Workshop

Fibromyalgia Syndrome

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ABSTRACT. The fibromyalgia syndrome (FM) workshop at OMERACT 8 continued the work initiated in the first FM workshop at OMERACT 7 in 2004. The principal objectives were to work toward consensus on core domains for assessment in FM studies, evaluate the performance quality of outcome measures used in a review of recent trials in FM, and discuss the research agenda of the FM working group. An initiative to include the patient perspective on identification and prioritization of domains, consisting of focus groups and a patient Delphi exercise, was completed prior to OMERACT 8. Patient-identified domains were, for the most part, similar to those identified by clinician-investigators in terms of symptoms and relative importance. However, patients identified certain domains, such as stiffness, that were not included by physicians, and emphasized the importance of domains such as dyscognition and impaired motivation. Many of the principal domains agreed upon by the clinician-investigators, patients, and OMERACT participants, including pain, fatigue, sleep, mood, and global measures, have been used in clinical trials and performed well when viewed through the OMERACT filter. The research agenda items reviewed and approved for continued study included development of objective "biomarkers" in FM, development of a responder index for FM, and coordination with the WHO's International Classification of Functioning Disability and Health (ICF) Research Branch and the US National Institutes of Health's Patient Reported Outcome Measures Information System network (PROMIS) to develop improved measures of function, quality of life, and participation. The OMERACT process has provided a framework for identification of key domains to be assessed and a path toward validation and standardization of outcome measures for clinical trials in FM. (J Rheumatol 2007;34:1415–25)

Key Indexing Terms:
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Fibromyalgia syndrome (FM) as defined by the American College of Rheumatology 1990 definition for clinical trials is a chronic widespread pain condition with characteristic tender points on physical examination, often associated with a constellation of symptoms such as fatigue, sleep disturbance, headache, irritable bowel syndrome, and mood disorders[1]. Whereas surveys in the United Kingdom have identified the phenomenon of "chronic widespread pain" in up to 11% of the population at any given time[2], epidemiologic work in the US suggests that FM, when including the requisite tender

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point count, is present in 2% of the adult population (3.4% of the female population)[3]. A prevailing theory of pathogenesis is dysregulation of pain pathways leading to central sensitization and marked by neurotransmitter, neurohormone, and sleep physiology irregularities[4-8]. Uncertainties regarding pathophysiology and absence of validated objective markers of disease activity limit progress in therapeutic approaches to FM.

The treatment of FM has included both nonpharmacologic therapies such as exercise, massage, cognitive behavioral therapy, and others, and pharmacologic therapies, which primarily affect neurophysiologic function, often in a variety of combinations. These include medications traditionally used as antidepressants, analgesics, muscle relaxants, antiepileptics, and others[7,9-14].

There is currently no therapy formally approved by the European Agency for the Evaluation of Medicinal Products or the US Food and Drug Administration for the pain of FM or the syndrome as a whole. Because there have been virtually no standardized or validated outcome measures for FM, there has been uncertainty about which key domains of the condition should be measured and whether measures for pain, sleep, fatigue, or other symptoms used elsewhere in clinical research would be applicable in FM. Other key research problems have included the influence of comorbid psychiatric conditions, gender, disability, and other factors on outcomes. Yet another problem has been how to effectively demonstrate improvement of multidimensional function as well as pain. Despite these uncertainties, a number of large controlled trials have been conducted in FM in recent years, comprising analgesics, antiepileptics, drugs that augment serotonin and norepinephrine function, and components that modulate sleep, to name a few, and which have effectively distinguished placebo and treatment response in domains such as pain, fatigue, sleep, and function[7,9-12]. Given this success and the large unmet need to have approved therapies for FM, a group of FM clinician-investigators and industry researchers met to try to achieve consensus on a set of core domains to be assessed in clinical trials and evaluate the quality of outcome measures used to assess those domains so that they may be validated in FM. These, in turn, will be helpful to regulatory agencies involved in approving emerging therapies for FM. The group conducted a workshop at OMERACT 7 in May 2004[15]. This work continued as a workshop at OMERACT 8.

Workshop Objectives and Intended Outcomes

The objectives of the FM workshop at OMERACT 8 were to further the work initiated at OMERACT 7[15] and achieve the following goals: (1) work toward consensus on the "core" domains to be assessed in FM clinical trials and longterm observational studies; (2) further evaluate the performance characteristics of outcome measures used to assess these domains in clinical trials; and (3) identify and frame, where possible with existing data, the ongoing research agenda of the workshop.

