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**Assessment of physical function and participation in chronic pain clinical trials:
IMMPACT/OMERACT recommendations**

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Abstract

Although pain reduction is commonly the primary outcome measure in chronic pain clinical trials, physical functioning as part of health-related quality of life (HRQOL) is also important. A challenge in designing chronic pain clinical trials to determine efficacy and effectiveness of therapies is obtaining appropriate information about measures of the impact of an intervention on an individual's physical function. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) and Outcome Measures in Rheumatology (OMERACT) convened a meeting to discuss and deliberate measurement considerations for physical functioning and activity in research on chronic pain. **The primary purpose of this article is to synthesize evidence and discussions on the scope of physical functioning to inform future work on refining physical function outcome measurement. We address issues in assessing this broad construct as an outcome in chronic pain clinical trials and provide examples of frequently used measures of relevant constructs.** Chronic pain investigators can assess physical functioning using patient-reported outcome (PRO) measures, performance-based measures, and objective measures of activity. This paper aims to provide support for the use of these outcome measures, covering broad aspects of functioning, including work participation, social participation, and caregiver burden, which researchers should consider when designing chronic pain clinical trials. Investigators should consider the inclusion of both PROs and performance-based measures as they provide importantly different but also often complementary information. The development and consistent use of reliable and valid PROs and performance-based measures of physical functioning may expedite development of improved pain treatments, and standardization of these measures has the potential to facilitate comparison across studies. We provide recommendations to stimulate future methodological research to develop tools that are more robust, address consistency and standardization, and engage patients early in the tool development process.

Keywords: OMERACT, IMMPACT, pain, physical performance measures, patient-reported outcomes, physical functioning, physical activity, accelerometer, work, employment, HRQOL, social participation, caregiver burden, clinical trials

1. Introduction

There is little question that the presence of chronic pain has impact on all areas of functioning, including emotional, social, as well as physical.^{53,61,170,186} With the persistence of pain, the extent and depth of these consequences expands and evolves. Focus groups and surveys have shown that physical functioning is altered in people living with chronic pain, with the majority of participants expressing functional problems in activities or increased symptoms during or following the activity.¹⁹¹ Physical functioning outcome measures are important because they provide data on the impact of pain and treatment effects beyond symptom reduction alone, moving into the impact on individuals' lives beyond symptoms, a primary concern for patients.¹⁹¹ The objective of this article is to synthesize current evidence and expert deliberations and discussions (held at a joint Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)/Outcome Measures in Rheumatology (OMERACT) meeting) to present considerations and recommendations for the comprehensive assessment of physical functioning and related outcomes in chronic pain clinical trials. Although many additional factors may affect functioning, we included participation and caregiver burden as contextual outcomes because they have received scant attention in other reviews.

Central to the deliberations at the meeting was the concept of the relationship between physical functioning and “participation” and restrictions in activities of daily living (ADLs). The aim was to better define and contextualize these relationships and to discuss whether chronic pain clinical trials should consider participation as an additional patient-centered domain in outcome measurement. Hammel et al.⁷⁹ found that individuals in their study conceptualized participation as a cluster of values (e.g., active and meaningful engagement/being a part of, choice and control, access and opportunity/enfranchisement, personal and societal responsibilities, having an impact and supporting others, and social connection, inclusion, and membership). People living with chronic pain may view the outcomes of a pain intervention to be more clinically meaningful if the outcomes assessed include evaluation of their ability to

participate in various activities, in addition to pain and performance in clinic or laboratory assessments.

In a previous article, IMMPACT recommended that in order to assess HRQOL, physical, emotional, and social functioning should be included as core outcome domains in all chronic pain clinical trials.¹⁹⁰ Investigators should include measures of physical functioning that provide evaluations of meaningful aspects of an individual's life, including the ability to carry out ADLs such as household chores, walking, work, and self-care, as well as strength, endurance, and flexibility.¹⁹⁰ These aspects have been categorized in an interrelated arrangement of domains in the International Classification of Functioning, Disability, and Health (ICF)²¹⁰ (see Figure 1 for the model and Table 1 for ICF Chapters), in which physical functioning is found at the level of very specific task demands (taking a step), broader acts (walking a block), or participation restrictions (role functioning, meeting physical demands of work). Physical functioning is an important independent outcome domain. However, to date, the literature has failed to reveal a strong linear relationship between decreased pain and increase in activity.¹⁸⁹ Outcome measures of physical functioning, activity, and social functioning can be useful in establishing the global impact of treatment and whether the adverse effects of a treatment affect the potential benefits of pain reduction. Although the discussions that provided the basis of our recommendations focused on analgesic clinical trials, the issues discussed in this article have implications and are relevant for research on the efficacy and effectiveness of interventions for patients with chronic pain more broadly.

2. Methods

IMMPACT convened a meeting in collaboration with the members of the OMERACT Pain Working Group to **review the evidence and discuss the issues in measuring the broad construct of physical functioning as an outcome domain in chronic pain clinical trials in order to inform future work on refining investigators have frequently been used in clinical trials (see below). However, the authors do not endorse any specific measures given the limitations discussed.**

Prior to the meeting, two systematic literature searches were undertaken reviewing the evidence for physical functioning measures, one aimed at PRO measures and the other at observer, laboratory, and other performance-based outcome measures of pain-related physical functioning (Table 2); the results are presented in Tables 3 and 4. We have included references in these tables so the reader can examine the studies and ascertain the metrics, methods, and patient groups.

The meeting brought together an international group of participants from academia, government agencies, industry, and public advocacy organizations selected based on research, personal experience living with pain, and clinical expertise relevant to evaluating physical activity and functioning. There were 28 academic and related participants, including 22 from the United States of America (USA), 3 from Canada, and 3 from the United Kingdom (UK). There were 9 government participants, 2 patient representatives from the USA, and 7 industry participants, all of whom were from the USA.

