Best pharmaceuticals for children act [BPCA]

Overseeing a Pediatric Drug Development Program…even during times of crisis

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Perdita…

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

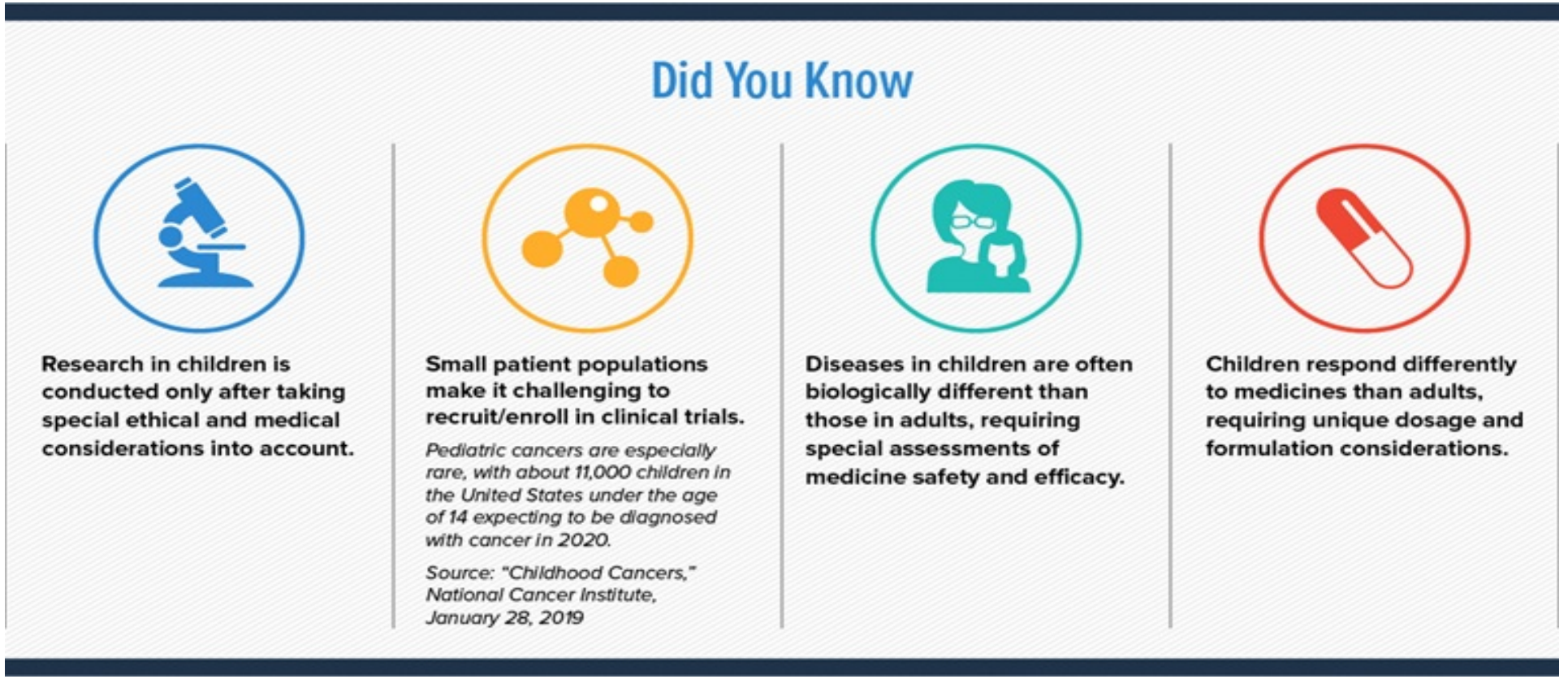
Drug Development

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
- This model disintegrates during times of disaster/crisis

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

Considerations: Unique Challenges



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

Adults	Characteristic	Children
Many	**Number of Trials**	Few (may only be one/ average 2.2 per compound)
Large (thousands)	**Population Available**	Small (hundreds)
May enroll large number	**# Participants/Site**	Few enrolled
Not a major issue	**Ethical Consideration**	Determines feasibility of studies
Testing of volunteers part of drug development	**Available Population**	Healthy children cannot be used for testing
Feasible in large number	**Recruitment**	Pediatric patients difficult to recruit
Participation in study easier to arrange		Logistics of study participation requires coordination around family, school, and work schedules.
Less of a problem	**Intersubject Variability**	A major problem, particularly in infants **(Ontogeny)**
Cost per patient less than in pediatrics		3 or 4 times the number of studies needed to cover developmental continuum