Methods

These objectives were accomplished in oral presentations reviewing work from the steering committee, in breakout groups that discussed the content of these presentations, in reports of group discussions to the workshop as a whole, and in voting on domains in the workshop and in the final plenary session. Preparatory work by members of the OMERACT FM steering committee was accomplished during the 2 years since OMERACT 7 in committees focused on domains and outcome measures. Following the clinician-investigator Delphi conducted prior to OMERACT 7, the domain work was advanced by patient focus groups and a subsequent patient Delphi. The committee members also conducted a literature review of all therapy trials in FM, an up to date summary of the performance characteristics of measures used in recent clinical trials in FM, and a focused review of objective biomarker data in FM. Other items on the research agenda undertaken by the steering committee, as reported in the workshop, included development of a composite responder index for FM and improved patient-reported measures of function, quality of life, and participation, being developed in conjunction with the NIH-PROMIS network and the WHO ICF Research Branch.

Domains of Assessment in FM (L.M. Arnold, R. Bennett, D. Clauw, L. Crofford, D. Goldenberg, S. Martin, P. Mease, I.J. Russell, D. Williams)

Several steps have been taken to establish a prioritized set of domains of FM from which a core set recommended to be investigated in clinical studies can be established. Prior to OMERACT 7, the steering group identified a group of domains that were prioritized in a Delphi exercise among FM clinician-investigators and formed the basis for discussion and voting at the OMERACT 7 workshop (see below). It was also recommended that the perspective of patients on important domains be obtained and integrated in deliberations on the core set. A series of patient focus groups were held, followed by a patient Delphi exercise (see below). The results of both Delphi exercises were presented at the OMERACT 8 FM workshop and in the review of the workshop in the final plenary session of OMERACT 8. Voting occurred in both settings, the objective being to provide guidance to the steering group regarding further development of a finalized core set.

Clinician-investigator Delphi. Prior to OMERACT 7, the FM workshop steering group developed a set of 40 potential domains of assessment for FM clinical trials. Between December 2003 and April 2004, fifty-one FM experts were approached to participate in a Delphi exercise to prioritize these domains, and 23 completed 3 rounds of this exercise. A Delphi exercise was felt to be a good method to derive expert opinion[16-19]. The results of this process were presented at OMERACT 7, followed by a presentation of clinical trial results and breakout discussions, with subsequent voting on domain prioritization. Table 1 shows the most highly prioritized domains of the Delphi exercise and the OMERACT 7 voting[15].

Table 1. Comparison of pre-OMERACT 7 Delphi scores and OMERACT 7 ratings. A. Median scores (points assigned out of 100 possible) for the top 12 domains identified by FMS clinician-investigators in a Delphi exercise conducted prior to OMERACT 7. B. Percentage of OMERACT 7 attendees who agreed these domains were essential to assess in clinical trials of FMS (with addition of "Multidimensional function").

A

Domain	Median Delphi Score
Pain	16
Fatigue	10
Patient global	10
Sleep quality	8
Health related quality of life	5
Physical function	5
Treatment side effects	5
Depression	5
Tender point intensity	2
Dyscognition	2
Anxiety	2
Clinican global	1

B

Domain	OMERACT 7 Participants,%
Pain	100
Patient global	94
Fatigue	85
Health related quality of life	76
Multidimensional function	75
Sleep quality	70
Depression	65
Treatment side effects	58
Physical function	42
Tender point intensity	18
Dyscognition	21
Anxiety	21
Clinican global	23

In general, there was considerable consensus between the clinician-investigators who participated in the Delphi and the OMERACT group as a whole. The OMERACT group discussion included focus on the importance of assessment of multidimensional aspects of function, which is being addressed in the research agenda by liaison with the WHO-ICF and NIH-PROMIS groups. It was also agreed that it would be optimal to include the patient perspective in development of consensus on the core domains of assessment. To this end, patient focus groups have been conducted and a patient Delphi was performed prior to OMERACT 8.

Patient focus groups on FM domains. The initial stage of gaining a patient perspective on FM domains involved patients from Cincinnati, Ohio (L.M. Arnold), Ann Arbor, Michigan (L.J. Crofford) and Seattle, Washington (P. Mease). In each of the 3 centers 2 focus groups of 7–10 FM patients [n = 48 total fulfilling American College of Rheumatology (ACR) criteria] were conducted by group moderators from MAPI Values, an outcomes research organization (made possible by a grant from Pfizer Global Research and Development, Ann Arbor, MI). The focus groups were conducted between July 2004 and September 2004. As part of the discussion, patients were asked to identify their FM symptoms and describe how FM affected important areas of functioning. They were asked to indicate the symptoms or impairment that they would most like treatment to improve. The focus groups were audiotaped and transcribed for analysis. All identifying information was removed from the transcripts. A detailed description of the process and outcome of the focus groups will be published separately.

The patients identified pain as a key domain, as well as fatigue and disturbed sleep. Other important domains included depression, cognitive impairment (decreased concentration, disorganization, memory problems), and social and occupational dysfunction. Notably, the domains identified by the patients are generally consistent with several of the important domains identified by clinician-investigators in the previously described Delphi exercise. The patient findings also underscored the need to assess multidimensional aspects of function, as recommended by OMERACT 7 workshop attendees.

