BEST PHARMACEUTICALS FOR CHILDREN ACT [BPCA]

IMPLEMENTATION AT THE NIH

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BPCA Legislative Overview*

BPCA Legislation

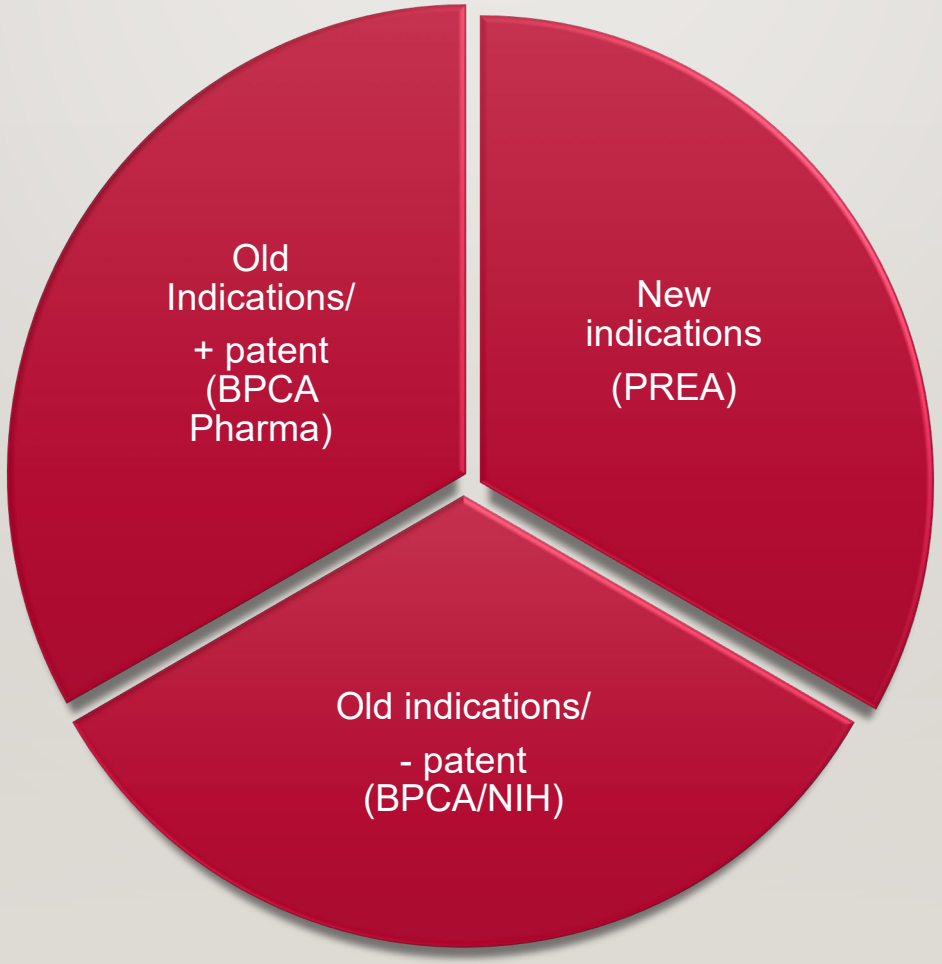
FDA (*on-patent)

- Pharmaceutical Companies' Drug Studies
- Pediatrics Division Oversight

NIH (*off-patent)

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

Pediatric Labeling



NIH BPCA IN A NUTSHELL

- PRIORITIZATION
- Sponsor Clinical Trials
- Submit data to FDA and public domain
- Drug Label Change

BPCA Overall Vision: LABEL +

PRACTICAL/FEASIBLE PRIORITY LISTS

BETTER CLINICAL STUDIES

PHARMACOLOGY FOCUSED RESEARCH

EXPANDED TRAINING (WORKFORCE)

IMPROVING CARE (I.E., DATA DISSEMINATION)

PRIORITIES*

- 150 Drugs (Prioritized) Listed to date
- 50 Specific Therapeutic Categories
  - 17 overarching areas
  - HTTPS://BPCA.NICHD.NIH.GOV

