Application of Master Protocols to Pediatric Anesthetics and Analgesics

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Pediatric Trials Network
Leading the Way

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

A project of the Best Pharmaceuticals for Children Act

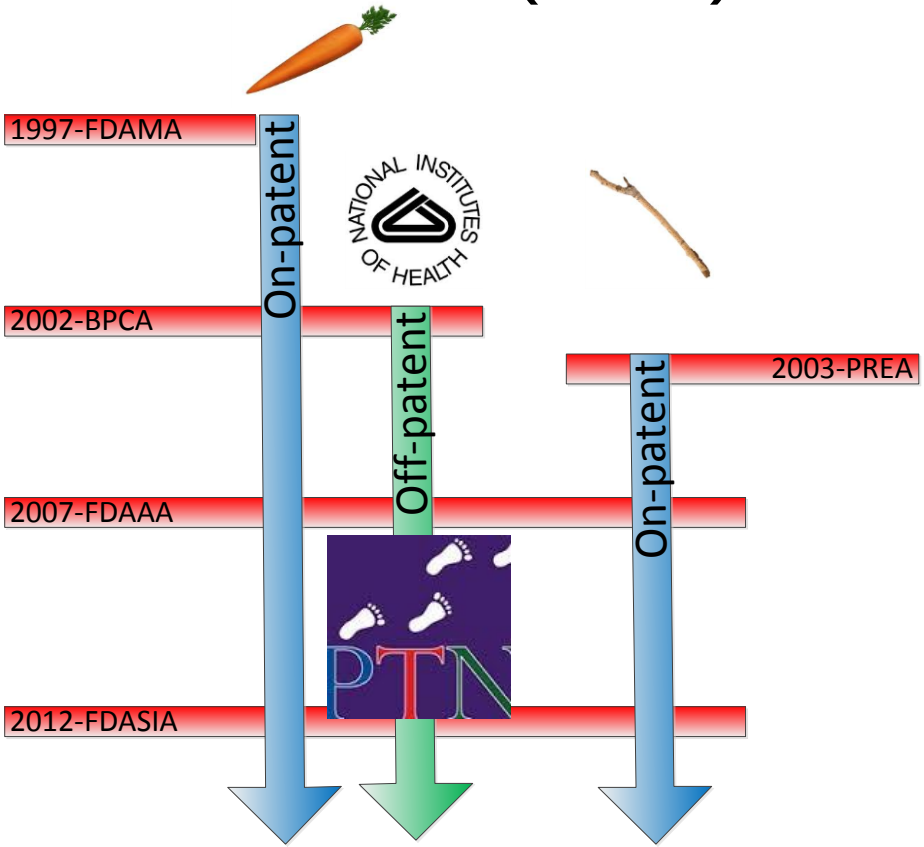
Disclosures

- None

Overview

- Example of master protocol from the NICHD Pediatric Trials Network
  - Anesthetics and analgesics in children
- Extrapolation of efficacy
- Resultant study design
- Leveraging existing data and networks

Pediatric Trials Network (PTN)



Challenges of pediatric trials

- Sick population
- Low rates of parental informed consent
- Limited blood volume
- Rigid sampling schedules

Minimal Risk Methods used in PK Trials in Children

- Low PK sample volume
  - Ultra-low volume multiplex assays
  - Dried blood spots (DBS)
- Sparse and supplemental sampling
  - Scavenge
  - Population PK analyses
- Sampling windows
- Uncontrolled environment
  - Sampling per standard of care
- Leveraging existing data
- **Master protocols**

PTN and master protocols

- POPS: Opportunistic PK study
- Staph Trio
- SCAMP
- LAPS
- Anesthetics and Analgesics

Anesthetics and analgesics in children

- Anesthesia and analgesia in infants and children are frequently used to alleviate pain and anxiety and provide adequate conditions for surgery
- Dosing and safety of many of these drugs in children are supported by limited or no data
- Multiple short and long term side effects are reported, but the majority of the reports come from animal data or retrospective clinical studies