At the start of the meeting, background lectures provided overviews of the following topics: (1) United States Food and Drug Administration (FDA) guidance for the development and evaluation of PRO measures (A.S.); (2) an FDA perspective on review of outcome measures for drug approval and labeling (E.P.); (3) a conceptual overview defining physical function (D.B.); (4) PRO measures of physical functioning (A.M.T.); (5) clinician, observer, laboratory, and other outcome measures of physical functioning (K.P.); (6) actigraphy (K.V.P.); (7) social participation outcome measures (D.W.); (8) work participation outcome measures (M.G.); (9) outcome measures involving caregiver burden (J.M.); and (10) interpretation of the clinical importance of improvements in patient reported and “objective” assessments of physical functioning (D.J.C.). Slides supporting these presentations are available on the IMMPACT website: <http://www.immpact.org/meetings/Immpact17/participants17.html>. We recommend that readers view the slides, as appraisal of the evidence is more detailed than we are able to cover in depth in the present article.

Using the information presented in the background lectures, the subsequent discussions during extensive question and answer sessions, and informed by the background readings, participants deliberated on physical functioning outcome measures, including participation and caregiver burden as contextual factors. The rationale for the meeting was to examine the scope of physical functioning and the issues affecting it in order to provide recommendations and a research agenda for a detailed and thorough plan of activity following the meeting. The meeting was recorded and transcribed to retain ideas about important content and structure. A.M.T., K.P. and K.V.P., the lead authors, prepared a draft manuscript that reflected the deliberations. They circulated the initial draft to all participants for consideration and comment on content, structure, and proposed recommendations. The lead authors revised the manuscript iteratively until all authors approved its content. In this paper, we have incorporated the most salient points of these discussions.

3. Physical functioning: primary outcomes

3.1. Patient-reported outcome (PRO) measures

Authors often use different terms interchangeably in describing physical functioning without defining them precisely. Therefore, it is often unclear whether a particular outcome measure in a clinical trial is assessing organ-level impairments, task completion, or interference with specific activities. A number of studies indicate that different interventions used to treat chronic pain may have differential effects on physical impairment, activity limitation, as well as restrictions in participation.¹³ Ideal PRO physical function outcome measures differentiate among these to illustrate the true value of an intervention.¹³

A conceptual model for pain and physical functioning needed, for this initiative, to integrate the key concepts of the ICF with additional features that have particular clinical relevance, for example, the disease defining component(s), the mechanism of action of the treatment that an investigator is studying, and the primary outcome warranting study.

Understanding of physical functioning requires consideration of the individual's environment and

context (see Tomey & Sowers¹⁸⁵). Physical functioning is considered as the person's capacity in set situations, however it also can acknowledge that persons can manage barriers to functioning such as stairs, temperature, and neighborhood accessibility by aids and adaptations or avoidance of them. Investigators must consider the physical functioning of an individual within the appropriate context to permit comparisons across respondents. For example, individuals with chronic conditions (pain or other sources of limitations in physical functioning) often learn to accommodate their condition through adaptations of techniques or learning to work around any limitations. Whether or not adaptations are considered is, for example, an important conceptual question and depends on the research question.

Investigators can achieve the measurement of physical functioning using a number of methods each providing a certain 'window' on the concept. These can range from direct observation and monitoring devices, to PROs. The FDA defines PRO measures as, "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else".¹⁹³ As illustrated in Tables 3-4, there is a plethora of PRO measures of physical functioning, some generic and others disease specific, each with its own strengths and weaknesses. In evaluating such measures, several points are particularly noteworthy (see also Williams et al.²⁰⁶). A primary consideration is the content validity of the instrument. None of the currently available measures is sufficiently comprehensive, covering all key domains of physical functioning. Some questionnaires focus solely on physical functioning, whereas others include multiple domains in which physical functioning is only one component or subscale of the assessment tool (Table 3). However, there needs to be a balance between comprehensiveness and respondent burden. It may not be feasible to ask patients to complete a very lengthy PRO measure or sets of measures.

Advanced psychometric methods, such as Item Response Theory (IRT) and the use of Computer Adaptive Testing (CAT), have the potential to reduce respondent burden by increasing the efficiency of the assessments.^{40,81,122} The National Institutes of Health Patient

Reported Outcome Measurement Information System (PROMIS) is an important development that may make a significant contribution to clinical trial data capture as it evolves.^{3,4,21,30,34} It is a domain-oriented, mixed method approach to health outcomes intended to facilitate within- and between- disease comparisons, that included patient input from the earliest stages (see <http://www.immpact.org/static/meetings/Immpact17/Williams.pptx>). The PROMIS investigators developed items using advanced psychometric qualitative and quantitative methods. PROMIS uses IRT, which enables CAT, in order to improve precision latent trait estimation while also minimizing patient respondent burden. PROMIS physical functioning (PF) items may act as a standard for comparative effectiveness research (Patient-Centered Outcomes Research Institute has funded such research). PROMIS PF measures are available for both adults (full bank = 121 items) and pediatric populations (PF-mobility = 23 items, PF-upper extremity = 29 items); they are also available as part of a PROMIS Profile (29, 43 or 57-item versions).

It is also important to consider the target population of a PRO. The experience might be different across populations (chronic episodic versus chronic constant pain), and attribution within the PRO might need attention to match with a target population. Researchers should ask whether appropriate normative information is available regarding the sample included in a particular target study. Various investigators have developed questionnaires for a range of populations; however, limitations experienced by some groups may not be applicable to others:

- Instruments developed for use with adults over 18 and under a certain age may not be appropriate for use with older adults and are likely to be virtually completely irrelevant for children and adolescents;
- measures developed on native language speakers may not be transferrable to second language samples;
- and measures of physical functioning developed specifically for use with patients with low back pain might not be the best instruments to use with a sample of patients with neck and shoulder pain.

- Further, as role and job responsibilities have evolved over time, the initially applied measures may become less applicable as respondents' current roles and employment evolve.

