Perinatal Arterial Stroke(PAS): A Multi-site RCT of Intensive Infant Rehabilitation (I-ACQUIRE)

Warren Lo, M.D.,
Nationwide Children's Hospital & The Ohio State University

Sharon Landesman Ramey, Ph.D.,
Virginia Tech Carilion Research Institute, Virginia Tech (Roanoke)

Stephanie DeLuca PhD, Amy Darragh PhD, Jill Heathcock, PhD,
Max Wintermark MD, and Craig Ramey, PhD

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BACKGROUND FOR I-ACQUIRE

- Pediatric arterial ischemic stroke occurs most frequently in infants
  - Estimated incidence of neonatal stroke 1:2500 – 1:7700 live births
  - Incidence of presumed perinatal stroke likely similar
- No consensus rehabilitation for infants with post-stroke hemiplegia
  - Wide array of approaches
    - Weekly low-dose therapy is typical (not evidence-based)
    - Consensus from systematic reviews that constraint-induced movement therapy (CIMT) efficacious in older children with hemiparesis
      - CIMT is considered high-intensity and actively shapes voluntary control
  - No adequately powered RCT of CIMT in infants (< 24 mos)
  - No RCT of signature CIMT focused on infants after stroke
- Our team developed safe & feasible pediatric constraint (CIMT) protocol – known as ACQUIREc (DeLuca, Ramey, & Echols [2006])
  - High therapy dosage of 3 or 6 hrs/day X 20 days
  - Operant conditioning techniques utilizing infant principles of learning
    - Individualized activities & reinforcements, both uni- and bimanual
    - Parents included in treatment planning and delivery

PUBLIC HEALTH IMPACT OF I-ACQUIRE PHASE III TRIAL

- **In U.S., 3400+ new cases/year of Perinatal Arterial Stroke (PAS)**
- **High likelihood of lifelong motor and cognitive impairments, especially hemiparesis**
- **Immense cost burden for families, the healthcare and education systems, and society**

If I-ACQUIRE(at one or both doses) proves efficacious, then the field will have the critically needed Phase III confirmatory evidence to transform rehabilitation and improve clinical outcomes for infants with PAS.

I-ACQUIRE SPECIFIC AIMS

- **Primary Aim:** **Determine the efficacy of I-ACQUIRE at 2 dosage levels compared to U&CT to increase upper extremity skills on the hemiparetic side.**
- **Secondary Aim:** **Determine the efficacy of I-ACQUIRE at 2 dosage levels compared to U&CT to improve use of the hemiparetic upper extremity in bimanual activities.**
- **Exploratory Aim:** **Explore the association between I-ACQUIRE treatment at Moderate and High Doses and gross motor development and cognition (i.e., cross-domain effects of treatment).**

DESIGN FOR PHASE III I-ACQUIRE

Eligibility Screening and Enrollment (N=240)
Perinatal Arterial Stroke (PAS) diagnosis
with confirmatory MRI & hemiparesis (8–24 mos)

Random Assignment (centralized) to
I-ACQUIRE DOSAGE GROUPS

Moderate Dose I-ACQUIRE (N=80) 3 hr/day x 20	High Dose I-ACQUIRE (N=80) 6 hr/day x 20	Usual & Customary Tx (UCT) (N=80) documented

Baseline (pre-treatment) Assessment Battery
Blinded Assessments (video) & Parent Ratings

Implementation of Treatment Protocol (4 weeks)
Active Central Monitoring & Therapy Logs

Post-treatment Assessment Battery: Immediate & 6 mos.
Blinded Assessments (video) & Parent Ratings

UCT Parents offered choice of
I-ACQUIRE Dosage (Crossover)

DETAILS ABOUT ENROLLMENT FOR I-ACQUIRE

- **Inclusion criteria:**
  - **8-24 mos old**
  - **Perinatal AIS confirmed with clinical MRI (high-quality, standardized)**
  - **Hemiparesis at mini-MACS II, III, or IV level**
  - **Parents able to participate in home-based intervention and parent Tx component**
    - **present at least 1 day/wk for therapy and 40-60 min/day at home**
- **Exclusion Criteria:**
  - **Fragile medical health, prior recipt of CIMT ≥ 2 hrs/day x 10 days, Botox within 3 mos**

- **In prior studies of ACQUIRE, parent willingness to enroll is high (93-95%) and attrition rate is low (5-7%)**
  - **Most attrition occurs prior to starting treatment (reasons not related to Tx)**
  - **After starting treatment, attrition about 3% in current trials**

GOING FORWARD

- **Identify 12-13 sites with interest, resources, patient volumes**
  - **Access to research therapists/assessors – We will help through our national network with OTs and PTs**
  - **Anticipated ability to recruit 20 subjects/site over study duration of 3.5 yrs**
  - **Willing to go to homes or have available home-like facilities where out-of-town families can live for 4 weeks (e.g., extended stay hotels, furnished apaetments, Ronald McDonald house) Note: Proposal does not have funding to pay for lodging**

- **Anticipate training therapists and assessors for 6-7 sites at onset then remaining sites after 9-12 months into the project; Travel and salary needed for training are covered by the grant**
- **Eager to meet with new StrokeNet sites and existing sites to have individualized conversations; Copy of the full grant application is available for all who are interested.**

