Clinical Trials in Children and Families: the ECHO ISPCTN in Kansas

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Intro to IDeA, ECHO, ISPCTN & SPeCTRE

Ann Davis, PhD, MPH, ABPP
What is IDeA?

- Institutional Development Award identified 23 states & Puerto Rico that received lower levels of support from NIH.
- Established by Congressional mandate in 1993 and managed by the National Institute of General Medical Sciences (NIGMS).
- Goal: broaden the geographic distribution of NIH funding for research.
  - Enhancing investigator ability to compete successfully for additional research funding through faculty development & institutional research infrastructure enhancement
  - Serving the unique populations of these states, such as rural and medically underserved communities.

What is ECHO?

- Environmental influences on Child Health Outcomes (ECHO)
  - Mission: understand the effects of a broad range of early environmental influences on child health and development
  - 2 aims:
    - Enhance the health of children and adolescents through research that may help inform healthcare practices, programs, and policies
    - Create a culture that helps teams of child health researchers work together to achieve the best results
- 5 key areas:

Research in Children

- Major gaps in research about and with children
- Clinical care of children often relies on adult research¹
- 2000 – congress authorized the Children’s Health Act of 2000
- National Children’s Study (NCS)
  - Pilot: 2009-2013
  - Ended prematurely in 2014
- Need a new approach

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ECHO = TWO Types of Research

**OBSERVATION:**
Understand what influences children's health as they grow and develop.

**INTERVENTION:**
Test how much making changes in children's lives will enhance their health.

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ECHO-wide cohort

Create the ECHO-wide cohort

- Start with ECHO-wide cohort
- Participate in a single data platform to conduct site-specific and national research
- Integrate site-specific data

- Goal: >50,000 children

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ECHO – Cohorts & ISPCTN

ISPCTN

- Cohorts contribute to a single data platform to conduct site-specific and national research
- Integrate site-specific data
- Goal: >50,000 children

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Source: ECHO Overview slides from echochildren.org
What is ISPCTN?

- IDeA States Pediatric Clinical Trials Network (ISPCTN)
- 18 sites, each in an IDeA State

Why target states with high rural and underserved populations?
- Infants and children living in rural areas and states are less likely than those living in other states to have a chance to enroll in clinical research

Goals of Network:
- Perform of state-of-the-art clinical trials with rural and underserved children
- Capacity building
- Success of network (over success of any one site)

ECHO ISPCTN

What is SPeCTRE 2.0?

- Sunflower Pediatric Clinical Trials Research Extension (SPeCTRE)
- 2.0 = We are in our second cycle of funding (through 8/31/25)
Goals of SPeCTRE 2.0

- 3 aims
  1. Improve pediatric research capacity through professional skills development of clinicians and researchers in Kansas
  2. Bring state-of-the-art pediatric clinical trials to children living in rural and underserved areas of Kansas
  3. Evaluate and improve clinical trials recruitment and performance in rural and underserved areas of Kansas

- Key performance metrics:
  - Time to contract
  - Time to IRB approval
  - Time to first patient recruited
  - Time to last patient recruited
  - Expansion of skills (individualized skill development plans)

Interested in research? How can we help you?

adavis6@kumc.edu

What is a Research Coordinator and what do they do?

Kristina Foster, MS, RN, APRN-BC, CCRP
Clinical Research Coordinator (CRC or RC)

- Person responsible for conducting clinical trials using good clinical practice under the guidance of a Principal Investigator
- The relationship is like….
  - Doctor is to nurse/APRN like
  - PI is to RC

Who are RC's?

- Variety of clinical and non-clinical backgrounds
  - Nurse, RT, Dieticians
  - Scientists, Lawyers 😊
- Analytical, methodical, attention to detail
- Investigative, intellectual, introspective, inquisitive
- Efficient organizational skills
- Independent (education, work, etc)
- Team player, collaborative
- Effective interpersonal/communication skills
- Project management

Training: Competency Domains

- Scientific Concepts and Research Design
- Ethical and Participant Safety Considerations
- Investigational Products Development and Regulation
- Clinical Study Operations
- Study and Site Management
- Data Management and Informatics
- Leadership and Professionalism
- Communications and Teamwork
What do RC’s do?