BPCA PRIORITIZATION PROCESS

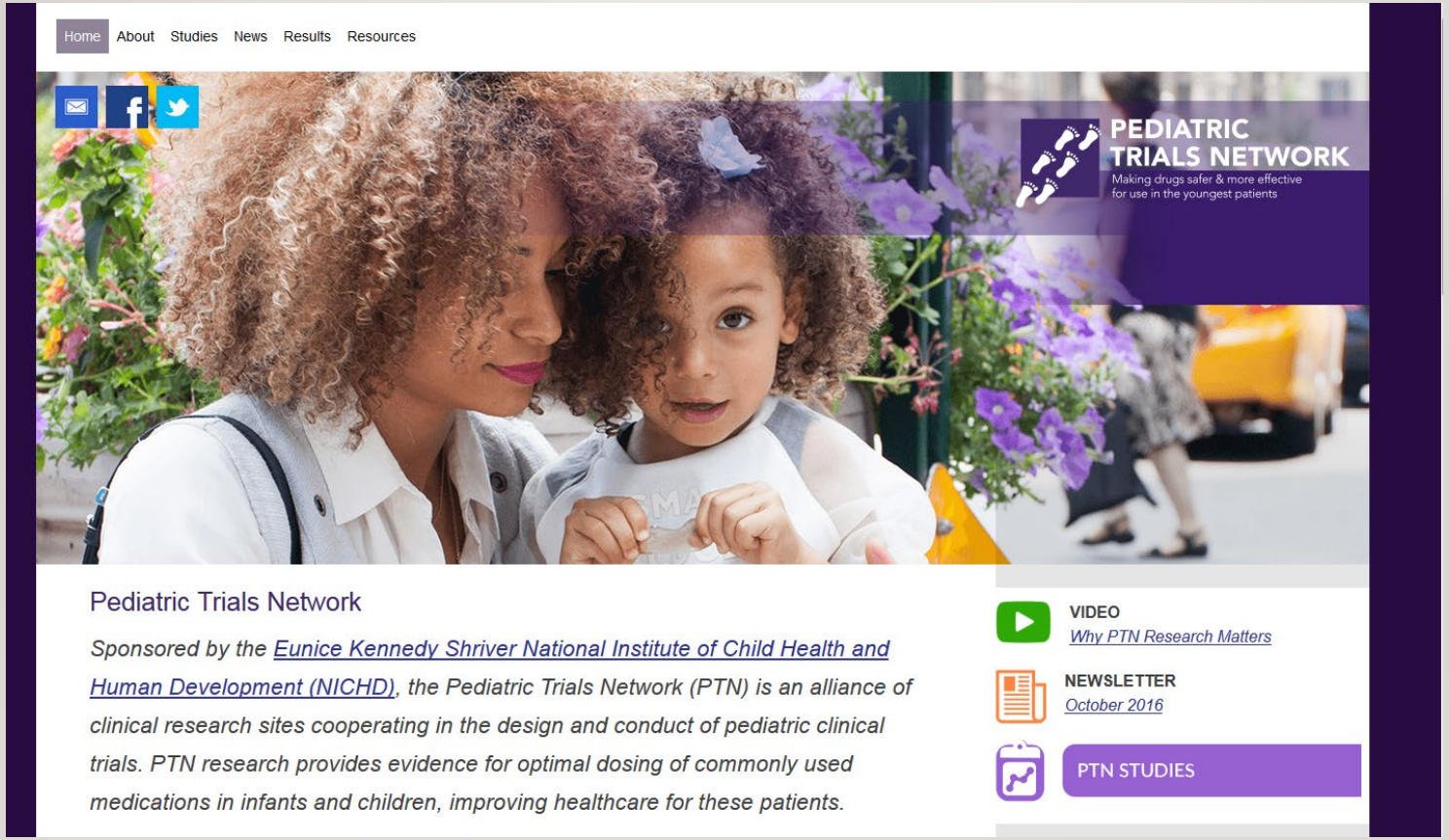
- BPCA Stakeholders
- NIH Liaisons
- Annual BPCA Meeting

- Volunteer reviewers
- Scored based on evidence, population, impact
- Three tiers of nominations
- BPCA NICHD Working Group review
- FDA review

- Updated list of priorities
- Top tiered/scored nominations
- Listed by therapeutic area

