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Topical Review and Recommendations

Core outcome measures for chronic pain clinical trials: IMMPACT recommendations

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1. Introduction

Many patients with chronic pain do not obtain adequate relief or experience unacceptable side effects from existing treatments. Moreover, even when clinical trials report positive outcomes, the long-term benefits of these treatments have not been demonstrated. Efforts to develop treatments that provide improved outcomes are therefore a priority for pain research. Because variability in outcome measures across clinical trials hinders evaluations of the efficacy and effectiveness of treatments, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has recently recommended that 6 core outcome domains should be *considered* when designing chronic pain clinical trials. These 6 core outcome domains were: (1) pain; (2) physical functioning; (3) emotional functioning; (4) participant ratings of improvement and satisfaction with treatment; (5) symptoms and adverse events; and (6) participant disposition (Turk et al., 2003).

The benefits of adopting these core outcome domains in clinical research on chronic pain would be augmented by the identification of optimal measures for assessing them. Such core outcome measures could be supplemented by measures specific to the situation or treatment being studied. Use of a standard set of outcome measures for chronic pain clinical trials would facilitate the process of developing research protocols, encourage development of multi-center projects in which all participating facilities agree to include these measures, provide a basis for determining the treatment outcomes that constitute clinically important differences, permit pooling of data from different studies, and provide a basis for meaningful comparisons among treatments of the clinical importance of their outcomes, particularly through systematic reviews (Jadad, 1998; Jadad and Cepeda, 2000).

IMMPACT-II was convened to develop consensus recommendations for specific measures of each of the IMMPACT core outcome domains. Although there have been recent attempts to recommend outcome measures for specific chronic pain conditions—including osteoarthritis (Bellamy et al., 1997), low back pain (Deyo et al., 1998), and neuropathic pain (Cruccu et al., 2004)—the only previous attempt to identify specific treatment outcome measures applicable to diverse chronic pain conditions was published over fifteen years ago (Williams, 1988). The objective of the present article is to present consensus recommendations for specific measures of each of the IMMPACT core outcome domains.

2. Consensus meeting procedure

The IMMPACT-II meeting was held on April 11–12, 2003 and included 35 participants from academia, governmental agencies, a self-help organization, and the pharmaceutical industry. The participants were selected on the basis of their research, clinical, or administrative expertise relevant to the design and evaluation of chronic pain treatment outcomes. Literature reviews of measures of the IMMPACT core outcome domains were commissioned specifically for the IMMPACT-II meeting and distributed to participants prior to the meeting. These reviews focused on measures that could be used in trials of all chronic pain conditions and did not examine measures that were specific to certain types of chronic pain. These background literature reviews and the slide presentations delivered at the meeting are available on the IMMPACT-II page at www.immpact.org/meetings.html. They should be consulted for detailed reviews and discussions of the measures that were considered, the evidence on which the present recommendations are based, and the reasons for selection or rejection of specific measures.

Among the criteria used in evaluating potential core outcome measures were: (1) appropriateness of the measure's content and conceptual model; (2) reliability; (3) validity; (4) responsiveness; (5) interpretability; (6) precision of scores; (7) respondent and administrator acceptability; (8) respondent and administrator burden and feasibility; (9) availability and equivalence of alternate forms and methods of administration (e.g. self-report, interviewer); and (10) availability and equivalence of versions for different cultures and languages (Fitzpatrick et al., 1998; Scientific Advisory Committee of the Medical Outcomes Trust, 2002). Responsiveness has been defined and assessed in numerous ways, but it most often refers to the ability of a measure to detect changes over time (Guyatt et al., 1987; Terwee et al., 2003). With respect to clinical trials, responsiveness has also referred to the ability of a measure to distinguish between treatments, in particular, between an active/experimental treatment and a placebo/control treatment. Although Hays and Hadorn (1992) have noted that responsiveness is a component of validity, the authors considered responsiveness a separate attribute of outcome measures because of its pivotal role in clinical trials.