3 key time points with different responsibilities:
1. Before starting the clinical trial
2. During the conduct of the clinical trial
3. After finishing the clinical trial

2 key themes:
- Adhere to research regulatory standards
- Adhere to ethical standards

What do RC’s do?

- **BEFORE the clinical trial:**
  - Answer/submit feasibility
  - Prepare research budgets
  - Assist with contracts
  - Maintain detailed records of study activities
  - Ensure necessary supplies/equipment are in stock and in working order
  - Regulatory documents
  - Submit to IRB (local/central)
  - Signatures (all study personnel)

What do RC’s do?

- **DURING the clinical trial:**
  - Oversee smooth running of the trial
  - Assist with subject recruitment
  - Engage with subjects
  - Recruitment/Screening/Enrolling/Retention
  - Understand concerns
  - Consent
  - Inform about study objectives
  - Monitor to ensure adherence to study rules/activities
  - Study payments
  - Collect/enter data
  - Manage research budgets
  - Maintain detailed records
What do RC’s do?

- AFTER the clinical trial:
  - Complete data entry, code, analyze
  - Complete regulatory binder
  - Study closeout activities
  - Participate in writing groups

“Five C’s” of a Good CRC

- COORDINATION
  - Time to study startup
  - Navigate strict eligibility criteria
  - Patient travel and other issues
  - Data monitoring and reporting
  - Promotion/awareness of clinical trials

- CONNECTION
  - Rapport
  - Accountability
  - Transparency
  - Empowerment

- COMMITMENT
  - Willingness to be challenged
  - Seeks ways to overcome obstacles
  - Exceeds minimal expectations

- COMMUNICATION
  - Ensure participant understanding
  - Develop synergistic relationships

- COLLABORATION
  - Develop partnership
  - Become a clinical research resource

Links:
- https://pima.mycarefocus.org/2018/07/12/what-is-a-clinical-research-coordinator/
- https://acrpnet.org/2018/08/14/the-anatomy-of-a-great-clinical-research-coordinator/
How to get involved in research

Kristina Foster, MS, RN, APRN-BC, CCRP

Getting Started

- Figure out what interests you – unique idea or patient population
- Find a mentor(s) who is/are conducting research
- Find collaborators (research networks, etc)
- Utilize NIH resources to find funding of interest
  - [https://grants.nih.gov/funding/searchguide/index.html](https://grants.nih.gov/funding/searchguide/index.html)
  - Don’t hesitate to reach out to NIH program officers for more info

NIH Resources

[https://researchtraining.nih.gov/infographics/physician-scientist](https://researchtraining.nih.gov/infographics/physician-scientist)
Training Requirements to Participate

- CITI Training
  - Institution specific training may vary slightly
- Good Clinical Practice (GCP)
- Human Subjects Protection (HSP)
  - May be specific 'special populations' modules to include
- Responsible Conduct of Research (RCR)
- License
- Current
- Current CV
  - Signed/dated copy

Perspectives of a new Site PI in the ECHO ISPCTN

Krishna Dummula, MD
Clinical Assistant Professor of Pediatrics
KU School of Medicine & UMKC School of Medicine

Challenges to conducting pediatric clinical trials

- Investigator Challenges
- Scientific Challenges
- Recruitment Challenges
- Administrative Challenges

Challenges to conducting pediatric clinical trials

- Investigator Challenges
  - Time and financial demands of clinical practice
  - Inadequate research training
  - Locating funding
  - The complexity of regulations and contracts
  - Lack of local supportive infrastructure
  - Data collection challenges
  - Securing protected research time from the institution
  - Overall shortage of personnel

