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Consensus Statement

Core Outcome Domains and Measures for Pediatric Acute and Chronic/Recurrent Pain Clinical Trials: PedIMMPACT Recommendations

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Abstract: Under the auspices of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), 26 professionals from academia, governmental agencies, and the pharmaceutical industry participated in a 2-stage Delphi poll and a consensus meeting that identified core outcome domains and measures that should be considered in clinical trials of treatments for acute and chronic pain in children and adolescents. Consensus was refined by consultation with the international pediatric pain community through announcement of our recommendations on the Pediatric Pain List and inviting and incorporating comments from external sources. There was consensus that investigators conducting pediatric acute pain clinical trials should consider assessing outcomes in pain intensity; global judgment of satisfaction with treatment; symptoms and adverse events; physical recovery; emotional response; and economic factors. There was also agreement that investigators conducting pediatric clinical trials in chronic and recurrent pain should consider assessing outcomes in

pain intensity; physical functioning; emotional functioning; role functioning; symptoms and adverse events; global judgment of satisfaction with treatment; sleep; and economic factors. Specific measures or measurement strategies were recommended for different age groups for each domain.

Perspective: *Based on systematic review and consensus of experts, core domains and measures for clinical trials to treat pain in children and adolescents were defined. This will assist in comparison and pooling of data and promote evidence-based treatment, encourage complete reporting of outcomes, simplify the review of proposals and manuscripts, and facilitate clinicians making informed decisions regarding treatment.*

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Key words: *Acute pain, chronic pain, children, adolescents, pediatric, clinical trials, randomized controlled trials, assessment, outcomes, health-related quality of life, physical functioning, emotional functioning, global ratings, adverse events, IMMPACT.*

The need for careful attention to pain in children and adolescents has been highlighted ever since Eland and Anderson²³ reported that children were not receiving analgesics for major surgery. Measures have been developed, treatments have been evaluated, and practice has changed. However, many children and adolescents continue to suffer from inadequately treated pain of all types.^{17,60}

Randomized, clinical trials (RCTs) are the gold standard method of evaluating interventions. They are also important in knowledge transfer, as a well-designed and well-publicized trial can promote changes in clinical practice.

Standardization of outcome domains and measures in pediatric pain RCTs would streamline designing and reviewing research protocols and articles, simplify and strengthen systematic reviews, and help clinicians make treatment decisions. However, any standardization is provisional, as the process of outcome measures development is dynamic and subject to frequent updates.

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has recently recommended 6 core domains be considered in clinical trials of chronic pain in adults⁷² and specific measures to assess each of these domains.²⁰ To encourage clinical trials in the pediatric population and to improve the interpretability and aggregation of data across pediatric pain trials, the Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (PedIMMPACT) was developed. Additional information concerning IMMPACT can be found at www.immpact.org.

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The PedIMMPACT group first obtained consensus on domains to be used for acute and chronic pain using the age groups of 3 to 6 years and 7 years and up. Next, the availability and adequacy of measures within each domain were considered. When there was insufficient empirical data available to make an evidence-based recommendation, consensus was sought among the participants.

PedIMMPACT recommends core outcome domains that should be considered in the design of all clinical efficacy or effectiveness trials of pharmacologic, behavioral, or environmental interventions. Our recommendations are presented to promote standardization of domains and measures for clinical trials in pediatric pain. One or more of these domains might, in any given trial, be justifiably excluded. We do not intend to imply that assessment of core domains be considered a requirement for regulatory approval of a product or for publication of a clinical trial. Furthermore, a researcher need not be limited by the domains of focus offered here. For example, targeted drug development for chronic pain conditions in children and adolescents may require assessment strategies that go beyond parameters discussed. A review of these factors exceeded the scope of this PedIMMPACT consensus meeting.

We endorse conducting trials according to Good Clinical Practice⁷³ and registration and publication of all trials, including trials that fail to show the hypothesized effect. We also support the CONSORT Statement¹⁶ to guide planning and publication of clinical trials. Behavioral trials should consider additions to the CONSORT Statement that are specifically applicable to pediatric behavioral trials.⁴⁸

Pain in neonates and infants was not considered because of the significant developmental differences between infants and neonates, on one hand, and children and adolescents on the other. PedIMMPACT also did not consider pain in cognitively impaired children because of differences in assessing these children. Efforts to develop standards for these populations will be the focus of future PedIMMPACT meetings.

Methods

The consensus group was constructed to represent the broadest spectrum of expertise in pediatric pain while

keeping the group small enough to accomplish the goals and to permit free-ranging discussion and debate. We used a consensus strategy that consisted of a 2-stage Delphi poll¹⁸ that helped the group focus attention on relevant domains and measures during a 2-day consensus meeting (March 17–19, 2005). The consensus was refined using commissioned systematic reviews of self-report and observational measures of pain intensity. We finalized consensus through post-meeting consultation among the group using e-mail. Finally, we subjected our major findings to public review by the international pediatric pain community by means of dissemination on the Pediatric Pain Listserv (<http://pediatric-pain.ca/ppml/>), which is subscribed to by more than 450 researchers and clinicians who are working in pediatric pain in more than 45 countries. Suggestions obtained from this process were incorporated within our recommendations.

