Becoming A Resource:

Developing a Framework that Enables Pediatric Drug Development

NIH 409I BPCA Program

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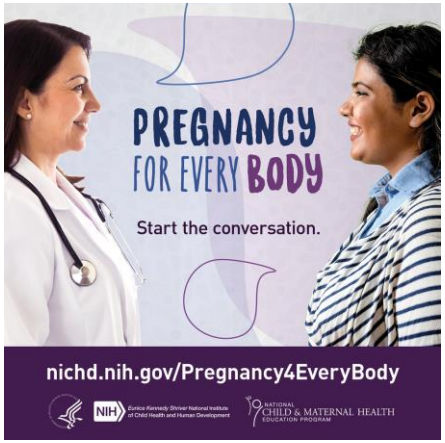
Perdita…

- Has no financial disclosures
- Will not be discussing any proprietary information

NICHD Mission

- To lead research and training to understand human development, improve reproductive health, enhance the lives of children and adolescents, and optimize abilities for all.
  - More population focused, Not specifically disease focused

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Group



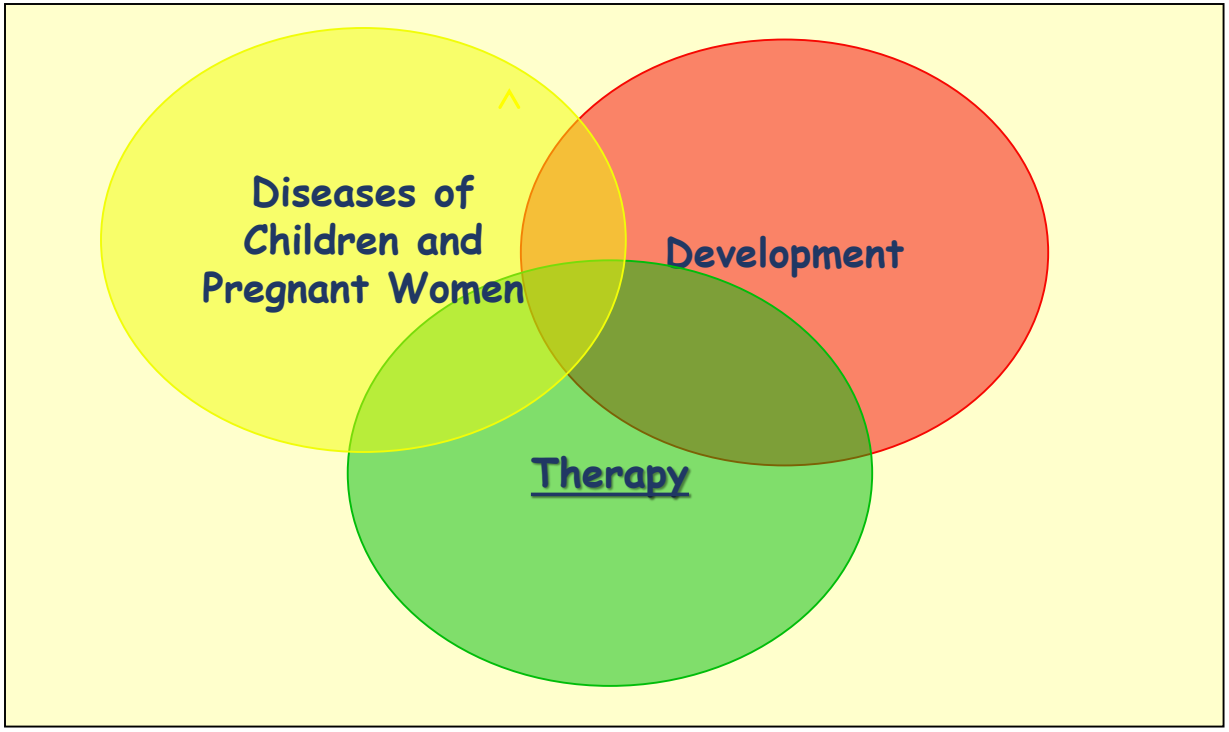
Intramural Division:
Conducting Research

Extramural Division:
Funding Research

https://www.nichd.nih.gov/about/org/der/branches

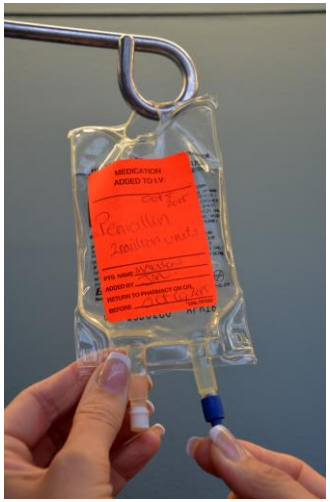
Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB)

Pediatric and Maternal Therapeutics



Therapeutics: Drug Development, Biologics, Devices
Basic, Translational, and Clinical Research

Drug Development



In general, pediatric drug development can be slow and patchy

- Primarily driven by adult drug development
- Problematic when the pediatric condition is different from the adult condition
- This model ultimately neglects neonates and rare pediatric conditions

Pediatric Drug Development: Challenges and Opportunities. Spandoni, C. Current Therapeutic Research. Vol 90. 2019

Considerations: Unique Challenges

Did You Know

Research in children is conducted only after taking special ethical and medical considerations into account.

Small patient populations make it challenging to recruit/enroll in clinical trials.

Pediatric cancers are especially rare, with about 11,000 children in the United States under the age of 14 expecting to be diagnosed with cancer in 2020.

Source: "Childhood Cancers," National Cancer Institute, January 28, 2019

Diseases in children are often biologically different than those in adults, requiring special assessments of medicine safety and efficacy.

