ANALGESIA

Patient-Reported Outcomes in Fibromyalgia
Multimodal Assessments for a Multifaceted Condition

ABSTRACT

Fibromyalgia is a chronic, complex pain condition characterized by widespread pain and a diverse range of symptomatic manifestations, including fatigue, sleep disturbance, dyscognition, diminished physical functioning, and mood disturbances. To date, patient-reported outcomes remain the best method for characterizing the many facets of fibromyalgia.
Introduction

Patient-reported outcomes are gaining traction as a highly effective option for capturing the impact of chronic illness and gauging treatment response. In clinical trials of chronic pain, patient-reported evidence is essential for establishing both efficacy and the potential advantages of an investigational drug over existing products. Moreover, with growing cost pressure and the need for product differentiation in a highly competitive market, sponsors are increasingly relying on patient perspectives to generate value propositions that go beyond traditional safety and clinical efficacy messages.1

Patient-reported outcomes are particularly important in conditions, such as fibromyalgia, where symptoms cannot be directly observed. Fibromyalgia has no cure, and no clear biomarkers are available to guide its management or measure response to therapy. Until there is a cure, treatment for fibromyalgia will be focused on managing symptoms and improving functional status, as well as quality of life. To date, the only way to know whether treatments are effective is to rely on patient self-report.

In this white paper, we will explore patient-reported outcome instruments that can be used for diagnosis, monitoring, and characterization of fibromyalgia. We will also discuss the use of patient-reported outcomes in clinical trials.

About fibromyalgia

Fibromyalgia is a chronic pain condition characterized by chronic, widespread pain accompanied by fatigue, sleep disturbance, cognitive dysfunction, diminished physical functioning, mood disturbances, and the presence of other chronic overlapping pain conditions (COPCs).2 Individuals with fibromyalgia often report diminished quality of life,3 diminished functional status,4 and

Individuals with fibromyalgia often report diminished quality of life, diminished functional status, and higher-than-expected healthcare utilization.
higher-than-expected healthcare utilization. Given the diverse range of symptoms in fibromyalgia, comprehensive assessment of all these components can be challenging.

**Epidemiology and pathophysiology**

An estimated five million U.S. adults suffer from fibromyalgia. Globally, the mean prevalence of fibromyalgia is 2.7 percent, with a female to male ratio of 3:1. In primary rheumatology clinics, referrals for fibromyalgia comprise 14 to 20 percent of new visits, making fibromyalgia the second or third most common reason for appointments.

Fibromyalgia is currently considered to be a central pain state and a diagnosis of exclusion. While peripheral input may play a role, central factors, such as central sensitization, are believed to account for much of the symptomatology.

**Patient-reported outcome measures for fibromyalgia**

Patient-reported outcomes (PROs), otherwise known as self-report measures, cover a range of consequences of a disease condition and its treatment as reported by the patient, including symptom experience, sense of well-being, functional status, treatment adherence, and treatment satisfaction. For the assessment of pain, PROs are often the only viable clinical endpoints because there are no objective physical or physiological markers of disease or treatment activity that can be observed or measured.

Currently, PROs remain the best method for characterizing the many facets of fibromyalgia. Numerous attempts to identify biomarkers – including genetics, autoantibodies, cytokines, hematological findings, oxidative stress, neuroimaging, and neuropathology – have produced mixed results. To date, there is no pathophysiological index with sufficient sensitivity and specificity to serve as a biomarker for fibromyalgia. However, PRO data may help identify different fibromyalgia phenotypes and uncover potential biomarkers that help match treatment to the underlying mechanism of disease.

The use of PROs in fibromyalgia can take several forms, depending upon the purpose of assessment:

- Diagnosis
- Symptom monitoring
- Phenotyping/characterization
- Outcomes for clinical trials

**PROs for diagnosis**

Fibromyalgia is difficult to diagnose, and despite its prevalence, many people with fibromyalgia have been misdiagnosed or even labeled as malingerers.