Finally, it is important to consider that a range of contextual factors, in addition to pain, will likely influence PRO measures of physical function and participation. Various models of health and disability emphasize that a range of personal, health, social, political, and environmental factors often relate to PRO measures of function and performance. Although this makes them more complex to include in studies, the IMMPACT/OMERACT recommendation is that researchers should consider them. A previous IMMPACT recommendation, that we endorse, is that investigators consider using both a disease-specific physical functioning measure and a generic measure to be able to compare results across populations with different disorders.⁵² Investigators should also consider inclusion and exclusion criteria that capture specific contextual factors. This will increase the generalizability of the outcomes to certain contexts; however, generalizations to groups without certain contextual factors will be limited. It also may mean that investigators need to complete multiple studies to address a range of contextual factors and this may not be feasible. Qualitative studies may help in understanding the contextual factors better.

A range of self-reported measures of physical functioning has appeared in the literature; we divided these measures and approaches into broad categories (Table 3), with the clinical, observer, and laboratory tools grouped by sub-domain (Table 4). We did not intend for the lists included in Tables 3 and 4 to be exhaustive as there are many disease and location specific instruments, but rather to illustrate measures that researchers have used in clinical trials in persons with chronic pain.

3.2. Performance-based measures

Researchers generally recognize that self-report and performance-based measures appear to provide different but complementary information. Performance-based measures assess discrete

physical actions in a standardized manner across study participants and sites, so that investigators can compare physical functioning across different clinical populations and countries. Investigators are increasingly using performance-based measures in observational and intervention studies, particularly in older adults¹⁴⁶, as they can assess physical functioning in a standardized manner. For these measures, investigators ask participants to perform a specific task and they then evaluate these in an objective manner using predefined criteria, such as recording the number of repetitions completed or the time to complete a task. The development and use of performance-based measures aimed to address limitations in self-report measures of physical functioning that can be prone to contextual and psychosocial bias. Some performance-based measures have amassed a considerable amount of normative data and have established minimally clinically important differences (Table 4).¹⁶

Performance-based tasks, however, may not be relevant to the particular needs of individuals or capture their real-world limitations and environment. The perceptions and motivation of the respondents are also important to consider as they affect their behavior. Performance-based measures (e.g., 6MWT¹⁶, Timed Up and Go test –TUG¹⁵⁰, Short Physical Performance Battery – SPPB⁷⁷) are not devoid of subjectivity and behavioral responses as they depend on effort. Many factors, such as fear of pain or injury, lack of motivation due to emotional distress, and learned behavior may be independent of actual physical ability and could influence performance on such voluntary tasks; but investigators can, nevertheless, use these measures to provide a more objective assessment of the total impact of pain. Training and retraining of study staff in test administration are critical for maintaining standardized, reliable assessments of physical performance.

A number of systematic reviews have been published describing performance-based measures of physical functioning specifically pertaining to pain. For example, in collaboration with members of OMERACT, the Osteoarthritis Research Society International (OARSI) has assessed measurement properties of many performance measures specifically developed for

use with patients who have hip or knee osteoarthritis pain.¹¹⁰ Currently, there are few performance-based tests that are widely used for any specific pain condition and their use in chronic pain clinical trials has been very limited. This is an important future direction for research in order to establish normative data in the field of pain research.

Researchers have developed a growing number of methods to assess task-related physical performance (e.g., functional capacity examinations using devices and instruments such as dynamometers and force plates) directly. Each of these approaches targets a particular physical function or set of physical functions (e.g., range of motion, muscle strength, gait speed and pattern). It is beyond the scope of this article to review each of these measures and their strengths and weaknesses. The references we used in this paper have been included to support further consideration of physical function outcomes. Once again, we encourage the interested reader to examine the appropriate references to inform their decisions regarding the appropriateness of any measure for their purposes. However, we will discuss a more general measure of activity, accelerometry (actigraphy) in greater depth in the next section to illustrate some of the complexities, strengths, and weaknesses inherent in technologically advanced measurement devices.

3.2.1. Actigraphy/Accelerometry

Actigraphy, also called accelerometry, is becoming more widely used both in research and for clinical applications to monitor physical activity objectively. Accelerometers are small, lightweight devices that can measure acceleration along 1, 2, or 3 axial planes and provide time-stamped data on intensity of physical activity and sedentary behavior. These data provide valuable complementary information to PROs and performance-based measures of physical function.

Self-reported physical activity is typically subject to recall bias and biased estimation and reporting, and is poorly correlated with estimates from accelerometers. For example, self-reported data from the 2005-2006 National Health and Nutrition Examination Survey showed

that 60% of adults in the USA met physical activity guidelines of either 150 minutes per week of moderate activity or 75 minutes per week of vigorous physical activity, accumulated in 10-minute bouts.¹⁸⁷ In contrast, accelerometer data showed that fewer than 10% met these guidelines.¹⁸⁷ Weak correlations between self-reported and objectively measured physical activity have also been observed elsewhere.¹²⁸ It is likely that the self-reported and accelerometer data are measuring different dimensions of physical activity (e.g., perceived versus actual intensity of activity), but both methods can provide important information. We need additional research to understand the meaning of this discordance between self-reported measures of physical activity and actigraphy data.

The reliability of actigraphy is well-established.^{28,201} Validity studies show that accelerometer counts are moderately to strongly associated with oxygen consumption during activity using direct and indirect calorimetry.^{54,62,85} Further, actigraphy is strongly associated with measures of physical performance, such as the 6MWT, and predicts physical disability^{82,109} and mortality.¹⁵ Accordingly, actigraphy provides valuable objective data on the intensity and extent of physical activity and is increasingly used in studies of chronic pain. Currently, however, the interpretation of actigraphy data beyond general levels of activity and sleep¹⁷¹ is problematic, although this will likely change with the application of advances in machine learning to the data. Indeed, emerging methodological studies are now capitalizing on the richness of raw accelerometer data to classify time spent in different activities (e.g., walking, sitting, lying down). Newer devices are available that also include inclinometers to measure posture and more reliably quantify time spent in different activities.^{73,120}

Despite increasing use of accelerometers in observational studies of pain^{48, 133, 134,145,207}, relatively few studies have used these devices in clinical trials. One exception is a randomized, placebo-controlled, crossover trial of celecoxib for knee osteoarthritis, which showed that accelerometer data can be combined with pain intensity ratings as a composite outcome measure and that peak activity alone responded to treatment.⁵¹ Another example is an open-

label study of a transdermal fentanyl patch that showed greater improvement with actigraphy measures than with a numerical rating scale.¹ Actigraphy can be useful for evaluating sleep, and can serve as an efficient assessment of both daily physical function and sleep using a single device in the same individual. However, lax standards in activity metrics (e.g., counts) as well as differences in hardware and software across devices may hinder progress in using accelerometers. Researchers need to conduct further methodological work to establish good practices and standards for using accelerometers and analyzing the resulting data in chronic pain clinical trials.