Children respond differently to medicines than adults, requiring unique dosage and formulation considerations.

https://www.phrma.org/policy-issues/Research-and-Development/Pediatrics

Experience is generally repetitious

Implications of Unique challenges

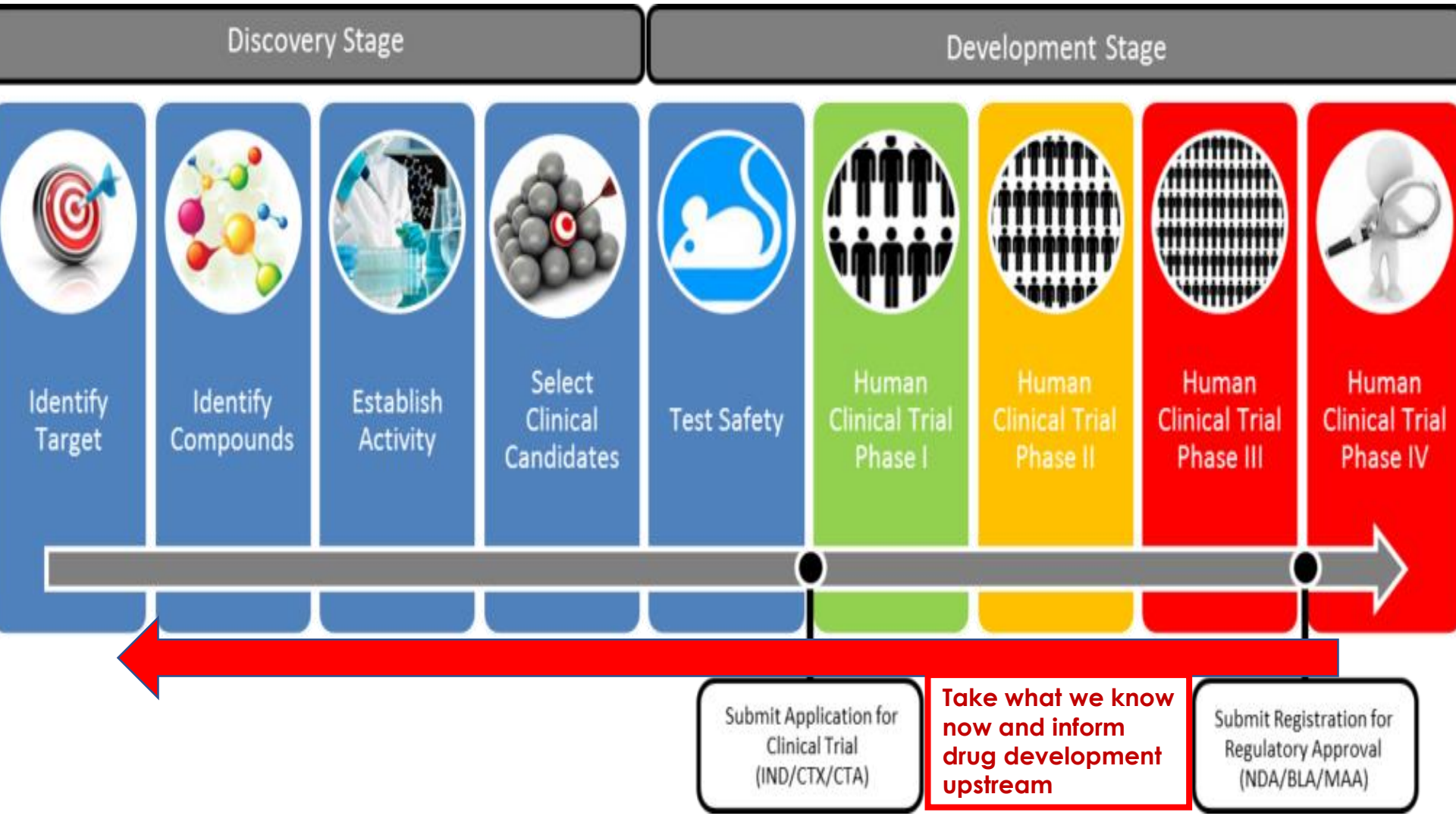
***Drug Development Tools Missing**
Delays in the availability of data to support usage