In 1990, the American College of Rheumatology (ACR) developed research classification criteria to help standardize selection of individuals likely to have fibromyalgia for the purpose of conducting research. These criteria required the presence of at least 11 tender points and chronic, widespread pain (see Figure 1). However, as women generally report more musculoskeletal tenderness than men, the concept of tender points led to a skewed perception that fibromyalgia was predominantly a female condition. When tenderness was replaced with widespread pain, the distribution of fibromyalgia still favored women, but by a smaller margin.
In 2010, the ACR released preliminary clinical diagnostic criteria for fibromyalgia, which view the condition as more of a syndrome. These new criteria eliminated the concept of tender points, but retained the requirement for widespread pain. They also, for the first time, placed reliance on patient-reported symptoms, such as fatigue, sleep disturbance, and cognitive dysfunction. Notably, the criteria also require a physician to first rule out other diagnoses that could account for the same symptoms.10

Figure 1. Tender points defined in the ACR 1990 Criteria for Fibromyalgia
Applying Quality by Design to the Rare Disease Population: Special Considerations

To support the conduct of research on fibromyalgia using the new clinical criteria, a fibromyalgia survey containing most of the diagnostic criteria was published in 2011. There are a number of practical differences between the actual diagnostic criteria and the survey criteria in that the survey can be:

- Mailed
- Completed online via an internet-based survey
- Completed in a research setting with a physician present

The survey criteria also allow the calculation of a continuously scaled Fibromyalgia Score so that there are varying degrees of fibromyalgia, which is consistent with both the fluctuating nature of the condition over time and the observation that some individuals report greater symptom burden than others.

### PROs for disease monitoring

Twenty years ago, there was little uniformity or standardization in the assessment of pain in clinical settings. However, in the mid-1990s, the American Pain Society championed the concept of pain as the fifth vital sign, a concept which was later adopted by both the Veteran's Administration and the Joint Commission. In clinical

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<table>
<thead>
<tr>
<th>Feature</th>
<th>1990 Classification Criteria</th>
<th>2010 Preliminary Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider pain to be a core symptom of FM</td>
<td>Yes</td>
<td>Yes – definition of FM is broadened to include other symptoms</td>
</tr>
<tr>
<td>Include assessment of other symptoms in diagnosis</td>
<td>No</td>
<td>Yes – Symptom Severity Scale covers fatigue, waking unrefreshed, etc.</td>
</tr>
<tr>
<td>Specify use of a tender point (TP) exam</td>
<td>Yes</td>
<td>No – a physical exam is recommended and may include a TP exam</td>
</tr>
<tr>
<td>Recognize the utility of a TP exam</td>
<td>Yes</td>
<td>Yes – although a TP exam is not required, the authors recognize the utility of a TP exam</td>
</tr>
</tbody>
</table>

**Figure 2. Comparison of the ACR 1990 criteria and preliminary 2010 diagnostic criteria**

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**Patient-Reported Outcomes in Fibromyalgia**
settings, this is often operationalized by having people rate their pain on a 0-10 numeric rating scale (NRS). Typically, pain greater than 4/10 triggers more comprehensive pain assessment.6

In fibromyalgia, use of the NRS as a means of disease monitoring is likely insufficient, given the spectrum of symptoms associated with the condition.14 The Fibromyalgia Impact Questionnaire-Revised (FIQR) is one of the few PROs developed specifically for fibromyalgia. The 21-question FIQR addresses three domains relevant to fibromyalgia:15

1. Function
2. Overall impact
3. Multi-dimensional symptomatology

The sum of the scores for each domain is called the FIQR total score. FIQR can be given weekly and takes only three to five minutes to administer. The development of this instrument was rigorous, and numerous studies support its validation.16

THE FIQR can be used both to monitor disease and as an outcome in clinical trials. In either case, a 14 percent change in the FIQR total score appears to represent a clinically meaningful change in the condition.17

The Fibromyalgia Score derived from the fibromyalgia survey can also be used to monitor disease if the continuous scale is used.

**PROs for phenotyping and characterization**

Although pain is the cardinal symptom of fibromyalgia, improvement in quality of life for people with fibromyalgia requires more than simply an improvement in pain. An internet-based survey of 2,596 individuals with fibromyalgia revealed that the intensity of fatigue, sleep disturbance, and cognitive dysfunction is often more severe and problematic than pain.18

Consequently, when characterizing fibromyalgia, there are six assessment domains to consider:2

1. Pain
2. Co-morbidities
3. Affective vulnerability
4. Beliefs and attitudes
5. Behavior
6. Environmental/social

To follow, we will explore each of these domains in more detail.

