

Platform trials for children: history, common goals, and a path forward

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Definitions

- Master protocols: answer more than one question at a time
 - Platform trial: multiple treatments or diseases are evaluated within the same protocol
 - Basket trial: one therapy is tested on more than one disease
 - Umbrella trial: multiple therapies are tested for a single disease
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- Regardless of your personal preference for any of the above, the meeting uses the term “platform trial” for the next 32 hours

Drug Development and Children

- Death of 13 children due to diphtheria anti-toxin from horse serum with tetanus in incubation phase; original Pure Food and Drugs Act (1906) prohibited misbranded drugs in interstate commerce, ultimately leading to the formation of FDA
- 1937 a company found that a great was to dissolve sulfanilamide was to mix in diethylene glycol; 107 people died, most of them children when and led to FD&C Act of 1938 (drug safe before marketing)
- 1962 Kefauver-Harris Drug Amendments to FD&C (effective + safety), in response to thalidomide, a product that harmed >10,000 children
- 2002 BPCA and 2003 PREA

Initial Results BPCA Exclusivity Program

- By 2006, 115 molecules had at least some data submitted
- 100 “key” labeling changes; 37 had substantially different dosing
- Most substantial differences in children under 2 years
- Uncommon to have substantial dosing differences in adolescents
- Implications of 1/3rd of molecules with substantial dosing difference
- Under estimate because very few of these studies included neonates (let alone neonates <30 weeks EGA)
- Never extrapolate dosing
- Safety assessment is risk : benefit analysis

Lessons Learned BPCA

- It is true that children are not small adults;
- But it is also true that children are not Martians
- Assess extrapolation of efficacy: full, partial, none
 - “Examples” Intra-abdominal infections; analgesia; premature infant BPD
 - “Typically” dosing & safety; some masking; well-powered trial
 - Topic areas for this workshop differ in approach extrapolation
- Divisions can change their approach to extrapolation

First Stage of Research

- Rounding in NICU
- STAMPEDE Trial 2005 oncology, now over 10,000 enrolled
- Opportunistic study of antifungals used in the NICU: moonlighting
 - Fluconazole 3mg/kg every 72 hours (9 or 10mg/kg/day)
 - Micafungin 1 or 1.5mg/kg/day (10mg/kg/d)
 - Voriconazole not data (therapeutic drug monitoring)
- Stage 1 of the 3 well-known stages of research:
 - 1) No one can do this (even though, someone in the world is doing it)

The Why



650g 24wk infant, lesions develop while on 7mg/kg lipid complex amphotericin; changed to voriconazole + micafungin

Total Number of Molecules Studied Under PTN 2010-2024

Abatacept	bumetanide	dexmedetomidine	gentamicin	levofloxacin	nalbuphine	remdesivir	tocilizumab
actinomycin D	buprenorphine	dextroamphetamine	granisetron	lidocaine	nicardipine	Ribavirin	topiramate
acyclovir	bupropion	diazepam	griseofulvin	lisinopril	nifedipine	rifampin	tranexamic acid
alfentanil	caffeine citrate	Diazoxide	guanfacine	lithium	norepinephrine	risperidone	trazodone
amikacin	calfactant	digoxin	haloperidol	lopinavir/ritonavir	olanzapine	rocuronium	TMP/SMX
aminocaproic acid	Canakinumab	dopamine	heparin	lorazepam	ondansetron	rosuvastatin	valganciclovir
amiodarone	cefdinir	doxycycline	hydrochlorothiazide	lurasidone	Oseltamivir	Ruxolitinib	valproic acid
amoxicillin	cefepime	duloxetine	hydrocodone	meropenem	oxcarbazepine	Sarilumab	vancomycin
amphotericin	ceftazidime	epinephrine	Hydrocortisone	metformin	oxycodone	sertraline	vasopressin
ampicillin	cidofovir	escitalopram	hydromorphone	methadone	pantoprazole	sevelamer	vecuronium
anakinra	ciprofloxacin	etomidate	hydroxocobalamin	methylphenidate	paroxetine	sildenafil	venlafaxine
aripiprazole	citalopram	fentanyl	hydroxyurea	methylprednisolone	pentobarbital	simvastatin	verapamil
Aspirin	clindamycin	fluconazole	Infliximab	metoclopramide	pip-tazo	nitroprusside	vincristine
atropine	clobazam	fluvoxamine	Interferon	metronidazole	poractant alfa	spironolactone	voriconazole
azithromycin	clonidine	fosfomycin	isotretinoin	midazolam	pralidoxime	sumatriptan	warfarin
baclofen	clozapine	fosphenytoin	ketamine	milrinone	pravastatin	terbutaline	ziprasidone
beractant	Colchicine	furosemide	Ketorolac	molindone	propofol	ticar-clav	zolpidem
bosentan	cyclobenzaprine	Gabapentin	labetalol	morphine	propylthiouracil	timolol	
Budesonide	dexamethasone	ganciclovir	levetiracetam	nafcillin	quetiapine	tobramycin	