4. Physical functioning: contextual outcomes

Poor physical functioning can lead to the inability to participate in or impede interpersonal relations. Thus, impaired social functioning may reflect poor physical functioning, and it can contribute to decreased function. In addition, increased caregiver burden associated with chronic pain may likewise contribute to or reflect poor physical functioning. These themes are important to explore in relation to physical functioning given that they are contextual factors within the conceptual framework and have had scant coverage in reviews.

4.1. Participation

Assessment of social participation largely evolved out of the ICF framework but the construct of social participation is not universally defined, and often confused with general participation, activities of daily living, support, and other social factors. For this general construct, there are many instruments with varying degrees of psychometric adequacy^{83,84,86,90,175,205} and in most cases, the construct is embedded within a more general scale or domain that is being assessed. Although the International Classification of Impairments, Disabilities, and Handicaps (ICIDH) framework is outdated, investigators are still making use of questionnaires based on it.

Studies have examined the impact of social support and its benefits and even deleterious influences^{59,158} on individuals living with pain and on functional disability.^{102,192,196} Emotional support tends to have a more beneficial impact in people living with pain than does

instrumental support (doing things for people) as the latter can lead to learned helplessness.¹² Studies have shown that both network size and quality of social support at diagnosis of rheumatoid arthritis patients, for example, predicts pain and functional status 3-5 years later.⁵⁵ Given the emerging relevance of social participation, we recommend that assessment of social participation be considered in chronic pain clinical trials when the investigator believes that this construct may be perceived as a moderator or mediator in shaping the outcomes for a particular population under study^{101,196} (See <http://www.immpact.org/static/meetings/Immpact17/Williams.pptx>). We identified 37 potential measures in the literature of which 17 were particularly relevant to the discussion. Table 5 lists some of the established measures covering this domain.

4.1.1.1. Participation in work and social activities within and outside the home

Participation in work, within and outside the home, and family, social, and leisure activities are important aspects of physical functioning. Measurement of work outcomes, including worker productivity, is complex; often these outcomes are characterized in terms of a variety of different theoretical frameworks (ICF^{31,165}). The factors contributing to participation go beyond pain, and health-related factors (see Table 1, ICF Chapters) and work participation outcomes (e.g., measures of work loss, absenteeism, and productivity) are interconnected. Therefore, it may be necessary for investigators to measure different types of work outcomes to evaluate these relationships adequately. It is not sufficient to consider compensated work outside the home alone because, for example, as few as 20-50% of people with rheumatoid arthritis may be working outside the home^{41,130,169} and retired people typically are not engaged in full-time paid work. However, they may volunteer or perform comparable activities (e.g., yard work, hobbies) without receiving financial compensation. For the purpose of this section, we will use the generic term “work” to describe activities within and outside the home, paid and unpaid. For school-aged children and adolescents, school attendance and participation in school-related activities are comparable to “work”. We will not discuss these in this article.

Investigators have used employment status as an outcome in many clinical trials, typically using a simple binary (yes/no) response. Sick leave or short-term disability is another potential outcome. Absenteeism (absent from work) and presenteeism (in work but unable to function due to illness) are also used as well as work scheduling (e.g., full to part time) and work disruptions (e.g., arriving late, leaving early). Large survey or population health data can separate some of these diverse factors, but it is challenging to determine what should be included as outcome measures in a clinical trial. Several validated instruments are available that assess changes in the activities that are important to patients, for example, the Work Productivity Survey (WPS, the only questionnaire to query family, social, and leisure activities as well as work within the home)¹⁴¹, the Work Limitations Questionnaire (WLQ)^{9,112,113}, and the Workplace Activity Limitations Scale (WALS).^{17,67,69} Such outcome measures should be considered for inclusion in clinical trials where there is an expectation that work will be affected by the treatment.

The fact that outcomes are interrelated raises the possibility of developing a global measure of participation or productivity for application to clinical trials (at least long-term trials where there would be sufficient time to expect that work would be affected). Pain can interfere with physical functioning and therefore work, and work can have an impact on pain; outcome assessments need to address this bi-directionality of work being both a cause and effect of pain and pain being a cause and effect of work loss. The work context (e.g., its physical demands and the accommodations and adaptations used to reduce pain and improve physical functioning) and the nature of the pain will make a difference in how participants will respond to work-related outcome measures. Given the complexities surrounding work participation measures, and the lack of clear definitions, the OMERACT Worker-Productivity Working Group was established to examine and understand the issues related to employment and select or develop relevant measures for clinical trials (please see Tang et al.¹⁸¹). As previously described, a number of measures can be used to assess the impact of pain on work functioning, within and

outside of the home, as well as overall productivity.^{17,67,162,176,181,182} However, work participation does need consideration in terms of other family, social, and leisure roles. The ongoing efforts of the OMERACT working group will make it possible for researchers to develop specific recommendations regarding the assessment of participation in chronic pain clinical trials. In the meantime, investigators can use the WPS, WLQ, and WALs to inform the results of chronic pain clinical trials. However, non-paid work is under studied; it needs its own research agenda to understand better the impact of pain on work that does not have monetary benefits.

4.2. Decreasing physical functioning and caregiver burden

Caregiver burden may be a result of decreasing physical functioning in the person living with pain or may lead to decreased physical function as the caregiver feels compelled to take on more responsibility. Therefore, caregiver burden may act as a proxy indicator of physical functioning in the patient living with chronic pain. Researchers should consider the amount of time a caregiver saves and the reduced burden in caring for a patient as physical functioning improves as potential outcome measures for a clinical trial in patients with chronic pain. These outcomes may be important to examine in those clinical trials where investigators anticipate such effects.

