

## Commentary

# What should be the core outcomes in chronic pain clinical trials?

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### Abstract

A consensus conference with representatives from academia, governmental agencies, and the pharmaceutical industry met and concluded that clinical trials designed to assess the efficacy and effectiveness of treatments for chronic pain should consider outcomes in six core domains: pain, physical functioning, emotional functioning, patient global ratings of satisfaction, negative health states and adverse events, and patient disposition. In addition, it was acknowledged that there are many secondary domains that might be of importance and should be included in trials depending on the nature of the treatment and population to whom the treatment is targeted.

**Keywords:** chronic pain, clinical trials, outcomes, patient global ratings, quality of life

### Introduction

Precise estimates of the prevalence of different pain syndromes in the USA are difficult to ascertain; however, there might be more than 30 million people with chronic or recurrent painful conditions. Nearly one-half of Americans who seek treatment with a physician report that their primary symptom is pain. This makes pain the single most frequent reason for physician consultation in the United States [1]. The US National Health Interview Survey determined that in the three-month period before the interview, 28% had experienced pain in the lower back, 16% experienced a severe headache, 15% had experienced pain in the neck region, and 4% had experienced pain in the face or jaw [2].

In 1995 and 1996 estimates of the cost of chronic pain (including treatment, lost work days, and disability) ranged from US\$150 billion [3] to US\$215 billion [4] each year. When viewing such global figures it is easy to overlook the impact that chronic pain has on the lives of individual sufferers. People with conditions such as low back pain, osteoarthritis, and postherpetic neuralgia suffer from pain that significantly impairs their quality of life, causing physical disability and considerable emotional distress.

Advances in knowledge of the neurobiology of pain have resulted in an explosion in the number of treatments that have become available. With the development of each new treatment come clinical studies designed to demonstrate its efficacy and effectiveness.

One method of increasing confidence in the effectiveness of any treatment comes from the aggregation of data across clinical trials. Efforts to perform such aggregations and to publish them in meta-analyses and systematic reviews have become common. However, clinical trials often incorporate idiosyncratic characteristics in samples included, methodological design, and outcome criteria, making it difficult to synthesize the data on treatment efficacy without making many compromises. The problem of integrating the many outcome studies is acute and the differences have impeded conclusions about the effects of different treatments. One way of facilitating conclusions based on clinical trials would be for a standard set of outcome domains to be used in clinical trials.

Over the past few decades there has been a growing realization that the traditional outcome domains of symptom reduction and safety are inadequate when

evaluating response to treatments for chronic disease states and symptoms that are as subjective as pain. Physical, emotional, and social functioning and patient satisfaction and perception of improvement have been identified as important targets of intervention when the treatment being evaluated does not cure a disease.

Development of a core set of domains and measurement procedures would facilitate the comparison and pooling of data while leaving investigators free to augment the core domains with others of their choice. Agreement on a set of core domains (and ultimately measures) should not constrain investigators and would provide a common approach for use across studies. For individual investigators it might be important to augment this core with measures of specific clinical effects or to experiment with new measures of the constructs (domains) included in the standard core. Thus it should be expected that the 'core' domains would be relatively stable whereas specific measures might change. An advantage of a consensually agreed core set of domains is that it would encourage more complete reporting of relevant outcomes, so that investigators do not simply report a single dimension or outcome while ignoring others. Another advantage is that it would encourage the development of cooperative multi-centered studies, which offer the prospect of large, rapid, and generalizable efficacy and effectiveness studies [5]. If different centers agreed to include assessment of core domains with a standard set of measures, the design and conduct of such cooperative trials would be facilitated. Finally, having a standardized set of outcome domains would simplify the process of designing and reviewing research proposals, manuscripts, and published articles.

IMMPACT is a consortium of professionals from academia, the Food and Drug Administration, the National Institutes of Health, the US Veterans Administration, and industry. The participants are engaged in research, clinical, or administrative activities relevant to the design and evaluation of chronic pain treatment outcomes and they represent anesthesiology, biostatistics, clinical pharmacology, epidemiology, geriatrics, internal medicine, law, neurology, nursing, oncology, outcomes research, patient perspectives, pediatric pain, physical medicine and rehabilitation, psychology, and rheumatology. The IMMPACT group meeting focused on the identification of a core set of domains that should be considered in all clinical trials of treatments for chronic pain.

### **Outcome domains**

The complexity of chronic pain suggests that multiple domains are relevant when evaluating the effects of treatment. Several considerations are important in deciding what domains should be considered in any clinical trial. The domains should match the purpose of the study, should measure positive and negative outcomes of

treatment, and should be appropriate for the chronic pain disorder and the population of interest (for example geriatric). A central issue is the identification of the set of domains that are clinically meaningful and that might be expected to change as a result of treatment [6].

### **Pain**

Although a ubiquitous phenomenon, pain is inherently subjective. The only way to know about someone's pain is by what they say or show by their behavior. There is an assumption that pain is highly associated with emotional and physical functioning and that a reduction in pain will inevitably lead to an improvement in function and patient satisfaction. This is often not the case. Numerous studies have demonstrated that pain and functioning are only modestly related (see [7]). Thus, although pain reduction might be the pivotal outcome for pain clinical trials, it is important to consider outcomes in addition to pain.

Pain is not an isolated symptom. Severe pain creates fatigue, impairs concentration, compromises mood, degrades sleep, and diminishes overall activity level. For many patients there is a point at which the pain reaches an interference threshold above which it seriously disrupts life and creates a cascade of related symptom burdens. Thus, there is a need for a way of assessing multiple areas of functioning and well-being. In addition to relieving clinical symptoms and prolonging survival, a primary objective of any intervention is improvement of functioning.