Pediatric Trials Network
Molecules from Platform 2018-2024

Summary Pediatric Trials Network Platform Trials
POPS: Pediatric Opportunistic PK Study
CUDDLE: Mother-infant dyads, breast milk
ECMO: extra-corporeal membrane oxygenation
Obesity: medicines commonly used in obese children
ANA: Anesthetics and Analgesics
AED: Anti-epileptic drugs

Product	Therapeutic area	IND	Start Up	Enrolling	CSR at FDA	Label negotiations	Next milestone
Ampicillin	Infectious Diseases	125,250					Label change 2018
Lithium	Psychiatry	73,844					Label change 2018
Mercy BabyTAPE	Devices	K191174					Label change 2019
Acyclovir	Infectious Diseases	106,153					Label change 2019
Doxycycline	Infectious Diseases	133,951					Label change 2020
Caffeine citrate	Neonatology	125,696					Label change 2020
TMP-SMX	Infectious Diseases	113,645					Label change 2020
Clindamycin	Infectious Diseases	115,396					Label change 2020 & 2021
Diazepam	Neurology	131,971					Label change 2021
Rifampin	Infectious Diseases	130,531					Label change 2023
Levetiracetam	Neurology	139,604					Label change 2023
Fluconazole	Infectious Diseases	76,813					Label change 2024
Oxycodone	Lactation/Pain	135,227					Label change 2024
Oxcarbazepine	Neurology	139,604					Label change 2024
Furosemide	Neonatology/Pulm	120,933					Label change 2024
Metronidazole	Infectious Diseases	108,209					Label change
Ondansetron	Lactation	135,227					Label change
Topiramate	Neurology	139,604					Label change
Nifedipine	Lactation/Cardiology	135,227					DASH submission
Valproic acid	Neurology	139,604					DASH submission
Timolol	Dermatology	129,154					DASH submission
Digoxin	Cardiology	141,063					DASH submission
Hydromorphone	Anesthesiology/Pain	136,790					CSR completion
Pip-tazo	Infectious Diseases	108,209					CSR completion
Aripiprazole	Psychiatry	132,329					CSR completion
Risperidone	Psychiatry	132,329					CSR completion
Sertraline	Lactation/Psychiatry	135,227					CSR completion
Azithromycin	Lactation/ID	135,227					CSR completion
Tranexamic acid	Lactation/Hematology	135,227					CSR completion
Escitalopram	Lactation/Psychiatry	135,227					CSR completion
Labetalol	Lactation/Cardiology	135,227					CSR completion
Metformin	Lactation/Endo	135,227					CSR completion
Ciprofloxacin	Lactation/ID	135,227					CSR completion
Methadone	Anesthesiology/Pain	119,459					CSR completion
Sildenafil	Neonatology/Pulm	226,396					Enrollment completion
Terbutaline	Pulmonology	144,549					Enrollment completion
Ketamine	Anesthesiology/Pain	136,790					Enrollment completion
Ketorolac	Anesthesiology/Pain	136,790					Enrollment completion
Morphine	Anesthesiology/Pain	136,790					Enrollment completion
Amoxicillin	Lactation/ID	135,227					Enrollment completion
Buprenorphine	Lactation/Pain	135,227					Enrollment completion
Bupropion	Lactation/Psychiatry	135,227					Enrollment completion
Citalopram	Lactation/Psychiatry	135,227					Enrollment completion
Cyclobenzaprine	Lactation/Pain	135,227					Enrollment completion
Duloxetine	Lactation/Psychiatry	135,227					Enrollment completion
Gabapentin	Lactation/Pain	135,227					Enrollment completion
Hydrocodone	Lactation/Pain	135,227					Enrollment completion
Levetiracetam	Lactation/Neurology	135,227					Enrollment completion
Paroxetine	Lactation/Psychiatry	135,227					Enrollment completion
Trazodone	Lactation/Psychiatry	135,227					Enrollment completion
Venlafaxine	Lactation/Psychiatry	135,227					Enrollment completion
Guanfacine	Psychiatry	154,035					Enrollment start
Bumetanide	Pulmonology	174,270					Enrollment start
Methotrexate	Rheumatology	173,907					Enrollment start
Urgent PC	Devices	Q220378					Enrollment start

What about labeling changes

Labeling Changes Using One or More Platform Trials

- **Acyclovir**
- **Ampicillin**
- **Clindamycin (2)**
- **Doxycycline**
- **Fluconazole**
- **Furosemide**
- **Levetiracetam**
- **Meropenem**
- **Oxcarbazepine**
- **Oxycodone**
- **Rifampin**
- **Trimethoprim-Sulfamethoxazole (TMP-SMX)**

Breast Milk Study 2018-2024

CUDDLE (BMS01)

