Fibromyalgia Syndrome

PHILIP J. MEASE, DANIEL J. CLAUW, LESLEY M. ARNOLD, DON L. GOLDENBERG, JAMES WITTER, DAVID A. WILLIAMS, LEE S. SIMON, C. VIBEKE STRAND, CANDACE BRAMSON, SUSAN MARTIN, TIMOTHY M. WRIGHT, BRUCE LITTMAN, J.F. WERNICKE, R. MICHAEL GENDREAU, and LESLIE J. CROFFORD

ABSTRACT. The objectives of the first OMERACT Fibromyalgia Syndrome (FM) Workshop were to identify and prioritize symptom domains that should be consistently evaluated in FM clinical trials, and to identify aspects of domains and outcome measures that should be part of a concerted research agenda of FM researchers. Such an effort will help standardize and improve the quality of outcomes research in FM. A principal assumption in this workshop has been that there exists a clinical syndrome, generally known as FM, characterized by chronic widespread pain typically associated with fatigue, sleep disturbance, mood disturbance, and other symptoms and signs, and considered to be related to central neuromodulatory dysregulation. FM can be diagnosed using 1990 American College of Rheumatology criteria. In preparation for the workshop a Delphi exercise involving 23 FM researchers was conducted to establish a preliminary prioritization of domains of inquiry. At the OMERACT meeting, the workshop included presentation of the Delphi results; a review of placebo-controlled trials of FM treatment, with a focus on the outcome measures used and their performance; a panel discussion of the key issues in FM trials, from both an investigator and regulatory agency perspective; and a voting process by the workshop attendees. The results of the workshop were presented in the plenary session on the final day of the meeting. A prioritized list of domains of FM to be investigated was thus developed, key issues and controversies in the field were debated, and consensus on a research agenda on outcome measure development was reached. (J Rheumatol 2005;32:2270–7)

Key Indexing Terms:
FIBROMYALGIA CHRONIC PAIN OMERACT OUTCOME MEASURES

Introduction and Background

Fibromyalgia (FM), as defined in the 1990 American College of Rheumatology (ACR) criteria[1], is a chronic, generalized pain condition with characteristic tender points on physical examination, often accompanied by a number of associated symptoms such as fatigue, sleep disturbance, headache, irritable bowel syndrome, and mood disorders. By this definition, FM affects at least 2% of the adult population in the US[2]. Although our understanding of the etiology of FM is evolving, evidence shows that the syndrome is influenced by factors such as stress, medical illness, and pain conditions in some, but not all patients, as well as a

From Swedish Medical Center and the University of Washington School of Medicine, Seattle, WA; Division of Rheumatology, Chronic Pain and Fatigue Research Center, Center for the Advancement of Clinical Research, University of Michigan, Ann Arbor, MI; Women's Health Research Program, University of Cincinnati College of Medicine, Cincinnati, OH; Tufts University School of Medicine, Boston, MA; US Food and Drug Administration, Rockville, MD; Center for the Advancement of Clinical Research, Chronic Pain and Fatigue Research Program, University of Michigan, Ann Arbor, MI; Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA; Division of Immunology, Stanford University, Portola Valley, CA; Pfizer Global Research and Development, Ann Arbor, MI, and Groton, CT; Novartis Institutes for Biomedical Research, Cambridge, MA; Global Product Safety, Eli Lilly and Company, Indianapolis, IN; Cypress Bioscience, Inc., San Diego, CA; and Rheumatology Division, University of Kentucky, Lexington, KY, USA.

P.J. Mease, MD, Head, Seattle Rheumatology Associates, Chief, Rheumatology Clinical Research, Swedish Hospital Medical Center, Clinical Professor, University of Washington School of Medicine; D.J. Clauw, MD, Professor of Medicine, Division of Rheumatology, Director, Chronic Pain and Fatigue Research Center, Director, Center for the Advancement of Clinical Research, University of Michigan; L.M. Arnold, MD, Associate Professor of Psychiatry, Director, Women's Health Research Program, University of Cincinnati College of Medicine; D.L. Goldenberg, MD, Chief of Rheumatology, Newton-Wellesley Hospital, Professor of Medicine, Tufts University School of Medicine; J. Witter, MD, PhD, Lead Medical Officer, FDA; D.A. Williams, PhD, Associate Professor, Medicine/Rheumatology, Director, Research Development, Center for the Advancement of Clinical Research, Director, Chronic Pain and Fatigue Research Program, University of Michigan; L.S. Simon, MD, Associate Clinical Professor of Medicine, Harvard Medical School, Beth Israel Deaconess Medical Center; C.V. Strand, MD, Biopharmaceutical Consultant, Adjunct Clinical Professor, Division of Immunology, Stanford University; C. Bramson, MD, Associate Director; S. Martin, MSPH, Associate Director, Pfizer Global Research and Development; T.M. Wright, MD, Deputy Head, Exploratory Clinical Development, Novartis Institutes for Biomedical Research; B. Littman, MD, Head, Experimental Medicine, Pfizer Global Research and Development; J.F. Wernicke, PhD, MD, Associate Director – Neuroscience, Global Product Safety, Eli Lilly and Company; R.M. Gendreau, MD, PhD, Vice President, Chief Medical Officer, Cypress Bioscience, Inc.; L.J. Crofford, MD, Professor of Internal Medicine, Chief, Rheumatology Division, University of Kentucky.

