above (19).

Finally, to test the robustness of the analyses, sensitivity analyses were conducted. For this purpose, all missing data were imputed by using multiple imputation with creation of 10 imputed datasets. Analyses of the imputed data yielded no different results and is therefore not shown. Statistical analyses were performed using Stata 13.1.

Results

Patient characteristics and PROMS

Characteristics of the study sample and PROMS are displayed in Table I. The vast majority of the group were female adults, and on group level all PROMS improved significantly after treatment.

Candidate responder sets

Review of existing literature yielded

Table II. Overview of responder sets for testing in multicomponent non-pharmacological treatment in FM.

Responder Sets	Health professional's judgment			Patient's perspective		
	Sensitivity (%)	Specificity (%)	ROC area	Sensitivity (%)	Specificity (%)	ROC area
Literature-based responder sets						
#1 NORMAN * Improvement of one half of the SD (baseline) in at least one of the six following: • pain • limitations in activities of daily living • patient's global assessment • illness perceptions • fatigue • sleep	95	15	.55	99	29	.64
#2 OMERACT-OARSI * High improvement in pain or in limitations in activities of daily living ≥50% and ≥20 SU OR * Improvement in at least 2 of the 3 following: • pain ≥ 20% and ≥ 10 SU • limitations in activities of daily living ≥20% and ≥10 SU • patient's global assessment ≥20% and ≥10 SU	61	65	.63	63	75	.69
#3 ARNOLD * Improvement in pain ≥ 30% and limitations in activities of daily living ≥10% and in at least 1 of the 2 following: fatigue or sleep ≥30%	17	95	.56	17	91	.54
Expert-based responder sets						
#4 EXPERT1 * Improvement in illness perceptions ≥15% and ≥10 SU OR * Improvement in at least 2 of the 3 following: • illness perceptions ≥10% and ≥5 SU • limitations in activities of daily living ≥10% and ≥ 5 SU • patient's global assessment ≥10% and ≥5 SU	80	50	.65	81	50	.65
#5 EXPERT2 * Improvement in illness perceptions ≥15% and ≥10 SU and limitations in activities of daily living ≥15% and ≥10 SU	41	85	.63	43	96	.69
#6 EXPERT3 * Improvement in illness perceptions ≥15% and ≥ 10 SU and improvement in limitations in activities of daily living ≥10% and ≥5 SU	45	85	.65	47	96	.71
#7 EXPERT4 * Improvement in illness perceptions ≥10% and ≥5 SU and limitations in activities of daily living ≥ 10% and ≥5 SU	54	80	.67	54	83	.68

