Bench to Bassinet: Challenges and Opportunities in Child Health Research

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Disclosures:

- Consultant – Otsuka Pharmaceuticals

Child Health Research

- The problem: pharmaceutical use in children
- The issues: clinical trials in children
- The initiatives: federal and non-federal
- The role of Child Health Investigators in the CTSA Consortium (former CC-CHOC)
- The opportunities: Point Person Project

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Child Health: the Current Problem

For the vast majority of therapies used on children every day in the United States and around the world, clinicians lack basic data to support decisions about the correct dosage, the best type of medication to use, and the appropriate situations to provide treatment.

(Pasquali, et al. Pediatrics 2012)

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Child Health Research: the Issues

- **Low recruitment to clinical trials** *(Pasquali et al, Pediatrics 2012)*
  - Review of ClinicalTrials.gov from 2005 to 2010 identified >60,000 registered trials, but only ~5,000 (<10%) in children <18 yo and ~300 (<1%) in newborns.
  - Factors:
    - Pediatric diseases relatively rare and very diverse (multi-center sites)
    - Lack of pediatric research infrastructure
    - Ethical issues associated with research in children (acceptable risk)
    - Difficulty in establishing valid clinical endpoints; high liability
  - Other issues
    - Limited enrollment (clinically meaningful, generalizable information)
    - The number of drug intervention trials in children declined over time; with fewer Phase 0 to II versus Phase III to IV trials.
    - Many trials enrolled patients outside the United States

Child Health Research: the Issues

- **Fragmented Infrastructure**
  - Currently a hodgepodge of existing networks (NICHD sponsors ~60 specialized child-maternal health clinical research programs); new networks designed for specific trials; and *ad hoc* networks formed by sponsors, e.g. pharmaceutical companies.
  - Cost of fragmentation:
    - Inconsistency in methods
    - Divergent terminology
    - Incompatible informatics platforms
    - Variability in data standards and quality
    - Cyclical infrastructures – repetitively built, dismantled, rebuilt
  - Need sustainable/scalable infrastructure (core tools, processes, people, data)

Connor et al. Sci Transl Med 2014

Child Health Research: the Issues

- **Data quality**
  - Need for universal best practices in pediatric data quality
  - Harmonizing of ontologies, nomenclature, and data standards
  - An interoperable platform for data collection, management, analysis, and validation
  - Robust methodology for information exchange with the electronic health record
  - Culture change: move from parochial to collaborative
  - Training: competencies in clinical informatics and data quality

Connor et al. Sci Transl Med 2014

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Child Health Research: the Initiatives

Federal legislative initiatives aimed at stimulating research in children (e.g. drug dosing, safety, and efficacy):

- The FDA Modernization Act (1997)
  - Includes the Pediatric Exclusivity Provision
- The Best Pharmaceuticals for Children Act (BPCA; 2002, 2007)
- The Pediatric Research Equity Act (PREA; 2003, 2007)
- The Creating Hope Act (2011)
- The FDA Safety and Innovation Act (FDASIA; 2012)

NICHD recently funded the Pediatric Trials Network

Child Health Research: the Initiatives

Pharma, federal agencies, advocacy groups, international efforts:

- Pharmaceutical Research and Manufacturers of America – development of ~300 medicines in development to address child health needs
- NCATS, NICHD, FDA Office of Orphan Product Development – all working to advance product development for rare diseases
- International Rare Diseases Research Consortium (IRDiRC)
- Europe - Pediatric Regulation requires applications for new medicines to include a Pediatric Investigational Plan (PIP)

Child Health Research: the Initiatives

Pediatrics Trial Network (PTN)

- Established by NICHD in 2010 to address knowledge gaps in pediatric therapeutics
- Contract-based clinical coordination center
  - Management and site performance
  - Clinical trial performance
  - Formulations development
  - Clinical pharmacology study design and data analysis
  - Device development and validation

https://pediatrictrials.org

Child Health Research: the Initiatives

Pediatrics Device Consortium (PDC)

- Instituted by FDA in 2009 to facilitate the development of pediatric devices; 7 sites funded in FY13
- Establish Centers of Excellence:
  - Provide resources and consultation for new pediatric devices and adaptation of marketed devices for use in children
  - Operational model:
    - By leveraging expertise, facilities, and existing relationships and deploying small funding awards, serve as a bridge/catalyst to connect diverse sectors, organizations

www.fda.gov/ForIndustry/DevelopingProducts forRareDiseasesConditions/PediatricDeviceConsortiaGrantsProgram.htm

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CTSA Program: Child Health Initiatives

- Child health: a focus of the CTSA Program since its inception in 2006.
- The CTSA Consortium Child Health Oversight Committee (**CC-CHOC**) established as one of the CTSA Consortium's leadership committees.
- Goals:
  1. Provide a national forum to identify collaborative opportunities for facilitating clinical and translational research on child health
  2. Set priorities for the development of collaborative efforts and standard approaches/metrics, with a focus on drug discovery and device development
  3. Coordinate CTSA-wide efforts on child health research
  4. Train new child health research investigators
- Researchers in 55/62 CTSAs have participated in CC-CHOC activities.