Address reprint requests to Dr. P.J. Mease, Seattle Rheumatology Associates, 1101 Madison Street, 10th Floor, Seattle, WA 98104. E-mail: pmease@nwlink.com

variety of neurotransmitter and neuroendocrine changes[3,4,4a]. Such changes include reduced levels of biogenic amines, increased concentrations of excitatory neurotransmitters, and alterations of hypothalamic-pituitary-adrenal axis and autonomic nervous system activity[5]. A range of treatments are employed to treat the various symptom facets of FM[3,4a,6]. These include neuromodulatory medications such as antidepressants, opioids, nonsteroidal antiinflammatory drugs, sedatives, muscle relaxants, and anti-epileptics. Nonpharmaceutical treatment modalities, including education, exercise, physical therapy, massage, and cognitive behavioral therapy, can be helpful for FM as well[4a,7-10]. Although some of these therapies have been tested in randomized controlled trials (RCT), there has been little standardardization of an approach to trials or of outcome measures used. This represents a challenge for regulatory agencies that have yet to approve a drug for FM. They must ask a series of fundamental questions: What constitutes meaningful symptomatic change for an FM patient? How can change be accurately and consistently measured in this population? How durable is the therapeutic effect?

Evaluating therapeutic effects in FM is difficult because of the many facets of the syndrome. Diagnostic criteria based on pain and tender points have been developed for research purposes and identify a group of patients with pain and tenderness[1]. However, subgroups of patients with differing intensity of symptoms have been reported, and the current criteria may be shown to be limiting as further understanding about pathophysiology emerges[4,11]. Outcome measures transplanted from pain, rheumatology, neurology, and psychiatry research are able to distinguish treatment response in individual symptom domains, but do not necessarily tell us if meaningful change has occurred, either in individual symptom domains or the syndrome as a whole. Further work is necessary to refine and validate these measures in FM, as well as develop composite measures or response criteria to address the multidimensional nature of the syndrome. As more potential treatments for FM are being tested, there is pressing need to develop and standardize valid and reliable instruments to measure outcomes, which will improve the comparative value of treatment trials.

A possible model for this endeavor in FM, in the field of pain medicine, is that of the IMMPACT group (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials)[12,13]. As a partnership between researchers, industry, and the US Food and Drug Administration (FDA), this group is addressing the question, "What should be the core outcomes to assess in chronic pain clinical trials?" The consensus of this group has been that key outcomes to consider should be pain, physical functioning, emotional functioning, patient global ratings of satisfaction, negative health states, adverse events, and patient adherence and disposition.

Review of Instruments of Assessment of FM

Disease-specific composite measures. A disease-specific composite measure has been developed and validated in FM. The Fibromyalgia Impact Questionnaire (FIQ), developed by Burckhardt and coworkers, consists of questions and visual analog scales regarding functional disability, pain intensity, sleep function, stiffness, anxiety, depression, and overall sense of well-being[14]. Criticisms of the FIQ are that it may underestimate disease impact and inadequately measure treatment effect in patients with mild symptoms, and it is not validated in men. In addition, the functional assessment has been criticized as containing items not routinely performed[15]. Nevertheless, the FIQ is responsive to change and has been translated into many languages[16]. Assessing function, a component of the FIQ, has proved difficult in this population. A number of instruments have been used, but have not been consistently responsive to change[15]. Although the FIQ has been used as a measure of overall health status in patients with FM, the functional component is oriented toward high levels of disability, resulting in a potential floor effect[15]. In a controlled trial of fluoxetine in FM, the physical impairment subscore of the FIQ did not significantly improve in the fluoxetine-treated patients compared with placebo, although the total score did significantly improve in the fluoxetine group. No other FM-specific instruments that measure function have been tested in clinical trials. The Medical Outcome Study (MOS) Short Form-36 (SF-36) has been used to assess some aspects of function and quality of life in trials of FM, with inconsistent results[17–25].