Patient ratings of FM domains. The focus groups provided qualitative information on important FM domains. To develop a more quantitative, reliable, and valid determination of patient consensus about the relative priority of different domains of FM, a patient Delphi exercise was conducted using data from the focus group discussions to generate the domain list. In addition to Seattle, Cincinnati, and Ann Arbor (D. Clauw, D.A. Williams) 2 sites were added, Lexington, Kentucky (L.J. Crofford) and San Antonio, Texas (I.J. Russell), the latter to include Hispanic patients in the study. Among the 5 centers, a total of 100 patients participated (20 at each site). The patient Delphi exercise was conducted between September 2005 and May 2006.

Patient Delphi. Of 100 patients participating in 5 centers, 86 took part through the second round of the 2-round Delphi exercise. Patients were presented the list of 40 FM domains distilled as most important from the focus groups and using language derived from transcripts of the focus groups. They were asked to award 100 points among these domains, based upon their judgment about the individual importance of the domain. After the first round results were tallied, each patient was re-presented with their first-round scoring, the mean

score of the whole group for each domain, and the minimum and maximum score. They were then allowed to reflect on their original response and re-respond, either by keeping their original score or changing it, if their review of others' responses led them to do so. The top-rated domains from the second round are presented in Table 2. A detailed description of the patient Delphi process and a variety of subanalyses will be provided separately.

The results of the patient Delphi exercise were, for the most part, similar to the results of the clinician-investigator Delphi. The domain of pain was ranked most highly in both, including the varied ways that patients described pain in the focus group discussions. Other domains ranked similarly highly included fatigue, sleep disturbance, multidimensional function, depression as a comorbid problem, and cognitive difficulty. This last domain was summarized in one word in the clinical-investigator Delphi, "dyscognition," whereas it was described in a variety of ways by patients, including "problems with attention or concentration," "disorganized thinking," and "memory problems." Aspects of function important to patients included the influence of the illness on making plans and accomplishing goals and tasks, including routine activities of daily living, as well as the motivation to accomplish things. Patients did not articulate phrases such as "patient global" or "health related quality of life" that would subsume a variety of domains that affect their overall sense of well-being, nor were they focused on treatment side effects as an important domain to measure in clinical trials. One domain ranked highly by patients but not by clinician-investigators was "stiffness." In breakout groups, patients described this as an important symptom. It is not described in the same way as the stiffness of rheumatoid arthritis but appears to have a different quality. It was felt that this deserved further research on how best to assess.

Review of Treatment Trials in FM and Assessment of Outcome Measures (S. Carville, A. Chappell, E. Choy, R.M. Gendreau, S. Martin, P. Perera)

The OMERACT workshop steering group and a multidisciplinary EULAR FM task force are working in collaboration to do a systematic review of all treatment trials of FM and assess the performance of outcome measures used in those trials. The members of the OMERACT workshop steering committee are noted above, representing 6 countries, consisting of rheumatologists, a psychiatrist, a psychologist, and a physiologist. The EULAR task force consists of rheumatologists, pain spe-

Table 2. Comparison of OMERACT 7 voting and patient Delphi: key domains. A. OMERACT 7 voting: FMS domains ranked as most important in clinician-investigator Delphi exercise performed prior to OMERACT 7. Percentage column shows percentage of OMERACT 7 attendees who agreed that these domains were essential to assess in FMS clinical trials. B. Patient Delphi: mean scores (points assigned out of 100 possible) for the top 14 domains identified by patients as important in FMS. Percentage column reflects percentage of patients who felt domains should be assessed.

A. OMERACT 7 Voting		**B.** Patient Delphi	
Domain	%	Domain/Item	Mean (%)
Pain	100	Pain or physical discomfort	6.9 (95)
Patient global	94	Joints aching or pain	5.7 (90)
Fatigue	85	Lack of energy or fatigue	5.5 (96)
HRQOL	76	Effect on sleep (difficulty falling asleep, staying asleep, or getting up in the morning)	5.3 (92)
Multidimensional function	75	Problems with attention or concentration (difficulty concentrating on things, difficulty thinking, "fibro-fog")	4.7 (91)
Sleep	70	Stiffness	4.2 (91)
Depression	65	Disorganized thinking (difficulty in expressing yourself, difficulty in answering questions quickly, or difficulty making plans)	3.6 (85)
Treatment side effects	58	Difficulty moving, walking, or exercising	3.5 (86)
Physical function	42	Having to push yourself to do things	3.1 (83)
Clinical global	23	Effect on ability to make plans, accomplish goals, or complete tasks	3.0 (79)
Tender point intensity	21	Feeling tender where touched	3.0 (77)
Dyscognition	21	Depression (disappointed, sad, resigned, or unmotivated)	3.0 (74)
Anxiety	21	Affected/limited in doing normal daily life and household activities	2.8 (82)
		Memory problems	2.6 (81)

Table 3. Effect sizes observed in clinical trials of therapeutic agents in fibromyalgia.