**Pain**

Historically, the only aspect of pain routinely assessed in fibromyalgia was intensity. Pain intensity was measured using NRS, visual analogue scales (VAS), or a faces approach. However, for people with fibromyalgia, there are other relevant aspects of pain, including quality, location/distribution, interference with functional status, and temporality.

*The McGill Pain Questionnaire (MPQ)* was one of the first instruments for measuring pain quality.19 The MPQ provides 78 pain descriptors, which grouped into 20 categories indicative of various types of pain. These categories can be scored along three dimensions of pain: sensation, affective, and evaluative. The MPQ also captures an NRS for current pain and offers a body map to assess pain location. Body maps are becoming increasingly important in helping to distinguish between single versus multiple comorbid pain conditions.20
The Brief Pain Inventory (BPI) is another commonly-used instrument that captures both pain intensity and pain interference. Like the MPQ, the BPI uses a body map to assess pain location. It also includes questions about the effectiveness of treatment.

painDETECT is a newer questionnaire that combines an abbreviated assessment of pain quality similar to the MPQ, an index of pain intensity assessment similar to the BPI, a body map, and an assessment of pain temporality. This instrument can also be scored to help differentiate the presence of musculoskeletal pain from the presence of neuropathic pain which, in fibromyalgia, can present in the same individual to differing degrees.

<table>
<thead>
<tr>
<th>Domain(s)</th>
<th>Instrument</th>
<th>Items</th>
<th>Score Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity</td>
<td>Visual Analogue Scales (VAS)</td>
<td>1</td>
<td>0 — 10</td>
</tr>
<tr>
<td>Intensity</td>
<td>Numerical Rating Scales (NRS)</td>
<td>1</td>
<td>0 — 10</td>
</tr>
<tr>
<td>Quality, Intensity and Distribution</td>
<td>McGill Pain Questionnaire (MPQ)</td>
<td>78</td>
<td>0 — 78</td>
</tr>
<tr>
<td>Intensity, Distribution and Interference</td>
<td>Brief Pain Inventory (BPI)</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Subscales:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain Intensity</td>
<td></td>
<td>4</td>
<td>0 — 10</td>
</tr>
<tr>
<td>Pain Interference</td>
<td></td>
<td>7</td>
<td>0 — 10</td>
</tr>
<tr>
<td>Quality, Intensity, Distribution and Temporality</td>
<td>painDETECT</td>
<td>9</td>
<td>-1 — 38</td>
</tr>
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</table>

Figure 3. Assessment of the pain domain in fibromyalgia
Co-morbidities

Comorbidities comprise diagnosable conditions and symptoms that tend to accompany chronic pain, including fatigue, sleep disturbance, and cognitive dysfunction. The concept of co-existing chronic pain conditions is now recognized by both the National Institutes of Health and the U.S. Congress as a set of co-aggregating disorders that share symptomatology and common mechanisms despite residing in anatomically distinct regions of the body. Fibromyalgia is considered to be one of these co-existing chronic pain conditions, now labeled as chronic overlapping pain conditions (COPCs) (see Figure 4).

The Complex Multi-Symptom Inventory (CMSI) is currently one of the best instruments for assessing for the presence of one or more COPCs in a given individual. The CMSI consists of two parts:

- A 41-item symptom screener
- The published diagnostic criteria for six of the 10 recognized COPCs

In practice, the patient is first asked to complete the screener, which contains specific items that trigger the administration of the full diagnostic criteria for COPCs that may be relevant for that individual. This process limits response burden by only administering relevant questions. Currently, an updated version of the CMSI that includes all 10 COPCs is in development.

The CMSI symptom screener can also be used as a tally of functional somatic burden, similar to the fibromyalgia survey. These co-aggregated symptom tallies have demonstrated utility in predicting both the onset and chronification of COPCs.