***Pharmacology (PK/PD) afterthought**
Market failures
Uncertainty of dosing, safety

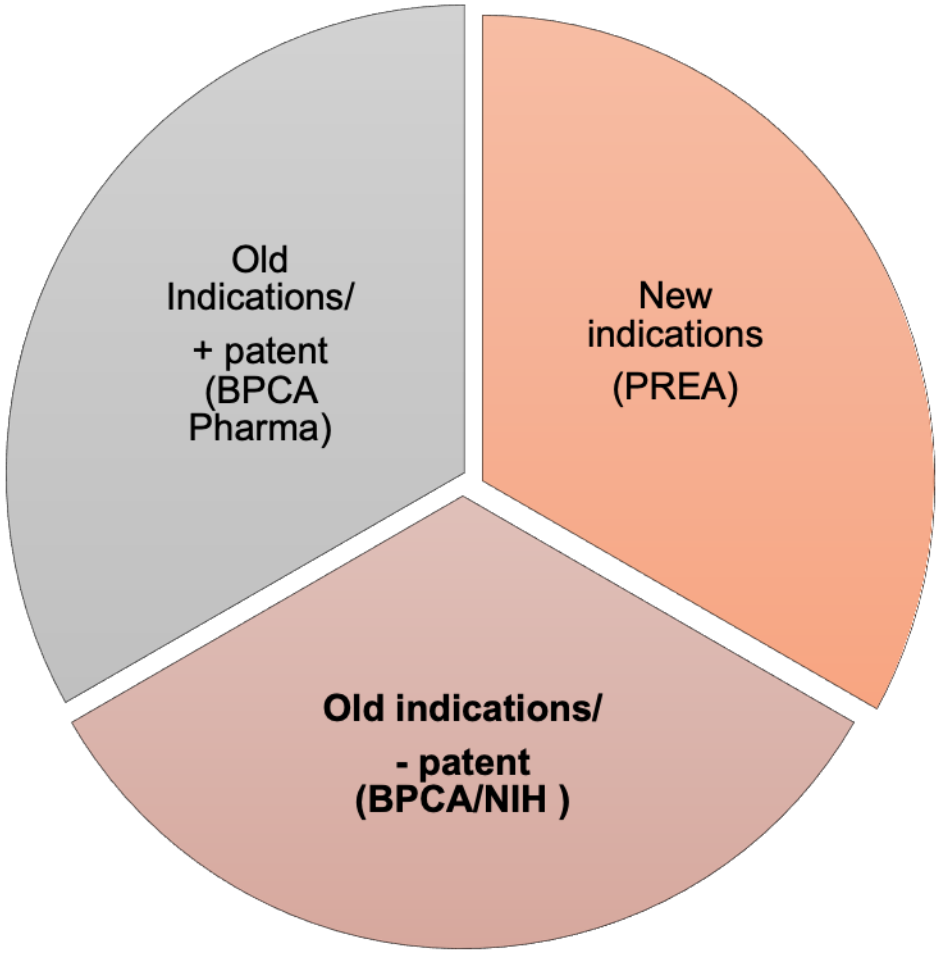
***Science advances limited**

**Failed Pediatric Drug Dev Trials*. Momper et al. Clin Pharm Ther. 2015

*IS IT TIME FOR A PARADIGM SHIFT IN PEDS DRUG DEVELOPMENT?



Pediatric Labeling



BPCA Legislative Overview

BPCA Legislation

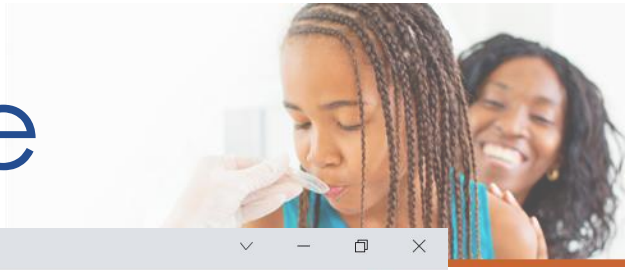
FDA
(*on-patent)

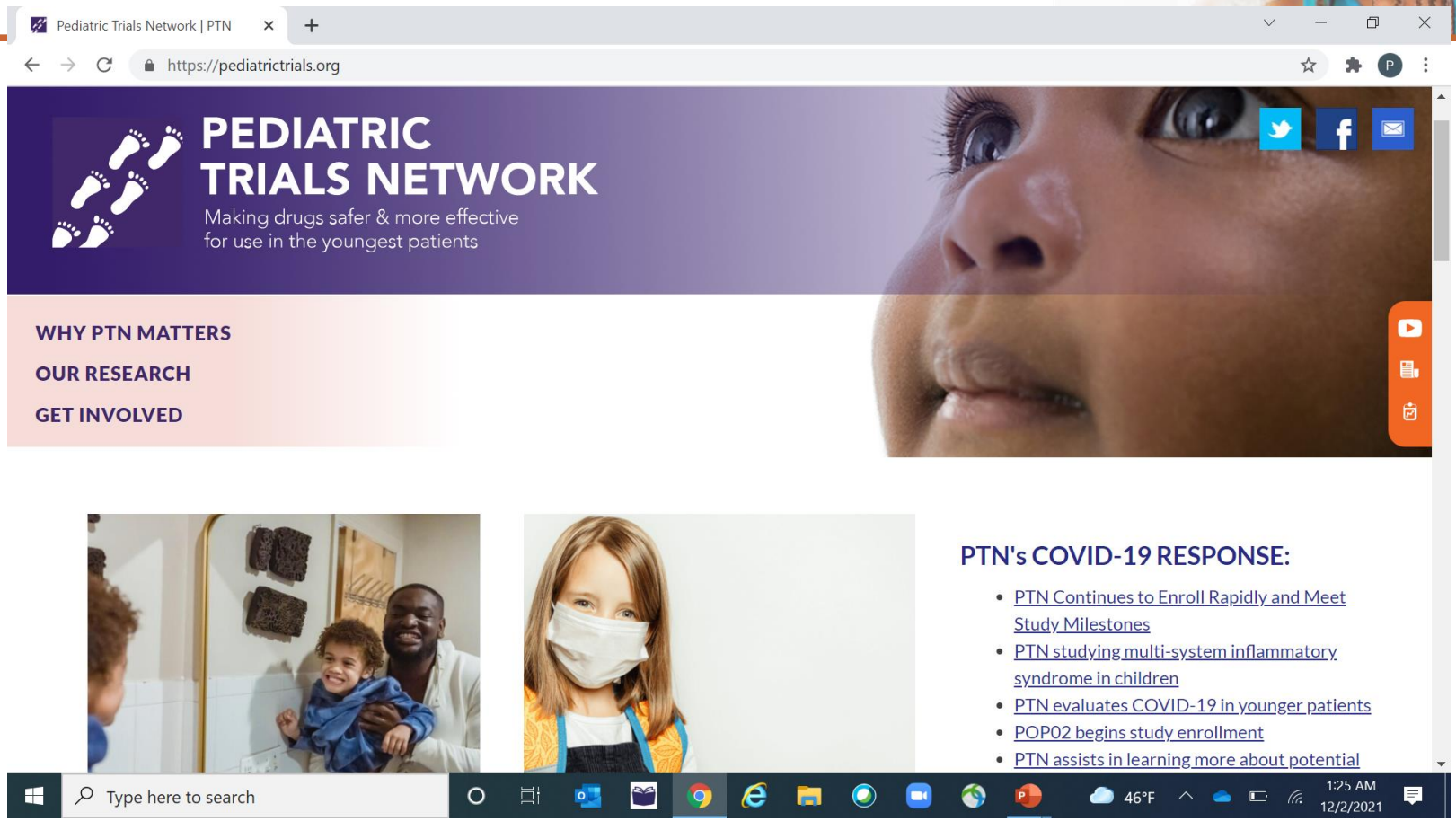
- Pharmaceutical Companies' Drug Studies
- Pediatrics Division Oversight

