Preliminary identification of key clinical domains for outcome evaluation in fibromyalgia using the Delphi method: the Italian experience

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SUMMARY

Objective: Fibromyalgia (FM) is a complex syndrome that, in Italy, affects at least 2% of the adult population. It is characterized by chronic widespread musculoskeletal pain often accompanied by multiple other symptoms. The aim of this study was to identify a set of clinical domains for FM considered relevant by both clinicians and patients using a consensus process.

Methods: Consensus was achieved using the Delphi method based on questionnaires and systematic, controlled opinion feedback. The Delphi exercise involved a panel of 252 rheumatologists and 86 patients with FM as defined by the American College of Rheumatology criteria. All of the patients and clinicians were asked to rank the relative different domains of FM in order of priority. The content validity index (CVI) was used to establish the percentage agreement. The importance of each item was ranked on a 0-3 Likert scale. The frequency, mean relevance scores, and frequency importance product were also calculated.

Results: The Delphi exercise showed that the domains ranked highest by patients were similar to those of the clinicians, with the exception of *tender point intensity* (considered relevant by the clinicians but not by the patients) and *environmental sensitivity* (considered important by the patients but not by the clinicians). A final 8-item model was developed which was considered to demonstrate adequate validity.

Conclusions: The Delphi exercises identified and ranked relevant key clinical domains that need to be assessed in FM research. On the basis of these results, a new patient-reported composite outcome index can be developed and used in clinical trials.

Key words: *fibromyalgia, Delphi method, pain scales, health-related quality of life, patient-reported outcomes.*

■ INTRODUCTION

Fibromyalgia (FM) is a complex syndrome which, in Italy, affects at least 2% of the adult population (1). It is characterized by widespread chronic pain, often associated with other symptoms such as fatigue, disturbed sleep patterns, functional limitations and cognitive impairment (2, 3). The presence of these symptoms and any comorbidity (4) significantly compromises the quality of life of FM patients (5-8). Defining the impact of symptoms on patients with FM can be a useful tool to evaluate pa-

tient activity and and social function, and response to treatment in research and daily clinical practice (9-14).
The group of experts in fibromyalgia of the OMERACT (Outcome Measures in Rheumatology) group, using working party and the Delphi methods, has recently examined the possibility of patients identifying principle clinical domains to be used as an evaluation tool in clinical trials (2, 15). Beginning with an initial list of 40 potential domains, the experts gave marks in terms of importance of each domain. In the same way, a similar selection was made by dif-

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ferent groups of patients with FM from different centers. The results from both the groups of experts and of patients were the same. The list of principal domains selected included: *pain*, *overall state of health*, *fatigue*, *quality of life* (QoL), *multidimensional function*, *sleep pattern* and *depression*. The so-called secondary domains included *physical function*, *tender points*, *cognitive impairment*, (lack of concentration, disorganized thoughts, etc.) and *anxiety* (15). This working method allowed us to sustain construct validity of the potential domains, while feasibility and the selective ability of the specific instruments to be used in its application were the subject of a separate systematic randomized controlled trial (RCT) (12, 16).

Use of the so-called patient reported outcomes (PRO) is the most accepted method of evaluating disease status, especially in conditions characterized by chronic pain (17, 18). This method is highly appropriate for use in FM (10) given that most of the clinical domains considered essential for evaluation of the disease, and defined as such by the experts of the OMERACT group (2, 15, 19) and of the Food and Drug Administration (FDA) (20), are patient centered.

In line with methods used by the OMER-ACT group (15, 20), this study was carried out using the Delphi method, and involved 252 rheumatologists and 86 patients with FM. The principle aim of the study was to reach a unanimous consensus on the list of health domains considered to be high priority both in a research context and in daily clinical practice, and considered to be useful for disease evaluation.

■ **MATERIALS AND METHODS**

Expert working parties
The items were generated in two successive phases. First, we carried out a literature review of clinical studies in FM in order to identify the principle outcome measures used. Clinical trials published up to September 2010 were downloaded from the internet using MEDLINE, CINAHL

and EMBASE search engines. A strategy of specific research was developed for each database using Cochrane filter for RCT and including articles published in English and in Italian between 1990 and 2009. The key words used were: "Fibromyalgia", "Chronic pain syndrome", "Widespread pain", "State of Health", "Multidisciplinary", "Patient care team", "Treatment of fibromyalgia" or "Management of fibomyalgia" and "Trial".