- Pediatric Trials Network
- Other BPCA Collaborations (other areas of research)

www.Pediatrictrials.org



WHAT THE BPCA PROGRAM BRINGS TO THE TABLE*…

Pharmacology expertise

PK/PD modeling, simulation, assay development and validation

Innovative research/trial design

*Standard of Care (SOC) and Opportunistic Trial Designs in Pharm

Obesity based dosing

Devices

Trailblazing efforts in pediatric REGULATORY research

Interaction and experience with MULTIPLE FDA review divisions (i.e., establishing pre-IND meetings)

Cost efficiency

Master Protocols

SOC protocols

Promoting Investigator Training

T32 Program

DCRI career development program

U54 Program

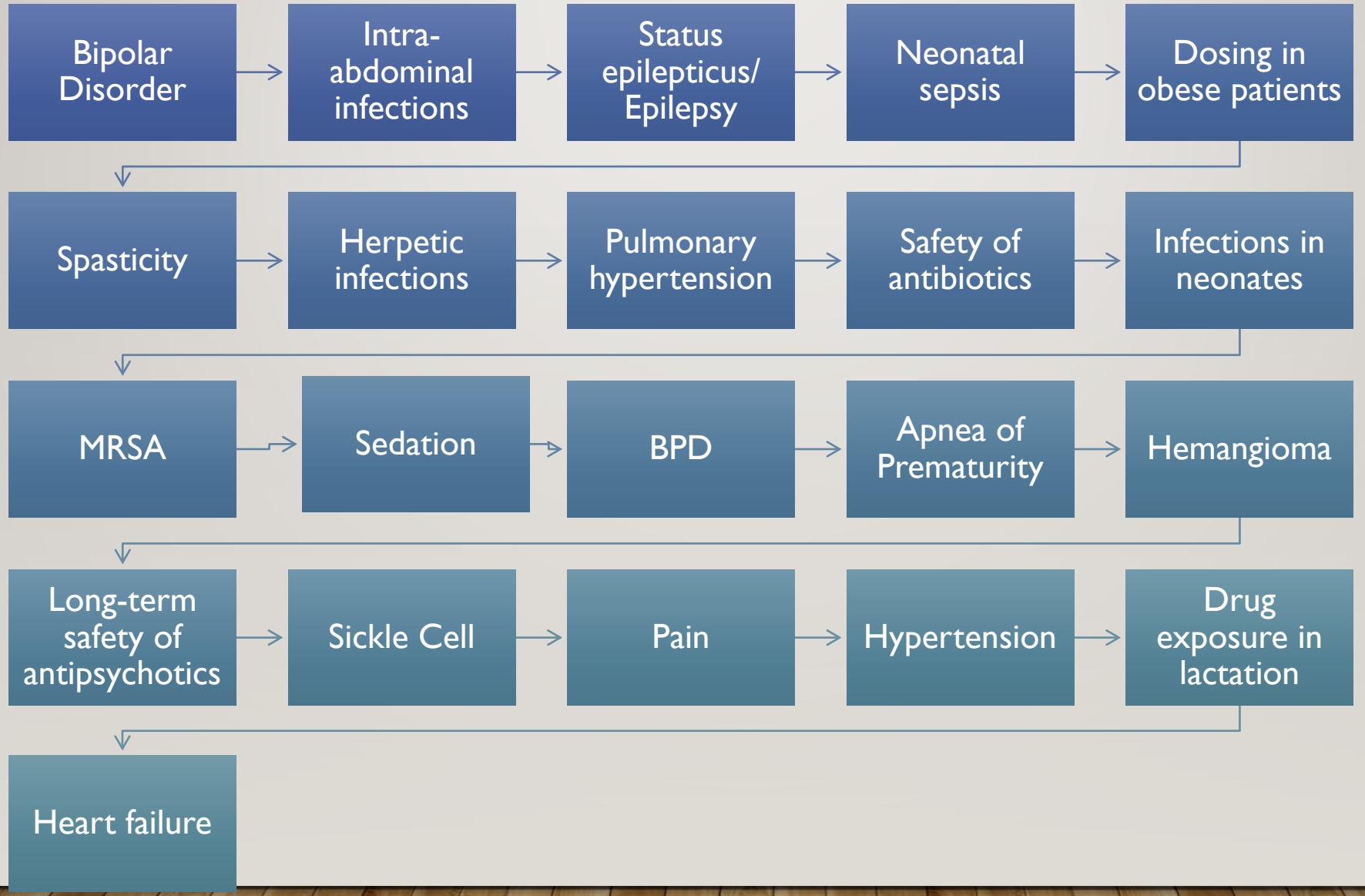
BPCA NIH CLINICAL TRIALS

120+ Drug Moieties studied to date

40 Clinical Studies to date

26 Studies submitted for Label Change to date

BPCA THERAPEUTIC AREAS



ELEVEN LABEL CHANGES TO DATE
(INCLUDING TWO DEVICES)