NIH
(*off-patent)

- Prioritization
- Clinical Trials (Sponsor/Submit)
- Pharmacology Training
- Translational Research

NIH BPCA Infrastructure





- Pediatric Trials Network (www.pediatrictrials.org)
- BPCA Data Coordinating Center
- Logistics Support Team, NIH, FDA

What the NIH BPCA Program has accomplished thus far

- 220 Drugs (Prioritized) Listed to date
- 50 Specific Therapeutic Areas Prioritized
  - HTTPS://BPCA.NICHD.NIH.GOV
- ~47 Clinical Trials conducted to date
- ~30 Clinical Study Reports submitted
- **17 Pediatric Label changes**
- 100+ publications to scientific literature

NIH BPCA LABEL CHANGES

Propylthiouracil
2010
(hepatotoxicity)

Sodium Nitroprusside 2012
(controlled blood pressure)

Meropenem
2014
(intra-abdominal infections)

Lorazepam
2016
(status epilepticus)

Lisinopril
2016
(hypertension in renal transplant patients)

Mercy TAPE
2016
(1st device trial for anthropomorphic)

Lithium
2018
(pediatric mania in bipolar disease)

Pralidoxime
(nerve agent exposure)

Acyclovir
2019
(herpetic infections in neonates)

Ampicillin
2019
(infections in neonates)

Mercy Baby Tape
2019
(2nd device trial)

Caffeine
2020
(apnea in preterm neonates)

Doxycycline
2020
(dosing and safety in infections)

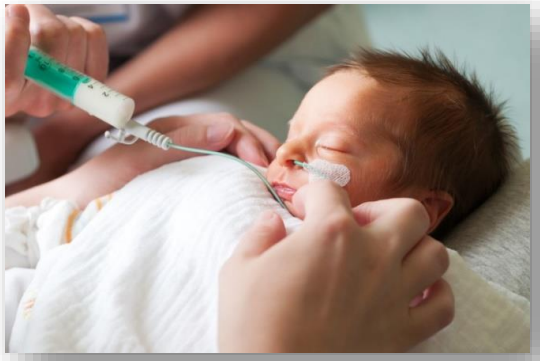
Clindamycin
2020
(dosing and safety in obese patients)

Bactrim
2020
(dosing and safety in infections)

Clindamycin
2021
(dosing and safety in infections)

Diazepam
2021
(PK modeling in status epilepticus)

