



# PEDIATRICS | ANALGESIA

## Designed Especially for Kids: Writing Protocols for Pediatric Analgesia Clinical Trials of Acute Pain

### ABSTRACT

Children are not little adults, and protocols for pediatric pain studies must take into account the unique needs of children to meet regulatory and ethical standards and protect this vulnerable population from untreated pain. Sponsors of pediatric analgesia clinical trials are tasked with designing studies that are both realistic to execute and sufficiently rigorous to support efficacy, safety, and dosing in children.



## Introduction

Performing research studies to evaluate analgesics in children is critical for determining the safety and efficacy of these medications in pediatric populations. According to the National Institutes of Health, 70 percent of the medicines given to children have only been tested in adults,<sup>1</sup> so there remains a significant need for pediatric-specific analgesic prescribing information based on clinical evidence to support efficacy, safety, and dosing in children. With the permanent extension of the Pediatric Research Equity Act of 2003 (PREA) in July 2012<sup>2</sup> and similar legislation in the European Union, an increasing number of sponsors are confronted with the task of conducting pediatric studies as an integral part of the analgesic development pathway.

Pediatric clinical trials typically require a different approach than adult clinical trials, as the differences between children and adults extend beyond anatomical and physiological differences

to communication barriers and emotional considerations. There are also significant developmental differences among children of different age groups.<sup>3</sup> In pediatric analgesia studies, the intrinsic scientific, ethical, and practical challenges of conducting clinical trials in children are further complicated by the need to protect these vulnerable patients from exposure to untreated pain.

Writing protocols for pediatric pain studies requires sponsors to do much more than simply cut and paste the protocol from adult trials. In order to meet regulatory and ethical standards, all aspects of the protocol – from study design and procedures to endpoints and informed consent – must be customized for children. A well-written protocol that takes into account the unique needs of children can facilitate regulatory approval, study enrollment, retention, and data quality. This paper provides insight on optimizing protocol writing for pediatric analgesia clinical trials of acute pain, with a focus on innovative study designs and outcome measures specific for children.

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## Pediatric analgesia trials are complicated by:

- 1 Lack of consensus on pediatric analgesia study designs and outcome measures
- 2 Limitations in pain assessment by surrogates
- 3 Limits on extrapolation of efficacy and risks from adult studies due to developmental differences

## Background

Analgesia clinical trials are inherently difficult due to the heterogeneous physiology and subjective measurement of pain, as well as marked variability among individuals in terms of pain perception and analgesic responsiveness.<sup>4,5</sup> These difficulties are magnified in clinical trials involving children, who may not be able to represent their own interests and whose participation in research with more than minimal risk must be justified by potential direct benefit.<sup>4,6,7</sup> In addition, pediatric analgesia trials are complicated by: (1) lack of consensus on pediatric analgesia study designs and outcome measures, (2) limitations in pain assessment by surrogates, and (3) limits on extrapolation of efficacy and risks from adult studies due to developmental differences.<sup>4,5</sup>

A pediatric analgesia clinical trial protocol must be carefully designed to meet the demands of scientific rigor and ethical conduct, as well as the unique needs of children. Optimizing pediatric acute pain protocols with carefully-planned, innovative study designs and outcome measures may help sponsors to address their regulatory and ethical obligations, while also improving study enrollment, retention, and data quality.

## Study design

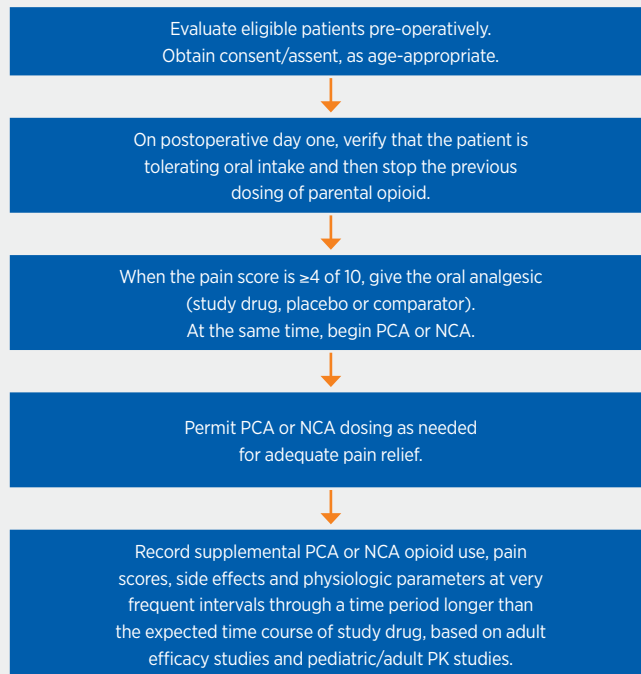
Parallel-group, placebo-controlled trial designs using pain scores as the primary efficacy outcome measure are commonly used to study analgesics in adults. However, these trials may be ethically problematic in children if exposure to more than minor pain occurs and if there are already effective, approved treatments for the condition being studied.<sup>4</sup> Pediatric analgesia study design must be appropriate for the stated objectives of the clinical trial and should consider the specific physiology, pharmacology, and normal daily activities for each age group being studied. Unsuitable designs can lead to slow enrollment and low retention, resulting in higher costs and approval delays.

