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ABSTRACT. Following development of the core domain set for fibromyalgia (FM) in Outcome Measures in Rheumatology Clinical Trials (OMERACT) meetings 7 to 9, the FM working group has progressed toward the development of an FM responder index and a disease activity score based on these domains, utilizing outcome indices of these domains from archived randomized clinical trials in FM. Possible clinical domains that could be included in a responder index and disease activity score include pain, fatigue, sleep disturbance, cognitive dysfunction, mood disturbance, tenderness, stiffness, and functional impairment. Outcome measures for these domains demonstrate good to adequate psychometric properties, although measures of cognitive dysfunction need to be further developed. The approach used in the development of responder indices and disease activity scores for rheumatoid arthritis and ankylosing spondylitis represents heuristic models for our work, but FM is challenging in that there is no clear algorithm of treatment that defines disease activity based on treatment decisions, nor are there objective markers that define thresholds of severity or response to treatment. The process of developing candidate dichotomous responder definitions and continuous quantitative disease activity measures is described, along with participant discussions from OMERACT 10. Final results of this work will be published in a separate report pending completion of analyses. *J Rheumatol* 2011;38:1487–95; doi:10.3899/jrheum.110277

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Fibromyalgia (FM) is characterized by chronic widespread pain and tenderness on physical examination, as defined by the 1990 American College of Rheumatology (ACR) Fibromyalgia Classification Criteria¹. Additional characteristic features include fatigue, sleep disturbance, cognitive dysfunction, and other somatic symptoms, which are included in the 2010 ACR Preliminary Fibromyalgia Diagnostic Criteria².

The prevalence of FM in the population is at least 2%,

occurring more frequently in women than in men³. Current evidence suggests that FM results from disordered central pain and sensory processing. Dysregulation of several neuropeptide and neurohormone networks has been identified, leading to a deficiency in pain inhibitory pathways and/or increase in facilitatory networks^{3,4,5}. The triggering and maintenance of FM appears to result from both genetic disposition and environmental influences such as emotional or physical stressors, or illness⁶.

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Over the last decade, several medications known to modulate these abnormal neurobiological pathways have been studied in randomized controlled trials (RCT) utilizing outcome measures to assess individual clinical domains of FM. These RCT have resulted in US Food and Drug Administration (FDA) approval of 3 medications, and review of another is under way. The FDA-approved medications are pregabalin, an $\alpha 2\delta$ modulator, and duloxetine and milnacipran, both serotonin-norepinephrine reuptake inhibitors^{7,8,9,10,11,12,13,14}. As these clinical development programs were getting under way, several issues were recognized, including a lack of consensus regarding the “core” set of domains that should be assessed in RCT, lack of standardization and validation of outcome measures to assess these domains in FM, and the absence of quantitative measures of disease activity and composite responder criteria as commonly utilized in other rheumatic diseases, such as rheumatoid arthritis (RA).

Establishing the Core Domain Set for FM

Recognizing these needs, a group of clinicians/researchers interested in FM formed a working group in 2003 that proceeded to conduct, through 2008, a series of OMERACT workshops and a module to define a core set of domains for assessment in FM RCT and longitudinal observational studies (LOS)^{15,16,17,18,19,20} (Figure 1). Initial elements of this project included an expert Delphi exercise, patient focus groups, and a patient Delphi exercise in order to better

understand those domains in FM considered important by both clinicians and patients^{15,16,17,18}. The key domains derived from this series of exercises were then examined by analyzing data from several RCT databases, and using multivariate regression modeling to identify the most important set of domains to assess, unique to FM. It was proposed and ratified at OMERACT 9 that the core domains that should be assessed routinely in RCT and LOS in FM included pain, tenderness, fatigue, sleep disturbance, patient global response, and multidimensional function. In addition, cognitive dysfunction and depression were considered important, but instruments to appropriately assess these in FM required further development and validation for use in FM. Items placed in the research agenda for consideration, as well as development of specific instruments to assess their influence in FM, included stiffness, anxiety, cerebrospinal fluid biomarkers, and indices derived from neuroimaging techniques.

