Clinical Outcome Assessments for Acute Pain Therapeutics and PTN/NICHD clinical trials for study of off-patent therapeutics

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KOA-APRIC

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Overview

I. CDER PFDD program

II. COA-APTIC overarching goals and objectives

III. COA-APTIC learnings to date

IV. Introduction to The Pediatric Trials Network (PTN) and its approach to studying off-patent analgesics in children and adolescents
CDER Patient focused drug development program

- “Systematic approach to ensure that patients’ experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation.”

- CDER Pilot Grant Program: Standard Core Clinical Outcome Assessments (COAs) and their Related Endpoints:
  - Develop methodologically-sound data collection tools are developed for use in clinical trials of an investigational therapy
  - Serve as a direct source of evidence regarding the benefits and risks of a drug
Identify or develop core sets of high-quality Clinical Outcome Assessments and endpoints to assess acute pain in clinical trials of pain therapeutics in infants and young children (0 – 3 years).
Two Phases of Project

○ UG3 Phase – Planning Phase
  • Indepth Qualitative Interviews:
    – Pediatric Clinicians
    – Caregivers
  • Literature reviews
    – Acute pain COAs and endpoints in pediatric trials
    – Validation evidence for COAs
  • Design Studies for UH3 Phase

○ UH3 Phase – Implementation Phase
  • Carry-out both qualitative and quantitative studies to validate COAs and endpoints for acute pain
Goal: To identify important aspects of acute pain assessment, treatment, and response to treatment in children who are 0 to <3 years of age, from a clinician and caregiver perspective.

Methods:
- One-hour, phone based Concept Elicitation Interview

Topics of Interest
- Pain expression behaviors and variation
- Types of non-pain distress (e.g. fear / anxiety)
- Differentiation between pain and non-pain distress
- Interventions for pain and non-pain distress
- Pain scales used
- Additional concepts to measure alongside pain (e.g. sedative effect)

Age categories: 0-<2 mo, 2 mo-<1 yr, 1 yr-<3 yr
Primary research question:

- What endpoints are being used to evaluate interventions for acute pain and/or distress in infants and young children (0 to <3 years old)?
Literature Review of Clinical Trials for Acute Pain Endpoints

Title and Abstract Screening: 16,271 articles (completed)
Excluded: 11,681

Full-Text Screening: 4,590 articles (completed)
Excluded: 2,515

Data Extraction: 1,313 articles (in progress)

Excluded: 442 conflicts left to resolve

Screened Out: 320

Screening for priority articles to extract first:
- Randomized Controlled Clinical Trial
- Acute pain outcome (must have a COA)
Literature Review of Existing COAs

- Characteristics
  - Name and abbreviation
  - Construct (e.g. distress (in ventilated children))
  - Type (ClinRo, ObsRo, etc)
  - Age range
  - Number of items
  - Response options (scale 1 – 5, presence or absence, etc)
  - Recall period
  - Time to complete
  - Score range (e.g. total score)
  - Languages
  - Additional comments
Lessons Learned

- Clinician and caregiver data highly variable and almost always dependent on context
- Existing COAs have limitations
  - Sparse content validity
  - No standardization for how long you monitor child for consolability; limited rigor around observation time
  - Lack of information on how individual items are performing
  - Very young kids are excluded from validity data
  - Prior validation studies failed to include racially and ethnically diverse populations
  - Many validation studies do not blind the raters to the painful event

- Minimal information on caregiver measures (ObsRo) but considerable potential benefit
Next steps to address existing gaps: prospective study

- Recruit a racially and ethnically diverse sample
- Mix of known very painful, minimally painful, non-painful but distressing procedures
- Prospective evaluation with multiple in-person and video raters
- Multiple ClinRo and new ObsRo
- Short term follow-up (multiple pain/distress states in one person)
- Two critical questions among many
  - Differentiate pain from distress
  - Differentiate levels of pain severity
Pediatric Trials Network (PTN)

- Sponsored by Eunice Kennedy Shriver National Institute for Child Health and Human Development
- “Create an infrastructure for investigators to conduct trials that improve pediatric labeling and child health.”
- Focus on off-patent therapeutics
- >100 clinical sites
- >40 clinical studies
- Multiple collaborators
- Innovative designs, thoughtful about feasibility
## PTN Successes