*Experience is generally repetitious

Implications of Unique challenges (can be magnified during times of disaster/crisis)

***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

BPCA Legislative Overview*

BPCA Legislation

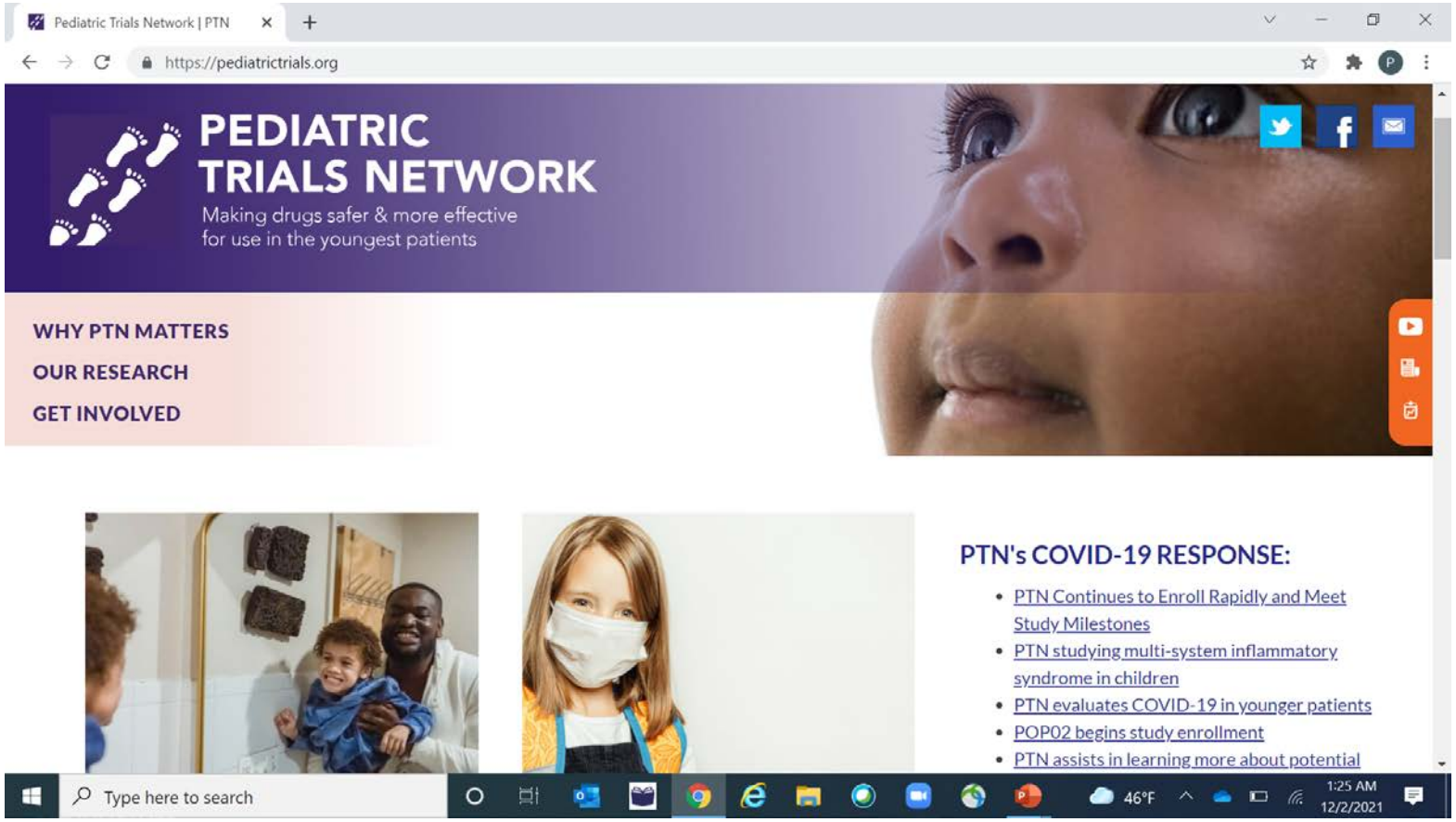
FDA (*on-patent)