Pain assessment. A standard tool of pain assessment is the daily pain diary, which is intended to assess pain intensity as well as the impact of pain on function[18]. The daily results are typically averaged on a weekly basis, and change from baseline to study endpoint is the primary outcome measure. Problems with this methodology include recall error, compliance with daily recording, and change in the patient's evaluation of pain intensity and impact over the length of the study. Efforts to deal with these problems have included use of the electronic diary and evolving methodologies of pain scaling methods[18]. The McGill Pain Questionnaire (MPQ) is a commonly employed pain questionnaire[26]. It includes 78 pain-related adjectives subdivided into sensory, affective, evaluative, and miscellaneous sensory qualities of pain. A shorter SF-MPQ, which includes 15 adjectives in sensory and affective categories, has been utilized in FM[26]. The SF-MPQ has been used in several trials and is able to distinguish drug versus placebo[19-22,24,25]. The Brief Pain Inventory (BPI) is a questionnaire that assesses intensity, impact, quality, relief, and patient perception of cause of pain[27]. It has been shown to be discriminant in recent FM trials[20,21]. The Leeds Assessment of Neuropathic Symptoms and Signs is an outcome measure designed to distinguish neuropathic and nociceptive pain. It was able to distinguish

quality of pain between patients with rheumatoid arthritis versus FM[28].

The manual tender point examination has been historically considered a key feature in the definition of FM[1]. However, validity and utility of the manual tender point examination is increasingly questioned: (1) Many patients who fall within the FM paradigm may have fewer than 11 tender points. (2) The manual tender point examination is limited by the relative lack of objectivity of the findings. (3) There is an uncertain relationship between the tender point examination and the underlying pathophysiology of the syndrome[4].

Although the manual tender point examination distinguishes FM patients from controls, its discriminant ability in clinical trials has been variable, suggesting that it may be useful as an entry criterion but not as an outcome measure. Dolorimetry, which may improve objectivity in tender point examination[29], has been shown to be responsive to treatment in a recent clinical trial[20]. Manual tender point intensity has been assessed utilizing the Fibromyalgia Intensity Score[30], in which the patient describes pain intensity on a 0–10 scale and the scores of 18 sites are averaged.

Fatigue assessment. The Multidimensional Assessment of Fatigue index, an 18 item questionnaire, has been used in FM trials[22,31,32]. The Multidimensional Fatigue Index, which similarly measures multiple aspects of fatigue including the emotional and physical, has been validated in a variety of populations and diseases, although not yet in FM[33]. Other instruments include the Functional Assessment of Chronic Illness Therapy[34] and the Fatigue Severity Scale[35]. The advantage of such tools is their ability to explore the multiple dimensions of fatigue. Simpler, single-question fatigue assessments are embedded within such composite instruments as the FIQ.

Sleep assessment. Multiple dimensions of sleep quality have been variably assessed in FM trials, including quantity, quality, ease of falling asleep, frequency of waking, and feeling refreshed upon awakening. Instruments include the MOS sleep scale[36], as well as single-question assessments of sleep quality in a daily diary format and embedded in the FIQ.

Quality of life and global assessment. Several instruments have been used to measure quality of life and global assessment in FM. The Patient Global Impression of Change[24], measured on an 11 point scale, and the Patient Global Impression of Improvement[20,21], measured on a 7 point scale, have been shown to discriminate treatment effect in FM. The MOS SF-36 used in most FM trials has 8 subscales assessing physical and mental function[37]. Several physical and mental subscales have been shown to discriminate treatment effect in FM[20-22,24].

Sexual function assessment. Sexual function is an important dimension of quality of life that is often overlooked in clinical trial outcome assessment. This domain can be improved as a person feels better with treatment, or sometimes worsened, e.g., as a side effect of some antidepressant or pain medications. A measure of sexual function has been utilized in one recent FM trial[24,38].

Assessment of psychiatric symptoms and comorbid psychiatric disorders. A number of screening tools for assessment of depressive and anxiety symptoms have been used in FM clinical trials, including the Beck Depression Inventory and the Beck Anxiety Inventory[39,40], the Hospital Anxiety and Depression Scale[41], and the Hamilton Depression Rating Scale[42]. The Mini International Neuropsychiatric Interview[43] and the Structured Clinical Interview for the DSM-IV Axis I Disorders[44] are structured diagnostic interviews that have been used for the diagnosis of comorbid psychiatric disorders in some FM trials. These structured interviews serve to exclude patients with certain psychiatric diagnoses for safety reasons, or stratify patients to observe if there are differences in treatment outcomes relative to these comorbid diagnoses. A comprehensive review of psychiatric measures in FM has been recently published[45].