Addressing Unique Challenges

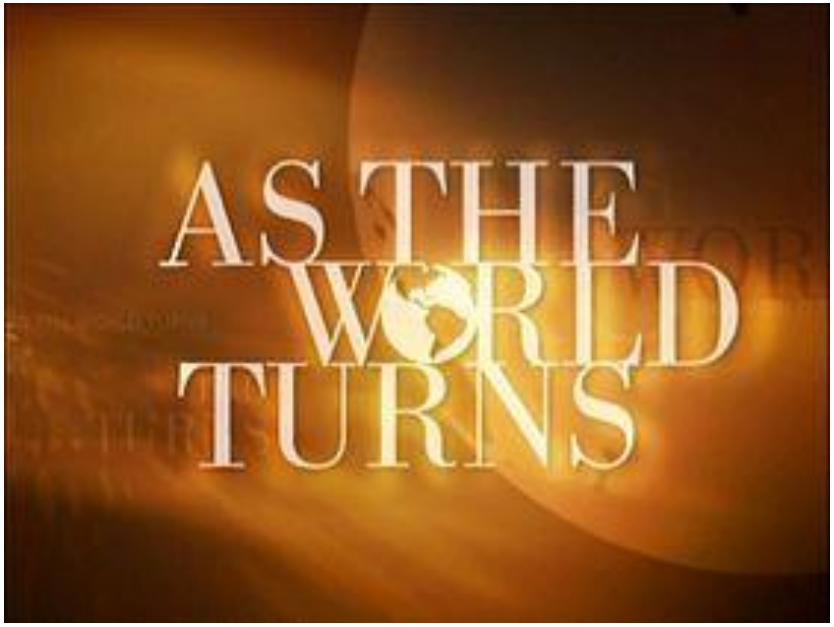


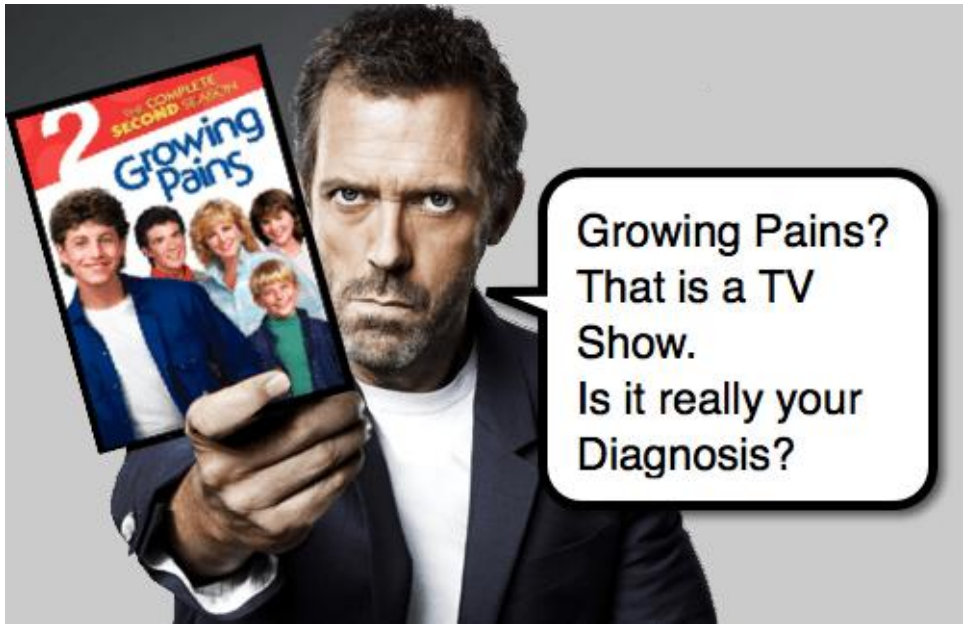
STORY: ACYCLOVIR

1 LABEL UPDATE CAN HAVE AN IMPACT

- Neonatal HSV: >50% mortality in infants with disseminated disease and delayed therapy; accounts for 0.2% percent of US neonatal hospitalizations and 0.6% of in-hospital deaths; blindness, seizures, learning disabilities are common in survivors
- Introduction of acyclovir as therapy: decline in one-year mortality by ~50%; reduces spread of disease; improved neurological development in survivors
- Despite clear need for treatment of neonates (including preterm), **no neonatal dosing data in the label** → early BPCA prioritization (2005)
- Clinical trial: PK and safety in preterm and term neonates; Cost < $1 million (2015)
- Updated FDA label to include dosing by gestational and postnatal age (2019)
- Global influence: Dosing in Neofax (clinician dosing guide); Health Canada label update

As the Program Matures





BPCA PROGRAM GOALS: LABELS +

- Novel Trial Designs
  - Opportunistic studies– drugs administering per standard of care, blood draws centered around clinical care, broad populations and indications
  - Master protocols: multiple drugs
  - Transition of clinical trial to registry for follow-up
- Understudied populations: neonates, children with obesity, critically ill children
- Diversity and Inclusion
- **Expertise with FDA**
- **Training and Educational Curriculum**

*This means that even with label changes, some needs remain.

Examples include:

- Development of appropriate study designs.
- Inconsistent and segmented data collection and data standards across therapeutic areas
- Need for informative data about which clinical trials do not achieve the intended goals and reasons why trials and preclinical research do not meet their goals
- Limited awareness of the need for, and processes to develop and validate PD measurements and biomarkers.
- Limited **team science approaches** in pediatric drug development (including clinical trialists, clinicians, statisticians, pharmacologists, epidemiologists, biomedical experts)

- **Resource guide of what is needed to improve the pipeline of science ideas and the conduct of pediatric drug development research (Quality Pharmacology)*

BPCA Revolution: What else can WE do?

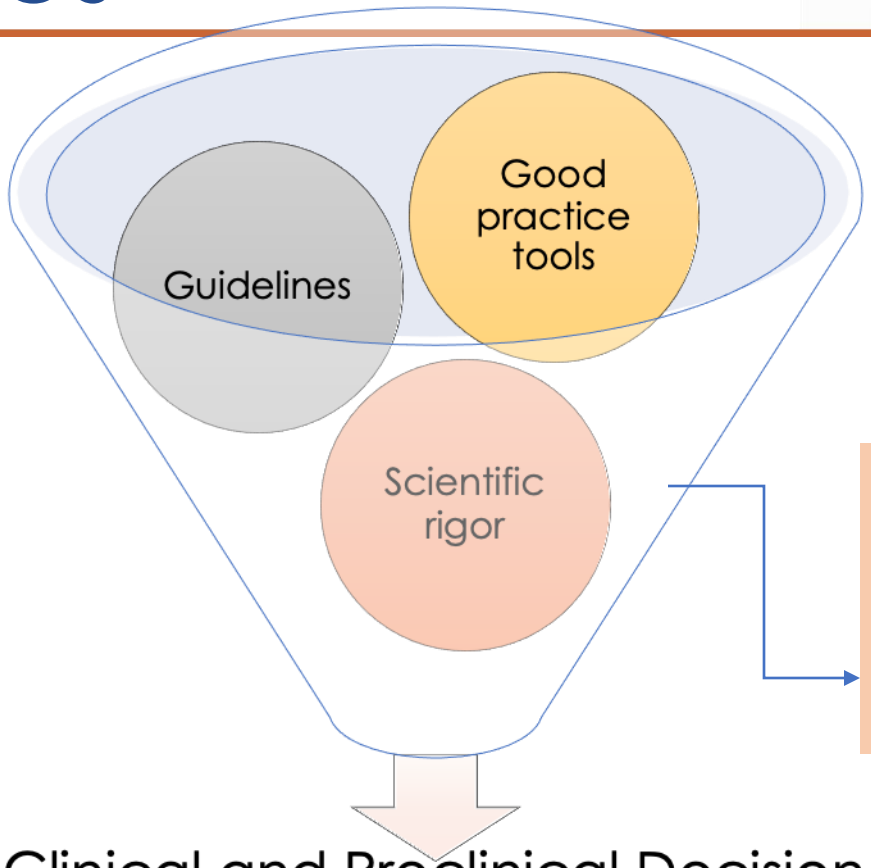
- Label

- Translate Research into Clinical Practice/More Patient Engagement
- Addressing Remaining Gaps in Pediatric Therapeutics in a practical way
- ?Can we become a resource: i.e., Where do people go to get information on how to do this type of research?