Outcome Measures for FM Domains

As described, the recommended core domains to measure in RCT and LOS of FM are pain, fatigue, sleep disturbance, patient global assessment [often measured as patient global impression of change (PGIC)], and multidimensional function. A variety of outcome measures have been utilized in FM trials to assess these domains (Table 1). Performance characteristics for the instruments included in Table 1 (e.g., discrimination, and effect sizes) have been evaluated in

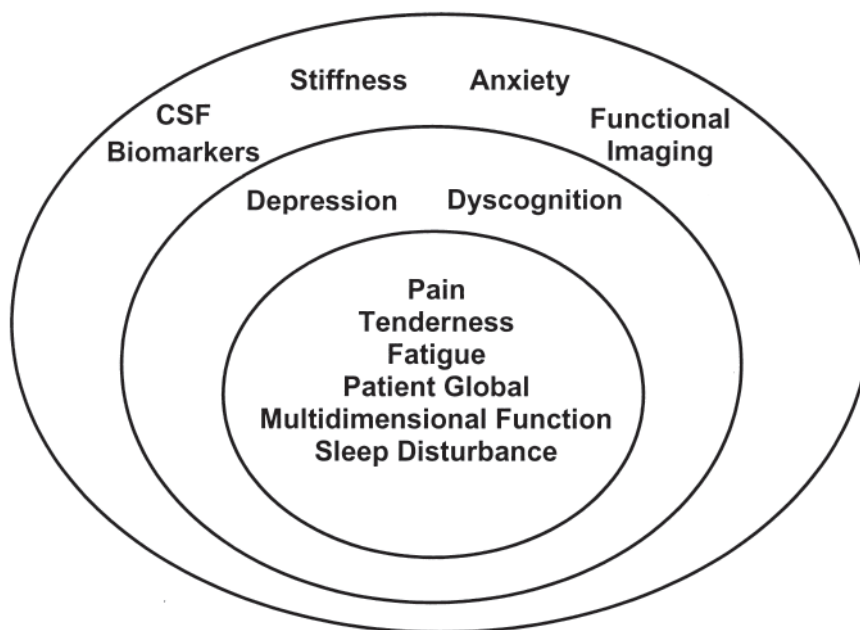


Figure 1. Core set of domains for fibromyalgia (FM). Concentric circles indicate the hierarchy of domains. Inner circle includes the core set of domains to be assessed in all clinical trials of FM. The second circle includes the outer core set of domains to be assessed in some but not all FM trials. The outermost circle includes the domains on the research agenda that may or may not be included in FM trials. CSF: cerebrospinal fluid. From Mease, *et al.* J Rheumatol 2009;36:2318-29²⁰.

Table 1. Outcome measures used in clinical trials.

Pain	Visual analog scale (VAS) pain, paper diary VAS pain, electronic diary Numeric rating scale (NRS), daily diary Fibromyalgia Impact Questionnaire (FIQ) pain Brief Pain Inventory, pain severity scores Medical Outcomes Study Short-Form 36 (SF-36) bodily pain
Tenderness	Dolorimetry — tender point threshold
Fatigue	VAS fatigue, daily diary Fibromyalgia Impact Questionnaire fatigue SF-36 vitality Multidimensional Fatigue Inventory (MFI) Multidimensional Assessment of Fatigue
Sleep	NRS of sleep quality, daily diary FIQ morning rested feeling Medical Outcomes Study sleep scale Jenkins' Sleep Problems Scale
Depression	Beck Depression Inventory (BDI) Hamilton Depression Rating Scale FIQ depression Hospital Anxiety and Depression Scale (HADS) depression MFI motivation
Anxiety	FIQ anxiety HADS anxiety
Cognition	Multiple Abilities Self-Reported Questionnaire MFI mental fatigue
Stiffness	FIQ stiffness
Physical function	SF-36 physical function FIQ physical function BDI pain interference with walking
Social function	SF-36 social function Sheehan Disability Scale (SDS) social and family life scales BDI pain interference with relations with other people
Work function	SDS work/school scale FIQ ability to do work BDI pain interference with work
Activity	BDI pain interference with activity MFI reduced activity SF-36 role emotional, role physical
Quality of life	EuroQol Questionnaire 5 dimensions

accord with the “OMERACT filter”: truth, discrimination, and feasibility. In a recent study by Choy and colleagues from the OMERACT FM working group, specific outcome measures used in the RCT of 4 pharmacological agents used to treat FM were analyzed for content, construct, criterion, and discrimination validity¹⁹. Outcome measures were mapped onto the following domains: pain, patient global assessment, fatigue, health-related quality of life, multidimensional function, sleep, depression, physical function, tenderness, cognitive dysfunction, and anxiety. For measures with subscales, such as the Medical Outcomes Study Short-Form Health Survey (SF-36) and Fibromyalgia Impact Questionnaire (FIQ), individual subscales and component scores were mapped and analyzed separately^{21,22}.