Assessing fatigue or sleep disturbance. There are several instruments for assessing fatigue or sleep disturbance, including (see Figure 5):

- Questionnaires available from the Patient Reported Outcomes Measurement Information Systems (PROMIS) Assessment Center™ website
- The Medical Outcomes Study (MOS) sleep scale
- The Pittsburgh Sleep Quality Index (PSQI)
- The Multidimensional Fatigue Inventory (MFI)

Fatigue, like pain, has multiple dimensions that require comprehensive assessment. The recently-developed PROMIS FatigueFM Profile is a 16-item measure consisting of four, four-item short forms of self-reported fatigue severity. Initial analysis of this PRO shows excellent internal reliability, but further work to evaluate the validity of this new measure in individuals with fibromyalgia is needed.

<table>
<thead>
<tr>
<th>Co-morbidities</th>
<th>Chronic low back pain</th>
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<tbody>
<tr>
<td>Temporomandibular disorders</td>
<td>Myalgic encephalomyelitis/chronic fatigue syndrome</td>
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<tr>
<td>Irritable bowel syndrome</td>
<td>Interstitial cystitis/painful bladder syndrome</td>
</tr>
<tr>
<td>Chronic tension-type headache</td>
<td>Endometriosis</td>
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<td>Migraine</td>
<td>Vulvodynia</td>
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Figure 4. Recognized chronic overlapping pain conditions
<table>
<thead>
<tr>
<th>Domain</th>
<th>Instrument</th>
<th>Items</th>
<th>Score Range</th>
</tr>
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<tbody>
<tr>
<td>Sleep</td>
<td>PROMIS Sleep Disturbance Short Form 8a</td>
<td>8</td>
<td>8 — 40</td>
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<tr>
<td>Waking</td>
<td>PROMIS Sleep-Related Impairment Short Form 8</td>
<td>8</td>
<td>8 — 40</td>
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<tr>
<td>Sleep</td>
<td>Medical Outcome Study (MOS) sleep scale</td>
<td>12</td>
<td>—</td>
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<td></td>
<td>Subscales:</td>
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<td></td>
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<td></td>
<td>Sleep Disturbance</td>
<td>4</td>
<td>1 — 6</td>
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<tr>
<td></td>
<td>Snoring</td>
<td>1</td>
<td>1 — 6</td>
</tr>
<tr>
<td></td>
<td>Shortness of Breath</td>
<td>1</td>
<td>1 — 6</td>
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<tr>
<td></td>
<td>Sleep Adequacy</td>
<td>2</td>
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<td></td>
<td>Somnolence</td>
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<td>Sleep</td>
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<td>Sleep Duration</td>
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<td></td>
<td>Sleep Efficiency</td>
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<td>0 — 3</td>
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<td>Sleep Disturbances</td>
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<td>0 — 3</td>
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<td></td>
<td>Use of Sleep Medication</td>
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<td>0 — 3</td>
</tr>
<tr>
<td></td>
<td>Daytime Dysfunction</td>
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<td>0 — 3</td>
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<td></td>
<td>Global Score</td>
<td>18</td>
<td>0 — 21</td>
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<tr>
<td>Fatigue</td>
<td>PROMIS Fatigue Short Form 8a</td>
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<td>8 — 40</td>
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<tr>
<td>Fatigue</td>
<td>Multidimensional Fatigue Inventory (MFI)</td>
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<td>—</td>
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<td>Subscales:</td>
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<td></td>
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<tr>
<td></td>
<td>General Fatigue</td>
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<td>4 — 20</td>
</tr>
<tr>
<td></td>
<td>Physical Fatigue</td>
<td>4</td>
<td>4 — 20</td>
</tr>
<tr>
<td></td>
<td>Mental Fatigue</td>
<td>4</td>
<td>4 — 20</td>
</tr>
<tr>
<td></td>
<td>Reduced Motivation</td>
<td>4</td>
<td>4 — 20</td>
</tr>
<tr>
<td></td>
<td>Reduced Activity</td>
<td>4</td>
<td>4 — 20</td>
</tr>
</tbody>
</table>

Figure 5. Instruments for assessing fatigue or sleep disturbance
Assessing cognitive dysfunction. The Multiple Ability Self-Report Questionnaire (MASQ) is a 38-item inventory that assesses perceived cognitive difficulties across the dimensions of:

+ Language ability
+ Visual-perceptual ability
+ Verbal memory
+ Visual memory
+ Attention/concentration

Due to its length, the MASQ can represent a considerable response burden.