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)

Propylthiouracil
(hepatotoxicity)

Pralidoxime
(nerve agent exposure)

Acyclovir
2019
(herpetic infections in neonates)

Ampicillin
2019
(infections in neonates)

Mercy Baby Tape
2019
(2nd device trial)

WHAT WE HAVE LEARNED
CTS REQUIRE A LOT MORE THAN YOU THINK…

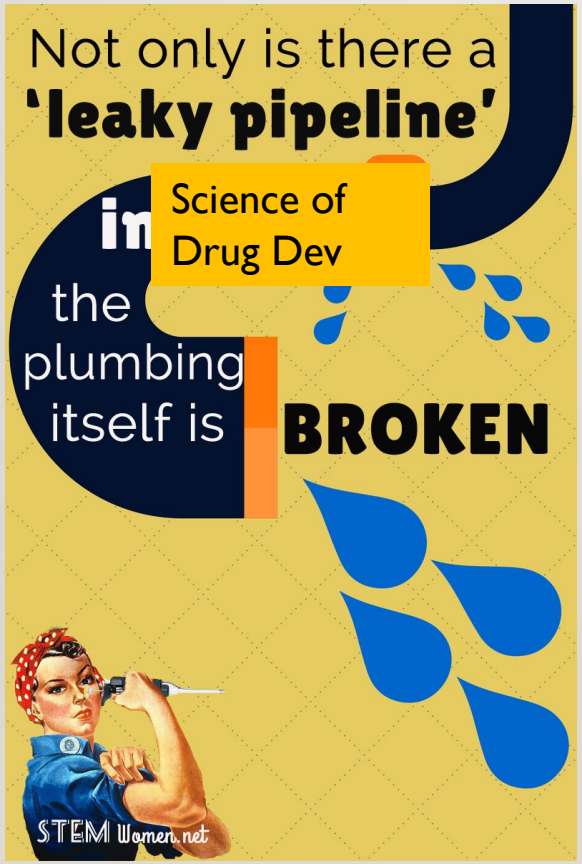
- Need Funded Infrastructure
- Need Data Science Experts
  - Biostats
  - Informatics
- Need Support Team
  - Patient Access (Study Coordinators)
  - Research Office Support
- Need a Good Question…

Practical Challenges in Pediatric Drug Dev Trials

- Performance*:
- Validated Outcome Measures
- Challenging Trial Designs
- Blood sampling Issues: Limited blood volume
- Sick population – increased variability
- Variability in site enrollment and site outcomes
  - Clinician concerns/beliefs about therapies and trials
  - Competing research priorities
- Lack of trained pediatric clinical investigators *(for regulatory drug trials*)*
- Lack of pediatric clinical pharmacology expertise

BPCA EXAMPLE:
25 YEARS AFTER LEGISLATION….