Participants

There were 3 groups of stakeholders represented: Academic research, government funding and regulatory agencies, and the pharmaceutical industry. The academic participants were selected by the organizers to represent the interdisciplinary international pediatric pain clinical research community and included representation from anesthesiology, clinical trials methods, epidemiology, neurology, nursing, pediatrics, pediatric oncology, psychology, and rehabilitation medicine. The meeting was chaired by the senior author (McGrath), who was assisted by the 2 coleaders of previous IMMPACT meetings (Turk and Dworkin) and was attended by a total of 26 professionals, all of whom are coauthors of this report. The representatives from industry were all scientists and not directly involved in marketing. Each company was allowed 1 participant in the consensus process. The representatives from the United States Food and Drug Administration and the National Institutes of Health were involved in assessment of interventions used in children and adolescents for pain. Each participant was instructed to speak for himself or herself as an individual and not as a representative of any organization. All participants were involved in the Delphi poll, the consensus meeting, post-consensus consultations, and approved the manuscript and all revisions. Because this was a professional consensus meeting with voluntary participation, it was deemed that there were no human subjects concerns, and institutional review board approval was not sought.

Developmental Issues

We believe that consideration of developmental processes is critical for understanding children's pain. Development includes biological, psychological, and social processes that all must be considered when designing a pediatric pain trial. Children change in their cognitive, emotional, and physical capabilities during the entire pediatric age range. Age is only a rough approximation of development but is often the most appropriate proxy.

There are differences across the age span in type and incidence of pain, abilities to provide self-reports, as well

as the role of child and family factors. For example, children of different ages tend to vary in the nature and frequency of different procedures and surgeries, and there is evidence that most children below 4 years of age are unable to use standard self-report scales of pain intensity. There are other clear developmental features of pain. Pain, as measured by self-report and by behavior during blood draws, for example, decreases with age from 6 years through the teenage years, with girls reporting more pain than boys over the age range.^{27,28,74} The role of parents in pain management also changes with development.⁷ In addition, the incidence of recurrent pain follows a clear developmental sequence. Headache, for example, increases dramatically with age. Before puberty, recurrent headache occurs at a low rate, and there is a slightly greater incidence of headache in boys than girls.^{66,74} With the onset of puberty, the incidence of both migraine and tension type headaches increases dramatically, and females assume the much higher incidence of headache that is shown in adult studies.⁶⁶ For these reasons, we made each of our decisions with developmental issues clearly in mind. We considered evidence of developmental change in the relevance of specific outcome domains and the appropriateness of specific measures and generally preferred measures that have been shown to be valid across a broad age range. In certain circumstances, however, different measures are more appropriate for different ages.

Process

A 2-stage Delphi poll¹⁸ was conducted before a 2-day consensus meeting that discussed the results of the poll and made final recommendations.

The Delphi poll was conducted by e-mail and asked participants to rate the outcome domains that had been suggested in the original IMMPACT recommendations⁷² and to recommend others. This information was solicited for acute pain and for chronic pain in 2 age groups (3–6 years and 7–16 years). The participants were also asked to suggest possible measures for each domain. The results from the first poll were summarized and were supplied to the participants for the repeat poll. The Delphi poll results were used as a guide to structure the discussion at the consensus meeting.

The meeting reviewed the results of the Delphi poll and discussed acute pain domains and measures and then went on to examine domains and measures for chronic and recurrent pain. Because of the wealth of research on measures of pain intensity and the need to carefully consider the extensive data available, systematic reviews were commissioned that reviewed scales for measurement of pain by self-report and by observation of behavior. The self-report review⁶⁷ was performed by a team headed by Jennifer Stinson and the behavioral measures review⁷⁹ was conducted by a team headed by Carl von Baeyer. The team leaders were chosen for their expertise in pain measurement and because they had not been involved in the development of any measures that their group reviewed and they were present at the consensus meeting. These background literature

Table 1. Core Outcome Domains Recommended for Consideration in Clinical Trials of Pediatric Acute Pain

Pain intensity
Global judgment of satisfaction with treatment
Symptoms and adverse events
Physical recovery
Emotional response
Economic factors

reviews^{67,79} are available on the PedIMMPACT page at www.immpact.org/meetings.html. On the other hand, consensus group members who had developed particular measures were allowed full participation in all discussions during the meeting or consultations. During our deliberations, we considered but were not constrained by the work of previous IMMPACT consensus articles on domains and measures in chronic pain in adults.^{20,72}

A consultation was held with the wider pediatric pain community. Two announcements with a summary of our consensus were placed on the Pediatric Pain listserv (<http://pediatricpain.ca/ppml/ppmlist.html>), and recipients who requested a full copy were sent a copy of the draft consensus document. The comments were reviewed by the senior author, and suggestions were incorporated. Consensus was refined by e-mail exchanges with the other authors after the meeting.

Results

The domains to be used in a clinical trial should correspond to the objectives of the study, include the full range of outcomes of interest, and be appropriate for the problem and for the populations studied.⁷² We selected domains to recommend for consideration in pediatric clinical trials that would meet these criteria, would be clinically meaningful, developmentally appropriate, and responsive to intervention.

Criteria for selection of measures were based on those used by Dworkin et al²⁰ and on previous work.^{26,64} These criteria include (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 (eg, self-report, interviewer); and (10) availability and equivalence of versions for different cultures and languages. In addition, we empha-

sized the developmental appropriateness of each measure.