Recently, the Multidimensional Inventory of Subjective Cognitive Impairment (MISCI) was developed specifically for fibromyalgia and other widespread pain conditions. This 10-item inventory provides indices for cognitive concerns in the areas of mental clarity, memory, attention/concentration, executive functioning, and language. In two studies of adults with fibromyalgia, results from the MISCI correlated strongly with results from the MASQ, with a much lower response burden.

Affective vulnerability

Pain is defined as both a sensory and affective experience, and emotion is considered to be central to the very experience of pain. Historically, the phenotype of fibromyalgia included the high prevalence of comorbid affective disorders. As such, it was common to use instruments such as the Beck Depression Inventory-II (BDI-II), the Center for Epidemiological Studies Depression Scale (CESD), the Patient Health Questionnaire (PHQ), and the General Anxiety Disorder-7 (GAD-7) to identify the presence of negative affective symptoms. Each of these instruments can be scored to reveal either a probable diagnosis of an affective disorder or a continuous measure of negative affect. As the diagnosis of fibromyalgia does not require the diagnosis of a comorbid affective disorder, the continuous measurement of emotion is preferable when assessing the role of affect in fibromyalgia or any other chronic pain condition.

The Positive and Negative Affect Scale (PANAS) is unique in that, in addition to characterizing pain by negative affect, it introduces the ability to assess positive emotion, which may represent an element of resilience that can serve to buffer or even diminish the perception of pain. The PANAS can be scored to derive an index of affect balance – a ratio between positive and negative emotion – that is associated with well-being in fibromyalgia.

Affective vulnerability may also be assessed with instruments that evaluate stress, trauma, and personality, such as the:

+ Perceived Stress Scale (PSS)
+ Childhood and Recent Traumatic Events Scales (CTES/RTES)
+ NEO Personality Inventory-Revised (NEO-PI-R)
+ International Personality Item Pool (IPIP)
+ Ten-Item Personality Inventory (TIPI)

Beliefs and attitudes

A person’s beliefs and attitudes about pain can directly influence his or her affect and functional status. Further, catastrophizing is a common cognitive style for individuals with fibromyalgia.
<table>
<thead>
<tr>
<th>Domain</th>
<th>Instrument</th>
<th>Items</th>
<th>Score Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catastrophizing</td>
<td>Pain Catastrophizing Scale (PCS)</td>
<td>13</td>
<td>0 - 52</td>
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<td>Subscales:</td>
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<tr>
<td></td>
<td>Rumination</td>
<td>4</td>
<td>0 - 16</td>
</tr>
<tr>
<td></td>
<td>Magnification</td>
<td>3</td>
<td>0 - 12</td>
</tr>
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<td></td>
<td>Helplessness</td>
<td>6</td>
<td>0 - 24</td>
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<tr>
<td>Locus of control</td>
<td>Beliefs About Pain Control Questionnaire (BCPQ)</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Subscales:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Internal Control</td>
<td>5</td>
<td>5 - 30</td>
</tr>
<tr>
<td></td>
<td>Powerful Others</td>
<td>4</td>
<td>4 - 24</td>
</tr>
<tr>
<td></td>
<td>Chance</td>
<td>4</td>
<td>4 - 24</td>
</tr>
<tr>
<td>Self-efficacy</td>
<td>Arthritis Self Efficacy Scales (ASE)</td>
<td>20</td>
<td>-</td>
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<tr>
<td>Coping strategies</td>
<td>Coping Strategies Questionnaire (CSQ)</td>
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<td></td>
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<td>Subscales:</td>
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<tr>
<td></td>
<td>Diverting Attention</td>
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<td>0 - 36</td>
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<td></td>
<td>Reinterpreting Pain Sensations</td>
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<td>0 - 36</td>
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<td></td>
<td>Coping Self-Statements</td>
<td>6</td>
<td>0 - 36</td>
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<td></td>
<td>Ignoring Pain Sensations</td>
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<td>0 - 36</td>
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<td></td>
<td>Praying/Hoping</td>
<td>6</td>
<td>0 - 36</td>
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<td></td>
<td>Catastrophizing</td>
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<td>0 - 36</td>
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<td></td>
<td>Increasing Behavioral Activity</td>
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<td>0 - 36</td>
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<td>Ability to Control Pain</td>
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<td>0 - 6</td>
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<td></td>
<td>Ability to Decrease Pain</td>
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<td>0 - 6</td>
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<td>Pain Beliefs</td>
<td>Survey of Pain Attitudes (SOPA)</td>
<td>57</td>
<td>-</td>
</tr>
<tr>
<td>Pain Beliefs</td>
<td>Pain Beliefs and Perceptions Inventory (PBPI)</td>
<td>16</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 6. Instruments for assessing beliefs and attitudes about pain\(^2\)