CTSAs: Facilitating Child Health Research

Initiatives

- Engage investigators in regulatory-oriented clinical trials through a structured system of interactions among consortium-participating institutions.
- Formalize new models of institutional review board (IRB) processes for multicenter clinical trials.
- Characterize obstacles to the recruitment of pediatric subjects into clinical trials.
- Develop metrics for pediatric clinical trials.
- Advance education in child and maternal product development.

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CC-CHOC Strategic Priorities:

1. **The Point Person Project:** designed to ensure that connections are made to respond to collaborative opportunities among industry, research networks, and investigators with relevant expertise for protocol and trial development and implementation.

2. **Federated IRB model**: effort to provide a thorough and flexible IRB process to facilitate multi-site pediatric clinical trials, through the harmonization of policy and regulatory aspects of child health research, including efforts to standardize relevant terminology, case definitions, diagnostic criteria, and core outcome measures.

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CC-CHOC Point Person Project

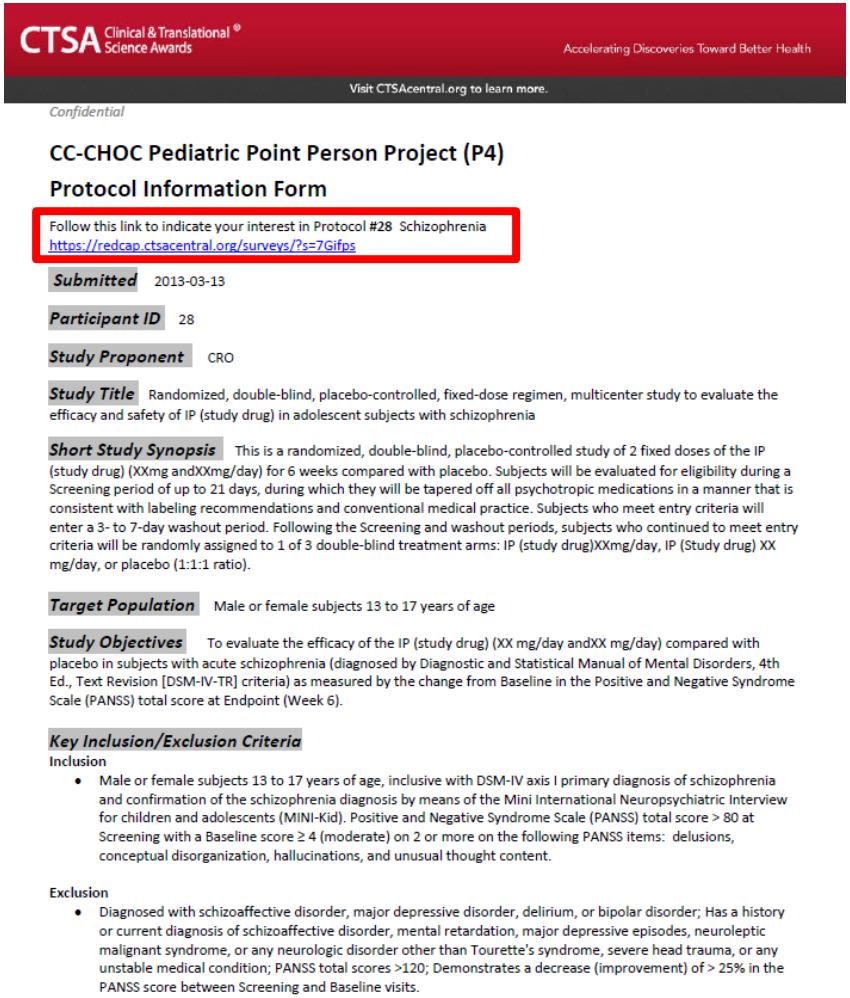
- **Point Person ("navigator") at each CTSA site**
  - Designed to review & respond to child health collaborative clinical research opportunities from a central source using a structured format
  - Direct opportunities to local investigators with expertise & potential interest
- **Pilot project launched in 2012**
  - One year pilot with information dissemination to all Point Persons, structured teleconferences for interested parties and follow up
- **Evaluation**
  - Survey (responses from 85% of 55 CTSAs with CH programs)
  - Review of progress of submitted protocols