Drug	Duration	Pain				Sleep	Fatigue		Mood		Global		Function
Outcome	No. of Studies	Pain VAS	SF-36 Bodily Pain	Tender Points	Morning Stiffness	Sleep	Fatigue	SF-36 Vitality	Mood Anxiety	Mood Depression	Patient Global	FIQ Total	SF-36 Physical Function
A*	1-8 weeks	0.45	0.39	0.29		0.73	0.33	0.31	0.26	0.23	0.48		0.27
B*	Average across 9 studies	0.52		0.29		0.66	0.45				0.66		
C*	1-12 weeks	0.95		0.48	0.52		0.57						
D*	1-12 weeks	0.35		0.44	0.32		0.02				0.29	0.19	
E*	1-12 weeks Dose A Dose B	 0.48 0.48		 0.41 0.29		 0.35 0.30				 0.15 0.25	 0.40 0.37	 0.50 0.46	
F§	1-12 weeks	0.39	0.39	0.22	0.32	0	0.13	0.15	0.27	0.13		0.37	0.33
G§	1-9 weeks	0.49		0.18								0.11	
H*	1-12 weeks	0.53	0.35		0.73	0.27	0.09	0.05	0.25	0.40	0.50	0.27	0.40
I§	1-9 months			(count) 0.6								0.6	
J§	1-14 weeks	1.48		0.50			0.79		0.23	0.44	1.26	1.00	(M-HAQ) 0.49
K*	1-8 weeks Dose A Dose B	 0.38 0.38	 0.51 0.51	 0.34 0.35	 0.54 0.55	 0.57 0.56	 0.58 0.53	 0.28 0.05	 0.09 0.01	 0.13 0.19		 0.51 0.43	 0.42 0.28
OMERACT filter	Truth											✓	
	Discrimination	Medium to high	Medium	Small to medium	Small to medium	Medium	Medium	Small	Small	Small	Medium	Small to medium	Small
	Feasibility	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Truth: ✓ indicates instrument has been validated in FMS. Only the Fibromyalgia Impact Questionnaire (FIQ) has been formally validated in FMS; other measures are in process of being validated. Discrimination: indicates sensitivity to change assessed by effect size (0.2-0.49 = small, 0.5-0.79 = medium, > 0.8 = large). Feasibility: ✓ indicates instrument is feasible as it has been used in FMS clinical trials.

* Effect size calculated using the following method: difference in mean endpoint score divided by pooled SD of the change. § Effect size calculated using the following method: difference in mean endpoint score divided by baseline SD.

cialists, experts in rehabilitation, a neurologist, an occupational therapist, a bio-scientist, psychiatrist, epidemiologist, and a patient representing 11 European countries. The group at OMERACT 7 reviewed several recent pharmaceutical clinical trials and developed a table of effect sizes seen in various domains (Table 3)[9,17,20-26]. This was updated for OMERACT 8 with data from recent trials of pramipexole, duloxetine, and sodium oxybate. The EULAR task force has conducted a systematic review of Medline, Pubmed, EmBASE, CINAHL, PsycINFO, Web of Science, Science Citation Indices, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews with the keywords "fibromyalgia," "treatment or management," and "trial," including both pharmacological and nonpharmacological interventions. Studies were excluded if they did not utilize the ACR classification criteria, were not clinical trials, or included patients with chronic fatigue syndrome or myalgic encephalomyelitis. Most of these have been reviewed[9,27-33] (see Table 4 for a summary of studies). From the 162 selected trials, where possible, data were extracted on sample size, randomization, blinding, duration of disease, duration of treatment, and change in pain assessed by visual analog scale (VAS) and Fibromyalgia Impact Questionnaire values, other outcome measures, instruments used, and change values

Table 4. Studies identified in the systematic review.

