The **MPRINT** Hub: Advancing Frontiers in Health through **Maternal and Pediatric pReScision In Therapeutics**

A collaborative effort of the Obstetric and Pediatric Pharmacology and Therapeutics Branch

Aaron C. Pawlyk, Ph.D., Branch Chief
The Problem

Physicians and patients must sometimes make decisions on medication and vaccine use without rigorously conducted regulatory studies and approval.
Up to 59% of the U.S. population comprises people who typically are not included in research studies (pregnant women, children, older people, and those with intellectual and physical disabilities).
Why are Pregnant Persons and Children Underrepresented?

- Real and perceived ethical concerns
- Real and perceived concerns over safety risk
- Practical challenges to inclusion in clinical trials
- Lack of workforce experienced with these populations

The MPRINT Hub is a new initiative that continues OPPTB’s efforts to provide new knowledge, tools, and training to address these factors.
Bridging the Gap

Basic Research, Therapeutic Discovery, Non-clinical Development

Science: Therapeutic research & Implementation

Inclusive Product Development

Inspired by talk by Dr. Suzie McCune 11/21/19
Goal: Lead efforts to develop, test, and evaluate new and existing therapeutics and devices to find safe and effective solutions that meet the unique needs of pregnant and lactating women, children, and people with intellectual and physical disabilities.
NICHD Strategic Plan
Aspirational Goals

- Facilitate application of precision medicine
- Train the next generation of scientists
Pharmacology
The branch of medicine concerned with the uses, effects, and modes of action of drugs.

Pharmacokinetics
What the body does to the drug.

Pharmacodynamics
What the drug does to the body.

Pharmacogenetics
How genetics affects pharmacokinetics and pharmacodynamics.
What is Needed for Precision Medicine?
A Big Step Forward: Legislation on Pediatric Drug Trials

Best Pharmaceuticals for Children Act & Pediatric Research Equity Act

- FDA (*on-patent)
- NIH (*off-patent)
- Pharmaceutical Companies’ Drug Studies
- Pediatrics Division Oversight
- Prioritization Clinical Trials (Sponsor/Submit)
  Pharmacology Training Translational Research

Led to creation of OPPTB in 2004
What the BPCA Clinical program brings to the table... Doing trials BETTER!

Pharmacology expertise
PK/PD modeling, simulation expertise, assay development and validation

Innovative research/trial design
Standard of Care (SOC) and Opportunistic Trial Designs in Pharm
Obesity based dosing
Master protocols

Trailblazing efforts in pediatric REGULATORY research
Interaction and experience with MULTIPLE FDA review divisions (pre-IND meetings)

Cost efficiency
SOC protocols
Junior Investigators
Subsidize site costs

Promoting Investigator Training
T32 Program
DCRI career development program

Need to bring such expertise to the broader community, expand into maternal populations, address gaps, and continue to build and train the workforce.
One Answer: The Pediatric Trials Network

“Create an infrastructure for investigators to conduct trials that improve pediatric labeling and child health.”

–Sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

–Success defined by improving dosing, safety information, labeling, and ultimately child health

–Focus on off-patent therapeutics

Dr. Perdita Taylor-Zapata  
Ms. Francine Mahase  
Dr. Antonello Pileggi  
Infinity Conference Group

www.PediatricTrials.org
PK + safety
low $s

PD (efficacy)
mid $$s

PD (efficacy)
high $$$$s

Source: GAO analysis of FDA data and a 2016 collaborative study by Biotechnology Innovation Organization, Biomedtracker, and Amplion. | GAO-17-564
Current T32 Pediatric Clinical Pharmacology Training Program

Lecture Series
- Principles of Pediatric Clinical Pharmacology Course with approximately 29 lectures divided into 8 modules including FDA Corner

Collaboration
- Network allows interdisciplinary collaboration of clinical, translational, and basic investigators who research pediatric therapeutics

Career Development
- Unique training experiences to bridge the gap between scientific discoveries and clinical medicine, fostering career trajectories towards research and scientific enterprise

Mentorship
- PI/PDs with scientific background, expertise, and administrative and training experience to provide strong leadership, direction, management, and administration of the proposed research

Virtual Network
- Network of institutions linked by a website, fostering cross-institutions interactions and interdisciplinary collaboration

Research Experiences
- Training and experience in the methods and conduct of basic and clinical drug research in the different phases of pediatric drug development

Dr. George Giacoia
Dr. Lesly Samedy-Bates
Expansion of Training and Career Development Program

**Stronger Network**
- Combining Training Program (T), Individual Fellowships (F), and Career Development Awards (K)
- Expand to Maternal Clinical Pharmacology

**Leverage NICHD networks**
Pediatric Trials Network (PTN), MPRINT Hub, Maternal-Fetal Medicine Units (MFMU) Network, Neonatal Research Network (NRN), etc.

