Perinatal Arterial Stroke (PAS): A Phase III Multi-site Trial of I-ACQUIRE

First Investigators Meeting
Protocol Overview
1 May, 2019

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Nationwide Children's Hospital & The Ohio State University (OSU)

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Clinical MRI Center Director, Stanford University

Laura Bateman
National Study Coordinator, FBRI, Virginia Tech

I-ACQUIRE

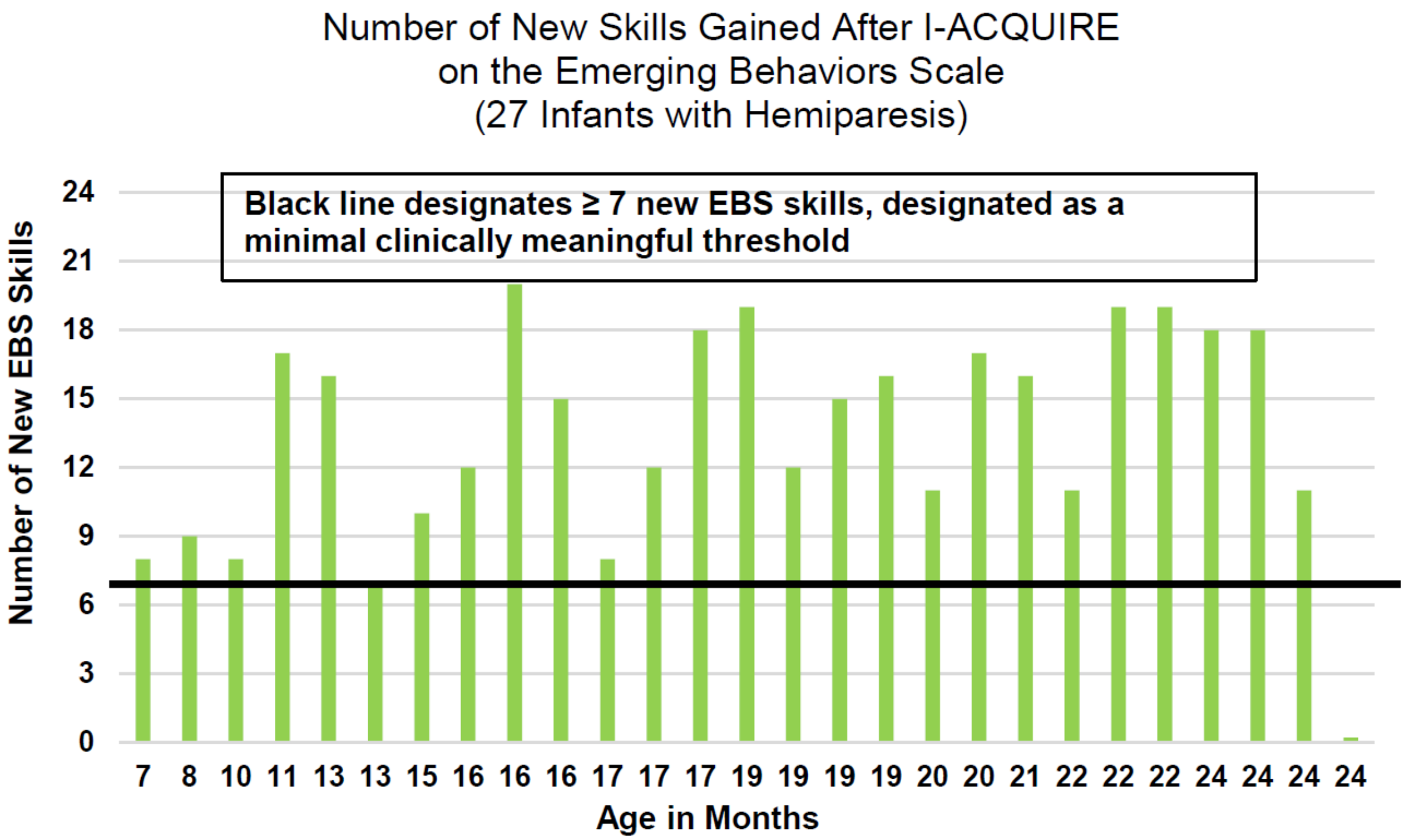
The primary locations of the 12 I-ACQUIRE Sites

Ann Arbor
Atlanta
Baltimore
Boston
Chicago
Cincinnati
Columbus
Houston
New Haven
Philadelphia
Roanoke
San Diego