## An alternative design: immediate rescue with patient- or nurse-controlled analgesia

In 2011, a scientific workshop sponsored by the U.S. Food and Drug Administration (FDA) proposed an alternative pediatric analgesic trial design integrating immediate rescue with patient-controlled analgesia (PCA) or nurse-controlled analgesia (NCA), using opioid sparing, rather than pain scores, as a surrogate primary efficacy endpoint.<sup>5</sup> Rescue-analgesic designs have been used successfully in pediatric analgesia efficacy trials evaluating nonsteroidal anti-inflammatory drugs (NSAIDs),<sup>8</sup> acetaminophen,<sup>9</sup> regional anesthesia,<sup>10</sup> oral opioids, and analgesic combinations<sup>11</sup> for acute, post-operative pain.

Immediate rescue designs maintain some of the scientific benefits of blinding, while addressing some of the ethical and practical challenges associated with parallel group, placebo-controlled designs. In these types of trials, patients with acute pain are enrolled and randomized to placebo and/or active comparator and study drug groups in a double-blind fashion. All study participants are given immediate access to either PCA or NCA, depending on age, motor capacity, and developmental readiness, for access to prompt rescue analgesia for unrelieved pain. Rescue analgesic dosing is based on weight and age. Although there is no consensus on what rescue analgesic should be used in this setting, the FDA scientific workshop suggested that there might be better discrimination between placebo and study drug using rescue opioids with more rapid onset and offset of action, such as alfentanil, fentanyl, or sufentanil.<sup>5</sup> In this immediate rescue design, differences in cumulative rescue dosing between placebo and active groups become the primary surrogate measures of efficacy and pain scores become secondary endpoints.<sup>5</sup> Comparison of analgesia sparing provides an objective measurement of the difference between the placebo and active control groups and does not require subjective judgments by the evaluator of the degree of pain for pain scores, which are more subjective and prone to bias or statistical variability.

**Figure 1: Outline of a pediatric oral analgesic efficacy trial design using opioid sparing as a primary endpoint.<sup>12</sup>**



### Advantages of PCA or NCA dosing

PCA dosing by family members is widely accepted in pediatric settings and there is established evidence of the safety of NCA in the management of acute pediatric pain.<sup>13,14,15</sup> The advantages of PCA and NCA include rapid relief of pain and the ability to deliver small incremental doses, thereby increasing assay sensitivity and reducing the risk of washing out differences between study groups compared to bolus rescue doses or continuous infusions.<sup>5</sup>

Eliminating basal infusions also minimizes the amount of analgesia delivered to study participants who experience little or no pain. However, protocols using an NCA and short-acting rescue opioid paradigm would require sufficient availability of study nurses to ensure prompt dosing at frequent intervals.

### Potential disadvantages of an immediate rescue design

From a scientific standpoint, rescue opioid use is an objective measure and cumulative rescue opioid use over a specified time period permits straightforward statistical comparisons between groups.<sup>5</sup> However, patients and surrogates tend to administer PCA or NCA as a compromise between pain and side effects, so opioid dosing may not be an accurate reflection of pain intensity. In addition, there may be complex pharmacodynamic interactions between the study drug and the rescue opioid which confound results.<sup>12</sup> Rescue opioid selection may also impact ethical or scientific aspects of the study. If onset of action is too slow or the dose is too low, study participants may experience pain for an excessive time period. If duration of action is too long, this may wash out group differences.<sup>12</sup>

### Other study design considerations

Sponsors may consider implementing pediatric analgesic safety and efficacy studies in two phases, with an open-label, single-dose, dose-selection phase followed by a double-blind, multiple-dose phase including an active comparator, using the immediate rescue design proposed by the FDA scientific workshop. In studies of oral analgesics, the study design should allow for intravenous analgesia until the patient has been cleared to transition to oral pain medication. This intravenous analgesia should be a medication that does not interfere with the measurement of metabolism of the study drug and does not have the study drug as a metabolite. In safety studies involving the youngest pediatric age groups, sponsors may consider beginning enrollment with older age groups and having an independent data monitoring committee evaluate safety from the data collected prior to proceeding with enrollment of the youngest patients.