We recommend that the domains and measures described below be considered for use in all clinical trials of the efficacy or effectiveness of pain interventions in children and adolescents. We present evidence-based recommendations for specific domains and measures when the research data support specific approaches and consensus recommendations when the evidence was insufficient to make evidence-based recommendations. We anticipate that as research progresses, our recommendations will need to be updated.

Acute Pain Domains and Measures

Acute pain can arise from (1) medical procedures ranging from immunization and simple venipuncture to debridement of skin in severe burns, (2) postoperative pain and other medical interventions, (3) injury, and (4) acute exacerbation of disease pain. These types of acute pain are quite different from one another in terms of time course and some of our recommendations vary, based on the particular features or nature of the acute pain.

PedIMMPACT recommends that the domains in **Table 1** be considered as core outcome domains in acute pain clinical trials in children and adolescents. We recognize that any one trial may not include all domains. Moreover, we wish to emphasize that we are not recommending that multiple domains necessarily be primary outcomes for individual trials. Measures of different domains are often not highly correlated,⁸⁰ and the specific research question should dictate which domains are measured and what domain(s) and measure(s) are selected as the primary outcome. However, the appropriateness of each domain should be considered during the design of all clinical trials with children and adolescents.

Pain Intensity

Pain intensity is an obvious core outcome domain for acute pain clinical trials. In pediatric pain, both self-report and behavioral measures of pain have been developed, validated, and widely used. Behavioral measures of pain were developed because children below the age of about 3 to 4 years cannot provide valid self-reports.³⁵

The PedIMMPACT group reviewed and accepted the recommendations in the commissioned literature report on self-report measures of pain intensity (**Table 2**). Extensive details on the justification for the selection of these measures are available in Stinson et al.⁶⁷

The Poker Chip Tool consists of a set of 4 red plastic poker chips, each used to denote a "piece of hurt." The

Table 2. Evidence-Based Recommendations for Self-Report Measures of Acute Pain Intensity in Clinical Trials in Children and Adolescents

AGE	TYPE OF PAIN	MEASURE	CITATION
3 to 4 years	Procedure-related and postoperative	Poker Chip Tool	Hester et al ³⁵
4 to 12 years	Procedure-related, postoperative, and disease-related	Faces Pain Scale-Revised	Hicks et al ³⁶
8 years of age and above	Procedure-related, postoperative	Visual Analog Scale	Scott et al ⁶⁵

child is asked to choose “how many pieces of hurt” they have right now. Children without pain would say they do not have any pieces of hurt. The first chip corresponds to “a little hurt,” the second chip indicates “a little more hurt,” the third chip means “more hurt,” and the fourth chip equals the “most hurt you could ever have.” The Poker Chip Tool is scored from 0 to 4.³⁵ The Poker Chip Tool has undergone extensive psychometric testing by various teams of investigators.^{30,32,69}

There are many different “faces” scales for the measurement of pain intensity. The Faces Pain Scale – Revised (FPS-R)³⁷ is a revised version of a scale originally developed by Bieri et al.⁶ It consists of 6 gender-neutral line drawings of faces that are scored from 0 to 10. It has been shown to have adequate psychometric properties.^{9,10,32}

We concluded that self-report measures of pain intensity are not sufficiently valid for children below 3 years of age. With children of 3 and 4 years of age, many will not be able to accurately self-report their pain and as a result, an observational measure should also be used. Consequently, the use of self-report of pain as a primary outcome in 3- to 4-year-old children may not be warranted.

The numerical rating scale (NRS), in which pain intensity is reported, for example, on a 0 to 10 scale. (NRS-11) or 0 to 100 scale (NRS-101), was seriously considered because of its ease of use and ease of charting. Despite the widespread use of the NRS in clinical practice, the lack of research on the NRS, except in the context of the Oucher⁵ in children and adolescents in acute pain precluded a recommendation for its use.

Readers will note the contradiction in recommending a visual analog score (VAS) but not an NRS when the VAS requires a higher degree of abstraction than the NRS and the VAS cannot be used in telephone follow-up. This anomaly in our recommendations has occurred because of the lack of psychometric studies with the NRS in children and adolescents. This is an area for further research.

Table 3 contains PedIMMPACT recommendations for observational pain scales that should be considered for acute pain trials. Different scales are recommended for different situations because they were designed for and validated in different circumstances. So, for example, the only observational measure recommended for use by parents is the Parents’ Postoperative Pain Measures¹² and the only measure recommended for consideration in children in critical care settings is the COMFORT scale.¹ More extensive justification of the selection of observational mea-

asures is available in the commissioned paper prepared by von Baeyer and Spagrud.⁷⁹

The FLACC scale⁵⁰ is a 5-item scale that raters use to score each of 5 categories, namely, (F) Face; (L) Legs; (A) Activity; (C) Cry; and (C) Consolability, which are scored from 0 to 2. There are extensive reliability and validity data on the FLACC.^{45,50}

The Children’s Hospital of Eastern Ontario Pain Scale (CHEOPS)⁴⁶ has raters assess 6 behaviors (crying, facial expression, verbal expression, torso position, touch, and leg position). There are extensive reliability and validity data on the CHEOPS.^{46,70}

The Parent’s Postoperative Pain Scale¹¹ is a 15-item scale in which parents are asked to report on changes from children’s usual behavior. The scale has been well validated.^{8,11,25}

The COMFORT Scale¹ measures alertness, calmness/agitation, respiration, physical movement, blood pressure change, heart rate change, muscle tone, and facial tension. Extensive validity data are available for the COMFORT Scale.⁷⁵

The Toddler-Preschooler Postoperative Pain Scale is an observational scale for measuring postoperative pain specifically for children aged 1 to 5 years. There are reasonable validity data for this scale.^{70,71} Studies have been limited to relatively short-term pain (mostly a few hours) from common surgeries. Although we believe extrapolation to longer term studies is reasonable, there are as yet no data available.

