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

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COA-APTIC

Kanecia Zimmerman, MD, MPH
Duke University School of Medicine
Duke Clinical Research Institute

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

COA-APTIC Overarching Goals and Objectives

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

Concept Elicitation: Clinicians & Caregivers

- 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

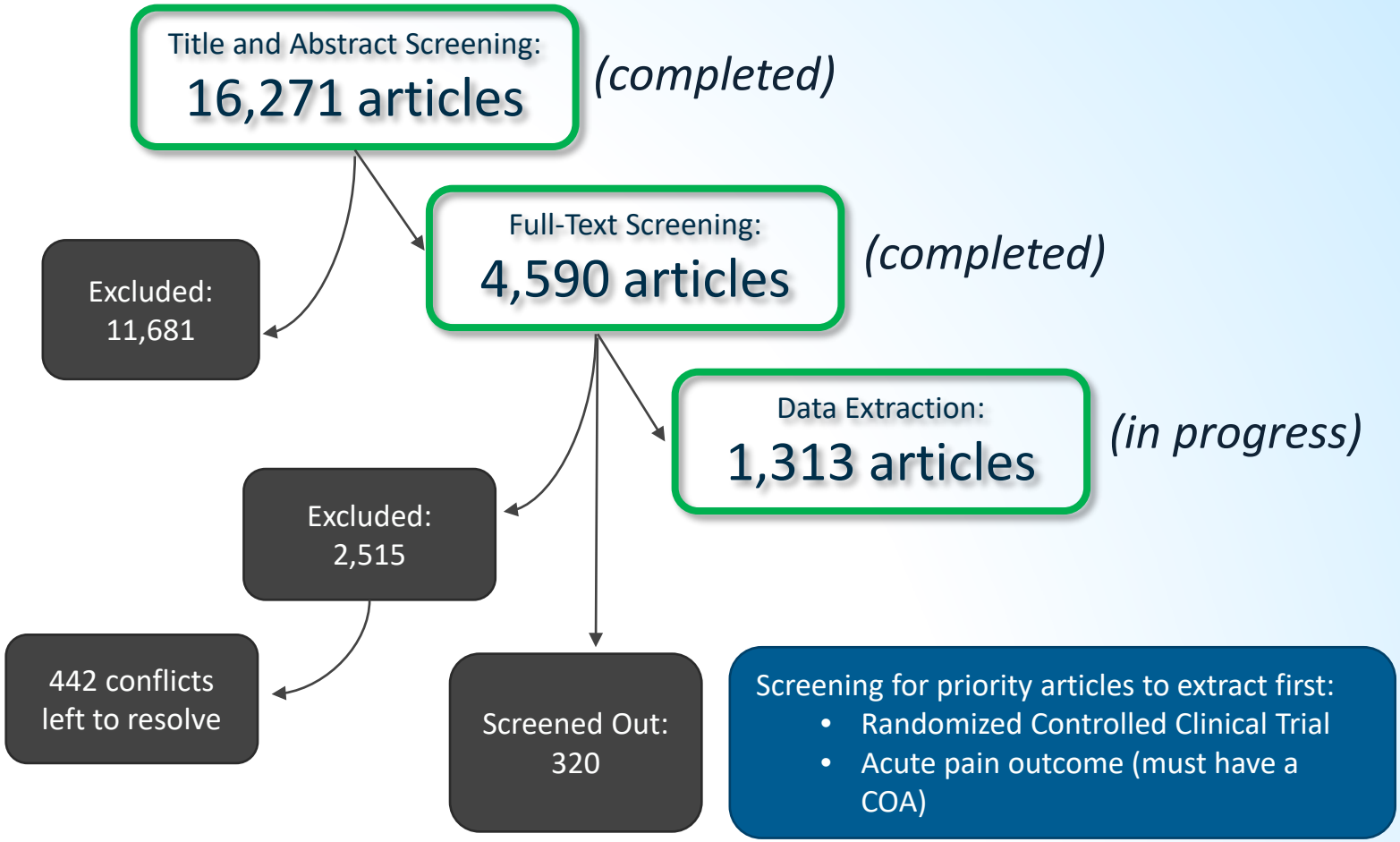
Pain expression behaviors and variation	Interventions for pain and non-pain distress
Types of non-pain distress (e.g. fear / anxiety)	Pain scales used
Differentiation between pain and non-pain distress	Additional concepts to measure alongside pain (e.g. sedative effect)

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

Literature Review

- **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



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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

Therapeutic Areas	**18** therapeutic areas studied 
Enrolled Participants	**>11,000** enrolled participants 
FDA Submissions	**26** product submissions to FDA 
Label Changes	**15** label changes 