In evaluating the extent to which the various measures reviewed in the background presentations fulfilled these criteria, appropriateness of content, reliability, validity, responsiveness, and participant burden were given the greatest weight. In particular, measures for which published information on these specific criteria were lacking were not recommended, and when such information was available for two or more relevant measures, recommendations were primarily based on comparisons of these five attributes. It is important to emphasize that even though basic information on reliability and validity is usually available for measures

that have been used in studies of patients with chronic pain, information on other important attributes of these measures is often lacking. The absence of data relevant to a measure's responsiveness, for example, must therefore be carefully distinguished from the availability of data that demonstrate its lack of responsiveness. Unfortunately, the absence of evidence is much more common than clear evidence of limitations for most of the criteria considered in evaluating outcome measures for chronic pain clinical trials.

Reliability, validity, and responsiveness can be condition or context specific and are not invariant properties of a measure. Although the authors considered evidence of the generalizability of these attributes to diverse chronic pain syndromes, in circumstances in which such data are lacking, it is important to evaluate the applicability of the measure to the chronic pain syndrome being investigated.

3. Core outcome measures for chronic pain clinical trials

The core outcome measures listed in Table 1 should be *considered* in the design of all clinical trials of the efficacy and effectiveness of treatments for any type of chronic pain. It is not the intention of these recommendations that use of these measures should be considered a requirement for approval of applications by regulatory agencies or that treatments must demonstrate statistically significant or clinically important benefits with all of these measures to establish evidence of efficacy or effectiveness. There may be circumstances in which use of some or all of these core outcome measures will not be appropriate, for example, in clinical trials in cognitively impaired individuals or in infants. As was true of the IMMPACT recommendations for core outcome domains (Turk et al., 2003), the present recommendations are most applicable to clinical trials to determine the efficacy or effectiveness of treatments for chronic pain and are made with the assumption that these trials will be conducted in accord with the principles of good clinical practice (International Conference on Harmonisation, 1996a; United States Department of Health and Human Services, 1997).

Table 1
Recommended core outcome measures for clinical trials of chronic pain treatment efficacy and effectiveness

Pain
11-point (0–10) numerical rating scale of pain intensity
Usage of rescue analgesics
Categorical rating of pain intensity (none, mild, moderate, severe) in circumstances in which numerical ratings may be problematic
Physical functioning (either one of two measures)
Multidimensional Pain Inventory Interference Scale
Brief Pain Inventory interference items
Emotional functioning (at least one of two measures)
Beck Depression Inventory
Profile of Mood States
Participant ratings of global improvement and satisfaction with treatment
Patient Global Impression of Change
Symptoms and adverse events
Passive capture of spontaneously reported adverse events and symptoms and use of open-ended prompts
Participant disposition
Detailed information regarding participant recruitment and progress through the trial, including all information specified in the CONSORT guidelines

3.1. Pain

There are various aspects of pain that can change as a result of treatment, and the results of reviews of the literature on pain assessment in adults (Jensen, 2003; Jensen and Karoly, 2001) support the recommendation that measures of pain intensity, the use of rescue treatments, pain quality, and the temporal components of pain should be considered when assessing pain outcomes. Self-report measures provide the 'gold standard' in assessing pain outcomes because they reflect the inherently subjective nature of pain, but they should be supplemented by careful assessments of the use of rescue treatments. Depending on the specific objectives of the clinical trial, other approaches to assessing pain can be considered, for example, overt expressions of pain and distress ('pain behaviors'; Keefe et al., 2001) and surrogate endpoints such as imaging measures.

3.1.1. Pain intensity

For most clinical trials of chronic pain treatments, a measure of pain intensity will provide the primary outcome measure. Each of the commonly used methods of rating pain intensity, including visual analogue scales (VAS), numerical rating scales (NRS), and verbal rating scales (VRS) are reliable and valid, and no one scale consistently demonstrates greater responsiveness in detecting improvements associated with pain treatment (Jensen and Karoly, 2001). However, there are important differences among VAS, NRS, and VRS measures of pain intensity with respect to lost data from patients failing to complete the measure correctly, patient preference, ease of data recording, and ability to administer the measure by telephone or with electronic diaries. VRS and NRS measures tend to be preferred over VAS measures by patients. Furthermore, VAS measures usually demonstrate greater amounts of missing and incomplete data than NRS measures, presumably because NRS measures are less abstract and easier to understand. Greater difficulty completing VAS measures is associated with increased age and opioid intake (Jensen and Karoly, 2001). Cognitive impairment has been shown to be associated with inability to complete NRS ratings of pain intensity (Jensen and Karoly, 2001). Patients who are unable to complete NRS ratings may be able to complete VRS pain ratings. There will, of course, be circumstances when self-reports of pain will be impossible and in these instances alternatives (e.g. observations of behavior, surrogate ratings) will have to be considered.