Univariate analysis showed overall at least moderate correlations, i.e., an r value ≥ 0.4 , between measures of the core set domains and the global measure of improvement (i.e., PGIC). Measures of depression were the exception, where

the correlation coefficient was less than 0.5. The ability to evaluate depression measures in these trials may have been limited by the fact that patients with moderate to severe depression were excluded from trials of 3 of the 4 compounds in this evaluation, yielding low baseline depression scores, and thus a limited range for correlational analyses. In multivariate regression analyses predicting PGIC, pain, fatigue, physical function, multidimensional function, and depression were retained as independent contributors of variance in all analysis scenarios, with r^2 values ranging from 0.41 to 0.671. Tenderness (separate from self-reported pain) was retained in the 3 trials in which it was assessed. Sleep was retained in 2 of the 3 possible models. Some issues regarding the applicability of several of the questions, such as “snoring,” in the most commonly used sleep instrument [i.e., the Medical Outcomes Study (MOS)] suggested that it might not be an ideal measure for FM. Stiffness was retained in 2 of 4 models, and cognitive dysfunction was not

retained, although it was only formally assessed in one of the clinical trial programs. Although this domain is considered an important one by FM patients¹⁸, and research has demonstrated impairment of cognitive function in patients with FM, particularly working memory²³, few clinical studies have assessed the domain. In one clinical trial program, a self-assessment cognition questionnaire was utilized and showed improvement in the treatment arm¹⁹. However, in a more recent clinical trial with a similar drug, in which more objective, computer-applied cognition-testing measures were employed, no difference between treatment and placebo was noted, and it is unclear whether this was related to treatment, the study population, or outcome measures utilized²⁴. More research is needed to determine how best to approach the assessment of cognitive dysfunction in FM and how its assessment fits in the core set of FM.

Conclusions for this exercise included a finding that existing assessment instruments adequately, if not ideally, measured the clinical experience of FM represented by the core set of domains identified by the OMERACT working group.

Development of a Composite Measure of Disease Activity (State) and Responder Index for FM

Background. The outcome measures described above assessed individual symptom domains of FM and by definition, no one measure evaluates the experience of FM in its entirety or provides an index of an overall multidimensional response to treatment. At the present time, there is no consensus on how to quantify FM disease activity state or response. Currently, those who are conducting clinical trials of medications in FM use a variety of outcome measures to assess the “core” (e.g., pain, fatigue, sleep, PGIC, and function) and “outer core” domains (depression, cognitive dysfunction, stiffness). The evaluation and use of patient-reported outcome (PRO) measures, as with any outcome measures, requires detailed understanding of the meaning of the outcome of interest. The FDA provides guidance on the use of PRO measures as endpoints in clinical trials. Current regulatory guidelines for approval of a medication for FM require that the therapy demonstrate efficacy for pain, with important co-primary or secondary measures including PGIC and physical function. While other measures are included in RCT, they do not significantly affect regulatory decisions regarding efficacy and often are not part of labeling.

It is difficult to compare standardized effect sizes of therapies across RCT (as is the case in a typical metaanalysis) due to differences in study designs and outcome measures. It is also difficult to assess the impact of various therapies on the overall state of FM due to the lack of consensus on composite measures of FM disease severity and/or response. For example, it may be desirable to demonstrate, by means of a standardized response measure, that a treatment has a favorable effect on multiple clinical domains of FM versus a

treatment that improves pain without benefit in other domains. A response index provides the advantage of dichotomizing a group of patients according to whether the individual person had a clinically important result or not on a binary metric. Interpretation of this binary metric is straight-forward and does not require an understanding of trial results either before or after a labeling claim has been granted. Thus, clinical decisions can be made on the basis of individual response, rather than upon inference from the patient’s response as part of a group mean²⁵.