RE-Thinking Our Role

- What we (NICHD BPCA) did…
  - Review of historical scientific needs from past prioritizations and BPCA working groups to determine gaps in knowledge and therapeutics that remain (2008-2018)
  - Review of roundtable analysis from past T32 Working Group (held in 2018)
- Questions that arose from this review…
  - Is it possible to develop **a generic framework** (with actionable items) that
    - **can be useful and utilized by various stakeholder involved in pediatric drug development/research and that**
    - **can subsequently be customized to specific therapeutic areas, indications, type of drug, developmental stages, phenotypic expression?**

Potential Framework Outcomes



Could also serve as a tool for the BPCA program in providing better use cases and proof of concepts

Clinical and Preclinical Decision support tools to improve the quality of clinical research and practice

QUALITY PIPELINE to various stakeholders

Pathway to a Framework

- How do we develop a framework of resources that a variety of stakeholders can benefit from?

Rationale

- What is the Goal?
  - This type of framework will **enable** pediatric drug development, not perform it.
- Why a Framework?
  - Keeps us all mindful of the Big Picture
- What could it do
  - **FIND RESOURCES (now):** Develop an annotated, selective, curated, collection of resources that will assist drug developers, researchers and clinicians with a universal resource of relevant topics before conducting pediatric drug development research
  - **ID WHAT'S MISSING (short-term):** Be a Call to Action for what gaps remain and what consensus still needs to be developed
  - **BE A PATHWAY 4 INTEGRATING APPROACHES (long term)**: Be a Signpost for bringing guidelines together for those who write grants and fund drug development research
  - **CONNECT PEOPLE (short and long-term):** Serve as a Platform for building or fostering more team science in Peds DD (documenting existing resources and remaining gaps)

SYSTEMATIC APPROACH

- Create Goals
- Identify Audience
- Establish Working Assemblies
- Develop Final Draft Document

Setting Framework Goals

The overarching call for a framework that enables pediatric drug development includes:

1) **The need to centralize and effectively advertise to the various contributors to pediatric drug development the large amount of good practice* tools and resources that currently exist in pediatric drug development.**
2) **The need to identify and address pathways towards closing remaining gaps in good practice (where more guidelines or methodological studies are needed).**
3) The need to promote integration between the various stages AND bridge collaborations between the various stakeholders of pediatric drug development (preclinical and clinical stakeholders; academia and industry).
4) The need to integrate approaches such as big data, real world evidence, the use of medical technology in drug development (e.g. m-health), patient and public involvement with research, and broader inclusion of diverse populations in trials.

*Good practice recommendations can be existing regulatory guidelines or existing well-constructed multi-stakeholder consensus documents.

Determining the Framework Audience

Stakeholders identified as those who could both benefit from and contribute to the framework development include:

- Clinical investigators
- Preclinical investigators
- Regulators
- Patients and patient advocates
- Industry and other institutions that:
  - Own assets for pediatric drug development (e.g., drugs, biomarkers, preclinical models, etc.)
  - Drive drug development (e.g., sponsors)
  - Support drug development (e.g., contract research organizations or academic research organizations)

Working Assemblies

Advancing Clinical Trials Designs
Ed Connor, M.D.
Christoph Hornik, M.D., Ph.D.

PD Biomarkers Research
Gregory Kearns, Pharm.D., Ph.D.

PK Modeling that Informs Dosing
Edmund Capparelli, Pharm.D.
Daniel Gonzalez, Pharm.D., Ph.D.

Pediatric-Friendly Formulations
Karen Thompson, Ph.D.

Pharmacoepidemiology Studies
Jonathan Davis, M.D.

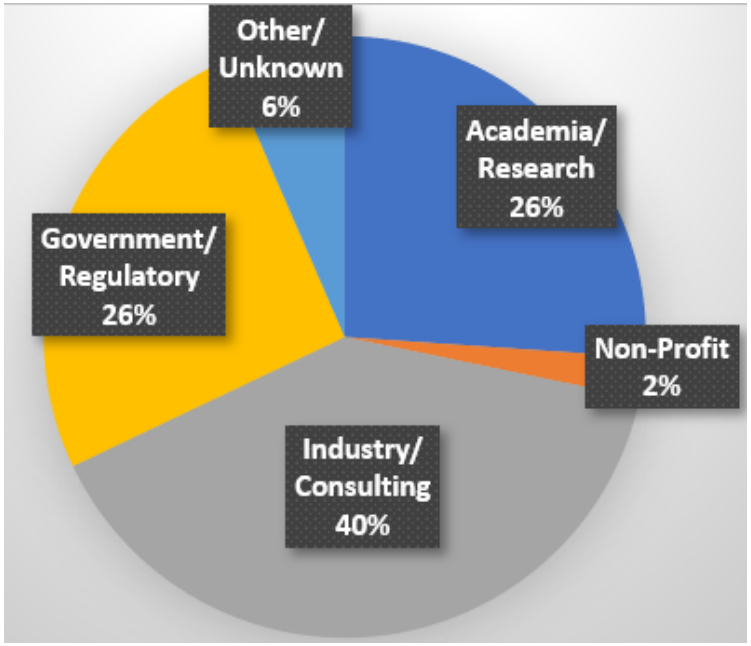
Quantitative Systems Pharmacology
Gilbert Burckart, Pharm.D.
Jeremiah Momper, Pharm.D., Ph.D.

Assembly Discussion Points

- Where can a stakeholder go to find documents about **good practice**?
- Which **guidelines or consensus documents** can be recommended (based on rigor and authority (or other criteria)?
- Which documents should be **read first**? Which documents **unlock the field** for people not familiar with a field?
- *Which guidelines or consensus documents are missing and need to be developed?*
- *Which methodological research gaps remain?*
- *What about patient and public involvement, and diversity/inclusion?*

Assembly Participation

- 408 unique participants attended at least one call.
- 184 **active** participants:
  - Academia/Research: 48 (26%)
  - Government/Regulatory: 47 (26%)
  - **Industry/Consulting: 73 (40%)**
  - Non-profit: 4 (2%)
  - Other/Unknown: 12 (7%)
- Average 39 active participants per assembly
- Average participant was active in 1.3 assemblies.