Responder analyses. What constitutes a "meaningful" response in FM? Regarding pain response, Farrar has published a pooled analysis of patients with chronic pain of various etiologies, including FM, treated with pregabalin. In this analysis, a 30% reduction in the pain intensity score was considered a clinically important difference, and a 50% reduction was associated with the highest degree of improvement[46]. Regarding response of the syndrome as a whole, 2 groups have proposed different composite criteria sets, which are a weighting of measures such as pain, tender point assessment, function, and sleep quality[47,48]. These proposed sets have not been used in recent clinical trials nor recommended by regulatory agencies. However, they are examples of a potentially valuable composite criteria set for evaluating FM as a whole, and not just individual domains of the syndrome.

Delphi Exercise on FM Domains

Objective and background. A Delphi exercise among FM researchers was conducted prior to the OMERACT workshop to develop consensus on a prioritized list of key domains of the FM syndrome that should be addressed in clinical trials (Table 1 and Table 2). The steering committee of the workshop considered it important to have a framework of prioritized domains to present at the OMERACT workshop as a basis for discussion and for developing a research agenda on domains of inquiry and instruments of assessment in FM trials.

The exercise was modeled after a recently completed Delphi exercise conducted by GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis). The key elements of a Delphi process were in place: (1) Anonymity — questionnaires were E-mailed; (2)

Iteration — 3 "rounds" were conducted; (3) Controlled feedback — individuals were informed of the whole-group response after each round; and (4) Statistical group response — group judgment was expressed as the median; spread of opinion indicated strength of consensus[49-53].

Methods. A list of 40 potential domains was prepared through literature review and E-mail discussion by steering committee members (see Table 1). After the domains were established, a selected group of FM clinicians and researchers was asked to participate in the consensus exercise. Fifty-one potential participants were contacted; 23 completed all 3 rounds of scoring. Each participant was e-mailed the list of 40 domains in Microsoft Excel spreadsheet format and asked to distribute 100 points among the domains, giving more points to domains they considered more important to evaluate. In 2 subsequent rounds the results of the group median, interquartile range, and total range of the earlier responses were E-mailed to each respondent, who could reflect on previous scoring and revise subsequent scoring if they chose. The participants were asked to rank the domains in each of 3 different contexts: (1) Symptom Modifying, i.e., as might be considered important in a clinical trial; (2) Clinical Record Keeping, i.e., as might be considered important in recording in a medical chart; and (3) Rehabilitation, i.e., as might be considered important regarding ultimate ability to improve or achieve remission. For the workshop, only data from the Symptom Modifying context were reviewed and discussed.

Results. The results are presented in Table 2. Pain was considered the key domain to be assessed, followed by fatigue, patient global, and sleep. Other key domains are indicated.

Table 1. Delphi symptom domains as a complete list.

Abuse, alcohol and/or drug use	Negative cognitive factors
Abuse, physical, sexual, and/or emotional	Noxious threshold
Anxiety diagnosis, current or previous	Pain
Arthralgias	Paresthesia/dysesthesia
Chest pain	Personality disorder
Comorbities, influence of	Physical functioning
Depression, current or previous	Productivity
Dyscognition	Restless leg syndrome
Family/social construct	Satisfaction
Fatigue	Secondary gain
Global clinician-rated improvement	Sexual function
Global patient-rated improvement	Sicca symptoms
Headache	Sleep quality
Health-related quality of life	Social functioning
Income	Socioeconomic status
Irritable bladder syndrome	Symptoms, number and level of
Irritable bowel syndrome	Tenderpoint count
Marital status	Tenderpoint intensity
Morning stiffness	Treatment side effects
Muscle fatigue or weakness	Unresponsivness to treatment

Table 2. Median Delphi scores for 12 domains identified for clinical trials of FM

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 diagnosis	2
Clinician rated global	1

FM Workshop Session at OMERACT 7

The Delphi exercise was presented, followed by a review of major clinical trials in FM, with a focus on the outcome measures used, in order to build an understanding of the key symptomatic domains that underlie the syndrome and their responsiveness to therapy. Trials chosen for review included those of tricyclic antidepressants (TCA)[19], fluoxetine[54], tramadol plus acetaminophen[23], tramadol[55], pregabalin[22], duloxetine[20], recombinant growth hormone[25], and milnacipran[24]. Some of these studies are unpublished except in abstract form, therefore the data have been anonymized in this report. The results were translated into standardized effect sizes by dividing the placebo-corrected difference by the pooled standard deviation using the method of Cohen[56]. Effect sizes of 0.2–0.49 are generally considered small, 0.5–0.79 are considered medium or moderate, and > 0.8 are considered large. These results are summarized in Table 3. Domains assessed, utilizing measures outlined previously, included pain (by VAS, multidimensional), fatigue (VAS, multidimensional), sleep (VAS, multidimensional), patient and clinician global assessment of change, function (by the FIQ), health-related quality of life (SF-36), depression, and anxiety. Effect sizes for all domains tended to be medium in size, and patients with FM show weaker correlations between improvement in symptoms and improvement in physical function than in other rheumatic diseases. These studies provide understanding of the responsiveness of FM to treatment and the endpoints most sensitive to improvements in symptoms and function.