Ciprofloxacin

Doxycycline

Levofloxacin

Amoxicillin

Duloxetine

Buprenorphine

Bupropion

Hydrocodone

Paroxetine

Levetiracetam

CUDDLE (Expansion)

Amoxicillin

Bupropion

Buprenorphine

Duloxetine

Hydrocodone

Levetiracetam

Paroxetine

BMS02 (Botswana)

Dolutegravir

Emtricitabine

Tenofovir disoproxil fumarate

Lamivudine

Overarching Lessons Learned

- PTN uses POPS as a funnel
 - Screening of: Investigators, Sites (300 across PTN trials), Molecules (145), Populations
 - Emerging and difficult populations—neonates (2,700 samples), ECMO (2,000), obesity (6,000), breast feeding (3,000), COVID
 - 33,000 biologic samples, >100 validated assays (>200 methods), >50 analyses completed and moving through FDA pipeline
- Extrapolation or Partial extrapolation—SCAMP <https://pubmed.ncbi.nlm.nih.gov/33902072/>
 - ≤33 wks EGA, <121 days old, cIAI were randomized to 1) ampicillin, gentamicin, and metronidazole; or 2) ampicillin, gentamicin, and clindamycin; or 3) piperacillin-tazobactam and gentamicin at doses stratified by postmenstrual age. (stricture and resistance)
 - Applicable to both extrapolation and partial extrapolation (128 randomized, 52 not randomized)
- Safety—LAPS, risperidone or aripiprazole, long-term safety vs 48 weeks, >500
- Pivotal study—ACTIV-1, enrolled 1,971 abatacept; infliximab; cenicriviroc; or placebo https://jamanetwork.com/journals/jama/fullarticle/2807333?utm_campaign=articlePDF&utm_medium=articlePDFlink&utm_source=articlePDF&utm_content=jama.2023.11043
 - International study

Lessons Learned 1

- Infrastructure and Collaboration
 - POPS1 in 2010, extensive pediatric-specific site infrastructure for opportunistic studies
 - Limited compensation, but the prospect of 20 therapeutics or more meant that each site could support a full time (money after enrollment)
 - Key stakeholder input including the NIH, PTN Steering Committee, and FDA, and continue with site selection, evaluation, activation, and training of sites
 - Vary by sponsor type (NIH v Industry), but we took into account what our sites could deliver
 - Regulatory-grade commercial laboratories for assay development, validation and processing
 - DCRI expertise in pediatric popPK methods
 - Flexibility in bioanalytical methods & procedures, e.g., scavenged sampling for drugs with documented stability, and collection of various types of samples, such as breast milk and plasma PK sample collection in BMS01
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- Industry application—collaboration, stakeholder input, pediatric PK/analysis

Lessons Learned 2

- Flexibility to fill critical knowledge gaps:
 - Opportunistic protocols can be designed to allow for studying variations in PK based on subgroup – i.e. patients on continuous renal replacement therapy, patients with obesity, and those with potential drug-drug interactions.
 - Flexibility in sampling schemes depending on DOI properties: the four antiepileptics in AED01 had wide variations in PK properties and the protocol allowed for varying sampling schemes.
- Industry application—flexibility and compromise around protocol details and sampling schemes, balancing the sites and disease, and the other partners

Lessons Learned 3

- Molecules in common clinical use:
 - when drugs are rarely prescribed, potential problem
 - COVID-19 pandemic, added 15 drugs for COVID and MISC
 - 33 sites; enrolled the first child patient in 6 weeks
 - some worked; and some failed;
 - additional sites cost more on the front end but key to success
- Industry application—some molecules will be more ‘popular’ than others; a subset of sites might be crucial for some molecules more so than others

Lessons Learned #4

- Align the goals of the study and the study setting:
 - Antipsychotic (LAPS) study, inpatient vs outpatient PIs
 - oversampling of young children,
 - where the ontogeny of metabolic enzymes, (CYP2D6)
 - unexpected exposures when adapting an adult popPK
 - had to pivot and now enrolled >500 children
- Industry application: CRO often talk about pediatric sites, but a pediatric site is really 15-20 sub-sites

Lesson Learned #5

- The current state of the electronic health record and the medication administration record, timing of drug administration is not rigorously recorded.
 - Calculating PK parameter estimates with short half-lives
 - Sites require training on the accurate documentation of timing of drug administration and sample collection. Very variable and not always correlated to children's hospitals or major medical centers.
 - Intensive sampling or documentation needs, and trained research-naïve sites on research processes and maintaining high data quality
- Industry implications—as many of you know, a pediatric department has 15 or more clinical divisions, and thus, 15 or more potential performance levels

The Why, Follow Up



Discharged home in a car seat; hearing, vision, and cognition (Bayley score) intact

The 3 known stages of research part 2

- The 3 well-known stages of research:
- 1) no one can do this;
- 2) someone should do this;
- 3) we have always done this.