*Criteria Developed

- **Set Parameters for identifying resources**
  - Resources submitted via Survey Monkey link
  - Criteria for inclusion:
    - Accuracy and reproducibility
    - Quality and breadth of science
    - Generalizability of recommendations
    - Applicability of recommendations to prescribed area
    - Robust, rigorous, and transparent process to develop recommendations

  - Resources scored, sorted, and adjudicated by respective assembly members via voting process via virtual meetings from March—August 2021.
  - Gaps that remain identified at later meetings

*Re-Asssessments

- For the early framework development, we allowed all comers for resource collection.
  - Articles
  - Presentations
  - Book chapters
  - Reviews

- All FDA guidances received a pass to be automatically included
  - However, guidances still reviewed by *NICHD team* for relevance.

- Resources such as background information, narratives and opinion papers originally considered low priority.
  - New category of additional resources added

- Public Access also considered and re-considered.

Finalizing Document

- Resources received (as of December 2021)
  - Systems Pharmacology: 22
  - Pharmacoepidemiology: 35
  - Biomarkers: 21
  - PK modeling: 20
  - Formulations: 72
  - Advancing Clinical Trials: 69

  ****And we were able to secure 2 resources that were NOT previously publicly available for public accessibility!**
- Resources categorized
  - Read this first
  - Helpful Explanations
  - Additional Resources
  - US Guidances

Snapshot of resource

BPCA Framework to Enable Pediatric Drug Development 2-15-22 (002).pdf - Adobe Acrobat Pro DC (32-bit)

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Home Tools BPCA Framework t... ×

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General Resources in Pediatric Drug Development (PDD)

Read this First

1) E8(R1) General Considerations for Clinical Studies
FDA. 2019.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e8r1-

Type here to search

Rain...

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2/17/2022

Gaps Remain

Advancing Clinical Trial Design (Hornik/Connor)

- **Digital endpoints** in clinical trials
- Patient reported outcomes (PROs)/observer outcomes
  - Developing digital tools to capture PROs (electronically)
- Remote, decentralized, or hybrid clinical trials
- Platform trials in pediatrics

Pharmacodynamic Biomarkers (Kearns)

- Drug response biomarker vs. Pharmacodynamic biomarker as a primary outcome
- **Validated biomarkers are available for pediatric patients/or clinical trials**
- Criteria for the selection of optimal biomarkers in pediatric clinical trials

PK Modeling (Gonzalez/Capparelli)

- Leveraging data to **assess the predictive performance of a model** once it's published
- Provide recommendations around the collection of PGx data and its integration into PK/PD models to account for the role of genetic variation
- Target attainment
- Dose optimization

Pharmacoepidemiology (Davis)

- Need for high-quality, high volume **pediatric databases exist**.
- Better integration of electronic data with an improved focus on necessary endpoints.
- More efficient, effective Electronic medical records (EMRs) linkages.

Pediatric-Friendly Formulations (Thompson)

- **Applicability of biochemical classification system (BCS) to pediatrics**
  - Extrapolation for efficacy and safety
- Ontogeny of some enzyme systems
- Understanding developmental status of organ systems metabolism/absorption in young children, particularly neonates.

Systems Pharmacology

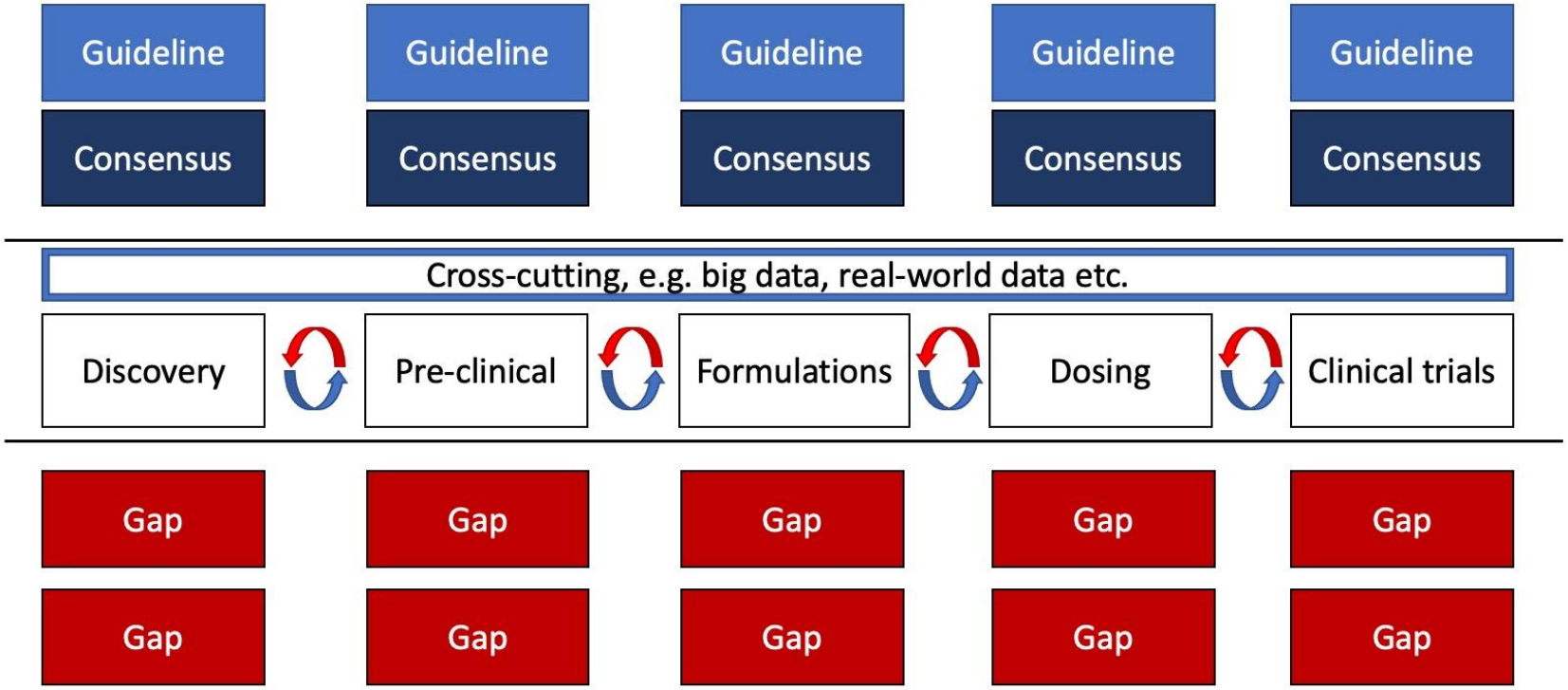
- Incorporating systems pharmacology training into pharmacology programs
- Characterizing the biochemistry of drug targets
- Investigating the origins of variability in drug response at the single-cell, organ and patient level that arise from differences at the level of the proteome, genome and environment
- Exploiting diverse clinical and omic data to create pharmacodynamic biomarkers that inform integrated, multi-scale models of drug response determinants in distinct patient populations
- Developing and supporting information exchanges for QSP, particularly in the area of clinical data and electronic medical records
- Developing new multi-scale computational models of pharmacological mechanism that span the divide between cell-level biochemical models and organism-level PK/PD models