Study Design Overview

Master protocol to study multiple anesthetics and analgesics in children

Objectives

- Determine PK of selected anesthetics and analgesics
- Evaluate the safety of anesthetics and analgesics
- Assess efficacy via surrogate endpoints (e.g., pain scores, PD endpoints)

Study design

- Prospective, multi-center, open label PK and safety trial
- Participants: 50 children per drug
- Intervention: Off patent anesthetics and analgesics that are prescribed per standard of care
- Duration of participation: ~7 days
  - 1-3 days of PK sampling
  - Up to 7 days of safety monitoring

Initial drugs

Analgesics

Hydromorphone

- Used for analgesia and anesthesia in children
- No FDA label

Anesthetics

Ketamine

- Used for analgesia and anesthesia in children
- No FDA label <16y

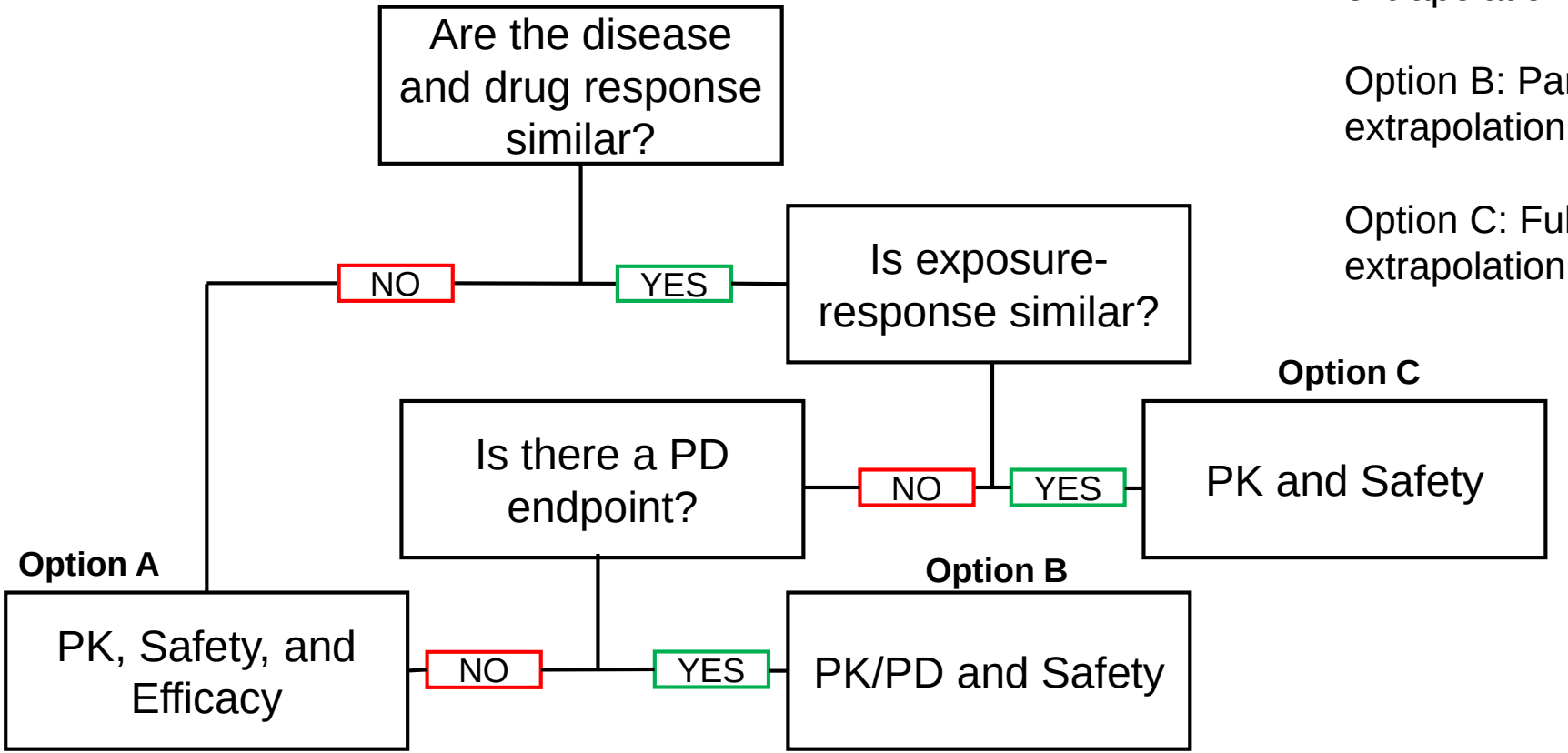
Labeling Pathway?