1. Networking of Fellows with Early Career Awardees for a unified program
2. Didactic training and seminar series to strengthen knowledge and foundation
3. Strategic coordination of maternal and pediatric clinical pharmacology training and education
Implementation Plan Submitted to the Secretary
August 2020, Posted on PRGLAC Website

Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

The 21st Century Cures Act established PRGLAC to advise the Secretary of Health and Human Services (HHS) regarding gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women. PRGLAC was tasked with identifying these gaps and reporting its findings back to the Secretary.

Federal members include the directors of NIH, NICHD, the Centers for Disease Control and Prevention, the HHS Office on Women's Health, and the Commissioner of Food and Drugs. Non-federal members include representatives from relevant medical societies, non-profit organizations, and industry.

https://www.nichd.nih.gov/about/advisory/PRGLAC
Maternal and Pediatric pReCision in Therapeutics Hub

MPRINT Hub is a service center and science catalyst:

• Provide knowledge and expertise to the scientific community

• Catalyze and accelerate maternal and pediatric therapeutics towards precision medicine

• Synergize with other resources and networks

• Build upon prior OPPTB efforts (PTN, OPRCs, RPDPs) and lay groundwork for future efforts

https://www.nichd.nih.gov/about/org/der/branches/opptb/mprint
The MPRINT Hub’s Place in the Ecosystem

Needs to Catalyze Regulatory Clinical Trials

- Centralized maternal and pediatric pharmacology knowledgebase
  - Common framework
  - ID’d knowledge gaps

- Tools to facilitate drug development in pediatric and maternal pharmacology
  - Biomarkers
  - Clinical outcomes
  - Enhanced modeling
  - Outcome measures
  - Technologies

- Education, training, outreach

Clinical Networks
- Clinical research
- Data & biospecimens
- Drug trials

Investigator Initiated Grants
- Basic Research
- Smaller studies
- Ontogeny
- ADME & tox

MPRINT Hub: Knowledge Core and Centers of Excellence

Structured Data and Knowledge Bases & Biorepositories e.g., DASH

Literature, Deposited Raw Data, Pharmacoepidemiology, Registries

MPRINT Hub:

- IMPAACT
- PTN
- NRN
- MFMU

Investigator Initiated Grants

- Basic Research
- Smaller studies
- Ontogeny
- ADME & tox
MPRINT Hub Components

**MPRINT KRCC P30:**
- administrative structure
- technical and scientific infrastructure
- responsible for knowledge aggregation and dissemination.

**MPRINT CET P50:**
- address key knowledge deficits
- conduct/facilitate novel clinical, translational, basic, and/or data sciences research.
Components of the Knowledge and Research Coordination Center

**Knowledge Base & Portal**
- Primary database, integrator, and analytical platform

**Pharmacometrics and Clinical Trial Design Core**
- Pharmacometric models and expertise for dose selection in maternal and pediatric clinical trials

**Outreach, Dissemination, and Training Core**
- Support of interactions between the MPRINT Hub and the broader scientific community

**Optional Core**
- Provide support services for other Cores

**Logistics Core**
- Overall logistic and administrative coordination for KRCC, CETs and future components
- Will oversee use of the Opportunity Pool funds
From Data to Knowledge

- Comprehensive knowledge repository for pediatric and maternal pharmacology.
- Organize knowledge into a cohesive framework.
- Present knowledge to multiple user types
- Identify gaps in knowledge.
Pharmacometric Modeling

- Goes beyond estimating dose by body size and weight.
- Incorporates detailed understanding of physiological processes.
- Requires high degree of technical expertise.

Goteborg University, online PK module
http://pharmguse.net/pkdm/index.html
PROPOSED PLAN FOR COLLABORATIVE APPROACH TO IMPROVE RIGOROUS APPROACH TO MATERNAL THERAPEUTICS

**Goals and approach:** leveraging synergistic investments

<table>
<thead>
<tr>
<th>NIH Programs</th>
<th>BMGF Programs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fogarty</strong></td>
<td><strong>Virtual Pregnancy</strong></td>
</tr>
<tr>
<td>The Fogarty Global Health Program for Fellows and Scholars supports U.S. university consortia to provide collaborative, mentored global health research training opportunities in low- and middle-income countries (LMICs).</td>
<td>The Virtual Pregnancy investment aims to establish an <em>in silico</em> resource based upon physiologically-based pharmacokinetic modeling. The technology would be informed by globally comprehensive data regarding placental transfer and maternal adaptation to pregnancy. The platform will support acceleration of development and safe implementation of maternal therapeutics in LMICs.</td>
</tr>
<tr>
<td><strong>MPRINT</strong></td>
<td><strong>Broad dissemination of RFP</strong></td>
</tr>
<tr>
<td>The MPRINT Hub is a national resource that aims to aggregate, present, and expand the available knowledge, tools, and expertise in maternal and pediatric therapeutics to the broader research, regulatory science, and drug development communities.</td>
<td>Virtual Pregnancy grantees supported to train and collaborate with MPRINT Hub</td>
</tr>
</tbody>
</table>

**Overarching goals of this collaboration:**

- Accelerate preclinical assessment of potential maternal therapeutics with a view toward global safety and generalizability
- Fill gaps in global pharmacogenomic data
- Support promising LMIC-based investigators