### Pediatric Initiative on Methods, Measurement and Pain Assessment in Clinical Trials recommended core outcome domains for acute pain:

- 1 Pain intensity, frequency, duration, and extent
- 2 Satisfaction with treatment
- 3 Symptoms and adverse events
- 4 Physical recovery
- 5 Emotional recovery
- 6 Economic factors

### Criteria for evaluation

An analgesia clinical trial's safety and efficacy endpoints might need to be adjusted for pediatrics. Efficacy endpoints commonly used in adult studies might not translate directly to children, and safety follow-up must almost always be larger and longer to detect any adverse effects on development as children grow. In pediatric analgesia trials, safety evaluation should include assessments of cardiac, respiratory, and neurological function.

There are a multitude of established pediatric pain measures, including pain intensity self-reports such as the Visual Analog Scale (VAS) or Faces Pain Scale; questionnaires and diaries such as the Varni-Thompson Pediatric Pain Questionnaire; and behavioral observation tools such as the Procedure Behavioral Rating Scale and the Observational Scale of Behavioral Distress.<sup>16</sup> Unfortunately, pediatric pain measures are inconsistently used across clinical trials, making comparisons of results difficult. In addition, different pediatric pain measures are designed for different age groups, so studies involving a broad range of age groups might require multiple pain measures that cannot be directly compared.

In order to assist in comparison and promote evidence-based treatment, the Pediatric Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (Ped-IMMPACT) has recommended core outcome domains that should be considered when designing pediatric analgesia clinical trials. For acute pain, these domains are: (1) pain intensity, frequency, duration, and extent; (2) satisfaction with treatment; (3) symptoms and adverse events; (4) physical recovery; (5) emotional recovery; and (6) economic factors.<sup>17</sup>

There are three approaches to measuring pain in children – self-report, observational, and behavioral or psychological. Patient self-report in combination with one or more of the other approaches is ideal,<sup>18</sup> but the developmental, communication, and

cognitive capacities of the pediatric populations studied must be taken into consideration. For example, behavioral measures are the most useful pain intensity measures for clinical research involving infants, pre-verbal children, and non-verbal children.<sup>5</sup>

Choosing appropriate self-report pain measures can be a complicated process, as optimal pediatric pain scales vary by age group. A systematic review commissioned by Ped-IMMPACT revealed that, of the more than 30 pediatric self-report pain intensity measures that exist, only six are supported by well-established evidence of reliability and validity and no single scale is optimal across age groups or pain types.<sup>18</sup> To facilitate protocol design, Ped-IMMPACT has provided recommendations regarding the most psychometrically sound and feasible self-report and observational pain measures to be used in clinical trials based on age, development, and type of pain.<sup>19,20</sup>

### Study population

In order to define the risks and benefits of a drug, sponsors are required to conduct studies in all patient populations likely to use the drug. Sponsors are reminded that when Written Requests regarding pediatric studies are issued by the FDA, it is the sponsor's responsibility to vet study feasibility. Under PREA, sponsors can apply for full or partial waivers of pediatric assessments if certain criteria are met.<sup>21,22</sup> For example, the FDA may request studies in neonates, but if sponsors can provide sufficient justification that these studies are not feasible, or that the drug will not have meaningful health benefits in that pediatric population, sponsors can apply for a waiver.

Children undergoing elective inpatient surgery are a preferred population for the study of analgesics in acute pain, as these patients can be prospectively enrolled in clinical trials. Unlike emergent settings, where the patient is already in pain, elective surgery settings allow investigators to approach eligible patients

and their families in a more objective context. In addition, since these patients will be admitted to the hospital, compliance with the study drug can be monitored and data collection is easier and more complete.