The search strategy produced 2,055 articles, of which 204 were selected on the basis of titles, summaries and key words, from which a total of 39 papers were subsequently selected. The list of items was re-examined for importance of content by a multidisciplinary task force of experts in FM: 25 rheumatologists, 4 orthopedic surgeons, 3 neurologists, 3 algologists, 2 psychologists, 6 physiotherapists and 3 occupational therapists. Each doctor was invited to decide which specific method they considered most appropriate to measure each clinical domain and to mark each item selected according to feasibility. In order to reduce the number of clinical domains, items were excluded from the list if:
a) they were related to gender;
b) they required use of special equipment;
c) they used terminology which was ambiguous or difficult to understand;
d) they presented alternatives to other items, duplicated them and/or were similar to them. The final list was made up of a pool of 58 symptoms/domains (*see Appendix*).

Final item selection
The number of items was reduced in order to avoid symptoms and/domains which were superfluous or repetetive. This was achieved by keeping 8-10 symptoms/domains considered to be the most important and representative of patients' general state of health. In the next phase, 252 rheumatologists, randomly selected from the list of 1,200 members of the Società Italiana di Reumatologia (Italian Society of Rheumatology) were interviewed through the internet (http://www.reumatologia.it).
Each rheumatologist was invited to make

their own independent selection, without any assistance, of the symptoms/domains they considered to be the most important and representative from the list of 58 symptoms/domains which had been identified by the task force. Response was 70.4% (252 of 538 contacted) representing a third of all rheumatologists interviewed. The content validity index (CVI) was used to establish the proportion/percentage of agreement between the experts. Lynn (21) recommended using a relevance evaluation scale for each item providing ordinal level data based on the Likert scale from 0 to 4 (4=highly relevant, extremely important; 3=very relevant, very important; 2=not very relevant, not very important; 1=not relevant, unimportant). Once scoring was completed, the CVI only included elements with a mark of 3 or 4, while all descriptors with a mark of 1 and 2 were not considered. The CVI formula was: CVI or percentage of agreement = the number of experts in agreement on items receiving scores of 3 or 4 divided by the total number of experts. The items were considered to have adequate content validity when agreement was 70% or over, and to be questionable or unacceptable when agreement among experts was 60-70% or less than 60%, respectively.

Patient working parties

The aim of this phase of the study was to reach unanimous agreement, in terms of priority and importance of the clinical domains, among patients diagnosed with FM according to the criteria of the American College of Rheumatology (ACR) (22). Rheumatologists involved in the study excluded diagnoses other than FM. Other exclusion criteria were: comorbidities such as to impede full participation in study procedures (terminal stage, such as, for example, advanced stage renal disease, cardiac insufficiency or neoplasms), alcohol abuse, significant cognitive impairment, or psychiatric symptoms which could have compromised efficient completion of the questionnaire.

After obtaining local ethics committee approval for the study, a group of 86 patients with FM were invited to take part and gave their signed informed consent. These patients were from three different rheumatology centers: the centers of northern, central and southern Italy. The patient group was considered to provide an adequate representative sample of the disease in terms of heterogeneity of the symptoms presented at the moment of inclusion in the study.

A rheumatologist experienced in developing measurement strategies presented each patient with the list of the 42 domains that were considered to be the most important in relation to FM. During the interview, each patient was asked to put the various domains in the order of priority (mean importance, MI) giving each one a score on the Likert scale from 1 to 3 (1=not relevant, not important; 2=not very relevant, not very important; 3=very relevant, very important). Mean values were then calculated for each item which had obtained a score of 2. Analysis considered frequency of each symptom, and the prevalence and domains which satisfied 60% or over of prevalence criteria. The frequency importance product (FIP) was, therefore, generated for each

Table I - Domains classified according to importance by clinicians.

Domain	Frequency	Mean importance (MI)	Frequency importance product (FIP)
1. Pain	79.0	2.85	225.2
2. Fatigue	78.6	2.65	208.3
3. Disturbed sleep patterns	74.6	2.70	201.4
4. Health-related quality of life (HRQL)	73.8	2.60	191.9
5. Depression	70.2	2.60	182.5
6. Anxiety	71.8	2.50	179.5
7. Memory lapse and lack of concentration	69.1	2.40	165.8
8. Tender points	60.2	2.20	126.4

item, multiplying the frequency by the MI assigned to each domain. For example, the FIP relating to the domain *pain*, estimated by clinicians to be the most frequent and with the highest range, was 225.2 (FIP *pain* = frequency 79% x MI 2.85 = 225.2) (Table I). The FIP represented, therefore, a composite, two-dimensional measurement particularly useful in establishing the extent of importance of a symptom or domain.

■ RESULTS

Use of the Delphi method among clinicians
Using the Delphi method, 252 rheumatologists evaluated the importance of each item. The items considered important (*pain*, *tiredness*, *disturbed sleep patterns*, *quality of life*, *physical function*, *depression*, *cognitive impairment*, *anxiety* and *tender points*) which reached a 60.2-79.0% agreement among clinicians were included in the final list. Table I shows the frequency, relevance and FIP of each item. Clinicians considered *pain* (FIP = 225.5), *tiredness* (FIP = 208.3), *disturbed sleep patterns* (FIP = 201.4) and *quality of life* (FIP = 191.9) to be the most important items.