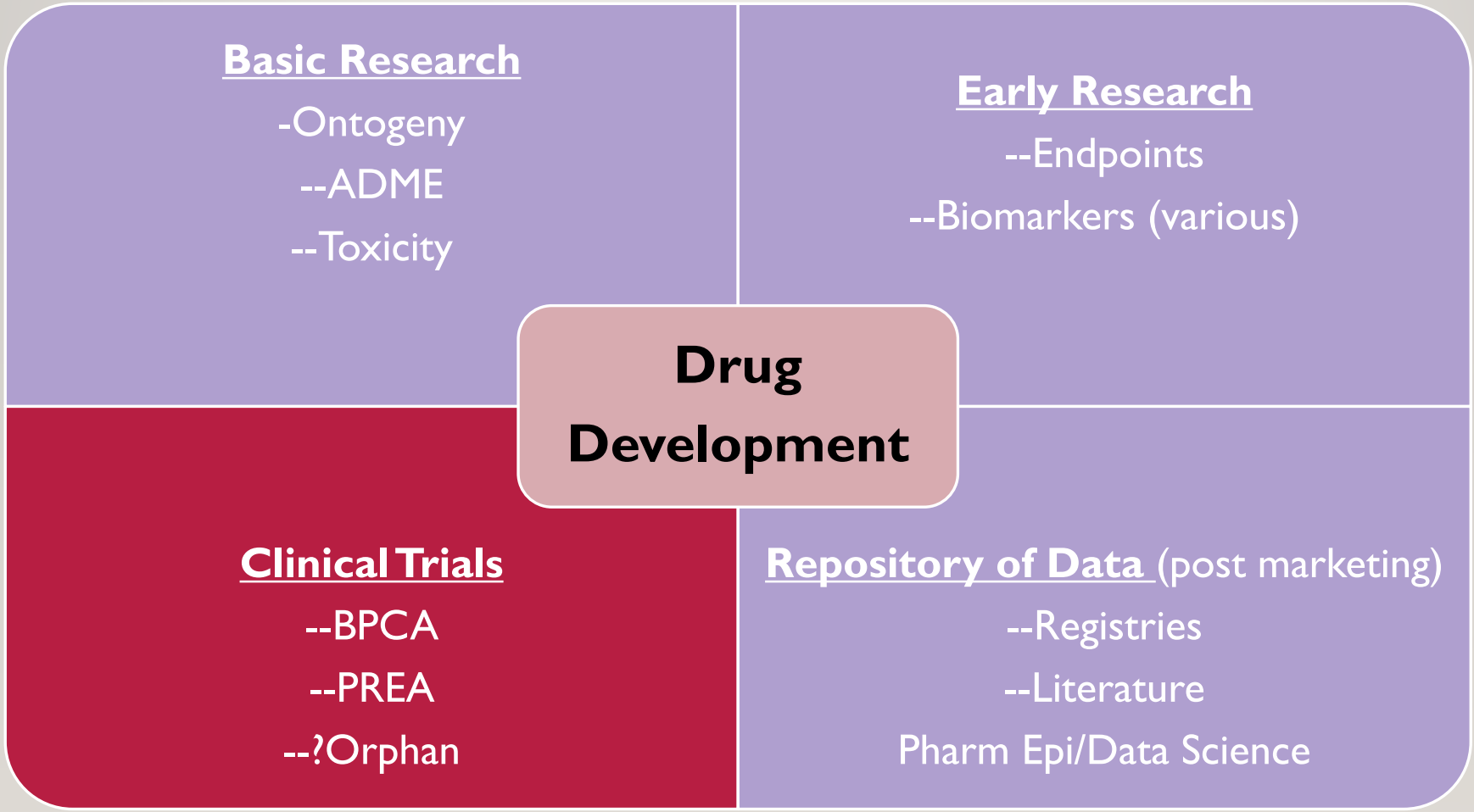
LABEL CHANGE +



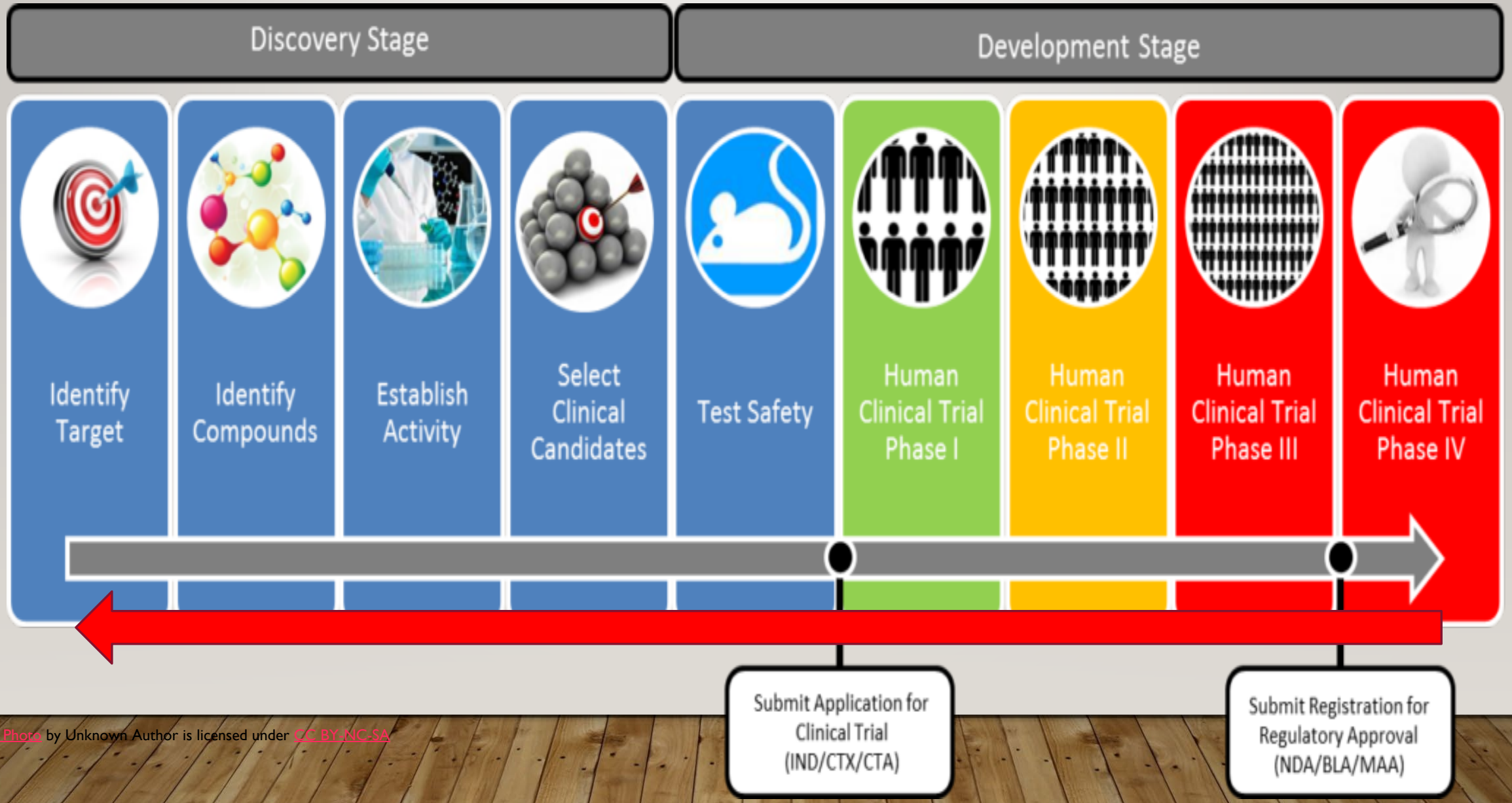
Scientific NEEDS:

- Basic Science
- Pharmacometrics (modeling, simulations)
- Pharmacogenomics (transporters, biomarkers)
- Outcome measures Endpoints (of disease & tx response)
- Clinical Trials Design
- Innovative Technology

OPPORTUNITIES IN DRUG DEVELOPMENT (WHAT WE WANT TO EXPAND GLOBALLY RELATED TO PEDIATRICS)



NEED PARADIGM SHIFT IN DRUG DEVELOPMENT



BPCA Deliverables

- **Labels**

- **Publications**

- **Dissemination**
  - Wide outreach to research institutions, societies
  - Clean, auditable data for Data sharing (DASH)
  - Novel trial designs
  - Collaborations

HOW TO GET INVOLVED

- PTN on-line surveys and concept sheet for new study ideas
  - https://pediatrictrials.org/for-health-care-professionals/
- Participate in BPCA Announcements and Priority Reviews
  - https://www.nichd.nih.gov/research/supported/bpca/activities
- Access BPCA related-data on DASH
  - https://dash.nichd.nih.gov/study/16018
  - https://dash.nichd.nih.gov/study/16020
- Program Contact
  - Perdita Taylor-Zapata, MD
  - taylorpe@mail.nih.gov
  - 3014969584