- Pharmaceutical Companies' Drug Studies
- Pediatrics Division Oversight

NIH (*off-patent)

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

*NIH BPCA Infrastructure



- Pediatric Trials Network (www.pediatrictrials.org) _Duke Clinical Research Institute
- BPCA Data Coordinating Center _EMMES Corporation
- Logistics Support Team, NIH, FDA (CDER PEDS)

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

Novel trial designs including Standard of Care (SOC) and Opportunistic Trials

Use of Master protocols

Trailblazing efforts in pediatric REGULATORY research

Engagement and experience with MULTIPLE FDA review divisions (meetings for trial designs and trial results)

Device trials

Cost efficiency

SOC protocols

Capitated payment system

Central trial coordination

Use of registries to support trial designs

Promoting Investigator Training

T32 Training Program

Junior Investigators involved in trials

Disaster related priorities

- Collaborations
  - Pralidoxime (organophosphate poisoning—literature-based updates
  - Hydroxycobalamine (cyanide assay dev in collab with NINDS)
- Dual-Purpose Studies
  - Midazolam
  - Doxycycline
- Personal Protective Equipment (PPE)

*Opportunistic Population Pharmacokinetics (PopPK)

- Empirical approach - measure drug levels in patients undergoing routine care
- Study many drugs within a single platform trial
- *With full pediatric extrapolation:* use data for pediatric label
- *With partial extrapolation:* design safer, efficient trials
- ‘Low hanging fruit’ approach, good BUT will only get us so far

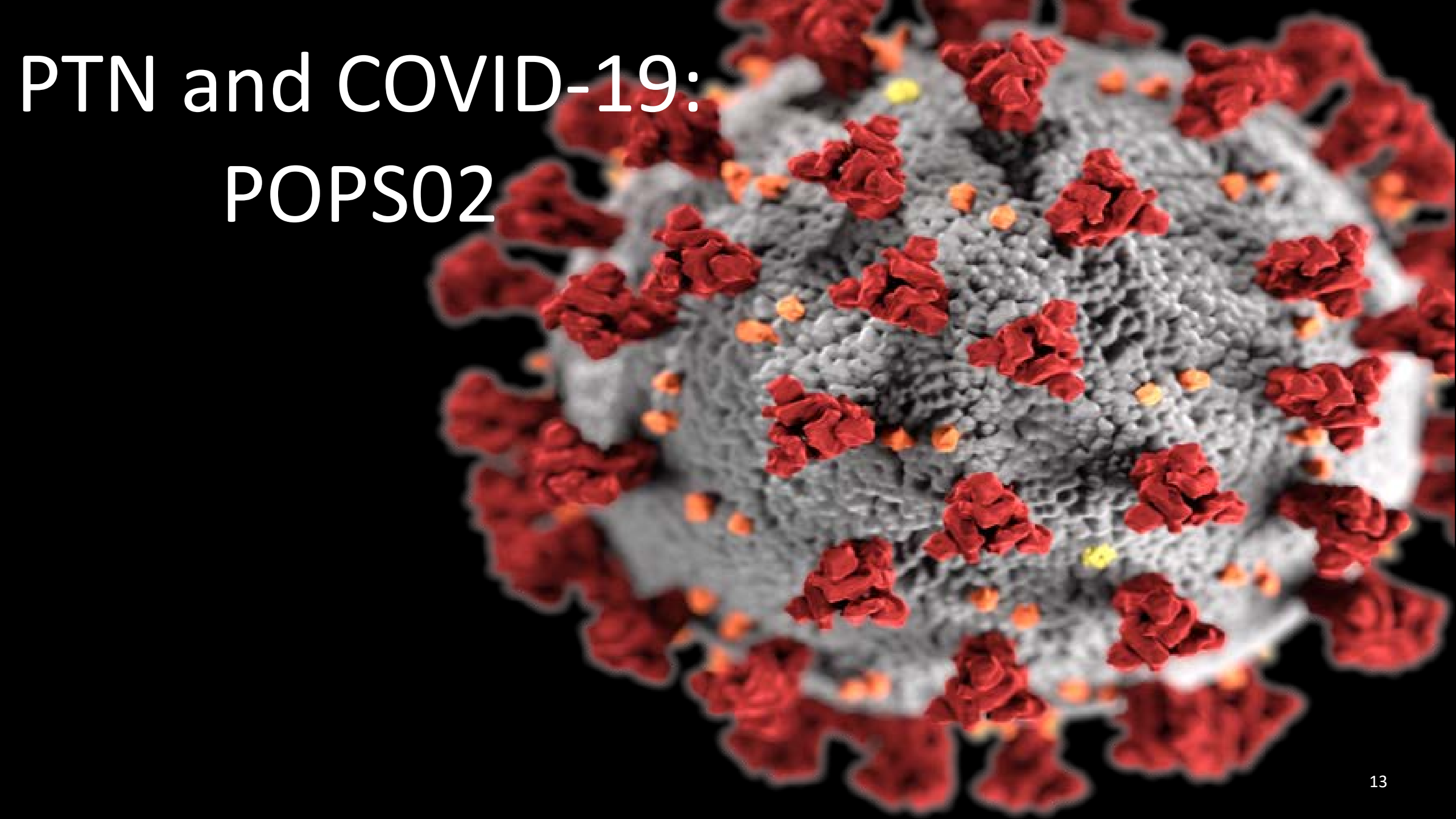
Pharmacokinetics of understudied drugs administered to children per standard of care (POPS)