Use of the Delphi method among patients
The study included 86 patients: 70 women and 16 men, mean age 43.9 years, range 22-68 years, female:male ratio 5:1, comparable and similar to other studies in the literature. The largest proportion of patients (58%) had been diagnosed with FM 1-4 years before the study began. Seventy-one percent of patients reported the onset of symptoms to have been over five years before, 35% did not work because of the disease, while 42% classified their state of health as "poor". Their level of education was generally low: 60.1% had only received primary school education (6-11 years of age) and only 19.9% had gone to upper secondary school (14-19 years of age). Most patients (77.9%) were married and lived with their family while 34% were housewives. Forty-one of the 86 subjects (52.6%) reported one or more comorbidity, in particular, cardiovascular disease (29.2%), and respiratory (14.1%) and metabolic (10.5%) problems.

Overall, classification of the domains selected by patients was the same as that proposed by the clinicians. *Pain* was the most important symptom (FIP = 282.2), while patients considered *tiredness*, *disturbance of sleep pattern*, *overall state of health*, *quality of life*, *depression*, *anxiety* and *cognitive impairment* (memory lapse and lack of concentration) to be equally important. *Tender points* were considered to be important by clinicians but not by patients. On the other hand, *excessive sensitivity to external stimuli* (sounds, lights,

Tabella II - Domains classified according to importance by patients.

Domain	Items	Frequency	Mean importance (MI)	Frequency importance product (FIP)
1. Pain	Pain or physical distress; painful joints; pain on palpation	97.3	2.9	282.2
2. Fatigue	Tiredness; low energy levels	93.6	2.7	252.7
3. Quality of sleep	Difficulty in sleeping; insomnia; frequent waking during the night	90.1	2.6	234.3
4. Multidimensional function	Difficulting in moving around, in walking or doing physical exercises; problems in carrying out daily routine activities, work and study, and impact on daily routine	89.8	2.6	233.5
5. Depression	Feeling sad, unmotivated, pessimistic, isolated, listless	81.5	2.4	195.6
6. Sensitivity to external stimuli	Sensitivity to sounds, light, smells and/or the cold	78.3	2.4	187.9
7. Anxiety	Feeling frustrated, worried, scared	76.1	2.3	175.0
8. Cognitive impairment	Memory lapse or difficulties in remembering things; loss of memory; lack of concentration	74.7	2.1	156.9

smells) were considered to be important by patients but not by clinicians. Patients did not take into consideration the domain *health-related quality of life* while the rheumatologists did. In spite of this, the impact of the disease on *physical function* was, however, considered to be important. In particular, reference was made to difficulty in moving around, walking or doing physical exercises, problems in carrying out daily routine activities, work and study, and the impact of the disease on daily life. The 8 items reached a prevalence of at least 70%, while the mean importance (MI) of marks given varied between 2.1 (*cognitive impairment*) and 2.9 (*pain*). The FIP of the 8 items is between 156.9 and 282.2. Clinicians summarized the last domain as *cognitive impairment* while patients described it in different terms such as, for example, "losing attention", "lack of concentration", "memory lapse" and "disorganized thoughts". The domains with the highest marks are shown in Table II.

■ DISCUSSION

In their definition of the classification of the 8 items considered to be important during the course of FM, a high percentage of doctors and patients generally gave *pain*, *tiredness* and *disturbed sleep patterns* the highest marks of importance. (23) This, therefore, confirms the importance of these domains, and suggests they should be included in evaluation criteria for this disease (19). It is interesting to note that these items represent the three domains which make up the "Fibromialgia Activity Score (FAS)" (24) self-evaluation scale, and as such are in agreement with recommendations proposed by the OMERACT group of experts in FM, the "Syndrome Workshop" (15, 19) and the IMMPACT (Initiative on Methods, Measurements and Pain Assessment in Clinical Trial) group (25). The other five domains selected by clinicians, including *depression* and *anxiety*, *state of health-quality of life*, *memory lapse* and *lack of concentration*, and *tender points*, are generally considered to be