THANK YOU

ADDITIONAL SLIDES

TRIALS-HISTORICAL

Drug/Indication /Prioritized	Time frame	Total Cost	Label change
Lorazepam- Sedation 2003	2003-2010	12 million	None
Lorazepam- Status* 2003	2006-2012	9 million	+ Label change
Lithium -Mania 2005	2005-2013	10 million	+ Label change
Meropenem- Intra-abd infections*	2005-2008	3 million	+ Label change
Baclofen -spasticity	2006-2009	6 million	None
Hydroxyurea 1 (baby Hug)-Sickle Cell Dx	Long time	Total amount unknown	Anticipated
Hydroxyurea 2 (PTN/BE)	2011-2014	1.4 million	Anticipated
Acyclovir -Herpes in Neonates*	2011-2015	770k	+ Label change
Ampicillin- Infection in Neonates*	2011-2013	250k	+ Label change
Lisinopril*	2011-2015	1.4 million	+ Label change
Pantoprazole	2012-2015	2 million	None

TRIALS-COMPLETED BUT STILL UNDER REVIEW

Drug/Indication /Prioritized	Time frame	Total Cost	Label
Fluconazole	2010-2015		Anticipated
Clindamycin-Infections (Antibiotic Safety study)	2013-2018 CSR submit Apr 2019	7.6 million	Pending
Clindamycin-Obesity	2012-2015	2 million	Pending
Caffeine-Apnea	CSR Mar 2019	1.2 million	Anticipated
Rifampin	CSR Sept 2019		Pending
Diazepam			Pending
Ondansetron	CSR Nov 2019		Pending
Methadone	CSR 2019		Pending
Bactrim	FDA docket Dec 2018		Unlikely
Doxycycline	FDA docket Dec 2018		Anticipated
Baby Tape			Approved

ONGOING TRIALS/UPDATES*

Drug/	Indication	Time Frame	Total Cost	Status
Opportunistic 1.0 (50+ drugs)	PK sampling of standard of care drugs and dose	2014-2019	~7 million	>2000 patients enrolled
Timolol	Infantile hemangioma-PK and safety of 2 doses	2015-2019	2.4 million	Enrollment ended Aug 2019
Antipsychotics safety (risperidone, aripiprazole)	Long term safety-weight and metabolic derange	2017-2021	9.9 million	Enrollment ends Fall 2020
Anti-epileptics (VPA, levetiracetam, topiramate, oxcarbazepine)	PK and safety of drugs in obese patients	2017-2020	1.4 million	Enrollment underway. Scheduled to end 2019
Sildenafil	PK and safety in neonates with PHTN	2014-2019	3.1 million	Cohort 1 enrolled. Cohort 2 pending
Furosemide	PK and safety of low vs high dose in neonates for BPD	2015-2019	1.2 million	Cohort 1 and 2 completed FDA safety review Revised study pending
Anesthetics (Ketamine, Hydromorphone)	PK	2017-2020	2 million	Enrollment underway
Breastmilk PK Study (10 Drugs)*	PK	2018-2021	5.5 million	1st enrollment October 2018
Digoxin*	PK and safety in single ventricle	FY 19	2 million	Protocol finalized. FDA meeting 10/18/18. Enrollment Aug 2019
Terbutaline*	PK and safety in ICU asthma	FY 19	Pending	Protocol dev in final stages
Opportunistic 2.0*	PK and PD studies of multiple drugs	FY 19	Pending	Protocol in development in final stages

Funding Overview

Resources

Project	Estimated Cost
PTN	~$12 million
DCC	$6 million
RPDP	$3 million
Training	$1.8 million
Co-funds	~$1.5 million
Logistics	$500,000
Repository	$50,000
Total Program projected cost	$25 million

NOTE

- Approximately 2 million of PTN costs for infrastructure (management, labs, consultants, etc.)