Class of treatment	Studies
Selective serotonin reuptake inhibitors	Anderberg 2000, Arnold 2002, Nørregaard 1995, Kee 2004
Tricyclic antidepressants	Carrette 1994 & 1995, Ginsberg 1996, Heymann 2001, Capaci 2002, Goldenberg 1996, Giordano 1999, Hannonen 1998
Dual reuptake inhibitors	Arnold 2004 & 2005, Nagaoka 2004, Vitton 2004, Sayar 2003,
5HT2/3 antagonists	Fäber 2000, Haus 2000, Hrycaj 1996, Müller 2000, Olin 1998, Samborski 2006, 2004a, 2004b, Späth 2004, Stratz 2000
Monoamine oxidase inhibitors	Hannonen 1998, Ginsberg 1998, Nicoledi 1996, Yavuzer 1998
Systemic analgesics	Graven-Neilsen 2000, McLean 2000, Raphael 2002, Russell 2000, Sörensen 1995, Bennett 2003
Topical analgesics	Scudds 1995, Janzen 1997, McCarty 1994
Tri-iodothyronine	Lowe 1997a, b, c
Individual pharmacological interventions	Paulson 1996, Aspergen Kendall 2004, Bessette 1998, Citera 2000, McLain 2002, Moldofsky 1996, Quijada-Carrera 1996, Rico-Villademoros 2005, Russell 1995, Scharf 2003, Volkmann 1997, Crofford 2005, Bennett 1998, Teitelbaum 2001, Holman 2005, Finckh 2005, Wood 2005
Aerobic exercise	Mengshoel et al. 1992, Nørregaard 1997, Nichols et al. 1994, Ramsay et al. 2000, Schachter et al. 2003, Richards et al. 2003, Gowans et al. 2001, Van Santen et al. 2002 a&b, Meyer et al. 2000, Da Costa et al. 2005
Strength training	Dupree Jones 2002, Häkkinen 2005, Geel 2002, Kingsley 2005
Mixed exercise	Bailey 1999, Dawson 2003, Isomeri 1993, Martin 1996
Pool-based	Altan 2004, Jentoft 2001
Dietary interventions	Bramwell 2000, Edwards 2000, Azad 2000, Kaartinen 2000, Merchant 2000, Deuster 1998, Merchant 2001
CBT	Neilson 1992, Singh 1998
CBT & exercise	Rivera-Redondo 2004, Mason 1998, Soares 2002, Goldenberg 1994, Mengshoel 1995
Education	Fors 2000, Oliver 2001, Nicassio 1997, Vlaeyen 1996
Education & exercise	Cedraschi 2003, Burkhardt 1994, King 2002, Gowans 1999, Mannerkorpi 2000, Zijlstra 2005, Lemstra 2005, Bailey 1999
Balneotherapy	Evick 2002, Yurtkuran 1996, Günther 1994, Zjilstra 2005
Homeopathy	Bell 2004a, b, c
Physiotherapy related	Brattberg 1999, Blunt 1997, Hains 2000, Field 2003
Meditation	Kaplan 1993, Astin 2003
Laser/light	Gür 2002, Pearl 1996
Acupuncture	Sprott 1998, Deluze 1992, Assefi 2005, Harris 2005
Magnets	Colbert 1999, Alfano 2001
Other nonpharmacological interventions	Almeida 2003, Alamo 2002, Chesky 1997, Huuhka 2004, Meuller 2001, Kendall 2000, Sverdrup 2004, Fors 2002, Bosch-Romero 2002, Theime 2003, Broderick 2005, Luckazer 2005, Biasi 1999, Keel 1998, Bennett 1996, Pfeiffer 2003, Creamer 2000, Worrell 2001

where available. The data extraction was verified by a second committee member.

There is an opportunity to synergize the work already carried out by the EULAR working group with the ongoing effort of the OMERACT working group. The OMERACT working group on FM has established key domains that should be assessed in randomized controlled trials, and will continue to report effect sizes for assessments in the available major FM studies (Table 3). Each outcome measure collected in the EULAR database can be mapped to a specific OMERACT domain. Outcome measures that have already been used in randomized controlled trials (RCT) are likely to be feasible and face-valid. Calculating their effect size (changes before and after treatment) assesses their sensitivity to change. Therefore data from the EULAR database as well as any available study results fulfilling the quality criteria as of April 2006 can establish whether there is any particular outcome instrument in each of the OMERACT FM domains that fulfils the 3 key aspects of the OMERACT filter, truth, discrimination, and feasibility. The work can be extended to determine the minimum clinically important difference for each selected outcome measure and contributes further to the development of a set of response criteria for FM.

This review revealed that for each of the key OMERACT domains, there are instruments that have been used in clinical trials. Many of these have been evaluated for validity and are feasible and sensitive to change in FM. Sleep is the one key OMERACT domain that lacks a sensitive measure in the systematic review, but in recent RCT, the Jenkins Sleep Questionnaire and the Medical Outcomes Study Sleep Scale performed well.

Research Agenda: Objective Measures in FM (D. Clauw, L.J. Crofford, D. Dadabhoy, I.J. Russell, M. Spaeth)

Evidence-based objective measures are valuable tools in clinical practice and research. Through a systematic review of the literature, potential biomarkers available for FM were evaluated. A summary of the various biomarkers was presented at OMERACT 8. Each objective measure was rated for category (clinical or research only) and for the strength and consistency of evidence supporting its use. The objective measures found to have the strongest evidence are described and summarized below. A detailed list of the primary articles reviewed for OMERACT 8 will be noted in an upcoming report on objective measures in FM.