MANY THANKS FOR GUIDANCE AND SUPPORT

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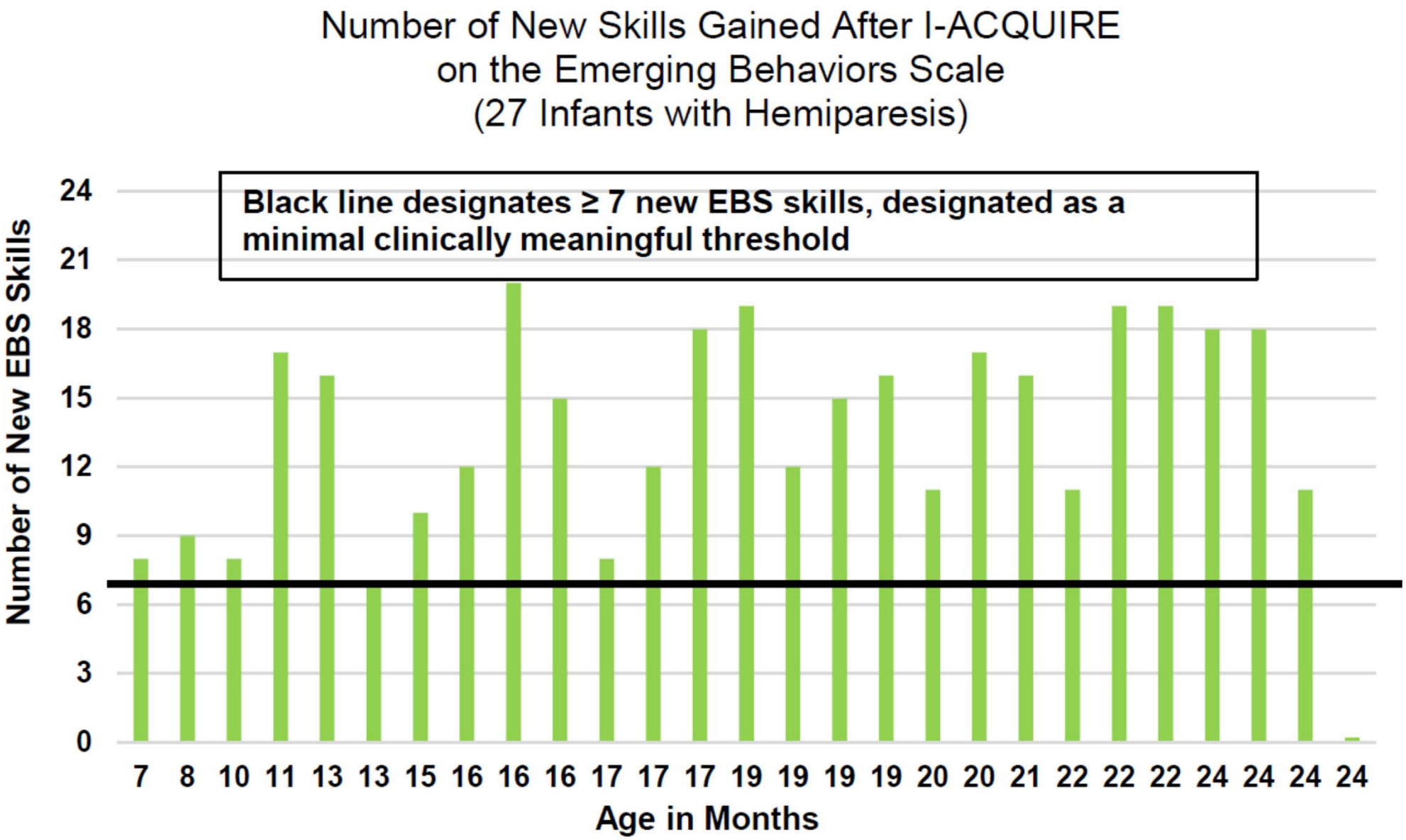
- **Rehabilitation Working Group: Steven Cramer, Steven Wolf, and multiple members of the working group**
- **StrokeNet DMSC: Caitlin Meinzer, Renee Martin, and Yuko Palesch**
- **NINDS: Scott Janis**


Number of New Skills Gained After I-ACQUIRE
on the Emerging Behaviors Scale
(27 Infants with Hemiparesis)
Black line designates ≥ 7 new EBS skills, designated as a minimal clinically meaningful threshold
Number of New EBS Skills
24
21
18
15
12
9
6
3
0
7 8 10 11 13 13 15 16 16 16 17 17 17 19 19 19 19 20 20 21 22 22 22 24 24 24 24
Age in Months

I-ACQUIRE
CORE TREATMENT COMPONENTS

- Constraint of the infant's less-impaired upper extremity for first 17 days of 20 treatment; cast is worn continuously
- High dosages of treatment – either 3 or 6 hrs/day, 5 days/wk for 4 weeks
- Operant conditioning techniques to shape and improve skills and abilities, combined with practice variation
- Provision of therapy in natural settings
- Emphasis on total body and bimanual activities (as well as traditional arm/hand therapy activities)
- Active Parent-Therapist Partnership
- Documentation of daily therapy sessions
- Transfer Package to promote future skill and motor development