Two types of single-item observational scales, global scales and behaviorally anchored scales, were considered but not recommended. Global scales require a single rating of the amount of pain by an observer. There may be anchors such as “no pain” and “severe pain.” Global scales, such as a VAS used by adults (parent, nurse, or research assistant) to rate children’s pain, have the advantage of being very simple to use. However, they may be prone to bias and poor validity because of the absence of any criteria for scoring pain. Van Dijk et al⁷⁶ reviewed the data on the VAS as an observational measure and concluded there were not sufficient data to recommend its use.

Behaviorally anchored pain intensity scales have been less widely used. They have several anchors of specific behaviors within a single item.^{38,59} There is insufficient evidence for their validity to recommend their use.

Often, measures of pain intensity are used in the context of the duration of the pain. So, for example, the average of multiple measures may be taken, or time pe-

Table 3. Evidence-Based Recommendations for Observational Measures for Acute Pain Intensity

AGE	TYPE OF PAIN	MEASURE	PRIMARY CITATION
1 year and above	Procedural pain; postoperative pain in hospital	FLACC: Face, Legs, Arms, Cry, Consolability	Merkel et al ⁵⁰
1 year and above	Procedural pain; postoperative pain	CHEOPS: Children’s Hospital of Eastern Ontario Pain Scale	McGrath et al ⁴⁶
1 year and above	Postoperative pain at home	PPPM: Parents’ Postoperative Pain Measure	Chambers et al ¹²
1 year and above	On ventilator or in critical care	COMFORT Scale	Ambuel et al ¹
1 year to 5 years	Postoperative pain	Toddler-Preschooler Postoperative Pain Scale	Tarbell et al ⁷¹

riods with pain above or below some level may be examined. The purposes of the study will likely dictate the way that duration of pain is assessed.

Global Judgment of Improvement and of Satisfaction With Treatment

Global judgment of satisfaction with treatment allows patients or patient surrogates to provide an aggregate of their perspective of all aspects of the treatment experience. Patient global ratings of satisfaction have not often been used in pediatric pain trials and thus it is a challenge to assess the value of this domain in pediatric pain. However, patient global ratings are widely used and perceived as very useful in adult pain trials²⁰ and in clinical trials for other problems. Patient global judgments focus on the patients' experience and thus are, by their nature, patient-oriented.

Both global ratings of improvement from the beginning of the trial and global ratings of satisfaction with treatment have been used extensively in the adult literature.²⁰ A recent meta-analysis of adult pain trials¹⁵ summarized data from 150 randomized, double-blinded trials included in 11 systematic reviews of single-dose, oral analgesics for postoperative pain and found that global satisfaction measures were highly correlated with more fine-grained measures. Different formulations of the global satisfaction question did not appear to be important.

The major issue with global ratings of satisfaction with treatment is the concern that the ratings will mean something different from one patient or surrogate to another. Some may focus exclusively on the relief of pain, whereas others may consider side effects of the treatment. There are no data on the relationship between patient global satisfaction questions and proxy ratings by parents. In the case of children below about 8 years of age, only proxy measures are available.

PedIMMPACT recognized the lack of sufficient information regarding patient global satisfaction with treatment ratings in pediatric pain trials on which to base an evidence-based recommendation and emphasizes the need for more research in this area. However, PedIMMPACT supports the use of patient global or proxy global satisfaction measures that are standardized so as to maximize the chances that all individuals are using the same components to determine their responses.

The consensus was that global satisfaction should be ascertained by posing a global question about satisfaction with treatment with indications of what should be considered in the answer, for example, "Considering pain relief, side effects, physical recovery, emotional recovery, and economic considerations (if appropriate), how satisfied were you with the intervention your child received?" A common metric such as an NRS-11 (rating of 0–10) could be used. Following this rating, the reason for the rating should be ascertained. For adolescents, the questions could be posed directly to them.

Given the importance of patient and parent satisfaction in the uptake of any treatment and the importance of adherence to treatment, especially in recurrent and

chronic pain, we were surprised with the lack of research on this area in pediatric clinical trials. Such research is greatly needed.

Adverse Events and Symptoms

All clinical trials with pharmaceuticals are required to analyze and report adverse events. This is less common in behavioral clinical trials and precludes the understanding of the harm-benefit balance of these trials.²⁴ We recommend that adverse events be routinely ascertained in behavioral trials as well as those of biomedical treatments.

Treatment-emergent adverse events refer to newly emerging signs, symptoms, laboratory findings, or diseases that occur after treatment is initiated. All treatment emergent adverse events should be reported.