PRINCIPLE 2: WELL-DEFINED OBJECTIVE CRITERIA*

- ***Each nomination scored 1 through 9 on each of the criteria***

Criterion	Definition	Considerations
Evidence	*Consideration of evidence already available on the nomination*	■ Existence of an unmet need in the research ■ Gap in the available evidence
Feasibility	*Consideration of the resources available to conduct the study and the ability to implement findings*	■ Study design: patients, sites and PI availability and expertise ■ Ability to implement findings ■ Time to realize benefit

PRINCIPLE 2:WELL-DEFINED OBJECTIVE CRITERIA (CON'T)*

- ***Each nomination scored 1 through 9 on each of the criteria***

Criterion	Definition	Considerations
Population	*Consideration of the different populations that may benefit from research*	■ Address diverse and broad range of populations ■ Address needs of most vulnerable ■ Address health disparities ■ Global health impact
Impact	*Potential effect on children, society, and the delivery of care*	■ Disease prevalence, severity, cost ■ Frequency of use ■ Potential for multiplicative effect across therapeutics areas ■ Availability of alternative treatments

PRINCIPLE 3: LEGITIMACY & FAIRNESS INCLUDES A NUMBER OF COMPONENTS

Transparency	■ Final list of Pediatric Needs and prioritization process published on BPCA website and in *Federal Register*
Broad Stakeholder Input	■ Public and stakeholders of existing networks submit Therapeutic Areas & Pediatric Needs nominations ■ Groups involved include physicians, researchers, consumer advocates, payers, and patient representatives
Dynamic Process	■ Process, criteria, and weights to be re-evaluated annually ■ Incorporate stakeholder feedback ■ Provide confirmation that the process is meeting its objectives
Leadership	■ OPPB leads prioritization process and implementation ■ Responsible for monitoring, evaluating, and improving the process

SAMPLE NOMINATION FORM

1. Please identify and list the proposed drug, biologic, or medical device to be investigated, along with the proposed pediatric indication of concern.	**Drug: Tacrolimus** Biologic: Medical Device:
2. Please list the proposed Therapeutic Area in which the proposed drug, biologic or medical device is to be investigated and the potential impact of a study in this area.	Immunosuppression in Childhood onset systemic lupus erythematosus (SLE)
3. Please submit a single sentence that frames your research question about the use of the drug, biologic, or medical device. Be sure to include the specific indication and outcome measure to be investigated.	Gaps in knowledge/ labeling for these agents include 1) efficacy and safety data in specific pediatric populations (age, gender, race, and ethnicity), 2) optimal dosing intervals, 3) early predictors of therapeutic response, and 4) data on when medications can safely be discontinued without causing disease relapse.
4. For the proposed nomination, what study design would be most effective in providing the needed evidence in pediatrics?	Primary research using prospective data collection without randomization (e.g., observational study)
5. Understanding that there is the potential for ethical concerns with research involving pediatric populations, please describe any potential ethical considerations relevant to the nominated research study.	No concerns
6. Please describe any existing evidence available regarding the proposed research question and the feasibility of the proposed research question, as it relates to the following considerations:	There are studies of tacrolimus in adults with lupus nephritis from Asian / Pacific-rim countries showing efficacy (Bao et al. J Am Soc Nephrology 2008; Chen et al. Am J Kidney Dis 2011; Yap et al. Rheumatology 2014; Liu et al. Ann Intern Med 2014), and there are pediatric studies of tacrolimus after kidney transplantation (Trompeter et al. Pediatr Nephrol 2002; Filler et al. Pediatr Transplant 2005, 2014; Koren et al. Pediatr Transplant 2014; Lin et al. J Pediatr Surg 2015; Michael et al. Pediatr Transplant 2016). The required studies are feasible. The MWPNC (Midwest Pediatric Nephrology Consortium), CARRA (Childhood Arthritis Rheumatology Research Alliance) both have the necessary infrastructure and expertise in pediatric lupus research. Both are or will be recruiting pediatric SLE patients into prospective registries. Collaborative projects such as LuCIN (Lupus Clinical Investigators Network) and the KHI (Kidney Health Initiative) have expressed interest in pediatric research.
7. Please describe any other information you would like to share that supports your nomination.	Scientific needs for pediatric physicians managing cSLE patients include PK data in specific pediatric populations, such as children with high-grade proteinuria and/or nephrotic syndrome, or children in renal failure, or on dialysis. For example, data is badly needed for anuric children with nephritis and cSLE who no longer make any urine. In addition, long-term follow studies or registries would be beneficial to study efficacy and safety. Although there is general agreement that nephritis is a poor prognostic indicator in cSLE, it remains unclear when the presence of lupus nephritis warrants changes in how we use tacrolimus.

FACING CHALLENGES…BREAK THE CYCLE*