*External Review Process

- NICHD and Logistics Team Finalize Document
  - August- October 2021
- Recommendations submitted to a trans-NICHD governance committee for review
  - November 2021
- Updates presented at annual BPCA meeting
  - December 2021
- Final Recommendations submitted to NIH-wide committees (BPCA Liaisons and N-Perc Group)
  - Target February 2022

Sample Framework Design for Future Consideration—Web based

Schematic diagram to show the structure of the framework, including some of the possible modules



CURRENT DISSEMINATION

- BPCA and PTN Websites/List Servs
- NICHD Communications Office
- MPRINT Hub (as a distribution hub)
- **Your friends and colleagues…all ideas welcomed**

A Home ?

About NIH Collaboratory - Rethir

https://rethinkingclinicaltrials.org/about-nih-collaboratory/

Home About Resources Grand Rounds News Subscribe to Newsletter

NIH PRAGMATIC TRIALS COLLABORATORY

Rethinking Clinical Trials®

DESIGN VIEW CHAPTERS >

DATA, TOOLS & CONDUCT VIEW CHAPTERS >

DISSEMINATION VIEW CHAPTERS >

About NIH Collaboratory

Our Mission: Strengthen the national capacity to implement cost-effective large-scale research studies that engage healthcare delivery organizations as research partners.

Dr. David Shurtleff of the National Center for Complementary and Integrative Health (NCCIH) discusses the unique work of the NIH Pragmatic Trials Collaboratory.

https://rethinkingclinicaltrials.org

Rethinking Clinical Trials—with you…

- Pragmatic trials in small populations may not be the same as pragmatic trials in large populations
- Pediatric specificities
  - Consequences of development
- The framework is designed to bring stakeholders together across siloes

A Fit?

About NIH Collaboratory - Rethir

https://rethinkingclinicaltrials.org/about-nih-collaboratory/

DESIGN VIEW CHAPTERS >

DATA, TOOLS & CONDUCT VIEW CHAPTERS >

DISSEMINATION VIEW CHAPTERS >

What We Do

- Support the design and rapid execution of pragmatic clinical trial Demonstration Projects that address questions of major public health importance and engage healthcare delivery systems in research partnerships.
- Help to establish best practices and provide proof of concept for innovative designs in pragmatic clinical research.
- Provide technical support and pragmatic trial expertise for Collaboratory trials and initiatives via 5 Core Working Groups, each focused on a specific topic.
- Produce data, tools, and resources that are made available to the greater research community to promote partnerships with healthcare systems and propel a transformation in how clinical research is conducted.

450,000 opioid overdose deaths

in the United States from 1999-2018 (CDC)

Addressing the Opioid Crisis

In 2019, the NIH Pragmatic Trials Collaboratory began serving as the Resource Coordinating Center for a group of large-scale embedded pragmatic clinical trials (ePCTs) supported by the Pragmatic and Implementation Studies for the Management of Pain to Reduce Opioid Prescribing (PRISM), a program of NIH's Helping to End Addiction Long-term Initiative (NIH HEAL Initiative).

The PRISM trials will determine the effectiveness of multiple non-opioid interventions for treating pain and assess the impact of implementing interventions or

*Opportunities in Drug Development (Team Science)

Basic Research

-**Ontogeny**

--ADME

--Toxicity

NIH
Academia

Early Research

--Endpoints

--Biomarkers (various)

Pharma
Big/Small

Drug Development

Academia
CROs

Clinical Trials

--BPCA

--PREA

--?Orphan

PTN-off patent

IACT-on patent

Repository of Data

--Registries

--**Literature *(Framework)***

Pharm Epi/Data Science

Special Shout Outs

- Dr. George Giacoia/ Dr. Mark Turner
- Framework Assembly Leaders
  - Drs. Gil Burckart, Ed Capparelli, Ed Connor, Jonathan Davis, Danny Gonzalez, Christoph Hornik, Greg Kearns, Jeremiah Momper, Karen Thompson
- Framework Assembly Participants
- Infinity Conferences Logistics Team
- Dr. Aaron Pawlyk/OPPTB/NICHD leadership

Stay in Touch…We Will

BPCA Website

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BPCA Framework Distribution

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Thank you