On the basis of a review of the literature on pain measures prepared for the IMMPACT-II consensus meeting (Jensen, 2003) and discussions among the participants, an 11-point (i.e. 0–10) NRS measure of pain intensity is recommended as a core outcome measure in clinical trials of chronic pain treatments. In order to facilitate consistency among studies, the authors recommend that the specific format of this rating should include presentation of the numbers from 0 to 10, with 0 meaning 'No pain' and '10' meaning 'Pain as bad as you can imagine,' accompanied by the instructions "Please rate your pain by indicating the number that best describes your pain on average in the last 24 h" (Cleeland and Ryan, 1994). Depending on the specific aims and design of the clinical trial, pain during the past week can also be assessed using this scale, as could pain 'at its worst' or pain 'at its least'.

Investigators should also routinely consider including a VRS measure of pain intensity (none, mild, moderate, severe) as an additional pain outcome measure. Doing so makes it possible to compare the results of a clinical trial with the many studies, especially of acute pain, that have used such VRS measures. In addition, use of a VRS measure of pain intensity should limit the amount of missing data that results from some study participants having difficulty completing the primary NRS measure.

There are clinical conditions for which reliable, valid, and responsive measures of pain intensity that do not use an NRS are routinely used (e.g. the Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] VAS ratings in studies of patients with osteoarthritis; Bellamy et al., 1988). These circumstances should be distinguished from those for which no such measures exist and NRS ratings of pain intensity are recommended. When other measures of pain intensity are used, it may be useful to also administer NRS ratings to compare with other diseases or treatments.

In addition to analyzing and reporting absolute changes in pain intensity, it is recommended that the percentages of patients obtaining reductions in pain intensity from baseline of at least 30% be reported when an NRS (or VAS) has been used in a chronic pain clinical trial. This recommendation is primarily based on the results of an analysis of the relationships between changes in pain intensity and patient reports of overall improvement in ten clinical trials of chronic pain in patients with diverse diagnoses (Farrar et al., 2001). Importantly, these relationships were consistent across age, sex, treatment group (different dosages of pregabalin/placebo), the five clinical conditions, and whether study results demonstrated separation from placebo or not (Farrar et al., 2001). To permit comparisons with previous studies and meta-analyses, investigators may also wish to report the percentages of patients obtaining reductions in pain intensity from baseline of at least 50% (McQuay and Moore, 1998).

3.1.2. Rescue analgesics and concomitant pain treatments

The use of all pain-related treatments during the course of a clinical trial should be assessed, including rescue analgesics and any other concomitant pain treatments. This is a straightforward task in single-dose analgesic trials that prohibit the concurrent use of other medications, but it is more difficult in chronic pain clinical trials that allow concurrent use of pain medications and other treatments for pain (e.g. physical therapy) for weeks or months. Some chronic pain trials have allowed previously used pain medications to be continued throughout the trial, and dosage stabilization is often required before patients are allowed to enroll in such trials. However, when changes in the use of concomitant pain treatments are permitted, they can be considered as an outcome measure (e.g. Kieburtz et al., 1998).

Providing patients with access to rescue analgesics may make it easier to include a placebo group in treatment efficacy studies, since patients not obtaining adequate pain relief are provided with an analgesic. However, administration of rescue treatment complicates the interpretation of differences in pain ratings between patients taking placebo and active treatments because of the reduction in pain expected to occur in patients receiving rescue treatment. The use of rescue medications is affected by both patient and provider beliefs. Patients use rescue medications to achieve varying levels of pain relief, but also for other reasons, including improving sleep or reducing anxiety, preventing increased pain resulting from increased activity, and treating pain (e.g. headache) that may be unrelated to the clinical trial. When recording treatments used for pain during the clinical trial, it may therefore be desirable to distinguish analgesics used for relief of the disorder being studied from all other uses.