Scientific Challenges
- Inadequate understanding of methodology
- Pediatric populations display large heterogeneity
  - Different background diseases
  - Maturation aspects
- Identifying age-appropriate clinical outcomes
- Prolonged follow up needs
- Divergence between research physicians and community practitioners
  - Greatest challenge to translating study results into clinical practice

Recruitment Challenges
- Compared with adults, children have lower prevalence of diseases
- Eligible populations for research studies are often small and geographically dispersed
- Identifying large numbers of children with a phenotype of medical interest is challenging
- Limited involvement of community physicians in clinical research

Challenges to conducting pediatric clinical trials

- Administrative Challenges
  - Inadequate funding
  - Complex regulations and excessive monitoring
  - Overtly restrictive interpretation of privacy laws
  - Narrow incentive for physician participation
  - Training and retention of clinical investigators


Single Center Studies

- Determines feasibility and clinical relevance
- Identifies outcome measures, plausible effect sizes, and the designs most likely to succeed
- Possible conclusions:
  - Insufficient information to proceed with the new treatment strategy, or
  - Conversely, suggests that the accumulating evidence warrants a larger multi-center study or adopt the new treatment based on a cumulative meta-analysis.
- Runs the risk of overestimating treatment effect 1,2
- Often lacks scientific rigor or external validity required to support widespread practice changes 3
- Prerequisite to a multicenter trial

2. Bafeta et al., BMJ 2012;344:e813

Attributes of Multicenter Trials

- Rapid accrual of study participants
- Larger, more informative, sample sizes
- Shorter duration of trials
- Greater heterogeneity with respect to pre-randomization attributes of study participants and co-interventions
  - Hence, greater generalizability

Advantages of Clinical Research Networks

- Connect researchers who are physically separated
- Facilitate sharing of expertise and resources
- Exchange of valuable skills
- Increase research involvement
- Build research capacity
- Develop a research culture
- Benefits to participation in a research network
  - Access to large and diverse patient populations
  - Increased funding opportunities
  - Access to support staff who can facilitate the research projects
  - Opportunities for professional development
  - Mentorship by experienced researchers
- Increase research involvement
- Build research capacity
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Components of Multicenter Trials

- Principal Investigator / Steering Committees
  - Frame the research question
  - Assess scientific, ethical and financial feasibility
  - Create consensus
  - Create opportunity for input from potential collaborators without undue delay of the study
- Coordinating Center
  - Expertise in biostatistics, computing and epidemiology
  - Expertise in medicine and management
  - Responsible for the development of policies and procedures manual(s) and data collection forms
  - Organization of meetings and communications
  - Data management and data analysis

Components of Multicenter Trials

- Engagement of Clinical Sites
  - Determine feasibility
  - Estimate staffing needs
  - Gauge the level of institutional support
- Ensuring success of a multicenter study
  - Provide optimal time for site directors to understand the needs of the study
  - Give site directors an opportunity to contribute to the study protocol to enhance their commitment
  - May delay the study initiation but ensures consensus and leads to increased engagement
Responsibilities of a Site PI in a multicenter trial

- Supervise conduct including those delegated with trial activities
- Conduct study in accordance with protocol
- Satisfy and maintain adherence to local regulatory requirements
- Ensure adequate enrollment
- Maintain adequate training of site personnel
- Ensure integrity of study data
- Protect the rights, safety and welfare of patients
- Submit study documents: adverse events, progress reports, deviations from investigational plan

Mentz RJ and Peterson ED. Circulation. 2017 Mar 28; 135(13): 1185–1187

ESC NOW
Eating, Sleeping, Consoling for Neonatal Opioid Withdrawal

Krishna Dummula, MD
Clinical Associate Professor of Pediatrics
KU School of Medicine & UMKC School of Medicine

- Substantially impacts families, including pregnant women
- 5-fold increase in the incidence of neonatal abstinence syndrome (NAS) 2004 to 2014
- Incidence continues to increase
- Between 2010 to 2017, the estimated rate of NAS increased from 4.0 to 7.3 per 1,000 birth hospitalizations.