Caregiver burden may be different if the individual living with pain is a child rather than an adult (see Palermo et al.¹⁴³). Cultural and ethnic factors can play a major role, and investigators need to see outcome measures of caretaker burden in the context of the culture and ethnicity of the group that investigators are studying.

There are a number of tools to measure caregiver burden.^{50,58,75,89,100,125,167} However, to date this concept has not received sufficient attention, especially in the field of pain. Caregiver burden has been included as an outcome measure in phase 3 clinical trials in Alzheimer's disease, the index condition for studying caregiver burden²⁹, and such measures may have a role in later-phase pain clinical trials.

However, there are problems with caregiver burden assessment in clinical trials (see Lingler et al.¹¹⁶). There are certainly challenges in developing approaches that can isolate caregiver burden that is specifically attributable to pain from the burden associated with the condition causing the pain and impairment (e.g., neurological impairment due to motor or sensory loss or musculoskeletal impairment associated with a limb fracture or amputation). There are also challenges in discriminating burden associated with pain versus co-morbid mental health conditions, particularly emotional distress and depression.

There is the potential to develop reliable measures of caregiver burden associated with pain that are also responsive to change. To date, it is unclear whether caregiver burden associated with chronic pain is a contributing factor or a separate outcome of poor physical functioning. This may depend on the conceptual framework for physical functioning and on the specific intervention, an investigator plans to examine. However, we need further development of the theoretical basis for examining caregiver burden in chronic pain and definitions of caregiver outcomes. Therefore, caregiver burden may be an important outcome measure in future chronic pain clinical trial and hence its inclusion in the framework we propose.

5. Considerations regarding the use of physical functioning measures in chronic pain clinical trials.

Investigators need to give greater attention to the important role of conceptual models in framing physical functioning measures in chronic pain clinical trials. The models discussed delineate the various concepts that are relevant to physical functioning; the hypothesized relationships among the concepts, and a framework to support potential treatment targets.¹⁶⁰ Researchers should develop these early when considering physical functioning measures for use in clinical trials.

The ICF is a classification system of health and health-related domains, and used here as an example of a conceptual model. As the functioning and disability of an individual occur in a context, ICF also includes a list of environmental factors. We recommend that behaviors and tasks associated with a particular condition be mapped to the physical functioning outcome

measure(s) that would be used. Ideally, investigators should match a large proportion of behaviors and tasks relevant to a specific chronic pain condition to the outcome measures that they will use in the trial. If not, further consideration of which measures or methods to use is required. A number of mapping exercises have been published describing the process.^{44,45,88,172,176} These mapping exercises provide strong empirical support to recommend mapping to a conceptual model.

5.1. Outcome measures should include consideration of psychosocial factors that impact functioning

We have already noted that many if not most “objective” measures of physical functioning are dependent on individuals’ co-operation. These “voluntary” behaviors are potentially influenced by the range of HRQOL domains, including psychosocial factors (e.g., mood, attention, pain-related attitudes and beliefs)^{8,10,32,15119,23,35,47,87,103,123,152}, and thus cannot be considered to be “pure” measures of physical ability. Depression, pain-related fear, and catastrophizing are associated with increased interference, awareness of pain, and impaired disengagement from pain, and can moderate the effects of attentional coping leading to poor clinical outcomes.^{11,19,23,35,47,87,103,123,152,179,195} Similarly, fear of injury or harm has an influence on physical effort and activity.¹⁹⁹ Given such data, it is recommended that psychosocial outcome measures also be administered when assessing physical functioning, as changes, or the lack of changes, in physical functioning following an intervention may be accounted for by existing fear, catastrophizing, and depression. Therefore, investigators should interpret lack of improvement in physical functioning in chronic pain clinical trials taking into account whether participants’ scores are also elevated in the psychological domains. Psychosocial constructs and processes may be particularly relevant when considering measures of caregiver burden. Given the amount of research examining the impact of psychosocial factors on physical functioning, there is strong evidence to suggest that investigators should evaluate psychosocial factors in tandem with assessments of physical functioning.

5.2. Ensure outcome measures assess the core disease-defining concepts

When evaluating treatment benefits on physical functioning, outcome evaluations need to consider a range of measures, all of which are important; however, the interpretation of trial results depends on knowing how treatment affects the core disease-defining concepts. Figure 2 illustrates this. On the left, measures are specific and represent the core disease. However, moving towards the right, the measures address concepts that can be modified by many factors other than just the core disease. These measures may also follow a different time course than the core disease-defining concept, in that they may take longer to recover following an intervention. We recommend that investigators identify the core disease-defining concepts before more downstream effects, and that they match the core disease-defining concepts with measures that will be the primary outcomes in a clinical trial. Although this recommendation appears to be reasonable, further research is required to address the complexities involved in identifying the core disease-defining concepts in those living with chronic pain.¹⁶⁴

5.3. Assess performance properties for each physical functioning measure

Investigators should give careful attention to content validity and instrument design to insure that they present these precisely in their articles. A number of resources are available to support the identification of robust outcome measures for use in clinical trials including: OMERACT Filter 2.0²², COSMIN^{46,131}, and the PROMIS physical function domain.^{63,105} The International Society for Pharmaco-economic and Outcomes Research (ISPOR)^{127,147} also publishes consensus recommendations for the development and evaluation of measures. Investigators should match valid and reliable measures to the specific chronic pain condition being studied, and should include a generic measure of physical functioning to enhance interpretation of study outcomes by providing a context of data from other disorders. Considered together, the results of previous chronic pain clinical trials and on-going work provide sufficient evidence to support this recommendation.

5.4. The context of use of function measures and the environment of the respondent need to be identified

The presence of contextual factors defines the situation in which the abilities of individuals are being tested or quantified.¹²⁹ It is important to also consider the person as a contextual factor^{68,70}; for example, individuals adapting to their pain condition to conserve energy or accepting help from others. Differentiating whether a specific act (walking), identifiable task (walking outside), or participation (getting to work on time) is the outcome of interest is ultimately up to the investigators for a given study. Researchers will need to develop a general model of function to address capacity to function, the environmental pressures on that capacity, and the ability of coping and adaptation to modify the relationship between capacity and what study participants actually perform. In addition, it is essential to consider meaning; measures may miss what is truly important to those living with pain beyond what they are obligated to do on a day-to-day basis; for example, discretionary, recreational, and social activities.