Rescue medication consumption has been used as an outcome measure in clinical trials, with assessments including amount used and time-to-use (e.g. Chrubasik et al., 2003; Eisenberg et al., 2001). Scales have been developed that allow quantification of medication use in chronic pain patients based on dosage and medication class (Steedman et al., 1992), and composite measures have been proposed that combine rescue medication usage and pain intensity ratings into a single score (Lehmann, 1990; Silverman et al., 1993). Although these may be used to compare different treatment groups in clinical trials, the psychometric properties of such composite measures are not well established.

Despite the complex issues involved in the interpretation of rescue medication usage in a clinical trial, patients in a placebo group can be expected to take more of a rescue treatment than patients administered an efficacious investigational treatment. When considered together with pain intensity ratings, the amount of rescue treatment used by patients therefore can provide an important supplemental measure of the efficacy of the treatment being evaluated. For these reasons, assessments of rescue treatments are

recommended as a core outcome in trials where rescue interventions are available and permitted.

3.1.3. Pain quality and temporal aspects of pain

Pain has different sensory and affective qualities in addition to its intensity, and various measures of these components of pain can be used to more fully describe a patient's pain experience (Price et al., 1987). The efficacy of pain treatments may differ for various pain qualities. Measures of the affective and sensory qualities of pain may therefore identify treatments that are efficacious for certain aspects of pain but not for overall pain intensity. Assessment of pain qualities at baseline also makes it possible to determine whether certain patterns of pain characteristics moderate the effects of treatment.

Whereas pain intensity reflects the overall magnitude of the pain, pain affect can be viewed as reflecting the distress caused by the pain. Assessment of pain affect or unpleasantness is supported by the evidence that the affective component of pain can be empirically distinguished from pain intensity and may be differentially responsive to treatments (Jensen, 2003; Price, 1999). As with pain intensity, pain affect can be assessed with VAS, NRS, and VRS items having different anchors, for example, 'not unpleasant' and 'most unpleasant feeling possible'.

The Short-Form McGill Pain Questionnaire (SF-MPQ; Melzack, 1987) assesses 15 specific sensory and affective pain descriptors and provides a total score and sensory and affective subscale scores. This questionnaire is reliable and well-validated, and its sensory and affective subscales have demonstrated responsiveness in recent chronic pain clinical trials (e.g. Dworkin et al., 2003; Rowbotham et al., 1998). Because it assesses both specific sensory pain qualities and the affective component of pain, the SF-MPQ is recommended for inclusion in clinical trials as a secondary outcome measure to evaluate the effects of pain treatment on both sensory and affective qualities of pain.

Measures of the temporal aspects of pain—including variability in intensity; time to onset of meaningful pain relief; durability of pain relief; and frequency, duration, and intensity of pain episodes—have not received adequate attention in pain research. The available evidence indicates that measures of pain frequency have validity and represent a distinct dimension of pain (Jensen and Karoly, 2001). Frequency of 'breakthrough' pain (periods of severe pain superimposed on ongoing pain) is an important temporal aspect of pain that has been used as an outcome measure in clinical trials (e.g. Farrar et al., 1998). When appropriate, investigators should consider administering measures of the temporal aspects of pain as secondary outcome measures in clinical trials. The temporal dimensions that should be considered include patients' reports of the time to onset of meaningful pain relief and its durability as well as the frequency and intensity of episodes of breakthrough pain.

3.2. Physical functioning

Chronic pain interferes with daily activities, and it has been assumed that relief of pain is accompanied by improvement in function. However, many studies have demonstrated that pain intensity and physical functioning are only modestly associated (Turk, 2002), which supports the importance of including measures of functioning in chronic pain clinical trials. Measures of physical functioning typically assess multiple aspects of function, including activities of daily living. Disturbed sleep is prevalent in people with chronic pain, and its assessment is also important in chronic pain trials. Individuals with chronic pain consider both increased ability to function and improved sleep important treatment objectives (Casarett et al., 2001).

There are two broad types of measures of physical functioning and, more generally, health-related quality of life (HRQOL). Generic measures provide information about physical functioning and treatment benefits that can be compared across different conditions and studies; disease-specific measures assess problems associated with specific conditions that may not be assessed by generic measures and may also be more responsive to the effects of treatment (e.g. Dworkin et al., 2001; Guyatt et al., 1993). Because each of these approaches has strengths, use of both disease-specific measures, when available, and generic measures of physical functioning should be considered in designing chronic pain clinical trials.