Tramadol and tramadol/acetaminophen for the treatment of FM. Two trials, tramadol alone and tramadol in combination with acetaminophen, demonstrated modest efficacy in treating FM pain[23,55]. Tramadol/acetaminophen had modest effects on function as assessed by FIQ and SF-36. Tramadol alone did not improve function as assessed by FIQ total score. Tramadol/acetaminophen had no effect on sleep. Sleep was not assessed in the trial of tramadol alone.

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	VAS Pain	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 wks	0.78	0.55	0.29		0.82	0.46	0.42	0.20	0.19			0.22
B	Average across 9 studies	0.52		0.29		0.66	0.45				0.66		
C	1–12 wks	0.95		0.48	0.52		0.57						
D	1–12 wks	0.34		0.41	0.24		0.08				0.24		
E	1–12 wks	0.39	0.39	0.22	0.32	0	0.13	0.15	0.27	0.13		0.37	0.33
F	1–9 wks	0.49		0.18								0.11	
G	1–12 wks	0.51	0.4			0.25	0.41	–0.02	0.26	0.25			
H	1–9 mo			0.6								0.6	

Recombinant human growth hormone. Use of growth hormone (GH) in FM is based on studies showing that levels of insulin-like growth factor-1 (IGF-l, the mediator of GH activity) in patients with FM are lower than in age-matched controls. Whether lower IGF-1 is a result of the FM syndrome or involved in the causative pathway is not known; however, IGF-1 does play a role in muscle repair, and thus could conceivably be involved in the pathogenesis of FM pain[57]. A 9-month study of injectable recombinant human GH in patients with a low IGF-1 at entry showed improvements in FM symptoms as assessed by the FIQ total and tender points score[25].

Tricylic antidepressants. In a metaanalysis of TCA[19], most studies used a pain VAS or Likert scale as the primary outcome. Sleep, fatigue, tenderness, stiffness, and mood/anxiety were frequently assessed as secondary outcomes. Global assessment and a variety of health related quality of life (HRQOL) and functional assessments were measured. TCA generally had moderate effects on sleep and pain, with the effects on sleep generally slightly larger.

Selective serotonin reuptake inhibitors (SSRI). Although the effect of SSRI on pain has been marginal, one study of flexibly dosed fluoxetine showed improvement of pain, as measured by FIQ pain score, and statistically significant effects on fatigue and depression[54].

Serotonin/norepinephrine reuptake inhibitors (SNRI). Milnacipran was efficacious in treating the core symptoms of FM, including pain, fatigue, and mood[24]. Robust improvements were observed in the Patient Global Impression of Change, with modest effects on fatigue and functioning (measured by FIQ) and small effects on sleep. Patients demonstrated improvements in pain regardless of baseline major depressive episode status, but patients with depression had the largest placebo response on pain scales. Duloxetine, another SNRI, was tested in FM patients. In the first of 2 studies, significant improvement was demonstrated in the treated group utilizing the total FIQ score, but did not show significance in the co-primary outcome of FIQ pain score, nor was improvement noted in male subjects[20]. A secondary outcome measure of pain, the BPI, did show statistically significant improvement in the treated group. Duloxetine also improved several other symptoms associated with FM, including stiffness and tender points (measured by dolorimetry), as well as global assessment and several quality of life measures. Duloxetine improved pain symptoms regardless of baseline major depressive disorder status. A second study, utilizing the BPI as a primary pain endpoint and excluding male patients, did show statistically significant improvement[21].

Pregabalin. Pregabalin is an investigational agent that binds to the alpha-2-delta subunit of the voltage-gated calcium channel in the central nervous system. It is structurally related to gabapentin and is being developed for the treatment of FM and other indications. Pregabalin was studied in an 8 week RCT in FM and was efficacious in the treatment of pain, sleep disturbance, and fatigue[22]. The primary outcome was pain measured by an 11-point numeric rating score recorded in a daily pain diary. There was significant improvement in pain at the highest dose studied. Significant improvement in sleep was also observed as assessed by a sleep diary and the Medical Outcomes sleep scale. Significant reduction in fatigue was also reported. Patient global impression of change and 4 domains of the SF-36 were also improved.