The Opioid Epidemic
Consequence of abrupt discontinuation of chronic fetal exposure of opioids in utero

A constellation of neurologic, gastrointestinal, and musculoskeletal disturbances associated with opioid withdrawal
- Increased tone
- Tremors
- Poor feeding
- Poor sleep
- Poor consoling
- High pitch cry

Treatment
- Variable practices across hospitals
- Frequent use of opioids with various approaches
- Growing interest in non-pharmacologic management

Neonatal Opioid Withdrawal Syndrome (NOWS)

- Multiple knowledge gaps remain despite the severity of the problem
  - Optimal assessment tools
  - Optimal treatment approach – pharmacologic vs non-pharmacologic care
  - Optimal weaning approach for pharmacologic care
  - Long term effects of NOWS on children after prenatal exposure

NOWS Knowledge Gaps

- Young et al., 2021:
  - Cross-sectional retrospective study of 1377 infants
  - Born between 07/01/2016 to 06/30/2017
  - 30 participating hospitals nationwide
  - Site-to-site variation was measured across 3 major domains
    - Hospital characteristics
    - Maternal and infant characteristics
    - Management and outcomes
  - Considerable site-to-site variation in all domains
  - Incidence 4 to 423 cases per 1000 birth admissions
  - Delivery of care at various locations (Nursery/NICU/PICU/Floor)
  - Prenatal care (31%-100%)
  - Pharmacologic therapy (6.7%-100%); non-pharmacologic interventions (2.9%-90%)
  - Mean length of stay: 2-28.8 days
Combined effort of NICHD NRN and ISPCTN
- Launched in 2017 after finding wide variation of NOWS care in 30 research hospitals
- Since 2018, NIH has funded $47.6 million for ACT NOW
- ACT NOW Studies:
  - Eat, Sleep, Console
    - Compare infant outcomes before and after implementation of ESC, an approach prioritizing non-pharmacologic care
  - Weaning Trial
    - Compare rapid vs slow weaning among infants with NOWS treated with morphine or methadone
  - ACT NOW longitudinal study
    - MRI based study to evaluate brain structure and connectivity as well as developmental trajectories in early childhood

Advancing Clinical Trials in Neonatal Opioid Withdrawal (ACT NOW)

Finnegan Neonatal Abstinence Scoring Tool
- Used by 95% of institutions in the United States to:
  - Quantify the severity of withdrawal
  - Guide pharmacologic therapy
- Validity and reliability are not well established
- Lengthy tool
- Inherent subjectivity due to the complexity of the tool
- Tendency to overestimate need for pharmacologic therapy

Observer-rated scale used for last 40 years

ESC Care Tool
- Developed to standardize implementation of the assessment and management components of the ESC Care Approach
  - Simplified function-based assessment
  - Emphasizes non-pharmacologic therapies
  - Family centric approach
- Assessment includes:
  - Feeding effectively within 10 minutes of showing hunger
  - Sleeping undisturbed for ≥1 hour
  - Consoling within 10 minutes
Eating, Sleeping, and Consoling for Neonatal Opioid Withdrawal (ESC-NOW): A Function-Based Assessment and Management Approach

Lead Investigators:
Leslie Young, University of Vermont
Lori Devlin, University of Louisville
Stephanie Merhar, University of Cincinnati

ESC Care Approach

- Evidence to support the ESC Care Approach limited to regional quality improvement work
- Rigorous study of this care approach needed:
  - Unknown efficacy across diverse patient populations
  - Unknown impact on patient safety
  - Unknown effects on family well-being
  - Limited generalizability of published findings
Primary Objective
Determine if the ESC Care Approach will reduce the length of hospital stay in infants with NOWS when compared to usual institutional care with FNAST

Secondary Objective
Determine if use of ESC will improve infant neurobehavioral functioning and family well-being compared to usual institutional care with FNAST