On the basis of reviews of the literature on generic and pain-related measures of physical functioning prepared for the IMMPACT-II consensus meeting (Haythornthwaite, 2003; Stucki and Cieza, 2003) and discussions among the participants, use of a disease-specific measure of physical functioning is recommended in chronic pain clinical trials when a suitable and well-accepted one is available. Examples of such disease-specific measures of physical functioning are the WOMAC (Bellamy et al., 1988) and the Roland and Morris Back Pain Disability Scale (Roland and Morris, 1983). However, disease-specific measures of physical functioning have not been developed and validated for many chronic pain conditions. In clinical trials examining such disorders, use of either the Multidimensional Pain Inventory (MPI; Kerns et al., 1985) Interference Scale or the Brief Pain Inventory (BPI; Cleeland and Ryan, 1994; Cleeland et al., 1996) pain interference items (i.e. general activity, mood, walking ability, work, relations with other people, sleep, enjoyment of life) is recommended. The MPI and BPI interference scales both provide reliable and valid measures of the interference of pain with physical functioning that have been translated into many languages and studied in diverse chronic pain conditions in multiple countries.

The MPI and BPI measures of physical functioning have distinct advantages and disadvantages, and use of both may be considered when doing so would not impose an undue

burden on participants (a total of 16 items, 9 for the MPI and 7 for the BPI). The MPI Interference Scale does not assess sleep, and if this measure of physical functioning is administered, then use of a reliable and valid measure of the impact of pain on sleep is recommended. The BPI does include an item assessing pain interference with sleep, but also includes ratings of mood, social relations, and enjoyment of life. These three items may constitute a separate factor measuring affective state that is relatively independent of the remaining items (Cleeland et al., 1996). Few clinical trials, however, have examined BPI factors separately and so administration and analysis of only the three BPI activity items (general activity, walking ability, normal work) as a measure of physical functioning cannot be recommended until more data become available.

Regardless of whether a disease-specific measure of physical functioning or the MPI or BPI interference scale is used in a clinical trial, administration of a generic measure of physical functioning should be considered to obtain data that will allow comparisons with other disorders and that could be used in cost-effectiveness analyses (Thompson, 2002; Turk, 2002). The SF-36 Health Survey (Ware and Sherbourne, 1992) is the most commonly used generic measure of HRQOL and it has been used in studies of diverse medical and psychiatric disorders and in numerous clinical trials. The authors recommend the SF-36 as a generic measure of physical functioning because of the large amount of data available that permit comparisons among different disorders and treatments. The development of new HRQOL measures is an active area of research and these may offer improvements over the SF-36 and ultimately replace it (e.g. Chwastiak and Von Korff, 2003; Rogers et al., 2000).

In many chronic pain conditions, increased activity is accompanied by increased pain. Some patients limit their physical functioning because of pain, and their response to decreased pain may be to increase their activity until pain increases to its tolerated intensity. Other patients will tolerate increased pain to maintain a desired level of function and their response to decreased pain may be to report less pain as long as their level of function remains satisfactory. Although both situations represent true relief of pain, pain relief is reflected in increased activity with little change in pain intensity in the first, and in decreased pain intensity with little change in activity in the second. This issue has been addressed in some studies by examining combined measures of activity level and pain intensity to assess outcome (Malec et al., 1981; Peters and Large, 1990), but additional research on such composite measures is needed.

3.3. Emotional functioning

Chronic pain is often accompanied by symptoms of psychological distress and psychiatric disorders, including depression, anxiety, and anger (Fernandez, 2002). On the basis of a review of the literature of measures of emotional functioning prepared for the IMMPACT-II consensus meeting (Kerns, 2003) and discussions among the participants, the Beck Depression Inventory (BDI; Beck et al., 1961) and the Profile of Mood States (POMS; McNair et al., 1971) are recommended as core outcome measures of emotional functioning in chronic pain clinical trials. Both the BDI and POMS have well-established reliability and validity in the assessment of symptoms of depression and emotional distress, and they have been used in numerous clinical trials in psychiatry and in an increasing number of chronic pain clinical trials (Kerns, 2003). In research in psychiatry and in chronic pain, the BDI provides a well-accepted measure of the level of depressed mood in a sample and its response to treatment.