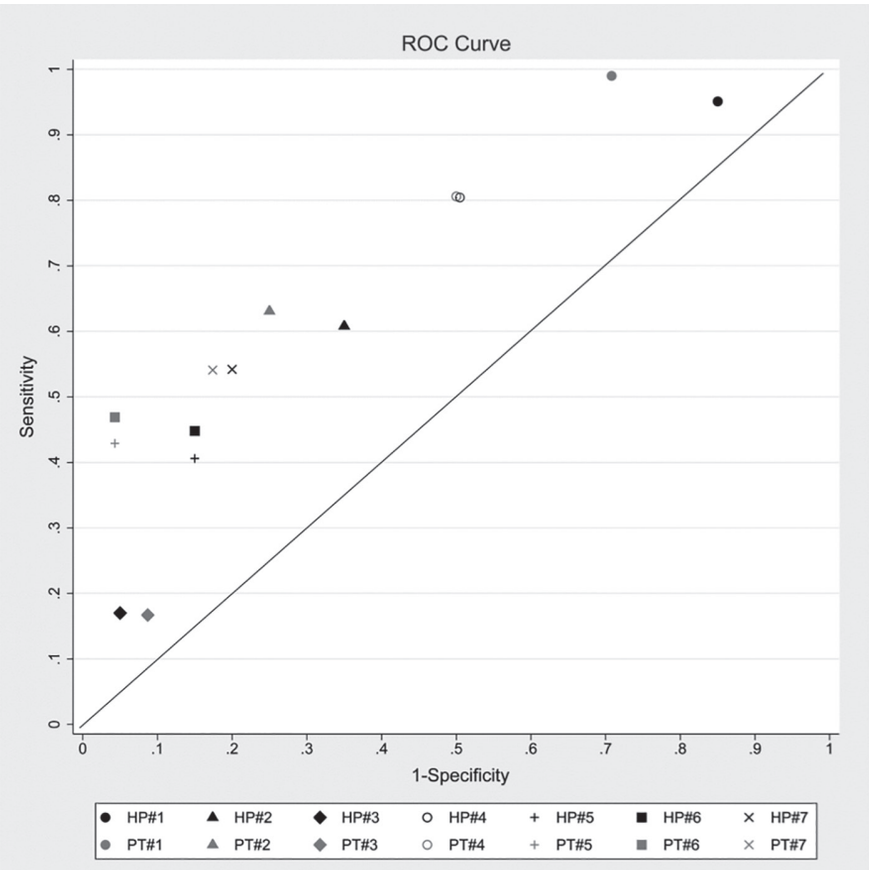

Fig. 1. ROC Curve of the responder sets against both gold standards.
HP: Health professional's gold standard; PT: Patient's gold standard; #: numbers correspond with numbers of the responder sets in Table II.

nine responder sets (7-12; 20-22) (Norman, Albright, Tubach, Felson, Paulus, Pincus, Dougados, Pham, Arnold). Three responder sets were found most important and eligible for testing in multicomponent non-pharmacological treatment in FM by the expert group; the sets of Norman, Pham and Arnold (Table II). Furthermore, 10 outcome domains were extracted from literature; pain, (physical) function, return to work, patient satisfaction, patient's global assessment (PGA), fatigue, sleep, depression, anxiety, and cognitions, and three additional outcome domains were formulated by the expert panel; illness perceptions, self-management skills, and limitations in activities of daily living (ADL). Of these 13 outcome domains, three domains were found most important by the expert panel to be incorporated in responder criteria for FM, and were: 1) PGA, 2) illness perceptions, and 3) limitations in ADL. Both absolute and relative change of outcome domains were considered important by the expert panel, and were therefore included in the responder sets. The magnitude of change of outcome domains was also discussed and defined; relative change percentages ranged from 10%–15%, and absolute change ranged from 5–10 standardised units (SU). Compared to existing responder sets, these change scores are small, as the expert panel expected limited change in the relevant domains for non-pharmacological treatment in FM. Eventually, the expert panel defined four new responder sets (Table II), with potentially relevant combinations of above mentioned outcome domains and change scores. In total, seven responder sets were tested against the gold standards; three literature-based sets and four expert-based sets.

Responder sets for FM and their sensitivity, specificity and ROC area

Sensitivity, specificity and ROC area for each responder set against both gold standards are displayed in Table II. The sensitivity and specificity of literature-based responder sets (n=3) ranged between 17%–95% and 15%–95% respectively, whereas the expert-based responder sets (n=4) performed slightly better with regard to sensitivity (range 41%–80%) and specificity (range 50%–85%).

Patient's gold standard performed slightly better than health professional's gold standard for all literature and expert-based responder sets, except for responder set #3 (Norman).

Of the literature-based responder sets the OMERACT-OARSI responder set with patient's gold standard performed best (sensitivity 63%, specificity 75% and ROC area = 0.691). Overall, the expert-based responder set comprising the domains illness perceptions and limitations in ADL (#6) with patient's gold standard performed best (sensitivity 47%, specificity 96% and ROC area = 0.713).

All responder sets' sensitivity and specificity scores are displayed in Figure 1.

Discussion

This is the first study that tested sets of responder criteria for multicomponent non-pharmacological treatment in fibromyalgia. Literature-based and expert-based sets were evaluated against both health professional's and patient's perspective on treatment success, reflected in two separate gold standards. The expert based set (#6), with both relative and absolute improvement in the domains of illness perceptions and limitations in activities of daily living, discriminated the best between patients' perceiving no improvement versus small to large improvement of daily functioning at six months after the start of treatment. With a sensitivity of 47%, specificity of 96%, and a ROC area of 0.71, this set performed at an acceptable level.

An important finding from our study was that, in general, responder sets that were defined by experts in the field of fibromyalgia (*i.e.* expert-based responder sets), performed slightly better than literature-based responder sets. Expert-based responder sets differed from literature-based sets in the way

that none of the expert-based responder sets comprised the domain of pain, and that formulated change scores in the expert-based responder sets were relatively small (10%–15% and 5–10 SU) compared to change scores in literature-based responder sets (10%–50% and 10–20 SU). The literature-based responder sets, defined by experts in the field of pharmacological care in osteoarthritis and fibromyalgia, were tested to investigate to which extent domains and change scores from pharmacological treatment were also relevant for non-pharmacological treatment. As the literature-based responder sets performed slightly worse, this suggests that experts' expertise is warranted for the careful formulation of responder sets in a certain health context, when no responder sets are available in that area yet.