Evoked potentials. Auditory, somatosensory, and visual evoked potential studies were reviewed. Reduced P300 amplitude during auditory discriminated task paradigm is the biomarker with the strongest current evidence of the evoked potentials[34]. Observed in 3 cross-sectional studies by 2 different groups, the reduced P300 amplitude measure appears promising, but larger studies by different groups with attention to standardizing methods are warranted. Currently, there are few and varied studies that evaluated somatosensory and visual evoked potentials, and the findings were inconsistent.

Neural imaging. The primary modes of imaging used in FM include functional magnetic resonance imaging (fMRI), single-photon emission computed tomography (SPECT), and positron emission tomography (PET). fMRI studies evaluating pain processing have the strongest current evidence of the neural imaging studies. Specifically, quantitative sensory activation of neural pain processing areas (SII, insula, ACC) has been noted in 5 cross-sectional studies by 2 different groups[35]. Notably, affected areas have been shown on imaging to be influenced by cognitive factors such as catastrophizing. In summary, the advantages of fMRI include the modality being less invasive and having high temporal and spatial resolutions. Disadvantages include cost and practicability as well as the inability to perform receptor-ligand studies, as can be performed in PET and SPECT.

Autoantibodies. The practicality of a blood test result that can be used as an objective marker makes this group of measures more attractive. Certain autoantibodies (e.g., antiserotonin, antiganglioside, antiphospholipid antibody) have been shown to be different in patients and controls, but the generalizability and sensitivity/specificity of these findings are not clear[36]. In chronic fatigue syndrome, investigators have noted a shift from a T1 to T2 immune response that may account for the increased production of nonspecific autoantibodies. As such, increases in concentrations of nearly any antibody may be seen in this spectrum of illness, and any autoantibody that would be considered for use as a diagnostic marker will require stringent controls to ensure its validity in this setting.

Genetics. Genetic studies have generally yielded noninformative or inconsistent results. Of the genetic markers, COMT haplotype and HLA linkage, reviewed in one study each, have shown an association[37].

Hypopituitary-adrenal axis. In basal and diurnal cortisol studies, the measure found most consistently was a flattened diurnal plasma cortisol with elevated trough, found in 3 of 4 cross-sectional studies by 2 of 3 groups[38]. Studies evaluating basal plasma cortisol, salivary basal and diurnal cortisol, and urinary cortisol have shown inconsistent results, but generally demonstrate normal to reduced basal levels. Since atypical depression can show reduced cortisol, biopsychological factors that influence cortisol levels may be contributing to the inconsistent results currently reported. In addition, studies have suggested that the presence of comorbid posttraumatic stress disorder and of early childhood abuse may dramatically affect these results and have been a confounder in previous studies. These factors need to be better elucidated and accounted for in future studies.

Biochemicals. There is significant evidence that elevated substance P in cerebrospinal fluid (CSF) is a reproducible marker of a number of different chronic pain states[39]. In contrast, normal substance P has been noted in chronic fatigue syndrome[40]. Difficulty in obtaining the measure (i.e., from the CSF) limits its clinical use.

The amino acid tryptophan, the cytokine interleukin 8, and the beta-adrenergic G-couple protein receptors all have been shown to be different in patients compared to controls in a couple of studies, but none was evaluated in longitudinal studies or by different groups[39,41,42].

Psychophysical testing. Psychophysical pain testing (sometimes referred to as quantitative sensory testing) is the best supported objective measure currently in the literature. Use of pressure pain thresholds, heat pain threshold, and tender point intensity/index is well established to differentiate patient groups from controls. The clinically used tests of pain thresholds, i.e., by tender point counts or dolorimetry, have been shown to be marginally biased, however, by cognitive and psychological factors (i.e., expectancy). These biases may be minimized by more sophisticated paradigms, but they are more difficult to use in routine clinical practice[43]. Studies suggest that pressure pain thresholds are more closely related to clinical pain reports than heat pain thresholds.

Diminished diffuse noxious inhibitory controls (DNIC) is a more recently investigated type of psychophysical study that has been noted in FM in 4 cross-sectional studies by different groups that used variable test and conditioning stimuli[44]. This suggests a defect in normal descending inhibitory pain signals in FM may be partly responsible for the augmented pain processing noted in these patients. Diminished DNIC have also been noted in other types of chronic pain, i.e., temporomandibular and hip osteoarthritis[45]. The normalization of DNIC after hip osteoarthritis surgery suggests that it may be an objective measure of chronic pain.

Muscle. Despite the interest in and investigation for objective peripheral muscle abnormalities, the results have remained variable and have not yet been reproduced by different groups. Additionally, there is great heterogeneity in the methods in evaluating for objective muscle abnormalities. To identify possibly useful objective measures, further investigations are necessary, preferably utilizing noninvasive procedures.