The POMS assesses six mood states—tension–anxiety, depression–dejection, anger–hostility, vigor–activity, fatigue–inertia, and confusion–bewilderment—and also provides a summary measure of total mood disturbance. Although the discriminant validity of the POMS scales in patients with chronic pain has not been adequately documented, the POMS has scales for the three most important dimensions of emotional functioning in chronic pain patients (depression, anxiety, anger) and also assesses three other dimensions that are very relevant to chronic pain and its treatment, including a positive mood scale of vigor–activity. Moreover, the POMS has demonstrated beneficial effects of treatment in some (but not all) recent chronic pain trials (e.g. Rowbotham et al., 1998). For these reasons, administration of both the BDI and the POMS is recommended in chronic pain clinical trials to assess the major aspects of the emotional functioning outcome domain.

The assessment of emotional functioning in patients with chronic pain presents a challenge because various symptoms of depression—such as decreased libido, appetite or weight changes, fatigue, and memory and concentration deficits—are also commonly believed to be consequences of chronic pain and the medications used for its treatment (Gallagher and Verma, 2004). It is unclear whether the presence of such symptoms in patients with chronic pain (and other medical disorders) should nevertheless be considered evidence of depressed mood, or whether the assessment of mood in these patients should emphasize symptoms that are less likely to be secondary to physical disorders (Wilson et al., 2001). Because the evidence indicates that measures of emotional functioning are adequately reliable, valid, and responsive when used in the medically ill (Kerns, 2003), the authors recommend that the principal analyses of the BDI and POMS in chronic pain clinical trials use the original versions without adjustment for presumed confounding by somatic symptoms. Depending on the specific objective of the clinical trial, supplemental analyses could be conducted to separately examine non-somatic and somatic aspects of emotional functioning.

3.4. Participant ratings of global improvement and satisfaction with treatment

Global ratings of improvement and satisfaction in a clinical trial provide an opportunity for participants to aggregate all of the components of their experience—pain relief, improvement in physical and emotional functioning, side effects, convenience—into one overall measure of their perception of the advantages and disadvantages of the treatment they received. Such measures reflect the 'disdisparate values and preferences of individual patients' (Gill and Feinstein, 1994) and in so doing provide an important measure of pain treatment outcome (Collins et al., 2001). Moreover, global ratings by patients of their improvement and satisfaction with treatment can be used to investigate participants' judgments of the clinical importance of changes in other outcome measures (Farrar et al., 2001; Fischer et al., 1999).

Many different approaches have been used to assess participants' overall evaluation of their treatment in clinical trials. On the basis of a review of the literature of measures of global outcome prepared for the IMMPACT-II consensus meeting (Farrar, 2003) and discussions among the participants, the Patient Global Impression of Change scale (PGIC; Guy, 1976) is recommended for use in chronic pain clinical trials as a core outcome measure of global improvement with treatment. This measure is a single-item rating by participants of their improvement with treatment during a clinical trial on a 7-point scale that ranges from 'very much improved' to 'very much worse' with 'no change' as the mid-point.

There has been widespread use of the PGIC in recent chronic pain clinical trials (e.g. Dunkl et al., 2000; Farrar et al., 2001), and the data provide a responsive and readily interpretable measure of participants' assessments of the clinical importance of their improvement or worsening over the course of a clinical trial. Impression of change scores using different verbal outcome categories have also been used to determine the minimally important changes in quality of life measures (e.g. Guyatt et al., 2002; Hägg et al., 2003). Although these measures appear to have validity, additional research is necessary to determine the relative extent to which ratings on the PGIC and similar measures reflect reduced pain, improvement in functioning, side effect burden, or other variables and whether this varies for different samples and treatments.

Other approaches to the global assessment of treatment response that have been used less frequently than the PGIC in chronic pain trials include ratings of participant satisfaction with treatment, prospectively conducted global ratings of disease state from which changes from baseline can be calculated, and global ratings of specific outcome domains, for example, global ratings of improvement in physical functioning or in overall side-effect burden (Middell et al., 2001). Single-item ratings of treatment outcome have both advantages and disadvantages when compared to multiple-item scales (Sloan et al., 2002), and additional research will be important to determine the optimal method for obtaining global ratings from patients.