In our study, the literature-based responder set for the pharmacological treatment of patients with fibromyalgia (FM30short) performed the worst, for both gold standards (12). This is an unexpected finding since the FM30short responder set reflects the focus of (non-) pharmacological treatment of fibromyalgia, which is a reduction of pain, fatigue and/or improvement in sleep (23, 24). Our finding suggests that successful treatment in non-pharmacological care of fibromyalgia cannot be fully captured in the domains of pain, fatigue and/or sleep, with relatively high change scores (up to 30%). Probably an indication that this FM30short responder set is not tailored enough for multicomponent treatment in fibromyalgia. Therefore, responder criteria might need to be aligned with other treatment goals of multicomponent non-pharmacological treatment of FM, such as improvement in illness perceptions (cognitive goal) or activity pacing (behavioural goal), and/or smaller change scores.

From all literature based responder sets, the OMERACT-OARSI responder set (#2) with patient's gold standard performed best (ROC area of 0.69). This could be due to relatively small (*i.e.* 20%) change scores on for example the domains of limitations in activities of daily living and patient global assessment of health status. In our study the sensitivity and specificity of this set reached 63%, and 75%, respectively. This relatively high specificity is a positive finding, since a high specificity is important for clinical practice (*i.e.* finding out which patients truly do not respond to treatment). Gaining insight in potential improvement in patient's health outcomes enables health professionals to evaluate treatment. If there is no improvement, current treatment could be adjusted. In this case other (pharmacological) treatment, tailored to the specific needs of the patient, should be considered.

In line with the explorative nature of our study, and as no valid objective gold standard exists to evaluate non-pharmacological multicomponent treatment success, we decided to test our candidate responder sets against two gold standards. In general, patient's gold standard performed slightly better across all responder sets than health professional's gold standard. Meaning that patient's experienced amount of improvement in daily functioning corresponded best with their experienced amount of change on the several outcome domains. An alternative explanation might be that common-method bias is present, as both the gold standard and the outcome domains were patient self-reported. This could have resulted in higher sensitivity and specificity rates, because of this shared measurement method. Furthermore, it also indicates that patient's perspective of change in daily functioning since the start of treatment and health professional's rating of general treatment goals (about for example activity patterns) are two different concepts. However, both perspectives are important in evaluating multicomponent non-pharmacological treatment of fibromyalgia, as treatment is an interactive, mutual process between health professional and patient.

A strength of this study is that our gold standards were taken six months after the start of treatment, whereas treatment was completed after approximately 2 months. This might be an indication that patients achieved important changes in daily functioning and activity patterns, and that this behaviour change was maintained over time.

A first limitation of this study is that perhaps not al potentially relevant outcome domains were measured. For example, knowledge of fibromyalgia, and self-management skills were indicated by the expert panel as being relevant outcome domains for multicomponent non-pharmacological treatment of fibromyalgia. These outcome domains were, however, not included in the responder sets, as reliable measurement instruments were not present at time the study was conducted. A second limitation was not investigating the measurement error of the measurement instruments that we used. Change scores always comprise of true individual change and some measurement error, therefore it remains unclear whether the changes in outcome measures defined in our study are a true treatment effect, placebo effect, or measurement error. We only investigated the performance of responder sets in an observational design, whereas an experimental design could have revealed possible placebo effects of treatment. Finally, we did not invite patients in the expert panel, which could have led to potential additional relevant outcome domains for patients not being represented in the responder sets.

A next step would be to validate the responder sets with acceptable, or close to acceptable performance (*i.e.* responder set #6 and #2) in patients with fibromyalgia receiving multicomponent non-pharmacological treatment elsewhere. Additionally, responder sets with combinations of (other) relevant outcome domains for fibromyalgia could also be tested. After reaching acceptable performance in external validity testing and feasibility testing, these responder sets then could be used in clinical practice to evaluate treatment effect. Alternatively, responder sets could also be used for comparative effectiveness research of health programmes. Overall, the responder set with illness perceptions and activities in daily living was best able to distinguish treatment success from treatment failure. Our current study was a first step to contribute to the knowledge of relevant outcome domains and change scores in multicomponent non-pharmacological treatment of patients with fibromyalgia.

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