© Bill & Melinda Gates Foundation
BMGF VIRTUAL PREGNANCY COLLABORATION AS A GLOBAL HEALTH SPOKE IN THE MPRINT HUB

Global health “spoke:”
- Establishment of virtual pregnancy models to inform use of therapeutics in pregnancy globally
- Ensure LMIC representation in pregnancy-focused pharmacometric modelling
- Capacity building for LMIC-based investigators
- Meets NICHD Strategic Plan Cross-Cutting goal in Global Health

Dr. Zhaoxia Ren (NICHD/OPPTB)
Dr. Hilary Gammill (BMGF)
Dr. Ping Zhao (BMGF)
Inclusion of Pediatrics in Existing Pharmacogenomic Resource

Pediatric PGx Dashboard

Legend: non-pediatric, pediatric, pediatric-only, BPCA

Clinical Annotations:
- 266 with pediatric VA's only
- 292 with at least one pediatric VA
- 4,855 clinical annotations

Variant Annotations:
- 2,084 pediatric
- 24,771 variant annotations

Label Annotations:
- 7 pediatric
- 371 FDA label annotations

Guideline Annotations:
- 30 pediatric
- 51 CPC guideline annotations

Automated Annotations:
- 831 pediatric
- 20,223 automated annotations

Literature:
- 6,970 pediatric
- 74,045 literature

Dr. Zhaoxia Ren (NICHD/OPPTB)
Dr. Aaron Pawlyk (NICHD/OPPTB)
Dr. Melissa Parisi (NICHD/IDDB)
Dr. Rongling Li (NHGRI)
Components of the Centers for Excellence in Therapeutics (CETs)

**Research Projects (#1)**
- At least one research project must be a clinical research project

**Research Projects (#2)**
- May be a clinical, basic/translational, or data science project

**Administrative Core**
- Provide oversight, support and management of Research Projects and Support Cores
- Work and coordinate with the MPRINT KRCC

**Support Cores**
- Support the Research Projects within the proposed CET
What the MPRINT CETs can Start Doing

- Develop ways to link parent/child EHR data and biosamples
- Assess effects of drugs on composition of breast milk
- Develop new devices and methodologies for precision dosing
- Build new pharmacometric models for predicting safety and efficacy of drugs in children and pregnant persons
- Determine and address causes of health disparities
- Educate and train the workforce, patients, and caregivers
Organization and Management of the MPRINT Hub

- Subject Matter Experts (SMEs) selected by NICHD to review the Hub annually.
- Hub will be governed by a Steering Committee with input from NICHD and SMEs.
- In negotiation with the NICHD, awardees will reprioritize and adjust activities, deliverables, timelines, and milestones on an annual basis.
Innovation in Safety Science

A goal to stimulate innovation in safety sciences that inform risk to pregnant persons, children, and adolescents.

New approaches informed by ADME and toxicodynamic variation due to: life stage, sex, genetics, and environmental factors.

Dr. Alison Harrill

**MPRINT Hub**

- Computational modeling
- Clinical trial design, risk communication
- Inter-individual variability, social determinants, mixtures

**Additional Branch Priorities**

- In vitro and adverse outcome pathways
- Cellular & organ-on-a-chip models
- Animal models for developmental and reproductive toxicology
Challenges of Pediatric Medical Devices

- Medical device development for children continues to lag behind that for adults.
- Some products are designed specifically for children, while others are borrowed from adult applications or produced for more general use.

Dr. Antonello Pileggi

Peiris, V. Pediatric Medical Device Development, Public Meeting and Workshop, August 13, 2018
System of Hospitals for Innovation in Pediatrics – Medical Devices
The National Innovation Ecosystem for Pediatric Medical Device Development

Multi-Stakeholder Engagement on FDA's Proposed Novel Framework

Virtual Public Meeting & Workshop
*February 9th - 11th 2021*

Recording available: [https://c-path.org/ship-md/](https://c-path.org/ship-md/)

**Executive Committee**
- Pre-Consortium Organization

**Coordinating Committee**
- Patient Advocacy
- Industry
- Children’s Hospital Association
- Payors
- Venture Capitalist
- Regulatory
- Academia
- NIH
- C-Path Institute

**Workstream 1**
- SHIP Boarding, Sailing, Exit

**Workstream 2**
- Criteria for Qualifying Hospitals

**Workstream 3**
- Reimbursement

**Workstream 4**
- Finance

**Workstream 5**
- Regulatory
Additional Needs in the Research Ecosystem

MPRINT Hub: Knowledge Core and Centers of Excellence

- PTN
- IMPAACT
- NRN
- MFMU

Integrative Research Resources
- Research infrastructure
- Conduct research
- Generate resources
- Training and workforce

Structured Data and Knowledge Bases & Biorepositories e.g., DASH

Literature, Deposited Raw Data, Pharmacoepidemiology, Registries
The MPRINT Hub is something new…

…and we’re building the bridge as we cross it!
Questions?