Investigators should not use physical functioning measures without appropriate consideration of contextual factors; they should collect relevant contextual information and present this information as part of the demographic and clinical description of the sample investigators plan to study. To ascertain how pain affects physical functioning from an individual perspective and weighing the contextual factors that are relevant will require a large body of evidence obtained initially from qualitative studies. This is, therefore, something that researchers will need to consider carefully as the evidence may not necessarily exist to guide the context of use of functional measures in specific patient groups.

6. Conclusions and specific recommendations

Physical functioning and activity are important components of health status¹¹⁹ and functional limitations in daily activities are common among adults with chronic pain.⁹¹ Researchers should develop physical functioning assessments for individuals with chronic pain within a conceptual model. Measures should be directed at the specific definition of physical functioning (i.e.,

activity, participation) that is of interest, and contextual factors and the environment should be considered. Investigators need to assess the appropriateness of a given measure for the specific research objectives of the research. There is a great deal of variability in the content and format of PRO measures of physical functioning, some of which undoubtedly reflects the diversity of painful conditions studied. Previous reviews have found variation in the number of recall periods used, inconsistencies in the development and validation methods of questionnaires, and limited, if any, discussion of the conceptual framework underlying the assessments. Therefore, future research needs to address these previous limitations to develop robust outcome measures for physical and social functioning.

Investigators did not develop most currently used measures with patient involvement, input, or perspective. We recommend the inclusion of patient input in the earliest stages of the development process. This can take the form of focus groups and qualitative studies to establish what are important outcomes for those living with persistent pain. Patient involvement is an important consideration in the FDA PRO guidance.¹⁹³ Future research will need to base physical functioning measures on a conceptual framework that includes patient input. Researchers can conduct Delphi studies combining the views of patients living with persistent pain, health professionals, and other stakeholders. OMERACT has a long history of working collaboratively with patient research partners using a variety of research methods and workshops to ensure that researchers accurately capture patient views and incorporate these into meaningful outcome measures.

We recommend that all chronic pain clinical trials include measures of physical functioning that are appropriate for the specific population investigators are studying and are valid and reliable; caution is needed, however, when extending the use of any measures, even well-established ones, to populations that differ substantially. There are many influences on physical functioning, including moderators and mediating processes. Given this, chronic pain clinical trials need to be able to demonstrate the robustness of their outcome measures not only

for reasons of data accuracy, but for the interpretation of the data and generalizability to clinical practice. Measures for pediatric populations are beyond the scope of this article and warrant dedicated consideration; however, many of the general assessment considerations discussed in this article also apply to children and adolescents.

As described in previous IMMPACT recommendations, investigators should give consideration to use of disease-specific measures combined with generic measures of physical functioning when designing a chronic pain clinical trial.¹⁹⁰ Investigators may not capture specific impairments inherent in a particular pain disorder with generic outcome measures. Therefore, disease-specific measures may more readily detect clinically important improvement or deterioration in functioning that is a consequence of the treatment under study. We recommend consideration of a combination of both types of physical functioning measures (generic and disease specific) such as those listed in Tables 2 and 3. There are 3 key domains in the realm of physical function assessment: self-reported physical functioning, measured physical function, and measured activity levels. As discussed in this article, each has strengths and weaknesses and until more outcome methods research has been undertaken, these 3 domains may all need to be assessed when physical function is a key outcome domain in a chronic pain clinical trial. Actigraphy is a more objective measure and with improvements in technology, this may become the definitive physical functioning measure in future trials. At present, however, it is important for research groups to ascertain what it is that they want to measure as an outcome and to identify valid and reliable tools that minimize bias.

Objective measures of physical functioning can complement PROs and provide some unique information. We recommend actigraphy as an objective measure of physical activity if additional research demonstrates that the measure captures the physical activity of interest. For performance measures of physical functioning, we suggest that investigators should consider the TUG¹⁵⁰, the 6MWT¹⁶, and the SPPB⁷⁷ if appropriate for the context of use. Other performance measures may be more relevant for a specific clinical trial, or may have better

measurement properties for a specific population (e.g., pediatric or geriatric populations) and investigators should also consider these. We listed a summary of the recommendations made throughout this article in Table 6.

Future research directions include: (1) examination of the discrepancies between PRO and objective measures of physical functioning; (2) assessment of caregiver burden and workplace participation; and (3) examination of sleep, emotional functioning, and sexual functioning and their relationships to the physical functioning outcomes discussed in this article. Although our emphasis was clinical trials, consideration of the issues raised in this article should inform research and facilitate comparison across studies of chronic pain more broadly by improving understanding of the impact of pain on functioning, as well as potentially advancing the development of effective treatments for patients with diverse chronic pain conditions.