3.5. Symptoms and adverse events

The assessment, analysis, and reporting of adverse events is an essential component of all clinical trials. Within the context of pharmacologic investigations, adverse events have been defined as "any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment" (International Conference on Harmonisation, 1995b, p. 2–3). Such events are unintended signs, symptoms, laboratory abnormalities, or diseases associated in a temporal manner with the use of a medication.

Clinical trial protocols should define the method of assessment and the rationale for that approach. In selecting the approach used for ascertaining adverse events and the methods used for recording and coding the terms used to describe these events (e.g. Medical Dictionary for Regulatory Activities, Brown, 2003), consideration should be given to the type and purpose of the trial, whether international regulatory requirements dictate certain approaches (International Conference on Harmonisation, 1995a,b, 1996b), the phase of development or post-marketing, and the total safety experience with the product.

On the basis of a review of the literature on the assessment of symptoms and adverse events prepared for the IMMPACT-II consensus meeting (Katz, 2003) and discussions among the participants, the authors recommend that, at a minimum, passive capture of spontaneously reported events and the use of open-ended prompts should be used in chronic pain clinical trials to assess adverse events. In describing the results of clinical trials, the incidence of individual adverse events and serious adverse events should be reported for each treatment group, including the percentages of participants who experienced treatment emergent adverse events of particular significance or with an incidence greater than placebo. It is also very important to evaluate and report the severity of adverse events as this may differ among treatments that have a comparable incidence of adverse events (Edwards et al., 1999).

Active capture using structured interviews or questionnaires to assess specific symptoms and adverse events that are relevant to the disorder or treatment being studied will often be more sensitive and more informative than passive capture or general inquiries (e.g. Anderson and Testa, 1994; Edwards et al., 1999). Depending on the objectives of a chronic pain clinical trial, active capture of selected symptoms and adverse events can be conducted at periodic intervals throughout the trial, including baseline and the conclusion of the trial, ideally by the same investigator.

It is important to recognize that the frequency, duration, intensity, distress, importance to the patient, impact on daily

function, and investigator and patient causal attributions can be assessed for symptoms and adverse events (e.g. Anderson et al., 1999; Portenoy et al., 1994; Wolfe et al., 2000). Such assessments provide information about the clinical importance of safety and tolerability outcomes.

The authors recommend that methods for active capture of symptoms and adverse events relevant to chronic pain and its treatment be vigorously explored. In developing comprehensive strategies to assess these events, consideration should be given to including participant ratings of frequency, severity, importance, and associated distress. In such research, it will be important to evaluate whether the use of these methods increases the reported incidence of clinically insignificant events that have no implications for tolerability, safety, and patient satisfaction with treatment.

3.6. Participant disposition

On the basis of a review of the literature on the assessment of participant disposition in clinical trials prepared for the IMMPACT-II consensus meeting (Turk, 2003) and discussions among the participants, the authors recommend that chronic pain clinical trials should collect and report comprehensive information on participant disposition, including detailed information regarding the recruitment of participants and their progression through the trial. Information on participant disposition is essential for the adequate evaluation of the results of a clinical trial and for interpreting the trial's conclusions regarding efficacy and safety.

Although the CONSORT (Consolidated Standards of Reporting Trials) guidelines (Altman et al., 2001; Begg et al., 1996; Moher et al., 2001) were developed to serve as a guide to reporting results of clinical trials, they also provide a valuable enumeration of the core elements of information on participant disposition that should be recorded when conducting trials (Goudas et al., 2001), including the numbers of participants who withdraw and are lost to follow-up as well as the reasons for withdrawal and loss. The following additional information can be valuable in interpreting the results of a clinical trial and should be collected and reported when doing so is feasible: (1) the recruitment process and the percentages of participants enrolled from each recruitment method; (2) the number of candidate participants who were excluded from participation and the reasons why; (3) the number of candidates who chose not to enter the trial and the reasons why; (4) the use of prohibited concomitant medications and all other protocol deviations that may impact the interpretation of the trial results; (5) the number and reasons for withdrawal from each treatment group, including deaths and patients lost to follow up; and (6) the types, rates, and reasons for non-adherence with treatment in each treatment group.