Behavior
There are a number of behavioral domains that may be relevant for individuals with fibromyalgia, but the most common may be physical functioning.\(^2\) The Medical Outcomes Study Short Form Health Survey-36 (SF-36) or some version of it has been used for assessment of physical and mental function in multiple fibromyalgia studies.\(^4\) Other measures of physical functioning with relevance for fibromyalgia include:\(^2\)

+ PROMIS physical functioning scales
+ Pain Disability Index (PDI)
+ Pain interference subscale from the BPI

Of note, outcomes such as health care utilization have shown higher correlation with demand for services and disability than with indices more specifically tied to symptomatology, underscoring the importance of assessing behavioral responses to pain.\(^45\)

Environmental/social
For rheumatological pain, both the quality and quantity of social support at initial diagnosis can be predictive of pain and functional status three to five years later.\(^46\) Consequently, social factors are often considered in the phenotypic assessment of fibromyalgia (see Figure 7).

PROs as outcomes for clinical trials
The use of PRO data in clinical trials has become more widespread, particularly for therapies developed to treat conditions such as chronic pain, where the objective is to ameliorate symptoms, facilitate functioning, or improve overall quality of life. In the context of a clinical trial, it is recommended that PRO data for pain be conducted daily for a daily pain score average.

In chronic pain, the use of PRO data as both primary and secondary endpoints to substantiate product efficacy is necessary for securing approval. While pain improvement is a requirement for product approval, it is not sufficient alone, as the U.S. Food and Drug Administration (FDA) also requires evidence of overall benefit and improvement in function.

In addition, regulatory scrutiny of the use of PRO data has escalated, and some of the PRO measures used to support approval or labeling in the past are no longer considered adequate. The FDA and European Medicines Agency (EMA) have imposed standards that call for a higher degree of scientific rigor in the development and evaluation of PRO measures, as well as the level of documentation required to support the use and validity of these instruments in confirmatory clinical trials.

Outcome Measures in Rheumatology Clinical Trials (OMERACT) is an international organization that seeks to refine outcome measurement issues, in part by identifying core sets of variables that should be collected and reported in any clinical trial involving rheumatological conditions.\(^47\) A task force within OMERACT conducted two Delphi studies – one involving individuals with fibromyalgia and the other involving clinicians treating fibromyalgia – to help establish consensus regarding the most relevant domains of assessment for fibromyalgia clinical trials. Other than some differences in the ordering of symptom priority between patients and clinicians, there was considerable consensus about the domains of relevance. The OMERACT domains included:\(^48\)

+ Pain
+ Fatigue
+ Functional status
+ Sleep
+ Mood
+ Tenderness
+ Stiffness
+ Dyscognition

The use of PRO data in clinical trials has become more widespread, particularly for therapies developed to treat conditions such as chronic pain, where the objective is to ameliorate symptoms, facilitate functioning, or improve overall quality of life.
### Domain | Instrument | Items | Score Range
---|---|---|---
**Home** | Dyadic Adjustment Scale (DAS) | 32 | 0 - 151
**Work** | Work Productivity and Activity Impairment (WPAI) | 6 | 0 - 100
- Percent work missed due to health
- Percent impairment while working due to health
- Percent overall work impairment due to health
- Percent activity impairment due to health
  | Participation Enfranchisement (PE) | 19 | 0 - 100
  | Multimodal | West Haven-Yale Multidimensional Pain Inventory (WHYMPI) | 54 | 0 - 100
- Pain Interference
- Support
- Pain Severity
- Life-Control
- Affective Distress
- Negative Responses
- Solicitous Responses
- Distracting Responses
- Household Chores
- Outdoor Work
- Activities Away from Home
- Social Activities
- General Activity

