Design Considerations for Single-Dose Analgesic Trials in Acute Pain
Recommendations from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials

ABSTRACT
When developing a clinical program to study an analgesic medication for acute pain, sponsors must take care to optimize the design of the early studies to increase the likelihood of successfully evaluating the drug’s efficacy and safety. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) provides guidance on the key design considerations applicable to acute pain clinical trials.
Background

Acute pain is generally defined as pain that occurs as a result of a known etiology and that is self-limiting over one to several days. Initial efficacy trials for medications intended to be used to treat acute pain are usually single-dose studies using a validated postsurgical model. The main objectives of these trials are: to explore a range of doses; to obtain data on onset, peak effect, and duration of effect; and to assess relative efficacy by comparing the study drug to a standard analgesic of known efficacy. When designing a clinical program to study an investigational drug with potential analgesic properties, sponsors must understand the drug’s pharmacokinetics, pharmacodynamics, target indications, and intended setting for use to select the most appropriate pain model, study design, and outcome measures.

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) is comprised of some of the most respected and influential researchers and clinicians in the field of pain medicine. In 2011, IMMPACT convened a meeting to put forth recommendations regarding the design of acute pain clinical trials. This meeting was attended by representatives from government, academia, industry, and patient advocacy groups. In this white paper, we summarize the key considerations and best practices governing the conduct of acute pain clinical trials, specifically with regard to study designs, assessment measures, and operational factors.
Pharmacology of the study drug

Preclinical or pre-human studies are extremely helpful in determining what clinical models might be the most valuable for initial proof-of-concept (POC) studies. Preclinical studies of the study drug may include in vitro assays, including receptor binding, human protein binding and primary hepatocyte in vitro systems, and animal models of acute pain. These studies can help determine whether a drug has anti-inflammatory properties, central or peripheral nervous-system activity or a novel mechanism of analgesic action. Preclinical studies also begin to characterize the pharmacokinetic (PK) properties of the drug and provide insight into the potential dosing regimen or optimal route of administration.1

It is worth collecting as much information as possible and investing time into analyzing the preclinical data to see if there are data that might help inform the design of a human POC study. The initial POC study should define the dose-response relationship, and comparator analgesics should be used as benchmarks for judging both assay sensitivity and the relative efficacy of the investigational drug.

Attributes of the drug

Early phase studies of the investigational drug help to define the primary attributes of the drug, including route of administration, pharmacokinetics (PK), and adverse event profile. PK studies include studies on bioavailability, single ascending dose (SAD), multiple ascending dose (MAD), and food effect. These studies provide some of the most revealing information needed for designing an acute pain study, especially for a new formulation of an already-approved drug. For example:

+ Does the new formulation have better bioavailability? If so, consider lowering the study dose.
+ Is the Cmax delayed significantly? For acute pain, pain relief should occur within an hour, but may be amenable to pre-operative dosing so that time to onset occurs simultaneously with offset of anesthesia. If Cmax is delayed significantly, the drug may not be suitable for treating acute pain.

Factors to consider in early-stage acute pain studies

Choice of model

When choosing the right model, sponsors must take into consideration all the attributes of the drug. If the drug is an opioid, a more severe pain model may be more appropriate for demonstrating differential efficacy of different doses. If the route of administration is oral, most models will suffice. However, if the drug is topical, the acute pain models that can be used are very limited.

The intended patient population or setting of medical use may also impact model selection. Intravenous products intended for the treatment of hospitalized patients are usually studied in more severe post-operative models, such as total knee replacement or total hip replacement where other co-morbidities must be taken into consideration. However, early POC or single-dose (SD) studies could be done in bunionectomy because of the pain severity and controlled environment.
If the PK of the drug show a slow onset, then sponsors may consider pre-operative dosing so the concentrations of the drug are available when anesthesia wears off. However, it is important to ensure that the study drug will not create surgical complications such as bleeding, impaired respiratory function, or decreased blood pressure. In addition, if PK studies demonstrate that certain doses of the drug cause adverse events to occur at a higher frequency, those doses will need to be avoided. Since lower doses may lead to less or no efficacy in more severe pain models, it may be necessary to adopt a higher-sensitivity model that creates milder pain in order to detect a signal.