Responder indices for FM have been previously proposed and tested in RCT. Simms and colleagues proposed a priori that a meaningful response was achieved if patients met 4 of the 6 following criteria: 50% reduction in pain, sleep disturbance, fatigue, improvement in patient and/or physician global assessment by 0–10 VAS scales, and increase of 1 kg in mean total myalgic score²⁶. Application of these criteria in a trial that compared amitriptyline, cyclobenzaprine, and placebo in FM patients demonstrated that about one-third of patients had at least short-term responses to active treatment; whereas only a fifth demonstrated this level of response in the placebo group²⁷. In another study, Simms, *et al* derived a responder index from a treatment trial that identified measures and cutoffs that best predicted response in treated versus placebo patients via a logistic regression analysis²⁸. The combination of variables that demonstrated the greatest area under the receiver-operating curve for response were (1) physician global assessment score ≤ 4 (0 = extremely well, 10 = extremely poorly), (2) patient sleep score ≤ 6 (0 = sleeping extremely well, 10 = sleeping extremely poorly), and (3) tender point score ≤ 14 (maximum possible tender point score 20). These criteria accurately identified patients treated with amitriptyline or cyclobenzaprine from controls. However, since pain itself was not one of the measures, the criteria lacked face, construct, and convergent validity.

Dunkl and colleagues evaluated the responsiveness of 4 outcome measures used in a clinical trial of magnet therapy, by assessing the ability of the measures to detect clinically meaningful change over a 6-month period. They assessed the degree of association between outcome change scores and patient global ratings of symptom change, ability of the scores to discriminate among groups of patients, ability of the scores to discriminate between those who improved and those who did not, and quantity of response²⁹. Based on cutoffs of outcome change scores for those patients who identified global rating of symptom change as “improved,” they proposed preliminary criteria for identifying responders in FM clinical trials: Achievement of at least 3 of 4 of the following: Fibromyalgia Impact Questionnaire (FIQ)²² total score < 45 , pain score < 5 (0–10), tender point count < 14 (out of possible 18) using dolorimetry, and tender point score (18×0 –10 intensity score) < 85 . These preliminary criteria identified responders in a trial of magnet therapy

with a sensitivity of 70.5% and specificity of 87.5%²⁹. However, they have not been validated in the context of other RCT, and there was no evidence that the magnetic therapy was an effective treatment for FM.

Composite responder indices have been used in recent RCT in FM. In the milnacipran FM trials, the protocol-defined primary outcome was response to treatment defined by 2 composite responder indices. The composite responder definition for “treatment of fibromyalgia” consisted of 3 components, which were all to be satisfied concurrently in a given patient: (1) $\geq 30\%$ improvement from baseline in [visual analog scale (VAS)] pain score, range 0–100, 100 indicating worst possible pain; (2) a rating of “very much improved” (score = 1) or “much improved” (score = 2) on the PGIC scale; and (3) ≥ 6 -point improvement from baseline in physical function [SF-36 Physical Component Summary (PCS) score]. For the “treatment of pain associated with fibromyalgia,” the composite responder definition included the pain and PGIC components described above^{12,13,14}.

In an earlier analysis by Farrar and colleagues³⁰ of responses in a variety of pain RCT conducted with pregabalin, it was established that achievement of either a 1 or a 2 score (which correspond to “very much improved” and “much improved,” respectively) on the PGIC (considered a clinically relevant measure of overall improvement and appropriate anchor) was associated with an approximately 30% improvement in pain VAS, which supported a view that this level of pain improvement was clinically relevant, exceeding the “minimum clinically important difference”³⁰. Both indices in the milnacipran RCT discriminated between active and placebo treatment. Other domains such as fatigue, sleep, cognitive dysfunction, and depression were measured separately. In a recent trial of sodium oxybate, a similar composite index was utilized, defining a responder based on $\geq 20\%$ improvement in pain VAS, $\geq 20\%$ improvement in the FIQ total score, and achievement of 1 or 2 in the PGIC³¹. This composite responder index discriminated active therapy from placebo. As in the milnacipran trials, other core domains were assessed as secondary outcomes. In both sets of RCT, as well as those with pregabalin and duloxetine, evaluation of $\geq 30\%$ and $\geq 50\%$ improvements in the single domain of pain demonstrated statistically significantly more response with active therapy than placebo.