**Figure 7. Instruments for assessing environment and social factors.**
Similarly, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has identified the domains of relevance for any clinical trial of a painful condition. IMMPACT recommends four core areas of assessment:

1. Pain intensity
2. Physical functioning
3. Emotional functioning
4. Overall improvement/well-being

While there is substantial agreement between OMERACT and IMMPACT regarding what domains should be assessed, neither organization dictates the specific instruments to be used in the assessment of each domain.49

ePRO diaries are the most common method of collecting daily pain scores, as well as other easily-answered measures, such as sleep and use of rescue medication. ePRO tablets or item response theory (IRT) websites are commonly used for in-office, or more lengthy assessments. These tablets and websites have the advantage of helping to decrease human case report form (CRF) entry error and clinical research associate (CRA) monitoring time.

Instruments for affective vulnerability are often used to screen for major depressive disorder as an exclusion criteria.

To date, fibromyalgia clinical trials have used a variety of different questionnaires to assess the relevant clinical domains. Despite this variability, one published study that combined datasets from large clinical trials, assessment approaches, and differing pharmacological agents identified the phenotype of a “fibromyalgia treatment responder.” This study suggested that, independent of the instrument used, a fibromyalgia treatment responder would demonstrate:42

1. Thirty percent improvement in pain
2. Ten percent improvement in physical functioning
3. Thirty percent improvement in at least two of the following domains: fatigue, sleep, depression, anxiety, or dyscognition

Of note, the 21st Century Cures Act, enacted in December 2016, recognizes the significance of the patient experience surrounding regulatory decisions and expands the concept of patient-focused drug development by laying out a framework for its application, guidance, and evaluation within the FDA. The 21st Century Cures Act also requires the FDA to develop and issue guidance documents for patient-focused drug development, as well as to report and publish online its review of patient experience data as part of approved drugs no later than June 1, 2021.

**Conclusion**

Patient-reported outcomes remain the best approach for assessing the many facets of fibromyalgia, whether for diagnosis, disease monitoring, phenotyping, or clinical trials. With its high variability and broad variety of symptoms, fibromyalgia requires instruments that can capture the waxing and waning of the conditions for accurate assessment. In the context of a fibromyalgia clinical trial, a multifaceted assessment is needed in order to adequately identify the potential of the intervention to not only improve pain, but also impact the multiple other clinical domains of relevance.
References

References (continued)


Scott Millard | Executive Director, Analgesia

Scott Millard has worked in the clinical research industry since 1991. Mr. Millard joined Premier Research in 1997 and has served in a variety of roles with increasing scope and responsibility inclusive of Senior Clinical Research Associate, Team Lead, Senior Manager, Project Manager, Senior Project Manager, Project Director, Senior Director, and Executive Director. Mr. Millard has served at a director level, managing project managers and sponsor programs for more than 13 years specialization in Analgesia and Rheumatology.

Mr. Millard is currently Executive Director, Strategic Development, Analgesia. He is a strategist who advises, consults, plans, and directs the design and strategy of new business opportunities and provides his expertise in the conduct of clinical trials. He is also responsible for developing strong relationships with existing and potential clients, clinical sites, and key opinion leaders.

Prior to joining Premier, Mr. Millard monitored for a large CRO and began his clinical research career in the Phase I arena at a large Phase I unit in Austin, first as a recruiter and then as an instructor.

Mr. Millard has a Bachelor of Science degree from the University of Texas and was certified as a CCRA (Certified Clinical Research Associate) in 1995 by the ACRP. He is a member of The Association of Rheumatology Health Professionals and American Pain Society, with recurring affiliations with IASP, DIA, and ACRP.

About Premier Research

Premier Research is a leading clinical development service provider that helps highly innovative biotech, medical device, and specialty pharma companies transform breakthrough ideas into reality. The company has a wealth of experience in the execution of global, regional, and local clinical development programs with a special focus on addressing unmet needs in areas such as analgesia, dermatology, medical devices, neuroscience, oncology, pediatrics, and rare disease. Premier Research operates in 84 countries and employs 1,250 professionals, including a strong international network of clinical monitors and project managers, regulatory, data management, statistical, scientific, and medical experts. They are focused on smart study design for advanced medicines that allow life-changing treatments.