### Inclusion of placebo arm

In acute pain trials – especially single-dose studies – inclusion of a placebo arm is essential. Ethical concerns raised by institutional review boards (IRBs), investigators, and patients can be addressed by:

- Clearly noting that placebo is being used in the study in the protocol and informed consent form
- Educating and training patients prior to drug administration about the inclusion of placebo as part of the study design so they report their pain as objectively as possible
- Making it clear that effective rescue medication is available on request for additional pain relief
- Assuring patients that no harm is expected to come from administration of placebo
- Training site staff on the placebo and its potential effect on patients

### Choice of active comparator

Whether or not an active comparator is needed may depend on the type of drug under investigation. For studies with reformulated, known analgesic drugs, it may not be necessary to include an active comparator. However, some formularies are requesting comparator studies for these drugs to determine their efficacy relative to less expensive, off-patent, or generic formulations of the same drug. Taking it a step further, including an active comparator as a positive control whenever possible helps to ensure model sensitivity.

For new chemical entities (NCEs), it is important to have at least one active comparator. In the absence of established standards, it is wise to choose a comparator with a mechanism of action that is similar to the treatment under study, as selecting an inappropriate standard may compromise the blinding of the study. If the investigational compound has a unique mechanism...
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of action, it would be ideal to include two active comparators that are known analgesics with different mechanisms of action (e.g., an opioid and an NSAID).

If the study will be used for regulatory purposes, choose a comparator that is already approved for the target indication using the dose – including any loading dose – that is in the drug labeling.

**Blinding**

Double-blind clinical supplies are the gold standard for acute pain clinical trials, as they help minimize placebo response and bias by investigators, site staff, and patients. Select comparators with the same route of administration to avoid the use of multiple placebos, if possible. When double blinding of supplies is not possible or if supplies are shipped in bulk to the sites, it may be necessary to use third-party, unblinded dosers whose sole purpose and only role in the study is to administer the drug.

**Single or multiple dose**

Both single-dose and multiple-dose studies have their pros and cons, which should be weighed carefully when designing an analgesic trial in acute pain. Keep in mind that both single-dose and multiple-dose trials will ultimately be required to adequately profile any new analgesic drug.1

Single-dose studies are valuable for establishing the efficacy, dose-response, onset, and duration of action of a novel medication. In addition, many of the models used in single-dose studies are amenable to PK/PD designs.2,3 However, single-dose studies cannot be used to definitively establish a dose regimen or the efficacy of the drug over several days or weeks.

Multiple-dose studies are best suited for pain models with longer-term pain. They are needed to provide a more complete safety profile for a novel compound, particularly if there is potential for cumulative toxicity.

**Figure 2. Pros and cons of single- and multiple-dose studies**

<table>
<thead>
<tr>
<th>Single-dose Studies</th>
<th>Multiple-dose Studies</th>
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<tbody>
<tr>
<td><strong>Pros</strong></td>
<td><strong>Pros</strong></td>
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<tr>
<td>Establish efficacy, dose-response, onset and duration of action</td>
<td>Establish a dose regimen</td>
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<tr>
<td>Amenable to PK/PD models</td>
<td>Establish efficacy of a drug over multiple days</td>
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<tr>
<td><strong>Cons</strong></td>
<td><strong>Cons</strong></td>
</tr>
<tr>
<td>Does not establish a dose regimen</td>
<td>Use of rescue and other confounding issues</td>
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<tr>
<td>Does not establish efficacy of a drug over multiple days</td>
<td>Needs to be a model with longer term durable pain</td>
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<td>Studies conducted at one center only are not generalizable to the target population</td>
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<td>No drop outs for intolerability</td>
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**Imputation of data following rescue**

There are three potential ways to account for data following administration of rescue medication in single-dose analgesic trials in acute pain:

1. Last observation carried forward (LOCF). This method carries forward the pain score just prior to rescue medication for all subsequent scheduled assessments.

2. Baseline observation carried forward (BOCF). With this method, the baseline pain score is carried forward for all scheduled assessments after rescue medication.

3. Worst observation carried forward (WOCF). This method carries forward the worst-observed score for all scheduled assessment following rescue medication.

For multiple-dose studies, the most commonly used way for imputing data following rescue is windowed LOCF. In this method, the pain score just prior to rescue medication is carried forward for all scheduled assessments after rescue medication, but only for the duration of time that pain intensity is thought
to be affected by the rescue medication. Another method that has been incorporated as a secondary or exploratory analysis, particularly for implantable drugs or devices, derives sensitive data to account for rescue medication used by patients multiple times over several days. This method requires integration of pain scores and the total amount of standardized rescue medication administered.