Autonomic reactivity. Tilt-table testing and heart rate variability were evaluated. The consistent and reproducible finding of lower heart rate variability in FM compared to controls (3 cross-sectional studies by 2 different groups) makes it a more useful measure than tilt-table testing[46]. Findings also suggest that aberrations in heart rate variability may predispose to FM symptoms[47]. Longitudinal studies evaluating change over time in autonomic reactivity would be useful.

Sleep and activity. In addition to sleep logs, polysomnography has consistently confirmed patient reports of hypersomnolence[48]. Actigraphy, although less intrusive, does not appear to be as sensitive a marker, but further investigation will be necessary.

In summary, except for psychophysical testing, no objective measure has been appropriately evaluated and shown to improve with improvements in clinical status in a longitudinal study (type I evidence). OMERACT will work toward a consensus on promising objective measures to be used in research and clinical arenas. An effort by different groups to systematically evaluate these measures in research trials to obtain useful, comparable results will be vital for progress in outcome research.

Currently, a metaanalysis of the data available on objective biomarkers is not warranted — the different studies are too dissimilar. Most biomarkers have too few reports with a small number of subjects. There is a need to identify biomarkers for future studies that have reproducibility and predictive value, practicability, and biological and temporal relevance in FM.

Research Agenda: Responder Index (L.M. Arnold, D. Clauw, L.J. Crofford, P. Mease, D. Goldenberg, D.A. Williams)

Once there is consensus about important domains, we will assess data from FM studies of pregabalin[24], duloxetine[21], milnacipran[26], and gabapentin (in progress) in FM that have utilized outcome measures for the domains of interest, as done during development of the core set of outcome measures for the ACR20[49,50]. We will use the criteria for selection of clinical trial outcome measures adopted by OMERACT as the OMERACT filter originally proposed by Tugwell and Bombardier[51].

Next, adopting the approach used to develop the ACR20[50] and the EULAR Response Criteria[52], we will use the core set of outcome measures identified by the above procedures and test several different definitions of FM state and improvement in a 3-step process:

Step 1. We will conduct a survey of 500 clinicians with extensive experience in treatment of FM. These clinicians will be drawn from members of the ACR and the International Myopain Society. From this pool, we estimate a 20% response rate to reach our goal of 100 respondents. Each will be presented with 10–12 sets of criteria for FM state and improvement constructed to have high face validity (based on consensus of the clinical investigators and consultants). Surveyed clinicians will rank the sets with respect to their perceived value in discriminating improved from non-improved patients.

Step 2. We will use clinical trial data from the pregabalin, duloxetine, milnacipran, and gabapentin trials to test the definitions of FM state and improvement.

Step 3. We will identify which improvement definitions characterize fewest placebo patients as improved.

We plan to include only data from studies of pharmacological agents because inclusion of data from behavioral or alternative medicine trials might add variance to the results, which might diminish the value of the responder index in large studies of the efficacy of pharmacological agents. Further, the responder indices such as the ACR20 are not used to evaluate treatment effects in studies of psychosocial interventions for patients with rheumatoid arthritis, because these interventions are not necessarily expected to produce outcomes similar to those produced by pharmacological agents. Thus, we propose to focus the development of the responder index for use in

pharmacological trials. Future studies could evaluate a responder index in nonpharmacological trials.

Research Agenda: Assessment of Multidimensional Aspects of Function, Quality of Life, and Participation in FM (A. Boonen, P. Mease, D.A. Williams)

Annelies Boonen and Alarcon Cieza are serving as liaison to the WHO-ICF (Research Branch) rheumatology working group, led by Gerold Stucki, and Dave Williams as liaison to the NIH-PROMIS network. The OMERACT FM group will participate in development of an ICF core set for FM, based on work done on the ICF in chronic widespread pain[53]. This process is being informed by the Delphi exercises on domains and contributes to the selection or development of measures to assess the "multidimensional function" domain, especially with regard to which subdomains must be included in such measures.

Existing outcome measures for FM have been criticized for having poor psychometric properties such as limited dynamic range (e.g., ceiling/floor effects), limited sensitivity to change over time, and inability to directly compare the effectiveness of differing interventions across multiple domains of meaningful clinical variables. Newer approaches to patient-reported outcomes depart from classical test construction by using item-response theory in combination with computer adaptive testing (IRT/CAT). This approach requires the development of large pools of well characterized test items, and uses computer algorithms to present the smallest number of items that will produce the most valid assessment of a particular outcome domain for a given patient[54-56]. The advantage of this approach is that a common assessment strategy can be used for each outcome domain of interest, it involves low patient burden, and it possesses superior measurement characteristics. David Williams is collaborating with the larger NIH/PROMIS project to develop refinements to the generic chronic illness assessment tool that can be applied specifically to FM.