Recently, Wolfe, *et al* published clinical FM diagnostic criteria, based on a study of 829 FM patients and controls, that were intended to update the 1990 classification criteria for research in FM^{1,2}. The 2 elements of the newly proposed diagnostic criteria are a Widespread Pain Index (WPI) and a Symptom Severity (SS) scale. The WPI represents the number of areas (0–19) where the patient has experienced pain in the past week. The SS scale (0–12) is composed of 3 symptom domains, fatigue, waking unrefreshed, and cognitive dysfunction, graded 0–3 in severity, and a fourth 0–3 score in which the evaluator rates the number of other asso-

ciated symptoms (41 are listed) as none, a few, moderate, or many. FM is present if the patient has a WPI ≥ 7 and SS ≥ 5 or a WPI 3–6 and SS ≥ 9 . Further refinement of this quantitative scoring system into a disease activity index may be a potential goal of this working group.

Approaches Taken in Other Disease States to Develop Disease Activity and Responder Indices

Rheumatoid arthritis. Because the approaches taken to develop disease activity and responder indices in rheumatoid arthritis (RA) served as a model for the FM work, the findings from the studies of RA are summarized briefly here. The Disease Activity Score (DAS), a continuous measure, was developed by observing the treatment decisions of rheumatologists managing a cohort of patients with early RA^{32,33}. Eighteen clinical and laboratory measures were collected monthly, for up to 3 years, by research nurses. A patient was considered to be in “high disease activity” if a new disease-modifying antirheumatic drug (DMARD) was initiated or one deemed ineffective was stopped. The patient was considered to be in a state of “low disease activity” if there was no change or start of a DMARD for at least one year. Factor analysis was done to reduce the number of variables, discrimination analysis was used to discriminate between high/low disease activity, and regression analysis was employed to define individual variables that explained the clinical outcomes. This analysis yielded the following formula: $0.54 \sqrt{\text{RAI}} + 0.065(\text{SJC}) + 0.33 \text{Ln}(\text{ESR}) + 0.0072(\text{general health})$, using the Ritchie Articular Index (0–53 tender joint count graded 0–3 in severity), a 0–44 swollen joint count, erythrocyte sedimentation rate (ESR), and patient-reported VAS general health assessment, with weightings of the domains to account for their variable importance in the overall score. A more simplified version of the Disease Activity Score (DAS) score, the DAS28 score ($0.56 \times \sqrt{\text{T28}} + 0.28 \times \sqrt{\text{SW28}} + 0.70 \times \text{Ln}(\text{ESR}) + 0.014 \times \text{GH}$), has largely supplanted the original DAS, in which 28 joints are assessed for tenderness and swelling, either ESR or C-reactive protein (CRP) may be used, in addition to the patient’s general health assessment³⁴. The establishment of the DAS system as an anchor has allowed the emergence of simpler measures for use in clinical practice, which does not require a calculator. These include the Simplified Disease Activity Index (SDAI), which is the arithmetic sum of the tender and swollen joint count, the patient and physician global assessment on a 0–10 VAS, and the CRP (mg/dl) and the Clinical Disease Activity Index, which is the same as the SDAI but does without the CRP so that it can be calculated at the time of patient examination³⁵. All these measures have established quantitative thresholds for high and low disease activity states and remission, which have helped to establish quantitative goals or targets for treatment. They involve physical examination, patient-reported factors, and laboratory elements.

The various versions of the DAS scoring system have been incorporated into a measure of response known as the EULAR (European League Against Rheumatism) responder index, which takes into account the degree of change from baseline and the disease severity state achieved at a selected timepoint, such as the endpoint of the study. Quantitative thresholds have been set such that a greater degree of change and better outcome yields a “good” response, little change and persistently active disease is considered nil response, and outcomes in between are considered “moderate.”

These scoring systems have been widely used in RA clinical trials and shown to be reliable and discriminative. They are variably used in clinical practice, more so in Europe than in the US, and are increasingly being used now that it has been shown that “treatment to target” (i.e., aggressively managing therapy to achieve a low disease or remission state) yields superior clinical outcomes and less damage and disability.

The ACR response criteria are categoric and based on the ACR core set variables³⁶. An ACR 20 response is constituted by a 20% improvement in tender and swollen joint count, as well as 20% improvement of 3 of 5 additional elements: patient global, pain, physician global, an acute-phase reactant (ESR or CRP), and the Health Assessment Questionnaire (HAQ), a measure of function. ACR 50 and 70 are analogous, requiring 50% and 70% improvement in these same elements. The ACR 50 and 70 do not add more discrimination ability, but do reflect the greater magnitude of results that are sought. The ACR 20 is commonly used as a primary outcome in RA studies. However the ACR approach examines only change from baseline, and does not inform the clinician about the current or past level of disease activity.