**Outcome measures in acute-pain studies**

The major efficacy domains assessed in acute-pain trials are pain intensity and pain relief. The primary outcomes measures that should be included in acute pain studies are:

1. **Pain intensity on a categorical Verbal Rating Scale** (VRS – none, mild, moderate, and severe) for qualification to get randomized in the study and for stratification purposes.

2. **Pain intensity on a Numeric Rating Scale** (NRS – a point scale of zero to 10) for baseline pain intensity for all subsequent scheduled pain intensity assessments. Baseline pain intensity is the benchmark against which all subsequent assessments are compared. The Visual Analogue Scale (VAS) is a potential alternative measure, but patients find it confusing as they are not familiar with the concept.

3. **Pain relief on a categorical scale** (none, a little, some, a lot, and complete) for all scheduled assessments after baseline.

Other measures of importance are time-to-onset of pain relief, reported adverse events, and the patient global assessment provided by the patient at the end of the study.

A standardized and reliable method for measuring onset of pain relief is the two-stopwatch method. In this method, two stopwatches are started when the initial dose of study drug is administered. The patient is instructed to stop the first watch when they first feel any pain relief (Time-to-Perceptible pain relief) and to stop the second watch when they have pain relief that is meaningful to them (Time-to-Meaningful pain relief).

The global assessment is the patient’s overall evaluation of the study medication, and it is generally assessed using a five-point categorical scale (poor, fair, good, very good, or excellent). However, an NRS, VAS, or Patient Global Impression of Change measure can also be used to capture a patient’s perceptions of the overall improvement in their pain since treatment initiation.

**Recommendations**

The IMMPACT group put forth 10 best practices and principles that should be factored into every short-duration, acute-pain analgesia trial:

1. **Use a placebo treatment group and an active comparator.** This design is recommended to assess the assay sensitivity of the trial and to benchmark the investigational treatment.

2. **Select an appropriate active comparator.** Choosing an active comparator that has a similar mechanism of action, route of administration, and adverse event profile to the investigational treatment assists in maintaining blinding to treatment assignment. For example, where possible, compare opioids to opioids and NSAIDs to NSAIDs.

3. **Utilize a randomized treatment allocation.** Acute pain trials should be conducted using randomized treatment allocation, typically as parallel group designs. Crossover design studies are generally not recommended in the acute pain setting due to the longer study durations required for such studies and the often self-limiting nature of the acute pain condition.

4. **Establish sufficient baseline pain.** Baseline pain intensity must be at least moderate to severe before initial dosing. Moderate to severe pain is defined as a VAS score greater of at least 50 mm or an NRS score of five or greater. Using moderate
to severe baseline pain as a trigger for initial dosing ensures that there is a sufficient baseline allow a treatment effect to manifest. Sponsors may also want to consider stratifying study participants by baseline pain so that comparable percentages of subjects with moderate and severe pain are assigned to each treatment group.

5. Include NRS measure of pain intensity or pain relief. These measures are easily and rapidly performed in most clinical and research settings, and should be included in all acute-pain clinical trials involving adults. Alternative scales such as VAS and VRS may have less assay sensitivity.

6. Schedule multiple early observation times. For treatment of acute pain, early onset of efficacy is critical. Setting multiple early observation times over the first 60 - 120 minutes after dosing helps to profile the onset of analgesic efficacy.

7. Collect and report all adverse events. All adverse events that are observed and reported must be recorded as they occur. The report must include a description of the adverse event, including its time course, duration, severity, need for treatment, and perceived relationship to the study drug. It is also important to describe in detail the methods used to collect the adverse event data.

8. Treat all study participants with identical regimens. All participants in acute pain trials should be treated with identical surgical, anesthetic, and perioperative care regimens. It is useful to include predetermined scripts for interviewing participants and answering their questions about the study methodology.

9. Assign the same coordinator to a patient. Whenever feasible, the same coordinator should be assigned to a participant throughout the evaluation period. Study participants should be isolated from each other and the study environment should be controlled as much as possible.

10. Employ trained study personnel. Only trained study personnel who use standardized pain-assessment methods should be used in acute pain trials.

Conclusion
Sponsors and investigators who are studying the effects of analgesic medications in acute pain are faced with a variety of study-design and methodological issues. By taking best practices and principles into consideration during the planning phase of clinical development, sponsors can increase their likelihood of conducting a successful study.

References
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