For pediatric pain, relevant studies of pharmacokinetics (PK) and safety are needed to provide a rational basis for dose calculation and patient selection. When selecting which pediatric populations should be included in an analgesia clinical trial, sponsors should consider the study drug's mechanism of action in order to determine the data needed to evaluate drug metabolism, dose response, and toxicity. Drug classes with well-understood mechanisms of action are likely to have similar efficacy at similar effect site concentrations in children older than two years of age compared with adults, as pharmacodynamic responses to opioids, local anesthetics, acetaminophen, and nonsteroidal anti-inflammatory drugs appear to be substantially mature by age two years.<sup>5</sup> For these drugs, PK and safety data for adolescents can often be inferred from adult data, decreasing the need to enroll this age group for PK and safety studies.

For drugs with less well-understood mechanisms of action or less well-established efficacy in adults, pediatric efficacy, PK, and safety studies should be conducted if there is a potential clinical role for these drugs in infants and younger children. If PK studies are required, sponsors may consider using a population PK methodology, which requires a larger number of subjects but minimizes the number of blood samples required from each patient. Sponsors may also consider utilizing blood drop assays, which require only a few drops of blood to assay concentrations and do not require venous access. The FDA scientific workshop

offers provisional recommendations on selection of patient populations for different drug classes and clinical indications, based on pediatric pharmacoepidemiology, expert opinion, and enrollment experience in previous pediatric analgesia trials.<sup>5</sup>

### Treatment regimens

An important objective of pediatric pain studies is to provide information on safe and effective drug dosing scales based on body size and organ development. Extrapolation of adult dosing for children based on a weight-scaled approach can lead to significant under- or over-dosing,<sup>22</sup> so age-related trends in pharmacokinetics and pharmacodynamics must be considered when designing dosing protocols. Pharmacogenomic variability can also dramatically influence drug efficacy and tolerability, particularly for drugs that act partially or almost entirely as prodrugs.<sup>5</sup>

Since pediatric data must be provided for all indications in which the drug will be used, or is anticipated to be used, in children, pediatric analgesia studies must address multiple pharmaceutical forms and routes of administration. Sponsors may need to reformulate their drug for administration to children. Considerable preclinical time and effort may need to be devoted to determining whether the pediatric version of a drug is best delivered orally in syrup form, nasally, transdermally, rectally, or via injection. When sponsors develop pediatric oral formulations, they need formulations that are: (1) easy to administer and swallow; (2) acceptable in taste, volume, and frequency of administration; and (3) appropriate in dosage and strength, with adequate bioavailability.

**When sponsors develop pediatric oral formulations, they need formulations that are:**

- 1** Easy to administer and swallow
- 2** Acceptable in taste, volume, and frequency of administration
- 3** Appropriate in dosage and strength, with adequate bioavailability





## Other protocol writing considerations

Many other aspects of the pediatric analgesia clinical trial protocol, such as site selection, study procedures, and informed consent, may need to be adjusted in order to keep the particular needs of children in mind.

### Study sites

When selecting pediatric investigative sites, pediatric-specific expertise and experience, access to an adequate number of patients who meet study criteria, and ability of a site to accommodate children and their families are key considerations.

### Study procedures

To facilitate enrollment and minimize discomfort, pain, and anxiety, the frequency and intensity of procedures outlined in the protocol should be minimized, especially for infant studies. Invasive procedures should be used only when clinically necessary. Sponsors may consider specifying the use of local anesthesia prior to needle-based procedures or an intravenous catheter to minimize needle sticks. Sponsors are also reminded that allowable blood volume and frequency of blood sampling during clinical trials differs across age groups. In the EU, there are very specific limits on how much blood can be drawn from children during clinical trials.<sup>23</sup>

### Ethical and legal considerations

The standards for obtaining parental consent for a child to participate in a clinical trial and the age of consent vary from state to state and from country to country. While parental consent is a legally binding requirement for participation in pediatric trials, it is also necessary to have an assent form to be signed by the child. Assent assures the child understands the potential risks and benefits of the trial. If pediatric assent is required, the study protocol should outline how this will be solicited and allow for appropriately trained personnel to obtain it.

## Conclusion

Designing and conducting analgesia clinical trials in pediatric populations is a complex undertaking that requires sponsors to juggle scientific, practical, and ethical challenges. Given the many factors that complicate pediatric analgesia clinical trials of acute pain, sponsors should commit sufficient time and resources to formulating a sound development strategy that incorporates a protocol design customized for children. Understanding PREA requirements and obtaining advice on designing and executing protocols specifically for children helps sponsors to ensure that studies are sufficiently rigorous and realistic to execute, with the ultimate goal of providing safe and effective relief for children with pain.

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