Dosages and duration of all treatments received by participants during the clinical trial should be recorded, including assessments of the use of rescue, concomitant, and prohibited medications and all alterations in prescribed treatment. Detailed information describing the extent to which each participant adhered to the protocol will make it possible for data analyses to be conducted that specifically examine efficacy in patients who adhered to the protocol. Such *efficacy evaluable* or *per protocol* analyses can sometimes be valuable in interpreting the results of intention-to-treat analyses, although the benefits of comparing randomized groups are lost. Although an important component of patient disposition, withdrawal from a clinical trial due to lack of treatment effectiveness can also be considered an endpoint (European Agency for the Evaluation of Medicinal Products, 2002; International Conference on Harmonisation, 2001).

Although reasons for withdrawal are usually provided in reports of clinical trials, this information is often inadequate. For example, 'drop out due to adverse events' may be given as a reason for withdrawal, but this is not informative without tabulation of the specific adverse events associated with the withdrawals. Similarly, 'withdrawal of consent' is commonly given as a reason for withdrawals, but this is impossible to interpret without description of the reasons why patients withdrew consent.

There are several factors that may compromise the integrity of the double-blind used in a clinical trial (Even et al., 2000). Participants' and investigators' guesses of which treatment was administered should therefore be assessed, and the reasons for the specific guesses (e.g. medication side effects or pain relief) should also be collected to assist in intepreting any unblinding that may have occurred (Moscucci et al., 1987; Turner et al., 2002).

4. Conclusions

The authors recommend that the core outcome measures listed in the table should be *considered* when designing clinical trials of chronic pain treatments. It must be emphasized, however, that the authors are not suggesting that the inclusion of these measures in a trial should be considered a requirement for publication in a scientific journal or by regulatory agencies. Furthermore, these recommendations are not meant to imply that positive results must be obtained for all of these outcome measures for a treatment to be deemed efficacious and safe.

Pain intensity and impairments in physical and emotional functioning are associated in patients with chronic pain, and improvement in pain has been associated with improvement in functioning and reports of overall benefit in some but not all clinical trials. There are many circumstances, however, in which improvement is found for measures of one or two of the core outcome domains but not others. There are undoubtedly many explanations for such results, including the generally modest relationships among the core outcome domains (Turk et al., 2003). Moreover, the statistical power of clinical trials is typically determined for the primary

endpoint, and it can therefore be expected that inadequate power may sometimes explain results for secondary outcome measures that are not statistically significant. Conversely, positive results for secondary outcomes in chronic pain trials such as physical and emotional functioning would not necessarily provide convincing evidence of efficacy or adequate demonstration within regulatory contexts to support additional efficacy claims.

It is important to emphasize that there will be clinical conditions or treatments for which one or more of these core outcome measures will not be relevant and should therefore not be included in a clinical trial. Future research may also identify other measures of these core domains that will be shown to have psychometric properties that are superior to the specific measures recommended in this article. The authors also expect that the recommended measures will typically be supplemented by other measures that are included for exploratory purposes or to evaluate treatment- or disease-specific issues (Turk and Melzack, 2001). Regardless of which measures are ultimately used, the reasons for selecting each of the specific measures that have been included in a clinical trial should be provided.

There are many decisions that must be made in administering outcome measures in chronic pain trials. For example, whether ratings of pain or the other measures discussed in this article are made using retrospective or serial assessments is a very important issue that may have implications for the ability of a measure to detect change (Fischer et al., 1999). These and other decisions will depend on the design of the trial, the resources available, and other considerations that are beyond the scope of this article.

In recommending specific core outcome measures, the authors acknowledge the important limitations of existing measures and the pressing need to develop improved methods for assessing chronic pain outcomes. For this reason, forthcoming IMMPACT recommendations will provide guidelines for developing improved measures of chronic pain outcomes and will identify the types of studies that are required to successfully develop such measures. Additional IMMPACT meetings will focus on methods to identify the clinical importance of changes in chronic pain outcome measures, and on approaches for combining multiple outcome measures to evaluate treatment efficacy and effectiveness. The use of standard outcome assessments has the potential to greatly enhance the validity, comparability, and clinical applicability of clinical trials of chronic pain treatments.

5. Disclaimer

The views expressed in this article are those of the authors. No official endorsement by the US Department of Veterans Affairs, US Food and Drug Administration, US National Institutes of Health, or the pharmaceutical companies that provided unrestricted grants to the University of Rochester Office of Professional Education should be inferred.

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