The hybrid ACR response measure combines the ACR 20, ACR 50, and ACR 70 scores with a patient’s mean improvement in core set measures and incorporates a continuous measure of change. The hybrid ACR measure was found to be highly sensitive to change and able to detect treatment differences in clinical trials. However, this revision to the ACR 20 has not yet been adopted for widespread use, and also fails to provide information about current disease activity³⁷.

Ankylosing Spondylitis

The Assessments in Ankylosing Spondylitis working group (ASAS) has developed response criteria and a criterion for “partial remission”³⁸. The ASAS 20 response criteria include improvement of $\geq 20\%$ and absolute improvement of ≥ 10 units on a 0 to 100 scale in ≥ 3 of the following domains: patient global assessment (VAS global), pain assessment (VAS total + nocturnal pain), function [Bath Ankylosing Spondylitis Functional Index (BASFI)], inflammation [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) — 2 morning stiffness questions], and

absence of deterioration (20% worsening) in a potential remaining domain. Other permutations, such as the ASAS 40, substitute a 40% change. Partial remission criteria are achievement of a value ≤ 20 in each of the 4 domains. These criteria have been used widely in clinical trials of AS and have been shown to be reliable and discriminative. Of note is that each of the elements is a PRO measure.

A process similar to the development of the DAS scoring system has recently been undertaken in the development of the Ankylosing Spondylitis Disease Activity Score (ASDAS)^{39,40,41}. A Delphi exercise was conducted among AS experts to prioritize core clinical domains that might be used in a disease activity index. The items selected in the Delphi (i.e., domains such as pain, inflammation, function, laboratory tests, patient global, peripheral signs, and fatigue, as measured by various BASDAI and BASFI questions, physical examination and laboratory) were further tested in the ISSAS (International Study on Starting Tumor Necrosis Factor blocking agents in Ankylosing Spondylitis) database. Clinical, physical examination, and laboratory data on more than 1200 patients were collected by a research nurse or physician, independent of the investigator’s decision to start an anti-tumor necrosis factor (TNF) medication. Of the 731 patients with adequate data for analysis, 49% were considered to have disease activity high enough to initiate anti-TNF therapy. Data reduction was accomplished by principal component analysis, demonstrating 3 key components of PRO, peripheral activity, and laboratory and weighting of factors by discriminant function analysis. Linear regression analysis was then performed, yielding a best 5-variable option of back pain, patient global, morning stiffness, and CRP/ESR. Three draft versions of the ASDAS were created, with permutations of these elements, with different weightings, and one that included the element of fatigue. All 4 showed better discriminant capability than measures such as BASDAI in various data sets and in trials of patients with TNF inhibitors.

Toward Development of a FM Responder Index and Disease Activity Scoring System

The processes used to develop indices in RA and AS are exemplary and several were employed by the FM working group, including an expert Delphi exercise, analysis of correlation of various clinical domains to patient global in RCT, as well as gaining the input of patients from patient focus groups and a Delphi exercise. However, several challenges were present in translating some methods to FM. Some of the previous methods used to develop disease activity measures involved analysis of “decision to treat” to define high and low disease activity. In FM, however, there is no clear algorithm of treatment to define disease activity based on treatment decisions and there are no objective markers to define thresholds of severity or response to treatment.

Building upon the work accomplished at OMERACT 7

to 9 and a US National Institute of Arthritis and Musculoskeletal and Skin Diseases/National Institutes of Health grant (AR053207; Arnold LM, principal investigator), the FM working group presented work on development of an FM responder index and disease activity score. The objectives were (1) to develop candidate composite responder indices for FM RCT, based on core domains ratified at OMERACT 9, and utilizing RCT databases; and (2) to explore candidate composite measures of disease activity.

The clinical domains used in the development of candidate composite responder indices were those agreed upon when deriving the FM domain core set in OMERACT 7 to 9^{15,16,19,20} and the identification of outcome measures used in clinical trials for domains of interest, whose performance characteristics were evaluated in OMERACT 7 to 9^{15,16,19,20}.