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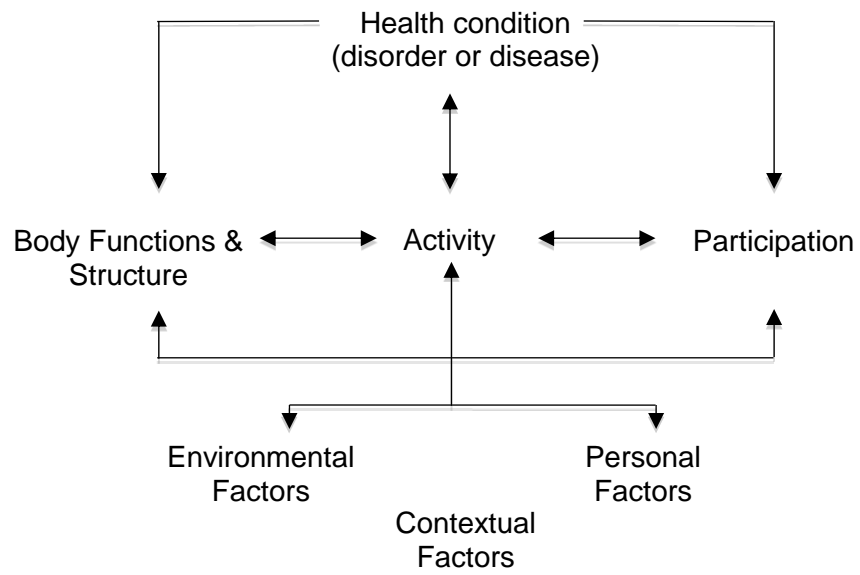
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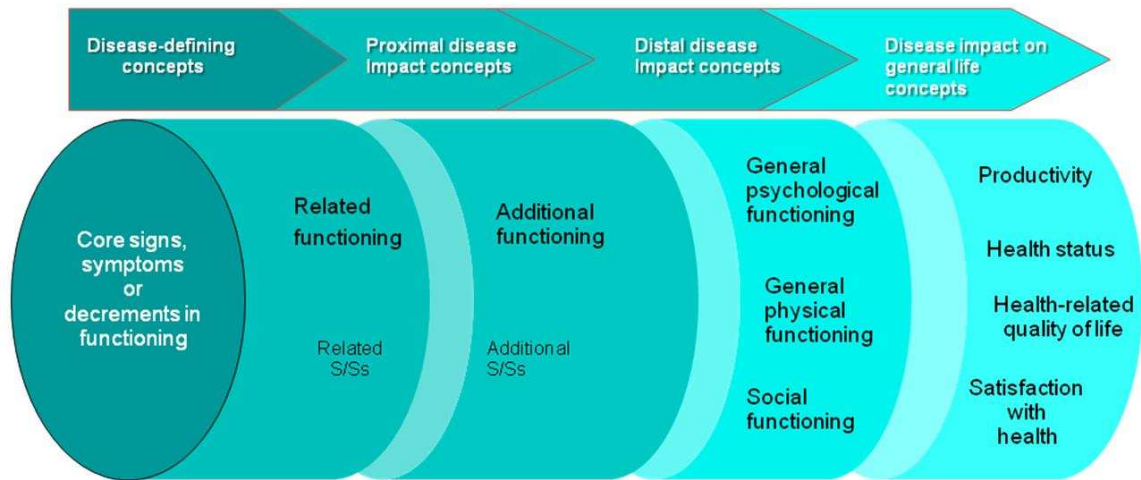
Figure 1. A model of disability that is the basis of ICF²¹⁰



ICF = International Classification of Functioning, Disability, and Health

Figure 2. Treatment benefit: What to measure?

Schematic diagram depicting the impact of inter-related domains and sub-domains of assessment for chronic diseases¹⁶⁸



S/Ss = signs and symptoms

Table 1. The ICF chapters²¹⁰

Body	
<p>Function:</p> <p>Mental functions Sensory functions and pain Voice and speech functions Functions of the cardiovascular, haematological, immunological and respirator systems Functions of the digestive, metabolic, endocrine systems Genitourinary and reproductive functions Neuromusculoskeletal and movement related functions Functions of the skin and related structures</p>	<p>Structure:</p> <p>Structure of the nervous system The eye, ear and related structures Structures involved in the voice and speech Structure of the cardiovascular, immunological and respiratory systems Structures related to the digestive, metabolic and endocrine systems Structures related to genitourinary and reproductive systems Structure related to movement Skin and related structures</p>
<p>Activities and participation</p> <p>Learning and applying knowledge General tasks and demands Communication Mobility Self-Care Domestic life Interpersonal interactions and relationships Major life areas Community, social and civic life</p>	
<p>Environment</p> <p>Products and technology Natural environment and human-made changes to the environment Support and relationships Attitudes Services, systems and policies</p>	

ICF = International Classification of Functioning, Disability, and Health

Table 2. Considerations for outcome measures: search strategies

<p>Outcome measures were identified searching electronic databases: Medline, Embase, PsychINFO, CINAHL</p> <p>Hand searching and backward chaining was undertaken</p> <p>Key words for patient-reported outcomes and performance measures: physical activity, functioning, function, motor activity, activities of daily living, activity, exercise questionnaire*, scale, tool, assessment, self-report, measure* chronic disease, chronic condition, pain, chronic pain, musculoskeletal, rheumat*, long term conditions, older adults</p> <p>Key words for observer, laboratory and other outcome measures: physical activity, physical function, physical functioning, exercise, motor activity, pain, chronic pain, musculoskeletal pain, performance measures, observation, six minute walk test, timed up and go test</p> <p>Inclusion criteria: research from 1980 to present day, in English, published in peer review journals</p> <p>Exclusion criteria: pre 1980 unless a seminal or key paper, studies looking at athletic performance, sports, children and adolescents, studies looking at the aging process devoid of long term conditions and in post-acute care rehabilitation.</p>

* In the place of a character in the search term indicates that any number of characters can be substituted in place of the asterisk