Study Objectives

Stepped-wedge cluster randomized design
- Randomization will occur at the site level (24 sites – Randomized to 8 blocks)
- Each site transitions from usual care to the ESC care approach
- Timing of transition from usual care to ESC randomly assigned

Sample Size
- Approx 2000 infants across 24 sites during the enrollment period
- No data collection during the transition period

Study Design
1. Currently use the FNAST or modification thereof for the assessment of withdrawal severity
2. Provide opioid replacement therapy as part of usual care for infants with NOWS
3. Have nurse management and administrative commitment to transition to the ESC care approach at the randomly allocated time

Site Inclusion Criteria
- Currently use the FNAST or modification thereof for the assessment of withdrawal severity
- Provide opioid replacement therapy as part of usual care for infants with NOWS
- Have nurse management and administrative commitment to transition to the ESC care approach at the randomly allocated time
Transition Period (3 Months)
- Offsite training of gold-star raters
- Training at the site by gold-star raters using didactics and videos on electronic platform
- Biweekly webinars with national experts
- Initial assessment of fidelity

ESC Intervention Periods
- Maintenance of fidelity assessed
- Random sample assessment with just-in-time training
- Monthly webinars with national experts

Caregiver participation (subject to consent) in post-discharge study activities to assess the impact of ESC on:
- Behavioral and development outcomes
- Parental competence and bonding
- Safety outcomes
- Infant growth

Data for the study collected via:
- Medical record review
- Online/telephone surveys
- One face-to-face visit at two years of age

Meet key research gaps identified by the National Institutes of Health (NIH) and the Government Accountability Office (GAO)
- Provide strong evidence regarding efficacy, safety and generalizability of the ESC care approach for management of infants with NOWS
- Determine the impact of the ESC care approach on early childhood and family outcomes
Direct Costs Reimbursement

- Compensation for:
  - Start-up-activities
  - Regulatory documents
  - Local IRB review (Note: Study is being conducted under a single IRB for sites that can cede)
  - Full Local IRB for sites not ceding to the central IRB
  - Study purchased licenses required for the questionnaires used in the trial

- Study purchased licenses required for the questionnaires used in the trial

Training Costs

- ESC Protocol Training (face-to-face travel expenses)
  - Each hospital was allowed up to 2 people to travel for 1 training
- ESC Care Approach Training (face-to-face travel expenses)
  - 3 people from each inpatient clinical location (i.e., newborn nursery, pediatric floor, NICU, etc.) were given gold star rater training
- Hospital Training Costs
  - Each hospital received funds to train all individuals who care for infants with NOWS
  - Estimated 200 nurses per site
  - Some will have more, others less; however, all should be trained
  - Training included modules and on-site training

With COVID, this training was all done remotely

ESC Study Enrollment Status – March 2022

- SPeCTRE had 2 enrolling sites
  - Advent Health Shawnee Mission
  - University of Kansas Medical Center
Learnings of a (new) Site PI

- Success of the study depends on fluidity with which collaborators work together towards a common vision
- Institutional support is essential
  - Physician and nursing buy-in is extremely important
  - Research institute’s help with contracting paperwork
  - Willingness of institutional IRB to cede to an external IRB
- At the site level, figuring out process more than science is a priority
- Understanding the structure and administrative paperwork can appear daunting for a new PI
- Having an experienced research coordinator is a blessing

Incentives to participating as a site PI in a network sponsored multicenter trial

- Upside
  - Contribute to improved patient care
  - Opportunity to learn new techniques
  - Develop collaborations
  - Opportunity to lead sub-studies
  - Contribute to peer-reviewed publications
- Downside
  - Academic credit not commensurate with effort
  - Authorship is a complex issue
  - No perceivable monetary benefit nor likely to gain protected research time

Strategies to improve engagement of clinicians in multicenter trials

- Involvement on study manuscripts (as appropriate based on study contributions)
- Letters of support to supervisors and/or institutional leadership for inclusion in the promotion process
- Access to career-building research education
- Trial activities constituting CME and/or MOC requirements
- Social media recognition