Candidate measures of the “core domains” were tested within RCT of 4 therapies: 3 recently approved by the FDA for the treatment of FM, and one currently under review. The goal was to identify which proposed responder indices best discriminated between active treatment and placebo and where feasible within the context of these RCT. In RCT to date, standardized effect sizes of benefit of various therapies have been similar⁴².

Prior to proposing candidate responder definitions, analyses evaluated the potential responsiveness of the domains identified as important to patients and physicians during OMERACT 7 to 9. Correlation analyses and multiple regression models examined the level of association of the study endpoints (representing most of the OMERACT recommended domains) with PGIC and patient global impression of improvement (PGI-I) across 10 RCT^{20,43,44,45,46}.

Outcome measures that most consistently demonstrated at least moderate correlations with PGIC and PGI-I included pain (r range 0.50 to 0.64), fatigue ($r = 0.4-0.68$), physical function/activity ($r = 0.37-0.56$), and sleep ($r = 0.40-0.64$)¹⁹. Weaker associations were observed for work function, social or family function, mood disturbance (e.g., depression or anxiety), cognitive dysfunction, tenderness, and stiffness.

These results indicated that the domains of greatest importance to patients and physicians demonstrated levels of responsiveness supporting their inclusion as components in candidate responder definition. Acknowledged limitations of these analyses included that most studies excluded patients with depression, measures of tenderness were not used consistently, stiffness was evaluated by a single item on the FIQ, objective and comprehensive measures of cognition were not employed, and cognitive function based upon self-report was utilized in only one trial program. As these limitations could affect analyses, it was determined that domains without moderate to high levels of responsiveness in the analyses, such as stiffness and symptoms of depression and anxiety, but of importance in treatment of

FM, would still be examined as components in some of the candidate responder definitions.

The group proposed candidate dichotomous responder definitions based on the OMERACT 9 domain core set and the PGIC and PGI-I analyses described above. These candidate definitions employed measures that were common across the RCT, such as pain VAS or numeric rating scales, PGIC, FIQ, and SF-36, as well as measures that were available in only one or 2 RCT, such as the MOS-Sleep and the Multiple Ability Self-Report Questionnaire^{21,22,47,48}. The candidate responder definitions and associated analytic results will be presented in full in a separate report pending completion of this work.

Discussion by OMERACT 10 Attendees

In a plenary session at OMERACT 10, the progress of the FM working group to achieve consensus on the core domain constructs, including patients participating at each OMERACT meeting and in focus groups, was reviewed as background. Methods and process for developing a responder index and a disease activity score were described and examples of candidate measures and exploratory outcomes were presented. A number of points and questions emerged in small-group and plenary discussions. For example, there was interest in determining if different measures of a clinical domain, if shown to perform reliably in RCT, could be substituted for one another in a responder index or disease activity score. Definitions of worsening and flare should be established. The symptoms of various comorbid conditions may overlap the symptoms defined in core domains of FM and thus influence either disease activity score and/or responder index. A question was raised whether OMERACT should be developing unified responder indices and disease activity state measurement for all chronic pain conditions, and not just FM. It would be important to get patient feedback on proposed responder indices and disease activity scores. These and other issues brought up in discussion will be considered by the FM working group.

Questions and Voting

OMERACT attendees were queried regarding their overall agreement with the direction and methodology of the FM working group in relation to development of a disease activity score and responder index. Approximately 70% agreed that a responder index and disease activity score for FM that included multiple domains was appropriate and should be developed further.

Conclusions

Having established a core set of domains to be assessed in RCT in FM, and ascertaining the performance characteristics of outcome measures to assess these domains, the FM working group is continuing to develop both an FM responder index and a disease activity score. Historical efforts to

develop FM responder indices and disease activity scores were reviewed, as were examples of the development of these measures in other diseases such as RA and AS. The process of developing and testing candidate measures was presented at the OMERACT module. These measures comprise domains considered core to FM assessed either by measures used across clinical trials (e.g., pain VAS, SF-36, FIQ) or potentially by measures that have not, but can be shown to be used interchangeably with those that have. A detailed presentation of the methods, content specifics, and recommendations for selection of candidate responders, indices, and disease activity scores will be presented in a separate report. Based on these efforts and ratification at OMERACT 10, it was concluded that the development of FM-specific measures of disease activity and responder indices is feasible with currently available outcome measures. The OMERACT FM group recommended implementation of responder approaches to assessment of outcomes in FM clinical trials.

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