<table>
<thead>
<tr>
<th>Therapeutic Areas</th>
<th>18 therapeutic areas studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled Participants</td>
<td>&gt;11,000 enrolled participants</td>
</tr>
<tr>
<td>FDA Submissions</td>
<td>26 product submissions to FDA</td>
</tr>
<tr>
<td>Label Changes</td>
<td>15 label changes</td>
</tr>
</tbody>
</table>

**Therapeutic Areas**

- Heart health
- Cancer treatment
- Mental health
- Infectious disease
- Chronic conditions
- Chronic kidney disease
- Diabetes
- Osteoarthritis
- Pain management
- Pulmonary health
- Neurology
- Nephrology
- Gastroenterology
- Cardiology
- Oncology
- Neurology
- Endocrinology
- Ophthalmology
- Pulmonology

**Enrolled Participants**

- >11,000 participants

**FDA Submissions**

- 26 product submissions to FDA

**Label Changes**

- 15 label changes
PTN sites
Pharmacokinetics of Anesthetics and Analgesics in Children and Adolescents (ANA01): Overall Study Design

- Pragmatic, multi-drug protocol of anesthetics and analgesics
- Similar baseline procedures for each drug
- Children 2 - <18 years of age (up to 75 participants/drug; 3 age cohorts and cohort with obesity)
- Drugs administered per routine medical care for indications labeled in adults
- PK, safety, confirmatory exposure-response relationships, and pediatric dose identification to match adult exposures
- Extrapolation from adult data per published recommendations

## Morphine: Full Extrapolation

<table>
<thead>
<tr>
<th>Population</th>
<th>PK</th>
<th>Short-term safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 2-&lt;18 years, receiving IV dosing via bolus or infusion for severe pain</td>
<td>Plasma concentration-time profile</td>
<td>AEs (Vital signs, nausea, hypoventilation, QTc prolongation)</td>
</tr>
</tbody>
</table>

### Proposed label changes:
1. Pediatric indication (age 2-<18) for management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate
Oxycodone

- Included: Receiving oxycodone (solution or tablet) for severe pain

- Excluded:
  - Received extended release oral oxycodone tablet
  - Receiving oxycodone for chronic pain
  - Tolerant to opioids, defined as a participant who has received daily opioids for at least the 7 days prior to the PK sampling dose at a dose of at least 1mg/kg of oral morphine (or equivalent dose of other opioid)
Labeling requirements

• Safety data across each of first three doses
  – Blood pressure
    *Every 30 minutes for the first hour*
  – Heart rate and Pulse oximetry
    *every 15 minutes for the first hour, then every hour until four hours after the dose*
  – Any clinically significant desaturation or value below 92% within the 4-hour time period that does not represent artifact on continuous pulse oximetry

• Identify dose that matches adult exposure
• Confirmatory exposure-response
Clinical reality

- Thousands of children receive oxycodone per standard of care every year
- Receipt of oral medication often means you are on the mend→ decreased monitoring and preparing to go home

*How do we get this done?*
The PTN solution

- Sites enroll in two cohorts:
  - Dose 1 and dose 2
  - Dose 1 and dose 3

- Flexible windows for PK sampling allows timing with standard of care blood draws (contribute to population PK model)

- Variable payment model for number of samples, timing of samples, etc

- Safety assessments recorded from medical record/electronic monitoring

- Assessment of analgesia:

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Baseline (within 1 hour prior to first DOI dose)</th>
<th>Post-dose (15 (±5), 30 (±10), 45 (±10), 60, 120, 180, and 240 (±15) minutes after DOI dose)a</th>
<th>Age Range (years)b</th>
<th>Ability to Self-Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numeric Rating Scale</td>
<td>X</td>
<td>X</td>
<td>&gt;8 to &lt;18</td>
<td>Able</td>
</tr>
<tr>
<td>Faces Pain Scale-Revised</td>
<td>X</td>
<td>X</td>
<td>3 to 12</td>
<td>Able</td>
</tr>
<tr>
<td>FLACC</td>
<td>X</td>
<td>X</td>
<td>2 to &lt;18</td>
<td>Unable</td>
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Questions
Contact information

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- For more information about the PTN and COA-APTIC:
  - https://pediatrictrials.org/
  - https://dcri.org/coa-aptic/