Cognitive behavioral therapy. A trial of cognitive behavioral therapy (CBT) in chronic multisymptom illness (CMI) showed correlation estimates between the SF-36 physical component scale and pain (0.34), general fatigue (0.40), and physical fatigue (0.42)[58]. This cohort with CMI had extremely low levels of self-reported function, like other cohorts with FM. CBT specifically aimed at improving physical function had only a marginally significant influence on self-reported physical function. This and other studies suggest weaker correlations between improvements in

symptoms (e.g., pain, fatigue, etc.) and improvement in function in FM than in other rheumatic disorders. A second clinical trial of CBT in FM using similar methods and outcome measures showed patients receiving CBT to be twice as likely to have a clinically meaningful improvement in physical functional status than standard care[59].

US regulatory perspective on FM. Jim Witter of the FDA Arthritis Advisory Committee highlighted the presentation and discussion of the committee's meeting on FM of June 23, 2003[60], and the US National Institutes of Health-FDA Guidance on Analgesics (under revision and currently not available). Unmet needs in chronic pain include a need for better understanding of clinical aspects of chronic pain and the pain mechanisms that may serve as treatment targets, and for standardized and validated methodologies of trial design and outcome measurement in FM. The FDA is currently considering 2 non-mutually exclusive approaches for new therapeutic agents seeking a claim approval for FM: (1) for symptomatic management of pain of FM, and (2) for the management of FM as an overall syndrome. To achieve the former, the drug would need to show statistical superiority in a predetermined pain measure(s). To achieve the latter, the drug would need to also show statistical superiority in its effect on a broader arena of symptoms and function of FM patients. Regarding recommendations as to a core set of domains to be considered in clinical trials of FM, the model of the IMMPACT recommendations was described[12,13]. Ultimately, a composite responder analysis, akin to the ACR-20 response criteria for rheumatoid arthritis, would be highly desirable for future trials of pharmacologic agents in FM.

OMERACT Workshop Consensus Voting

After reviewing the pre-OMERACT Delphi exercise and the data from clinical trials in FM patients, workshop attendees prioritized domains of assessment for clinical trials. Results are presented in Tables 4 and 5.

The key difference from the pre-OMERACT Delphi prioritization is a higher ranking of HRQOL and function, with a focus on multidimensional aspects of function rather than simply physical function. There was acknowledgment that aspects of function such as role, vocational, and emotional function may be of as great or greater importance in a patient with FM than physical function limitations. As in the prior Delphi exercise, pain, fatigue, and patient global sense of well-being ranked highest. The group also agreed that those domains ranked by at least 50% of workshop attendees should be considered key domains to assess in clinical trials, whereas those ranked lower should be considered to be measured, but that more research would be necessary to know how critical they would be, and how best to measure them. There was support for placing the concept of "participation" on the research agenda, i.e., developing an approach to measure ability of patients to participate in life activities and function. There was also support for further development of a new composite instrument and/or an outcome criteria set for FM, analogous to the ACR or DAS criteria sets used in rheumatoid arthritis. The group was split on whether this should be in the form of a responder analysis or on a continuous scale. It was recommended that the patient perspective be included in the prioritization of research domains, which could be accomplished by a future Delphi exercise with patients.

Table 4. Percentage of OMERACT workshop attendees who considered domains essential to assessment in clinical trials of fibromyalgia.

Domain	Respondents (%)
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
Clinician rated global	23
Dyscongnition	21
Anxiety diagnosis	21
Tender point intensity	18

Table 5. Voting results from FM workshop exercise. Attendees were asked to rank which domains that they thought were most important, and second and third most important to measure in FM studies.

Domain	Percentage of Attendees Who: Ranked First	Ranked Second	Ranked Third	Ranked in Top 3
Pain	64	13	16	93
Patient global	22	18	25	65
HRQOL	12	16	20	48
Fatigue	0	32	24	56
Sleep	2	13	4	19
Physical function	0	7	9	16

Conclusions

The primary objective of the FM workshop, to establish a prioritized list of domains key to FM research, was achieved with the ranking of the following key domains: pain, patient global, fatigue, HRQOL, function (multidimensional), sleep, depression, and treatment side effects. Other important domains, not considered as essential, included physical function, tender point intensity, dyscognition, anxiety, and clinician global assessment. This ranking is consistent with that achieved prior to the workshop in a Delphi exercise of FM researchers (Table 2). Highlighted is the multidimensional nature of the FM syndrome, with its key elements of pain, fatigue, sleep disturbance, and functional disability.