Serious adverse events—including death, hospitalization, prolongation of hospitalization, disability, or events requiring intervention to prevent these outcomes—are often quite apparent and require immediate reporting on appropriate forms to local ethics boards and regulatory agencies. Less serious adverse events are typically ascertained only if they are spontaneously reported by the patient or by the clinician caring for the patient. Often there is no particular strategy to measure either the occurrence or severity of the events. Measurement of both is important, as 2 interventions with similar occurrence of adverse events but different severity of adverse events are likely to be differentially accepted by patients.

The most typical method used for measuring adverse events can be characterized as passive, unstructured capture of events. Passive capture will minimize reporting of adverse events and may under represent the actual occurrence of adverse events.³ Standardized strategies to discern the occurrence and severity of adverse events will lead to more accurate reporting. One concern with using standard lists to enumerate adverse events is that they may prime affirmative responses. Thus, it is important to carefully balance the advantages and disadvantages of approaches that use open-ended inquiry compared with extensive lists of potential signs and symptoms.

No studies have been undertaken on standardized active capture of adverse events in the treatment of pain in the pediatric age range. We emphasize the need for research in this important area.

PedIMMPACT recognized that there is a lack of research on the assessment of adverse events in clinical trials with children and adolescents and that insufficient evidence exists for evidence-based recommendations. However, PedIMMPACT recommends that consideration be given in pediatric clinical trials to the active capture of symptoms and adverse events and that the severity and importance of each event be ascertained. Children older than 10 years may be able to be the prime informants. In younger children, parents or caregivers will have to be used to give proxy data. However, proxy data especially for nonobservable phenomena (eg, hot flashes, racing heart) may not be accurate. PedIMMPACT urges re-

searchers to develop appropriate measures in this very important area.

Physical Recovery

The domain of physical recovery includes those aspects of physical functioning that are influenced by the procedure or injury causing acute pain.⁴⁰ Physical recovery is not a relevant domain for short procedures, such as needle sticks. However, it is an appropriate domain that should be included for postsurgical trials and trials of pain management in injuries. The specific measure used in this domain in acute pain will depend on the study. For example, swallowing 50 mL of water might well be important in a study of pain management in tonsillectomy but not particularly relevant in a trial of pain in hernia repair. Possible measurements of the physical recovery domain include time to ambulation, time to resume swallowing, time to normal spirometry, oral intake, and time out of bed. The measure should be taken in a standardized way across all participants in a clinical trial. For example, assessment of swallowing should involve a specific set of instructions, a specific type and amount of fluid, and specified criteria for success.

Measures such as tolerance of physical therapy are problematic unless careful attention is paid to standardization. One child might be said to be intolerant of physical therapy because he or she did not want to go when asked, whereas another might be said to be intolerant to physiotherapy only if he or she cried and refused to continue with physical therapy. There is also a wide range of approaches to physical therapy. One center may have an aggressive and intrusive therapy program whereas another may have a less intense program.

Currently, there are no well-validated measures for assessing physical recovery in acute pediatric pain. Validated, standardized measures would simplify the job of the clinical trial investigator and facilitate comparisons across studies. The PedIMMPACT recommendation is that existing measures of physical recovery should be systematically assessed and that additional efforts should be devoted to developing measures of physical recovery that are appropriate for the purposes of evaluating interventions to control pain following procedures and injuries that have specific effects on physical functioning.

Emotional Response

The domain of emotional response includes all aspects of negative affect or distress secondary to pain. These emotions may include the affective component of pain as well as anxiety, depression, fear, distress, dysphoria, or unhappiness. The behavioral equivalents may be avoidance, withdrawal, or resistance. The maintenance of positive affect would also be considered as part of this domain.

If the affective component of pain is to be measured, on the basis of evidence, PedIMMPACT recommends use of the Adolescent Pediatric Pain Tool.⁶³ It is conceptually based on the McGill Pain Questionnaire,⁴⁹ uses a set of 56 words grouped according to sensory, affective, and evaluative qualities of pain, has been validated, and can be

used for children 8 years of age and over. In terms of single-item scales of the affective component of pain, we make an evidence-based recommendation to use the Facial Affective Scale⁴⁷ that consists of 9 faces that vary in the level of overt distress. This measure has been used with young children but it is not clear that the affective measures of pain are differentiated from intensity before about 8 to 10 years of age.

We recommend, on the basis of evidence, the following observational measures for the assessment of behavioral distress during procedures: Procedure Behavior Check List (PBCL)⁴⁴ and the Procedure Behavioral Rating Scale Revised (PBRS-R).³⁹ Both can be used for patients 1 year of age and older.

There are many measures of depression and anxiety in children. However, almost all validated measures have been used in the context of mental health problems and sometimes in the context of chronic illness or chronic pain. We recognized that simple measures of negative affect may be appropriate in the context of acute pain and that VAS or NRS measures have been used. However, we believed there was insufficient evidence to make a recommendation for the use in acute pain trials of VAS or NRS measures of negative affect at this time.

Economic Factors

PedIMMPACT determined that little research on economic factors has been undertaken in pediatric pain and thus no evidence-based recommendations were possible. However, as a consensus group, we recommend that economic factors should be considered for inclusion in clinical trials of interventions for acute pain. The exact measure used will depend on the purposes of the study but most likely will include both direct costs and indirect costs of different interventions. Direct costs include medical costs such as hospitalization, doctor's visits, and costs of drugs. Indirect costs include parental time off work, transportation costs, childcare, and incidental costs.