Protocol Number: NICHD-2019-POPS02

NCT Number: NCT04278404

- 200+ molecules (cumulatively)
- >5000 enrolled patients (<21 years)
- ~100 study sites
- ~40 enrollments/month (PRE-COVID)
- Gives real world PK data
- Can also inform Phase 2/3 trials
- Provides a model for site capacity
  - IDEA States Network
  - INCLUDE Network collaboration
- Special populations (neonates, obese, extracorporeal membrane oxygenation, continuous renal replacement therapy)
- Adaptable to various populations, indications, and even pandemics

PTN and COVID-19: POPS02



*March 2020 the Ultimate PIVOT… COVID-19

- We have had several cases where we have had to adjust to new policies (e.g. central IRB), or conducting new trials with static funds (i.e., the BPCA funding).
- HOWEVER, we have never had to deal with a global pandemic in our lifetimes
  - Are we OK?
    - A central area was generated on the website for all COVID-19 communications.
  - Do we continue?
    - No restrictions on enrollments were placed by the study sponsors.
  - How do we continue?
    - Sites were instructed to follow local requirements and recommendations regarding support of ongoing studies.
  - How do we contribute to understanding this pandemic?

POPS DATA and Timelines

- PK, safety and clinical data collection occurs for up to 90 days
- The SARS-COV-2 appendices(P&Q) collect:
  - demographics, medical history, presenting symptoms
  - SARS-CoV-2 confirmatory testing, results of diagnostic tests to evaluate organ dysfunction (e.g., laboratory data and echocardiogram)
  - clinical assessments and outcomes (including safety)
  - Information collected if NOT treated
  - information on drugs used to treat SARS-CoV-2, information on safety of therapeutics, and blood samples for pharmacokinetics, biomarkers, and genotyping.
- In the **overall POPS study**, there are **~1000 enrolled, 46 sites**
- As of 10/29/21: There are **~578** Sars Co-V-2 + patients, **378** participants have been enrolled under 9 drugs of interest for COVID.
- We have enrolled **146 participants suspected to have MIS-C and 9 with Kawasaki's Disease**.
- *October 2021, POPS became the first study in the CARING for Kids program to submit data to the ARING Data Platform

Some of the changes we experienced, made, and continue to adopt

- During 2020, Several sites withdrew from the PTN, indicating financial and/or logistical impact of COVID-19 as a contributing factor
- Sites supported by DCC-EMMES/PTN by:
  - Supporting essential documents required for site activation and participate execution of ICFs to be executed using DCC provided **electronic signature tools**
  - Uptake and adapting to **remote monitoring**
  - Obtaining **IRB waivers from the requirement of written consent for applicable studies** e.g., minimal risk studies
  - Obtaining **IRB approvals for telephone scripts** for the introduction of the study, and conduct of the consenting “discussions” prior to obtaining consent
- COMMUNICATE!

2022 and beyond…

Disasters happen, Prepare for the Pivot

INFRASTUCTURE (stable yet adaptable)

BUILD UPON YOUR STRENGTH

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
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