Table 3: Patient-reported outcome measures of physical functioning

Pain related physical functioning/activity measures	<p>The Pain Disability Questionnaire⁵ Chronic Pain Self Efficacy Scale⁶ Pain Self-Efficacy Questionnaire¹³⁶ Questionnaire for Physical Activity Decline in Pain (PAD)¹⁹⁷ Daily Activity Diary for Chronic Pain Patients⁶⁰ The Pain Disability Index¹⁵¹ The Multidimensional Pain Inventory¹⁰⁴ The Brief Pain Inventory⁴³</p>
General physical functioning/activity outcome measures	<p>London Handicap Scale⁸⁰ MOS 36-Item Short Form Health Survey (SF-36)²⁰⁰ The Impact on Participation and Autonomy (IPA)³⁹ The Impact on Participation and Autonomy Questionnaire (IPAQ)³⁸ The Physical Activity and Disability Survey (PADS)¹⁵⁵ The Physical Activity Questionnaire¹¹⁷ The Quality of Well-Being Scale, Version 1.04 (QWB)⁹⁶ The Sickness Impact Profile (SIP)²⁰ Work Limitations Questionnaire (WLQ)¹¹² Human Activity Profile⁴⁹ Motor Fitness Scale¹⁰⁶ Short Questionnaire to Assess Health-Enhancing Physical Activity (SQUASH)¹⁹⁹ PROMIS^{3,4,21,30,34}</p>
Activities of daily living measures	<p>Population Surveys of Chronic Disease and Disability (Section 1)⁶⁶ The Centres for Disease Control and Prevention's Healthy Days Measures (the CDC HRQOL-14)¹³² The Duke-UNC Health Profile¹⁴⁴ Katz Index of Independence in Activities of Daily Living⁹⁹ Rosow Breslau Index of Mobility¹⁶⁰ Nagi's Upper or Lower Extremity Functional Index¹³⁵</p>
Disease specific physical activity/functioning measures	<p>Bath Ankylosing Spondylitis Functional Index³⁷ Roland Morris Disability Questionnaire¹⁵⁷ Fibromyalgia Impact Questionnaire³⁶ Health Assessment Questionnaire⁶⁴ Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)¹⁸ Functional Status Assessment Instrument⁹⁴ The FAST Functional Performance Inventory¹⁵⁴ The Leisure Time Physical Activity Instrument (LPAI)¹²⁴ The McMaster Toronto Arthritis (MACTAR) Patient Preference Disability Questionnaire¹⁸⁸ The Physical Activity at Home or at Work Instrument (PAHWI)¹²⁴ Short Musculoskeletal Function Assessment Questionnaire¹⁸⁰ Modified Health Assessment Questionnaire (MHAQ)¹⁴⁹ Musculoskeletal Functional Limitation Index⁹⁸ Patient-specific activity scoring scheme¹⁷⁷</p>
Site specific physical functioning/activity measures	<p>Disabilities of the Arm, Shoulder and Head (DASH)⁹² QuickDASH⁷⁶ Boston Carpal Tunnel Questionnaire¹¹⁴</p>

	<p>Bournemouth Questionnaire^{25,26} Hip Injury and Osteoarthritis Outcome Score (HOOS)¹³⁷ Knee Injury and Osteoarthritis Outcome Score (KOOS)¹⁵⁹ Lequesne Hip and Knee Scores¹¹¹ Neck Disability Index¹⁹⁸ The Western Ontario Rotator Cuff Index^{107,108} The Oswestry Disability Index⁵⁶ Patient-rated Tennis Elbow Evaluation¹²¹ Foot and Ankle Ability Measure (FAAM)¹⁵⁶</p>
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Table 4: Clinical, observer, and laboratory tools grouped by sub-domain (online summary of some measures at <http://www.rehabmeasures.org/default.aspx>)

Mobility or Activity measures	Timed Up and Go (TUG) ¹⁵⁰ 6 minute walk test (6MWT) ¹⁶ Walk, Fast paced ⁷¹ Self-paced ⁴² Multi paced ²⁷ Actigraphy ²⁰¹
General physical functioning measures	Stair climb test ⁴² Chair stand test 5 times in a row (timed) ²⁴ Number of times in 30 seconds ⁹⁵ Balance One legged hop ¹¹⁸ Standing stork ¹⁴⁸
Multi-activity tests of physical functioning	Continuous Scale – Physical Function Performance Test (CS-PFP) ¹⁶⁶ Short Physical Performance Battery (SPPB) ⁷⁷ Physical Performance Test (PPT) ¹⁶³ Physical Activity Restrictions (PAR) ¹⁵⁴ Aggregated Locomotor Function (ALF) ¹²⁶ Functional Assessment System (FAS) ¹⁴⁰ Lin battery ¹¹⁵ Steultjens battery ¹⁷⁴ Stratford battery ¹⁷⁷
Site-specific physical functioning	Loaded forward-reach test for chronic low back pain ⁷ Shoulder Range of motion ²⁰³ Knee range of motion ¹⁴ Hand grip strength test ⁵⁷ Single leg hop test ¹⁴⁰

Table 5: Focused participation outcome measures

Groups	Measures
Social participation as a construct	Sickness Impact Profile ⁷² The Nottingham Health Profile ⁹³ Reintegration to Normal Living Index ²⁰⁸ Social Role Participation Questionnaire ⁶⁸ PROMIS Social Functioning ⁷⁸
Instruments that operationalize the ICDH model	Craig Handicap Scale & Reporting Techniques (CHART) ²⁰⁴ Perceived Handicap Questionnaire (PHQ) ¹⁸³ London Handicap Scale (LHS) ⁸⁰ Community Integration Questionnaire (CIQ) ⁹⁶
Instruments aligned to the ICF and included the concept of social participation	Assessment of Life Habits (LIFE-H) ¹³⁸ Participation Objective, Participation Subjective (POPS) ³³ Participation Survey/Mobility (PARTS/M) ⁷⁴ Participation Measure for Post-Acute Care (PM-PAC) ⁶⁵ Vestibular Activities and Participation (VAP) ² WHO Disability Assessment Schedule 2 ¹⁹⁴
Measures that address specific aspects of social participation	Life Satisfaction Questionnaire-9 (LSQ) ¹⁶⁴ Impact on Participation and Autonomy Questionnaire (IPA) ³⁹ Measurement of Quality of the Environment (MQE) ¹⁴² Participation Enfranchisement ⁸³ Work Limitations Questionnaire ^{17,162,181} Workplace Activity Limitations Scale ^{17,67,181}

Table 6: Summary of Recommendations

- Physical functioning assessments should be developed within a conceptual model
- Patient input should be included in the earliest stages of the development process for any outcome measure.
- Investigators should assess the appropriateness of any measure of physical functioning that they are considering for the specific population they are studying.
- Investigators should assess the appropriateness of a given measure for the specific research objectives of the research.
- Investigators should give consideration to use of disease-specific measures combined with generic measures of physical functioning when designing a chronic pain clinical trial.
- Consideration should be given to use of a combination of both types of physical functioning outcomes, that is, patient-reported measures and more objective assessments of activity or performance
- Investigators should consider actigraphy as an objective measure of physical activity if they can demonstrate that the measure captures the physical activity of interest.