Measurement of these costs will vary from study to study depending on the goals of the study. For example, early discharge from hospital might be one of the primary outcomes in a study that was designed to reduce hospital time, whereas cost of medication might be an appropriate outcome in a comparison of an expensive and less expensive drug. However, it is important to ensure that the complete range of appropriate economic costs is included.

Rescue medication or remedication is an inherent part of many single dose trials but very variable. In addition, the handling of data when remedication occurs is inconsistent.⁴ PedIMMPACT made no recommendations on rescue medication other than that the reporting should be clear.

Chronic and Recurrent Pain: Domains and Measures

There are many definitions of chronic pain, but the best accepted is to consider it pain that has persisted for 3 months or more or beyond the expected period of healing.⁵¹ Chronic pain conditions that are found in chil-

Table 4. Core Outcome Domains Recommended for Consideration in Clinical Trials of Pediatric Chronic and Recurrent Pain

Pain intensity
Global judgment of satisfaction with treatment
Symptoms and adverse events
Physical functioning
Emotional functioning
Role functioning
Sleep
Economic factors

dren and adolescents include, for example, complex regional pain syndrome and chronic daily headache. Recurrent pain is pain that is episodic but reoccurs. Typically, a time frame within which episodes of pain recur of at least 3 months is used. Examples of recurrent pain include migraine headache, episodic sickle cell pain, recurrent abdominal pain, and recurrent limb pain. Chronic and recurrent pain conditions can coexist, as in some forms of sickle cell disease pain, or can be independent. Chronic and recurrent pain can occur for known or unknown reasons.

Virtually all intervention research in chronic and recurrent pain has been conducted with adolescents. This reflects the increasing prevalence of chronic and recurrent pain that occurs in that age group. Thus, our recommendations must be considered with caution as applied to research with younger age groups.

Table 4 contains the domains that we recommend should be considered for measurement in clinical trials of chronic or recurrent pain. These domains are very similar to those recommended for consideration in clinical trials of acute pain. We used slightly different terms in 2 domains. We use the term physical functioning in chronic and recurrent pain versus physical recovery in acute pain. Emotional functioning was used in chronic and recurrent pain versus emotional response in acute pain. These differences reflect the longer time course in chronic and recurrent pain than in acute pain. We also recommend consideration of 2 domains, role functioning and sleep, in clinical trials for chronic and recurrent pain that were not recommended in acute pain.

For many domains, the same or very similar measures are recommended for use in acute and chronic pain clinical trials. In these cases, we refer the reader back to the previous discussion in the acute pain section of this article. However, several aspects of measurement are different because of the differing time course of chronic and recurrent pain versus acute pain. The attendees at the consensus meeting had available a prepublication version of a review of measures used to assess the impact of chronic pain on adolescents.²¹

Pain Intensity

Aspects of the pain experience are typically the primary outcome domain in treatment of chronic and recurrent pain. However, there may be occasions, such as in

multidisciplinary chronic pain treatment, when the most important outcome domain is disability. Disability spans the domains of physical, emotional, and role functioning.

We recommend the same self-report measures for assessing pain intensity in chronic and recurrent pain clinical trials as we have for acute pain (Table 2). However, the method of collection of pain measures may be different. In chronic and recurrent pain, investigators may be most interested in pain over a longer time span than in acute pain. The number of pain-free days or days in which pain does not reach a specific level (eg, 3 on a 5-point scale) may also be pain intensity end points.

Pain diaries are commonly used to assess pain symptoms and response to treatment in children and adolescents with recurrent and chronic pain. Diary methodologies have been shown feasible and valid with several recurring pain conditions including pediatric headache and sickle cell disease.^{19,56,62} Most pain diaries use an NRS-6, in which reports are made on a 0 to 5 scale. Varying anchors do not seem to make a difference in ratings.⁶² Other diaries may use faces scales or a VAS. Prospective diary methodologies may increase the validity of children's pain reports in comparison to retrospective interviews³¹ that depend on retrospective summarizing and averaging of symptoms. However, retrospective reports more closely reflect the clinical situation in which a clinician asks questions such as "How have you been doing?"

The developmental level at which a child is capable of self-report via a daily diary has not been adequately studied; however, children as young as 6 years have been included in diary studies. Until recently, pain diary methodology in children relied exclusively on conventional paper-and-pencil measures, which have been associated with several limitations including poor compliance, missing data, hoarding of responses, and back and forward filling.^{56,68} Recently, the electronic diary methodology was evaluated in school-age children and adolescents with chronic pain.⁵⁷ Advantages were found for increasing the accuracy of children's diary responses as well as in compliance using the electronic format compared to the paper format. These advantages in compliance are similar to those found in adult pain patients.⁶⁸ Electronic diaries have the disadvantage of being expensive, incorporate a number of logistical issues that must be resolved, and there is limited experience in their use. To our knowledge, there have been no pediatric clinical trials that have compared the responsiveness with treatment of paper-and-pencil versus electronic diary assessments. Therefore, PedIMMPACT did not have specific recommendation about the use of electronic diaries, but this methodology shows promise for future study.