Huskins et al. 2014

CC-CHOC Point Person Project

Structured Form

- Proponent
- Title
- Short study synopsis
- Target population
- Study objectives
- Key inclusion/exclusion criteria
- Enrollment details



CTSA Clinical & Translational Science Awards — Accelerating Discoveries Toward Better Health

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CC-CHOC Pediatric Point Person Project (P4)

Protocol Information Form

Follow this link to indicate your interest in Protocol #28 Schizophrenia
https://redcap.ctsacentral.org/surveys/?s=7Gifps

Submitted 2013-03-13

Participant ID 28

Study Proponent CRO

Study Title Randomized, double-blind, placebo-controlled, fixed-dose regimen, multicenter study to evaluate the efficacy and safety of IP (study drug) in adolescent subjects with schizophrenia

Short Study Synopsis This is a randomized, double-blind, placebo-controlled study of 2 fixed doses of the IP (study drug) (XXmg andXXmg/day) for 6 weeks compared with placebo. Subjects will be evaluated for eligibility during a Screening period of up to 21 days, during which they will be tapered off all psychotropic medications in a manner that is consistent with labeling recommendations and conventional medical practice. Subjects who meet entry criteria will enter a 3- to 7-day washout period. Following the Screening and washout periods, subjects who continued to meet entry criteria will be randomly assigned to 1 of 3 double-blind treatment arms: IP (study drug)XXmg/day, IP (Study drug) XX mg/day, or placebo (1:1:1 ratio).

Target Population Male or female subjects 13 to 17 years of age

Study Objectives To evaluate the efficacy of the IP (study drug) (XX mg/day andXX mg/day) compared with placebo in subjects with acute schizophrenia (diagnosed by Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Text Revision [DSM-IV-TR] criteria) as measured by the change from Baseline in the Positive and Negative Syndrome Scale (PANSS) total score at Endpoint (Week 6).

Key Inclusion/Exclusion Criteria

Inclusion

- Male or female subjects 13 to 17 years of age, inclusive with DSM-IV axis I primary diagnosis of schizophrenia and confirmation of the schizophrenia diagnosis by means of the Mini International Neuropsychiatric Interview for children and adolescents (MINI-Kid). Positive and Negative Syndrome Scale (PANSS) total score > 80 at Screening with a Baseline score ≥ 4 (moderate) on 2 or more on the following PANSS items: delusions, conceptual disorganization, hallucinations, and unusual thought content.

Exclusion

- Diagnosed with schizoaffective disorder, major depressive disorder, delirium, or bipolar disorder; Has a history or current diagnosis of schizoaffective disorder, mental retardation, major depressive episodes, neuroleptic malignant syndrome, or any neurologic disorder other than Tourette's syndrome, severe head trauma, or any unstable medical condition; PANSS total scores >120; Demonstrates a decrease (improvement) of > 25% in the PANSS score between Screening and Baseline visits.

CC-CHOC Point Person Project

- 24 protocols information forms received early 2012 - early 2013
- 23/24 distributed with 40/55 sites actively participating

Protocol form source:

- 15 (65%) CRO
- 6 (26%) Industry
- 2 (9%) Individual investigators

Disease Focus

- Wide range of disorders affecting children

- **Age Range**
  - Newborn to Adolescent (most ages 6-17 yrs)

CC-CHOC Point Person Project

Outcomes:

- 40/55 CTSAs with child health components responded:
  - 290 responses, mean 7 responses / site (range 0-18)
  - 74% indicated “interested” or “need more information”
- 15 protocols submitted by a CRO:
  - Contact made with 69 investigators at CTSAs, including 39 investigators new to the CRO
    - CDAs sent to 67, completed by 54 (81%)
    - Site information forms sent to 40, completed by 20 (50%)
- 16 CTSAs involved in selection, start-up, and or enrollment of at least 1 protocol

CC-CHOC Point Person Project

Next Steps:

- PPP currently paused; re-evaluation of the effort
- Proposed future roles
  - Collaboration among CTSA sites for funded studies, particularly publically-funded studies
  - Expert review and advice for studies in development
  - Subject recruitment and enrollment
- Design and implement robust project evaluation
- Interactions/collaborations with other child health networks

IOM Report: Recommendation 7

Strengthen Clinical and Translational Research relevant to Child Health

NCATS should collaborate with CC-CHOC to:

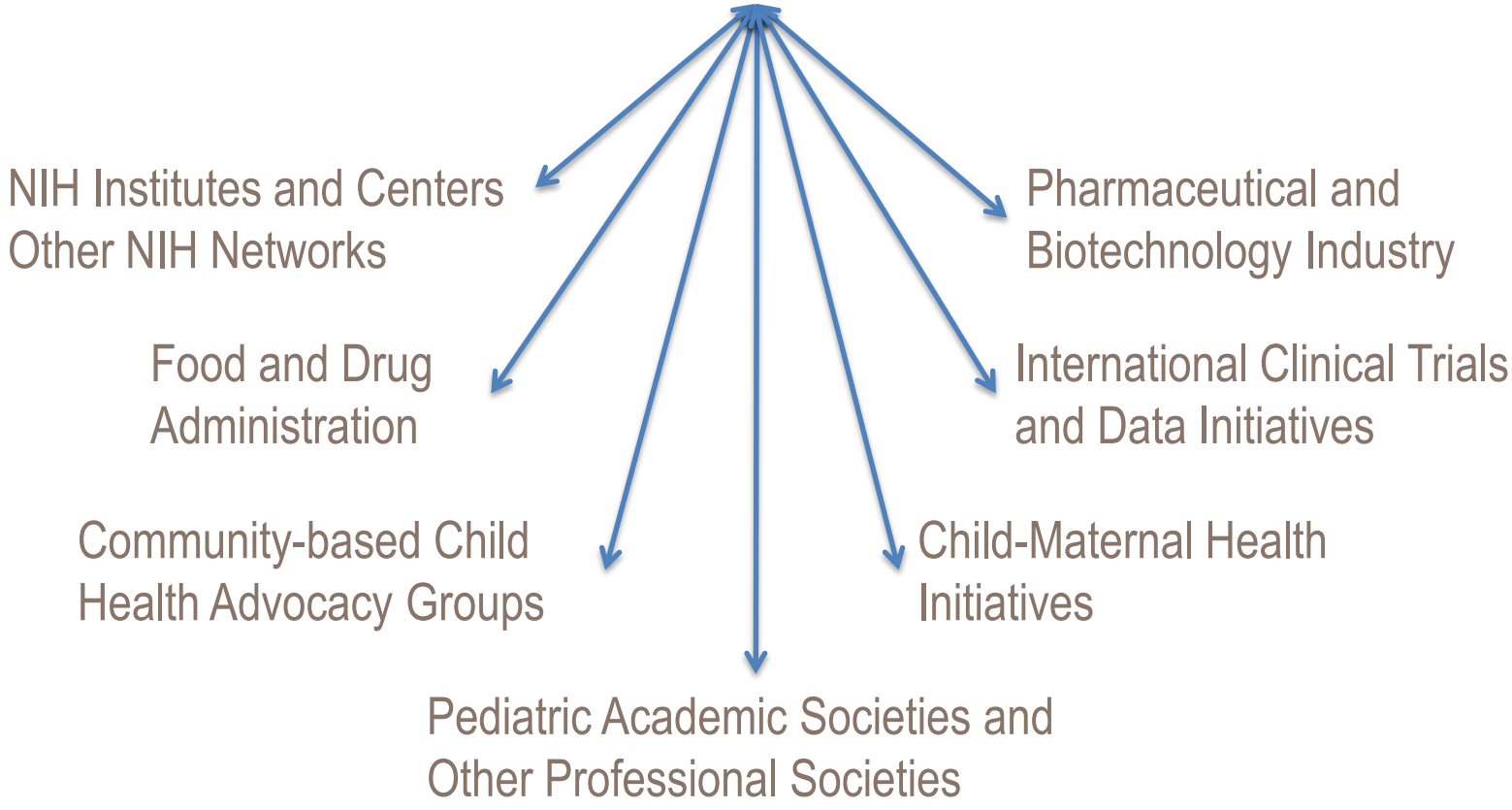
- Identify and designate CTSAs with expertise in child health research as leaders in advancing CTR relevant to child health and as coordinators for CTSA program-wide efforts and other collaborative efforts in this research;
- Promote and increase community engagement specific to child health by:
  - Raising awareness of the opportunities for children and families to participate in research efforts with clear information conveyed on the risks and potential benefits;
  - Involving parents, patients, and family members more fully at all stages of the research process, including identifying priorities and setting research agendas.

CTSA: an Organizing Nexus for Child Health Research

CTSI

Child Health Research Nexus

A facilitator of Child, Maternal, and Lifecourse Clinical and Translational Research



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