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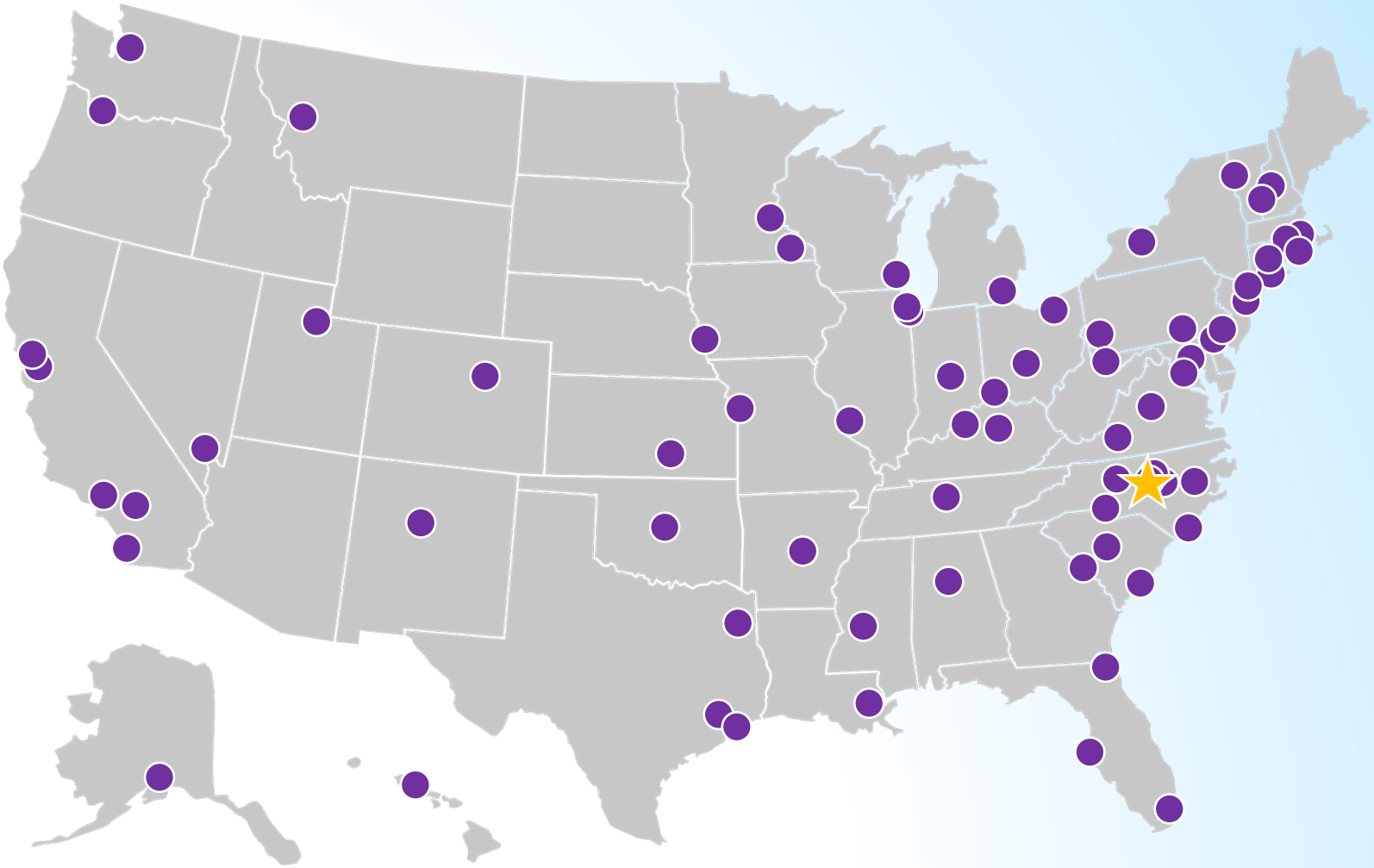
PTN sites



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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[1]

[1]Dunne J, Rodriguez W, Murphy D, Beasley N, Burckart G, Filie J, Lewis L, Sachs H, Sheridan P, Starke P, and Yao L. Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs. *Pediatrics* 2011 Nov;128(5):e1242-9.

Morphine: Full Extrapolation

Population	PK	Short-term safety
Age 2-<18 years, receiving IV dosing via bolus or infusion for severe pain	Plasma concentration-time profile	AEs (Vital signs, nausea, hypoventilation, QTc prolongation)

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:

Assessment	Baseline (within 1 hour prior to first DOI dose)	Post-dose (15 (±5), 30 (±10), 45 (±10), 60, 120, 180, and 240 (±15) minutes after DOI dose)[a]	Age Range (years)[b]	Ability to Self-Report
Numeric Rating Scale	X	X	>8 to <18	Able
Faces Pain Scale-Revised	X	X	3 to 12	Able
FLACC	X	X	2 to <18	Unable

Questions

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Contact information

- Kanecia Zimmerman, MD MPH
  - Kanecia.Zimmerman@duke.edu

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