Global Judgment of Satisfaction With Treatment

There is insufficient research to make an evidence-based recommendation. We suggest the same approach for measuring global judgment of satisfaction with treatment in chronic and recurrent pain as in acute pain,

that is, a global question with specifiers. The context will be different as chronic and recurrent pain conditions have a much longer time course than acute pain. Moreover, since we recommend somewhat different domains for chronic and recurrent pain, our recommended questions are somewhat different. We suggest wording such as "Considering pain relief, symptoms, adverse events, how your child is doing physically, emotionally, and in his or her roles as a student and family member, sleep and economic factors (if appropriate), how satisfied were you with the treatment your child received?" A common metric such as a rating of 0 to 10 (NRS-11) could be used. For adolescents, the questions could be posed directly to them.

Symptoms and Adverse Events

We recommend the same approach for measuring symptoms and adverse events in chronic and recurrent pain as in acute pain. The context will be different as chronic and recurrent pain conditions have a much longer time course than acute pain.

Physical Functioning

Physical functioning in chronic and recurrent pain is different than physical recovery in acute pain. The domain in chronic and recurrent pain is most likely to be focused on activities of everyday life. Children and adolescents with pain may be impaired in normal activities such as sitting or walking or in more vigorous activities such as running and other sports.

We recommend the use of the Functional Disability Inventory that was developed by Walker et al⁸¹ for measuring physical functioning in school age children and adolescents. This measure asks about being able to do a range of everyday physical activities. The psychometric properties of the Functional Disability Inventory have been well established with different populations.^{14,61,78}

We recommend use of the PedsQL (www.pedsq.org) developed by Varni et al⁷⁷ for assessing the physical functioning domain in younger children (less than 7 years). The PedsQL is a multidimensional scale with both parent and child report versions that measures (1) Physical Functioning, (2) Emotional Functioning, (3) Social Functioning, and (4) School Functioning. It is suitable for children and adolescents from 2 to 18 years.

Emotional Functioning

The emotional functioning domain in chronic and recurrent pain trials most often refers to depression and anxiety. These 2 components of negative affect are often related. Both anxiety and depression are elevated in children with chronic and recurrent pain,⁵⁴ but most children with chronic or recurrent pain do not have clinical levels of anxiety or depression.⁴³

There are several well-established measures for child and adolescent depression. We recommend the Children's Depression Inventory⁴¹ because of its psychometric properties and widespread use in pediatric pain studies. It is applicable from ages 7 to 17 years. We also recommend the Revised Child Anxiety and Depression

Scale (RCADS) developed by Chorpita¹³ as a measure of anxiety and depression separately and of negative affect when these 2 scales are combined. As noted above, we also recommend the PedsQL⁷⁷ for assessment of emotional functioning in younger children.

Role Functioning

Chronic and recurrent pain can significantly interfere with the roles that children and adolescents, like adults, perform. These roles include being a student, friend, employee, and family member. The nature of these roles changes with development. For example, absence from a job is typically not relevant in younger children but may be of more importance in some adolescents.

We recommend the use of school attendance as a measure of role functioning in school-age children. Because school attendance is mandatory, absence from school is an important measure of fulfillment of the role of student. We also recommend the PedMIDAS,^{33,34} which has been validated for measurement of role functioning in children ages 6 to 18 years with persistent headache. We recommend the PedsQL⁷⁷ for assessment of role functioning across the age span.

Sleep

The role of sleep in chronic and recurrent pain has not been widely investigated in children and adolescents. However, preliminary evidence with pediatric populations⁵⁵ and studies from the adult literature⁴² suggest that sleep disruption is common in chronic and recurrent pain. Walters et al⁸² found that more than half of children with pain-related conditions report difficulties sleeping. Palermo and Kiska⁵⁵ used self-report questionnaires in samples of adolescents with headache, juvenile idiopathic arthritis, or sickle cell disease and found that depressive mood was predictive of sleep problems.

We recommend the inclusion of sleep as a core outcome domain to be considered in chronic and recurrent pain clinical trials. However, it is not possible to recommend a specific measure of this domain because few clinical trials have included this outcome.

Most sleep researchers agree that the gold standard for measurement of sleep is night time polysomnography. However, polysomnography is intrusive and unrealistically expensive for widespread use in clinical trials. Actigraphy is another validated strategy for measuring sleep that uses a movement sensor.² Sleep diaries in which the child (or parent) keeps a record of the time to go to bed, fall asleep, and wake up are used but little validation work has been done. Recently, Gaina et al²⁹ have validated the sleep diary against actigraphy in healthy children aged 13 and 14 years. Finally, instruments such as the Sleep Habits Questionnaire,⁵³ which survey school age children on their sleep, may be useful.

Economic Factors

As in acute pain, economic evaluations have not been widely used and typically have been simplistic, hypothetical, or retrospective rather than comprehensive and prospective. For example, Hicks et al³⁶ reported, based solely

on improvement in relation to contact time with a health care provider, that online treatment for headaches and recurrent abdominal pain was 5.5 times more cost-efficient than would be face-to-face treatment.

The challenge of determining total costs and benefits of treatments in children and adolescents is even greater than in adults. Many of the effects on productivity are indirect. For example, it is usually the parent or guardian who does the driving and misses work to take a child patient for treatment. The impact of prolonged absences from school may not be appreciated until the effects on college or vocational training have been felt.