Voting in Workshop and Plenary at OMERACT 8

After discussion on these domains, outcome measures, and research agenda items in breakout groups that included members of OMERACT and patients with rheumatoid arthritis, psoriatic arthritis, and FM, the workshop members voted on the question of whether a domain should be part of the core set in FM clinical trials and longitudinal studies. They could choose either "yes" or "no" on whether the domain was essential to be assessed in a study or was optional and should be in the research agenda regarding its importance to be measured and needing further development of adequate assessment instruments. This decision may have been influenced by both the relative importance of the domain and the current adequacy of instruments to assess the domain (Table 5).

In the final plenary session of OMERACT 8, the workshop proceedings were summarized and further voting by the whole OMERACT 8 group took place. In this session, it was decided there would be 3 choices: (1) Is the domain "essential" to include in all studies; (2) Is the domain important to measure but not necessarily mandatory for all types of studies; or (3) Is the domain of uncertain importance to include in the core set, does it need clarification, or does it clearly not have adequate outcome measures such that it should be in the research agenda. Because information and evidence about the domains and outcome measures were not presented to the group as a whole (as might occur in a plenary module), this vote was understood to be used as guidance and not as a formal consensus. Table 6 shows the results of the voting in the workshop and plenary sessions.

Table 5. Workshop group responses (n = 37).

Domain	% of Positive Votes*
Pain	100
Fatigue	94
Patient global	94
Multidimensional function	86
Tenderness	74
Sleep	66
HRQOL	65
Dyscognition	61
Stiffness	60
Depression	47
Anxiety	47
Treatment side effects	38

*Percentage of FM workshop attendees who thought the domains identified in prior OMERACT 7 Delphi workshop and patient Delphi were essential to assess in clinical trials of FMS.

It is clear that the key domains of FM to be investigated in studies, domains endorsed by both clinician-investigators (as reviewed in OMERACT 7) and patients, include pain, fatigue, sleep disturbance, multidimensional function, quality of life, mood disorders, and cognitive dysfunction. An additional domain highlighted by patients is stiffness. As well, an important domain to assess in a trial of a medication would be treatment side effects, to determine the tradeoff with potential benefit. Not all these domains are considered essential in all studies. For example, cognitive dysfunction, anxiety, and stiffness may not be "core" enough or there may be uncertainty about how best to measure these domains, such that there would be merit in including their assessment, but it would not be essential to measure these domains in all trials.

Conclusions

Since OMERACT 7, there has been an advance in our understanding of important symptom domains in FM and additional data on instruments used to assess these symptom domains. It has been shown consistently that pain is the principal symptom to be measured, and good effect sizes have been demon-

Table 6. Full OMERACT 8 group responses (n = 104). All numbers are expressed as percentages of all persons attending final OMERACT plenary session. Column A: Essential for core set for all clinical studies. Column B: Necessary but not mandatory for all clinical studies. Column C: Research agenda (implying more research needed to define the domain in the context of FMS)

Domain	A	B	C
Pain	94	3	3
Fatigue	86	13	1
Patient global	81	12	7
Sleep	64	256	10
Multidimensional function	60	28	12
HRQOL	52	34	14
Tenderness	50	27	24
Depression	44	34	21
Treatment side effects	40	34	26
Anxiety	2s	43	35
Dyscognition	21	42	37
Stiffness	13	35	52

strated with instruments to measure pain in FM clinical trials. Other important domains include fatigue and sleep disturbance. Measures of these domains show reasonable effect sizes in clinical trials. There is considerable overlap between the opinion of clinician-investigators and patients regarding the identification and prioritization of key domains to be assessed in FM. Domains such as stiffness, dyscognition, function, and motivation are clearly important to patients but have not been as reliably assessed. It is desirable to demonstrate that FM therapy can improve function, including physical, social, and occupational function. Effect sizes of available instruments to measure various dimensions of function are variable and tend to be small, which suggests either that function may not be as responsive as other clinical manifestations of FM over 8–12 weeks of treatment or that the measures are not sensitive enough to detect treatment effects. In collaboration with the WHO ICF and NIH PROMIS projects, work is under way to develop more specific and sensitive instruments to measure the various ways in which FM affects function, quality of life, and participation in meaningful activities and to demonstrate change with effective therapy. Similarly, it is difficult to assess and measure change in the subtle cognitive dysfunction expressed by many FM patients, a challenge that is on our current research agenda. As we gain a clearer understanding of the neuropathophysiology underlying FM, more objective biomarkers of disease activity may improve our ability to diagnose and assess therapeutic progress. Tracking the developments in this arena is also on the research agenda of the OMERACT working group. The ability to measure clinically meaningful change in multiple dimensions of FM utilizing a composite responder index is desirable; this too is on the research agenda. It is reassuring to note significant agreement between clinician-investigators' and patients' rankings of important symptom domains. Establishment of consensus about symptom domains and development of outcome measures for FM clinical trials are critical steps toward the identification of effective treatments for FM.

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