There exist a variety of outcome measures, outlined in this article, to assess these domains and that have been used in FM clinical trials. Following further standardization and validation they will constitute the core of the upcoming research agenda for the FM research community. Further key research objectives will be to refine measures of the multidimensional aspect of functional disability, including role vocational, social, and emotional aspects, addressing the concept of "participation" as an outcome measure, to include patient perspective on what represents a clinically meaningful change in a domain or the syndrome as a whole. Toward this end, focus groups of FM patients are being developed to address the patient perspective and to serve as a nucleus for conduct of Delphi exercises. There is consensus that development and validation of a composite instrument and/or criteria set for fibromyalgia as a syndrome is of key importance. Several members of the Steering Committee are currently involved with an ongoing project to develop and validate such a measure. Results of these research efforts will hopefully be discussed in the next OMERACT session in 2006.

REFERENCES

1. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160-72.
2. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19-28.
3. Bennett RM. The rational management of fibromyalgia patients. Rheum Dis Clin North Am 2002;28:181-99.
4. Clauw DJ, Crofford LJ. Chronic widespread pain and fibromyalgia: what we know, and what we need to know. Best Pract Res Clin Rheumatol 2003;17:685-701.

4a. Mease P. Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. J Rheumatol 2005;32 Suppl 75:6-21.

5. Bennett RM. Emerging concepts in the neurobiology of chronic pain: evidence of abnormal sensory processing in fibromyalgia. Mayo Clin Proc 1999;74:385-98.
6. Barkhuizen A. Rational and targeted pharmacologic treatment of fibromyalgia. Rheum Dis Clin North Am 2002;28:261-90.
7. Busch A, Schachter C, Peloso P, Bombardier C. Exercise for treating fibromyalgia syndrome. Cochrane Database Syst Rev 2002;CD003786.
8. Burckhardt CS, Bjelle A. Education programmes for fibromyalgia patients: description and evaluation. Baillieres Clin Rheumatol 1994;8:935-55.
9. Burckhardt CS, Mannerkorpi K, Hedenberg L, Bjelle A. A randomized, controlled clinical trial of education and physical training for women with fibromyalgia. J Rheumatol 1994;21:714-20.
10. Williams DA. Psychological and behavioural therapies in fibromyalgia and related syndromes. Best Pract Res Clin Rheumatol 2003;17:649-65.
11. Giesecke T, Williams DA, Harris RE, et al. Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors. Arthritis Rheum 2003;48:2916-22.
12. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain 2003;106:337-45.
13. Turk DC, Dworkin RH. What should be the core outcomes in chronic pain clinical trials? Arthritis Res Ther 2004;6:151-4.
14. Burckhardt CS, Clark SR, Bennett RM. The Fibromyalgia Impact Questionnaire: development and validation. J Rheumatol 1991;18:728-33.
15. Wolfe F, Hawley DJ, Goldenberg DL, Russell IJ, Buskila D, Neumann L. The assessment of functional impairment in fibromyalgia (FM): Rasch analyses of 5 functional scales and the development of the FM Health Assessment Questionnaire. J Rheumatol 2000;27:1989-99.
16. Iverson M. The Fibromyalgia Impact Questionnaire. Arthritis Care Res 2003;49:S210-S213.
17. Henriksson CM. Longterm effects of fibromyalgia on everyday life. A study of 56 patients. Scand J Rheumatol 1994;23:36-41.
18. Gendreau M, Hufford MR, Stone AA. Measuring clinical pain in chronic widespread pain: selected methodological issues. Best Pract Res Clin Rheumatol 2003;17:575-92.
19. Arnold LM, Keck PE Jr, Welge JA. Antidepressant treatment of fibromyalgia. A meta-analysis and review. Psychosomatics 2000;41:104-13.
20. Arnold LM, Lu Y, Crofford LJ, Wohlreich M, Detke MJ, Iyengar S, Goldstein DJ. double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Arthritis Rheum 2004;50:2974-84.
21. Wernicke JF, Rosen AS, Lu Y, et al. Duloxitene in the treatment of fibromyalgia. Arthritis Rheum 2004;50:S697.
22. Crofford LJ, Rowbotham MC, Mease PJ.et al. Pregabalin for the treatment of fibromyalgia syndrome: Results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:1264-73.
23. Bennett RM, Kamin M, Karim R, Rosenthal N. Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study. Am J Med 2003;114:537-45.
24. Gendreau M, Mease P, Rao S, Kranzler J, Clauw D. Milnacipran: A potential new treatment of fibromyalgia [abstract]. Arthritis Rheum 2003;48 Suppl:S617.
25. Bennett RM, Clark SC, Walczyk J. A randomized, double-blind, placebo-controlled study of growth hormone in the treatment of fibromyalgia. Am J Med 1998;104:227-31.
26. Melzack R. The short-form McGill Pain Questionnaire. Pain 1987;30:191-7.
27. Cleeland C. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994;23:129-38.
28. Martinez-Lavin M, Lopez S, Medina M, Nava A. Use of the Leeds Assessment of Neuropathic Symptoms and Signs Questionnaire in patients with fibromyalgia. Semin Arthritis Rheum 2003;32:407-11.
29. Gracely RH, Grant MA, Giesecke T. Evoked pain measures in fibromyalgia. Best Pract Res Clin Rheumatol 2003;17:593-609.
30. Sinclair D, Starz T, Turk D. The Manual Tender Point Survey. [Internet] [Accessed July 14, 2005]. Available from National Fibromyalgia Association: http://fmaware.org/doctor/tenderpt.htm
31. Littlejohn G. A database for fibromyalgia. [Internet] 1993 [accessed July 14, 2005]. Available from Medical Pain Education:http://web-sites.golden-orb.com/pain-education/100130.php.
32. Belza BL, Henke CJ, Yelin EH, Epstein WV, Gilliss CL. Correlates of fatigue in older adults with rheumatoid arthritis. Nurs Res 1993;42:93-9.
33. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995;39:315-25.
34. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes 2003;1:79.

35. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The Fatigue Severity Scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121-3.
36. Hays R, Stewart A. Measuring functioning and well-being. In: Stewart A, Ware J, editors. Sleep measures. Durham, NC: Duke University Press; 1992:232-59.
37. Ware JE Jr, Sherbourne CD. The MOS 36-item Short-form Health Survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
38. McGahuey CA, Gelenberg AJ, Laukes CA, et al. The Arizona Sexual Experience Scale (ASEX): reliability and validity. J Sex Marital Ther 2000;26:25-40.
39. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988;56:893-7.
40. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71.
41. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67:361-70.
42. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62.
43. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59 Suppl 20:22-33; quiz 34-57.
44. First MB, Spitzer RL, Gibbon M, Williams JB. Structured Clinical Interview for DSM-IV Axis I Disorders — Patient Edition (SCID-I/P, version 2.0, 4/97 revision). New York: Biometrics Research Department, New York State Psychiatric Institute; 1997.
45. Turk DC, Monarch ES, Williams AD. Psychological evaluation of patients diagnosed with fibromyalgia syndrome: a comprehensive approach. Rheum Dis Clin North Am 2002;28:219-33.
46. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149-58.
47. Dunkl PR, Taylor AG, McConnell GG, Alfano AP, Conaway MR. Responsiveness of fibromyalgia clinical trial outcome measures. J Rheumatol 2000;27:2683-91.
48. Simms RW, Felson DT, Goldenberg DL. Development of preliminary criteria for response to treatment in fibromyalgia syndrome. J Rheumatol 1991;18:1558-63.
49. Jones J, Duncan H. Qualitative research: consensus methods for medical and health services research. BMJ 1995;311:376-80.
50. Linstone HA. The Delphi Technique. In: Fowles J, editor. Handbook of futures research. Westport, CT; London, England: Greenwood Press; 1978:273-300.
51. Oranga H, Nordberg E. The Delphi panel method for generating health information. Health Policy Planning 1993;8:405-12.
52. Pill J. The Delphi method: substance, context, a critique and an annotated bibliography. Socio-Econ Plan Sci 1971;5:57-71.
53. Rowe G, Wright G, Bolger F. Delphi. A reevaluation of research and theory. Technological Forecasting and Social Change 1991;39:235-51.
54. Arnold LM, Hess EV, Hudson JI, Welge JA, Berno SE, Keck PE Jr. A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. Am J Med 2002;112:191-7.
55. Russell I, Kamin M, Bennett RM, et al. Efficacy in tramadol in treatment of pain in fibromyalgia. J Clin Rheumatol 2000;6:250-7.
56. Cohen J. Statistical power analysis for the behavioral sciences. New York: Academic Press; 1998.
57. Bennett RM. Disordered growth hormone secretion in fibromyalgia: a review of recent findings and a hypothesized etiology. Z Rheumatol 1998;57 Suppl 2:72-6.
58. Donta ST, Clauw DJ, Engel CC Jr, et al. Cognitive behavioral therapy and aerobic exercise for Gulf War veterans' illnesses: a randomized controlled trial. JAMA 2003;289:1396-404.
59. Williams DA, Cary MA, Groner KH, et al. Improving physical functional status in patients with fibromyalgia: a brief cognitive behavioral intervention. J Rheumatol 2002;29:1280-6.
60. Center for Drug Evaluation and Research. CDER 2003 Meeting Documents: Arthritis Advisory Committee. June 23, 2003 [Internet. Accessed July 14, 2005] Available from CDER website: http://www.fda.gov/ohrms/dockets/ac/cder03.html#Arthritis