Comprehensive examination of economic factors will require assistance of health system economists or other specialists. However, sophisticated cost analyses that prospectively account for all costs are needed. It is not possible to recommend specific measures of this domain at this time.

Composite Domains and Measures

Composite domains, for instance, health-related quality of life, could include several domains, such as physical functioning, emotional functioning, and role functioning. A disadvantage of composite domains is that it is more difficult to know the specific changes that have contributed to a difference between groups.

Composite measures, in which a single instrument measures several different domains, have the potential to reduce the burden on patients and to make data collection simpler and easier for all. On the other hand, the content of composite measures may not match the specific needs of a given study. In some cases there is psychometric evaluation of each component, whereas for other measures there is no psychometric evaluation of subscales (or there may not be subscales). The individual subscales will not be interpretable if they have not each been psychometrically evaluated.

Our recommendations could be met using composite domains or composite measures. However, the composite domain should be relevant for the particular study. The composite measure should have appropriate psychometric validation to answer the questions posed in the study.

Review by the International Pain Community

A 2-page summary of the PedIMMPACT recommendations described above was distributed to the Pediatric Pain Listserv (<http://pediatricpain.ca/ppml/>). The posting to the listserv invited interested parties to comment. Eight comments were received, reviewed by the first author, and integrated into the text.

Discussion

Our consensus group of individuals representing academic research, government funding and regulatory agencies, and the pharmaceutical industry used a variety of consensus strategies (Delphi poll, consensus meeting, commissioned reviews, and public input) to develop a set

of core outcome domains and measures that should be considered when designing clinical trials for acute or chronic pain in children over the age of 3 years.

We are not suggesting that each of these domains and measures be required for submission to regulatory agencies or for publication in a scientific journal. Moreover, we do not suggest that positive results must be found for all of the domains and measures for a treatment trial to be considered positive. Importantly, the use of multiple outcome measures does involve unique interpretational and statistical issues.⁵² Although discussion of these issues is beyond the scope of the present article, they were the focus of a separate IMMPACT meeting and publication of recommendations is forthcoming.

It should be noted that the PedIMMPACT group focused on acute as well as chronic and recurrent pain in children to recommend assessment approaches for these problems. Although there may be overlap in specific assessment strategies, that should not be taken to mean that the etiology of acute and chronic pain syndromes are thought to be the same. Clearly for the latter, contextual factors often take on greater importance and should be assessed. Furthermore, as we better understand mechanisms underlying the onset and maintenance of chronic pain, identification of more specific assessment strategies will ensue. To date, however, such condition-specific targeted assessment approaches have not been developed and validated.

There will be clinical trials for which 1 or more of our suggested domains or outcomes are not appropriate. Better measures may also be developed. Additional domains and measures may also be used as process measures. However, the reasons for selecting each measure used in a clinical trial should be detailed. We also urge that the reasons for not selecting recommended domains and measures be explicated.

Clinical trialists will choose to have different domains as primary, depending on the focus of the trial. For example, in a rehabilitation-oriented intervention for chronic pain in adolescents, the domain of pain intensity would not be a primary outcome if the focus of the intervention was on increasing function. However, pain intensity would likely be a secondary outcome domain.

The major strengths of this PedIMMPACT consensus process were the breadth and knowledge of the consensus group and the extensive efforts used to develop these recommendations. These efforts included Delphi polling, a consensus meeting, commissioned systematic reviews, and an international consultation.

A limitation of the PedIMMPACT consensus effort that needs to be acknowledged is that many areas lack key research studies. This dearth was especially evident with respect to the selection of specific measures for several of the recommended core outcome domains. As a result, the pediatric clinical trialist is left in a serious quandary. Should measures of unknown reliability and validity be used which may thus risk the interpretability of the trial? Or should important outcome domains be ignored because of the lack of reliable and valid measures, precluding a complete picture of the effects of an intervention?

Clearly, this dilemma can only be solved by development and testing of appropriate measures. In the meantime, we encourage pediatric pain investigators to consider seriously the value of collecting and analyzing the data that we recommend. In many instances, testing of reliability and validity can proceed hand in hand with the use of data as outcomes. The use of a standard set of domains and measures will permit the pooling of data and facilitate establishment of the adequacy of the psychometric properties of these instruments.

We are confident that this process of identifying common domains and measures will strengthen the effort to develop appropriate measures and increase the number and quality of clinical trials in pediatric pain. Because clinical trials are keystone knowledge transfer vehicles, this probably will improve the care given to our young patients.

These recommendations will have a finite lifespan. We hope that our recommendations for specific measures will lead to refinements and innovations as research evaluates the application of well-established measures to new populations and as new measures are developed

to fill the serious gaps in the literature we have identified. For example, a new composite measure of chronic pain in adolescents, the Bath Adolescent Pain Questionnaire, has been developed by researchers in Bath, United Kingdom,²² but there are insufficient data to recommend this measure at this time. Similarly, Palermo et al⁵⁸ developed the Child Activity Limitations Interview, a measure of pain-related functional impairment in school-age children and adolescents that shows promise but requires further research before its use can be recommended.

In summary, PedIMMPACT was an international consensus process that recommended specific domains and measures for clinical trials in acute and in chronic and recurrent pain. These recommendations are based on the best available research and expert opinion and were developed to improve the quality, interpretability, and aggregation of clinical trials for the treatment of pediatric patient with pain.

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