### **Physical functioning**

Functional status typically refers to the ability to perform particular defined tasks such as walking a short distance, and social role functioning and participation in social interactions can also be assessed. A major decision to be made in assessing the impact of a treatment on physical functioning involves whether a generic or a disease-specific measure will be used. The tradeoffs between these two approaches have important implications for the interpretation of the results of a trial. Disease-specific measures of disability (for example WOMAC) are designed to evaluate the impact of a specific condition. Specific effects of a disorder can be missed by a generic measure, and disease-specific measures might therefore be more likely to reveal changes in disability that are a consequence of treatment. In addition, responses on disease-specific measures will generally not reflect interference in physical functioning associated with co-morbid conditions, which can confound the interpretation of changes in functioning occurring over the course of a trial when generic measures are used. However, generic measures make it possible to compare functioning and public health impacts of a disorder and its treatment with those of different conditions. Regardless of whether an investigator selects a generic or a disease-specific measure, physical functioning is a core outcome domain for clinical trials of pain treatment.

### **Emotional functioning**

Emotional state is a central feature influencing perception of satisfaction with life. The results of numerous studies suggest that higher levels of pain are usually associated with elevated levels of emotional distress, particularly depression and anxiety. Thus, emotional functioning should be considered as a core domain for pain clinical trials.

### **Patient global rating of improvement and satisfaction**

Patients' perceptions of change in physical and emotional functioning with treatment can vary considerably from the perceptions of health care professionals. Patients' preferences reflect the relative importance that each outcome has for them. The value, significance, and impact of a therapeutic change of a given magnitude can vary considerably for different patients and can be an important determinant of adherence to treatment.

By soliciting patients' preferences, investigators acknowledge the unique values of different outcomes and their aggregate for individual patients. Patients' values and preferences are what distinguish global ratings from other measures, and such ratings provide sufficient unique information to warrant inclusion in all clinical trials of treatments for chronic pain.

### **Symptoms and adverse events**

Most patients will experience some degree of side-effect burden with any pharmacologic treatment; the importance of monitoring adverse events in the evaluation of new drugs has long been recognized and is a component of all clinical trials. Two treatments may be equally effective and their adverse events not significantly different on a statistical basis, but patients might view the side effects of a treatment as sufficiently noxious to discontinue treatment or not comply fully with it [8].

The challenge is to find the dosage that maximizes pain relief and functional improvements and minimizes side effects. Investigators should consider broad-based measures rather than ones more limited in scope because the latter might underestimate the importance of symptom distress as perceived by the patient [8]. Moreover, investigators should determine not only the presence of side effects but also their severity and importance to the patient.

The usual strategy is to ask patients and clinicians to record the occurrence of any adverse events that might be attributed to the treatment. However, several studies (for example [9]) suggest that patients might not acknowledge the presence of many potentially important side effects spontaneously during open-ended inquiry. Although there might be many reasons for the differences (for example memory or embarrassment), the fact is that important side effects can be missed by the use of open-ended questions. Negative health consequences of

treatment using standard lists of symptoms that patients can rate with respect to presence, severity, and importance are a core domain that should be systematically assessed and reported in all clinical trials of treatments for chronic pain.

### **Patient disposition**

For a treatment to be effective, at least two things have to be present: the treatment must have an active ingredient that is likely to have a positive effect on the symptom or disease being treated, and the patient must adhere to the treatment regimen. Thus, in any clinical trial, patient adherence should be assessed.

Any concomitant treatments that patients initiate during the trial must be recorded because they indicate the effectiveness of the treatment or the presence of distressing side effects, and can interact with the treatment being evaluated. It is important to record the extent and duration of all pain-related treatments during the course of a clinical trial – not only the treatment being investigated, but concomitant treatments as diverse as rescue analgesics and visits for health care.

Significant percentages of patients enrolled in clinical trials drop out of studies prematurely. The IMMPACT group is in agreement with the CONSORT (Consolidated Standards of Reporting Trials) statement [10] about the importance of reporting data on patient attrition and loss to follow-up, and we emphasize that the reasons for nonadherence be provided and not just the percentage who fail to comply. Patient disposition, premature exit from a trial, nonadherence to treatment, and loss to follow-up form a core domain that should be reported as an outcome in all clinical trials.

### **Conclusions**

The core domains specified by the IMMPACT consensus – pain, physical functioning, emotional functioning, patient global judgment, symptoms and adverse events, and patient disposition – are generally consistent with the OMERACT-III [11] and adopted by the World Health Organization/International Leagues of Associations for Rheumatology (WHO/ILAR). Selection of measures of each domain from the many available should be based on the adequacy of normative data, psychometric properties (namely reliability, validity, and responsiveness – the ability to detect clinically meaningful changes), feasibility/practicality (for example, respondent and investigator burden: mode of administration, special training or material required for administration, complexity of response task, linguistic and culturally validated versions available), and appropriateness (consistency with study objectives; applicability to targeted disease, patient population, and/or treatment; compatibility with target decision maker's information needs).

Investigators who conduct clinical trials, the organizations that provide funding for such studies, and the regulatory agencies that review and ultimately approve new therapies for the public all share a commitment to identifying treatments for chronic pain that are more effective and have fewer adverse effects than those currently available. We hope that the IMMPACT process and the consensus recommendations that are developed will provide an example of the value of collaborative efforts between academia, government, and industry. The ultimate goal of such efforts should be to advance the science of chronic pain clinical trials and thereby provide improved treatments for patients suffering from chronic pain.

### Competing interests

None declared.

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