important also by patients (15, 19). However, with respect to clinicians, patients also consider *excessive sensitivity to external stimuli* to be important. The most important functional items, which were underlined by the patients, include effects of the disease on personal day to day planning, achieving routine objectives and completing daily tasks, even though they did not usually consider *health-related state of health* to be important. According to the OMERACT group of experts (15, 19). clinicians should consider *health-related quality of life* to be very important in order to adequately evaluate the much wider multidimensional aspect of *function* rather than simply *physical function*. It is interesting to note that while *rigidity* was considered to be an important domain by the OMERACT group of experts (2,.15, 19). by systematic revision (12,26) and in investigations conducted *via* internet (27). this was not among the domains selected by patients who took part in the study, who did not consider it to be important. In contrast, it is not surprising that *pain* was the domain selected most, often being the first symptom reported by the patient. However, even though it was classified in first place as an indicator of disease severity, *pain* is considered the principle criterion by 79% of the doctors interviewed. It should also be noted that an objective clinical evaluation made through investigation into *tender points* was reported by only 60.2% of clinicians and that all other criteria selected are to be considered "patient-centered". The variety of criteria available for FM, and the lack of a unanimous consensus agreement, underlines the need to validate an adequate means to measure disease severity. A recent study (8) which involved 788 patients with FM, defined *pain* and *tiredness* to be the most important symptoms in 54% of participants and to be the most characteristic signs of disease, while *fatigue* was chosen as the most important item by 28% of those interviewed. *Tiredness*, a common symptom among patients with FM (2, 15, 27) which often represents one of the most worrying problems, is a subjective experience which is described

as "extreme and persistent mental and/or physical weakness or tiredness". In spite of the fact that the causes of tiredness are little known, it has been increasingly used in recent years as a measurement of outcome in clinical studies (28). Since there is still no theoretical model, it remains difficult to define *tiredness* in FM. Along with *pain* and *tiredness*, *disturbed sleep patterns* is constantly referred to as important by patients and doctors (27, 29-33). These play a primary role in the disease course. Estimates of percentage of patients with FM affected by disturbed sleep patterns vary from 74 to 95-99% (34). It has also been shown that disturbed sleep patterns have a significant impact on amplifying pain and on the consequent negative impact on function and psychological-emotional well-being (32-34). It is not surprising, therefore, that both patients and clinicians underline the importance of improving the quality of sleep, together with treating pain.

Given the multidimensional characteristic of FM and the reported validity and usefulness of PRO in evaluating and monitoring these patients, we have recently developed the fibromyalgia assessment status (FAS) questionnaire which combines self-evaluation of the degree of *tiredness* and *pain*, and *quality of sleep* (on the basis of sites listed in the self-assessment pain scale, SAPS) into a single measurement, with scores ranging from 0 to 10 (23). This index includes the first 3 items considered to be important by both clinicians and patients, and can be used to evaluate disease severity and define response to treatment.

In conclusion, this study using the Delphi method of evaluation has shown that the domains considered to be the most important by patients are similar to those indicated by clinicians, with the exception of *tender points* (which were not considered to be important by patients). The final model of 8 items was shown to be have adequate construct validity.

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Appendix **Domains presented in the Delphi study**	
1. Low back pain	30. Involuntary movement
2. Irritable bowel syndrome	31. Vertigo
3. Restless leg syndrome	32. Impact on sleep (e.g. difficulty in falling asleep, insomnia, frequent waking during the night)
4. Tinnitus	
5. Cognitive impairment	33. Limiting/compromising normal daily routine activities
6. Morning rigidity	34. Impact on social life (e.g. less time for hobbies or free time, problems in traveling)
7. Fatigue	
8. Widespread chronic pain	35. Problems taking medication (e.g. side effects or intolerance)
9. Tender point	36. Impact on family life (e.g. relationship problems with partner or children)
10. Multidimensional function	
11. Memory lapse	37. Impact on work/study
12. Tingling extremities	38. Lack of or low sex drive
13. Constipation	39. Economic impact (e.g.. cost of medication, health insurance)
14. Dysmenorrhea	40. Problems driving (e.g. pain or fatigue or memory lapse)
15. Sjogren's syndrome	41. Anger or irritability
16. Raynaud's phenonemon	42. Frustration (e.g. due to function limitations, due to social relationships)
17. Physical weakness	
18. Widespread paresthesias	43. Anxiety (e.g. nervousness)
19. Temporomandibular joint dysfunction	44. Panic attacks
20. Losing attention or lack of concentration (e.g. difficulties in concentrating and following train of thought, "fibro-fog")	45. Chest pain
	46. Abdominal pain or cramps
	47. Urinary incontinence
21. Difficulty in moving around, walking or doing physical exercises	48. Strangury, dysuria, difficulties in urinating
22. Unable to do physical exercise	49. Shortness of breath
23. Depression (e.g. dissatisfaction, sadness, resignation or self-effacement, unmotivated)	50. Weight loss (<10 kg)
	51. Loss of appetite
24. Unmotivated	52. Loss of smell, taste or flavor
25. Disorganized thoughts (difficulty in expressing oneself, in prompt verbal response or in making personal programs and plans)	53. Difficulties in urinating
	54. Gynecological problems (women)
26. Numbness or tingling in the fingers and toes	55. Muscle pain, pain or cramps
27. Cephalea or migraine	56. Cold hands
28. Sensitivity to environmental factors (e.g. smells, sounds, lights, changes in temperature)	57. Swollen hands
29. Skin sensitivity	58. Swelling of other joints