Pediatric Decision Tree

Option A: No extrapolation

Option B: Partial extrapolation

Option C: Full extrapolation



Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs

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- 166 products
  - No extrapolation: 29 (17%)
  - Partial extrapolation: 113 (78%)
  - Full extrapolation: 24 (14%)

Extrapolation of efficacy: Analgesics

Complete Extrapolation of Efficacy

- Initially FDA did not accept that efficacy in children is same as adults
- FDA now accepts that it is appropriate to extrapolate efficacy down to age 2-4 years for
  - Opioids
  - NSAIDs
  - Acetaminophen
  - Local anesthetics

Extrapolation of Analgesics: Methadone

- PK and Safety of Methadone in Children
- Mixed indications (analgesia, opiate detoxification)
- Submitted data to FDA
- Requested surrogate measures of efficacy
  - Pain scores
  - Use of rescue medications

Implications for Anesthetics and Analgesics Master Protocol

- Collect age appropriate pain scores
- Record rescue medications

Extrapolation of efficacy: Anesthetics

Partial Extrapolation of Efficacy

- FDA considers anesthetics to be equally effective in children
  - Administered in controlled environment
  - Titrated to effect
- Focus of studies is Dosing (PK and exposure response) and Safety

Anesthetics – efficacy predicted with PD endpoint

- PK - Exposure match with adults
- Safety
- Efficacy
  - Collect sedation scores
  - Record rescue/concomitant medications

Study Population

Inclusion Criteria

- Children aged 2-<18 years
  - Target populations without labeling or for which data are scant
- Prescribed the drug of interest per standard of care

Exclusion Criteria

- Known pregnancy
- Extracorporeal life support (e.g., ECMO, dialysis)

Study Procedures	Baseline Assessments -72h to Day 0	Study Dose Administration Day 1-4	Post-dose Monitoring Day 2-8
Informed Consent	X		
Demographics	X		
Medical History	X		
Physical Exam	X		
Genotyping	X		
Laboratory evaluation	X	X	X
Dose Recording	X	X	X
PK sampling		X	
Adverse Events		X	X
Concomitant meds		X	X
Efficacy assessments		X	X

PK Sampling

- Timed PK sampling
  - 4-6 samples per child
  - Sample windows
- Alternative matrices
  - Dried Blood Spots
  - Scavenge Samples
  - Cerebrospinal fluid*
  - Urine*

* If collected per SOC

Surrogate Efficacy Measures

Pain

- Pain intensity scores
- Rescue analgesics

Sedation

- Sedation scores
- Rescue/concomitant anesthetics

PD endpoints

- Exposures associated with efficacy

PK Analysis Plan

- Collect “rich” timed PK data
- Combine with data from other trials
  - POPS
    - PK and Safety of Methadone (n=26)
    - POPS (n=65 methadone participants)
  - Other investigators

Lessons Learned and Future Directions

- Master protocols enhance efficiency
- Meet with FDA early to discuss study design
- Leverage existing data
  - Study X + PK and safety data from POPS
- Collaborate with existing networks
  - MASK Trial – PI David Warner
  - Pediatric Research Network for Pain – PI Gary Walco
- Long term safety of anesthetics and analgesics