Stroke in Infants and Current Treatment Approaches

- Pediatric arterial ischemic stroke occurs most frequently in infants
  - Incidence of Neonatal Arterial Ischemic Stroke (NAIS) is 1:2500 – 1:7700 live births
  - Incidence of presumed prenatal/perinatal stroke similar to NAIS (diagnosed at later ages after neuromotor impairment detected) **COMBINED INCIDENCE = 1:1250**
- No consensus rehabilitation for infants with post-stroke hemiplegia
  - Wide array of intervention approaches
    - Weekly low-dose OT and/or PT therapy is typical (not evidence-based)
    - Consensus from systematic reviews that constraint-induced movement therapy **(CIMT) is the most efficacious treatment for children with hemiparesis**
      - CIMT is considered high-intensity and actively shapes voluntary control
  - No adequately powered RCT of CIMT in infants/toddlers (< 24 mos)
  - No RCT of signature CIMT focused on infants/toddlers after stroke

I-ACQUIRE IS A SIGNATURE FORM OF CIMT TESTED IN MULTIPLE RCTs


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 Phase III Trial Specific Aims

- **Primary Aim:** **Determine the efficacy of I-ACQUIRE at 2 dosage levels compared to usual and customary treatment (U&CT) to increase upper extremity skills on the hemiparetic side *at both end of treatment and 6 mos post-treatment***
- **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 *at both end of treatment and 6 mos post-treatment***
- **Exploratory Aim:** **Explore the association between I-ACQUIRE treatment at Moderate and High Doses and gains in gross motor, language, and cognition outcomes (i.e., cross-domain or "spillover" effects of treatment)**

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Public Health Impact of I-ACQUIRE Phase III Trial

- **Estimated 3400+ new cases/yr of Perinatal Arterial Stroke (PAS) in U.S.**
- **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 evidence-based rehabilitation and improve clinical outcomes for infants and toddlers with PAS.

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DESIGN FOR PHASE III I-ACQUIRE TRIAL

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 or U&CT

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 (U&CT) (N=80) documented

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

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

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

U&CT Parents offered choice of
I-ACQUIRE Dosage (Crossover)

Inclusion/Exclusion Criteria for I-ACQUIRE Phase III Trial

- **Inclusion criteria**
  - 8-24 mos old at time when treatment delivered
  - Perinatal Arterial Ischemic Stroke (PAS) diagnosed
  - PAS confirmed with clinical MRI (high-quality, standardized)
  - Hemiparesis
  - Parents able to participate in home-based intervention
    - present at least 1 day/wk for therapy and 45 min/day practice at home
- **Exclusion Criteria**
  - Fragile medical health
  - Prior receipt of CIMT ≥ 2 hrs/day x 10 days
  - Botox within past 3 mos
- In prior studies of ACQUIRE, parent willingness to enroll is high (93-95%) and attrition rate is low (5-7%). Option of crossover (delayed) treatment is important.

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8 Core Treatment Components

(bold font represents core features of all signature forms of CIMT**)**

- **Constraint of the less-impaired upper extremity** for first 17 days of 20 treatment days. The lightweight cast is worn continuously.
- **High (intensive) dosage of treatment** – either 3 or 6 hrs/day, 5 days/wk for 4 weeks – provided by protocol-trained OTs or PTs (licensed, certified)
- **Operant conditioning techniques** to shape and improve skills and abilities, combined with practice variation; emphasis on play, self-help, fun, and use of a variety of individualized reinforcers
- Therapy in natural settings (e.g., home, child care center)
- Shaping includes total body/trunk and bimanual activities (as well as traditional arm/hand therapy activities)
- Parent-Therapist Partnership (formal module) all 4 weeks
- Daily therapy sessions documented
- **Transfer Package** to promote future skill and motor development

Save these 2019 dates: Upcoming I-ACQUIRE events

- Thursday, 18 April 2019 from 2:00 – 3:00 p.m.: Webinar about the Clinical Trial Agreement (CTA) and Payment Schedule (U of Cincinnati)
- Thursday, 25 April 2019 from 2:00 – 3:00 p.m.: Webinar about the Central Institutional review Board (CIRB) Process and Local Site Compliance (U of Cincinnati)
- Tuesday, 30 April 2019 in Chicago/Hilton Chicago O-Hare Airport (7:00 – 8:30 p.m.): Evening reception for I-ACQUIRE Study team and local site PIs, Co-Is, and Study Coordinators
- Wednesday, 1 May 2019 in Chicago/Chicago O-Hare Airport (8:30 a.m. – 4:00 p.m.): First Meeting of Local Sites and I-ACQUIRE national team
- Sunday, 16 June 2019 – Monday, 17 June 2019: First meeting of Parent Council in Roanoke
- Monday, 17 June 2019 (evening orientation) in Roanoke – Friday, 21 June: Required training for I-ACQUIRE therapists
- Mid-June to mid-July 2019: Required training (webinars and calls) for assessors
- 1 August 2019: Open to consent, randomize, schedule, and implement assessments and treatments

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Some unique aspects of I-ACQUIRE in StrokeNet

- First pediatric trial in StrokeNet
- First trial to engage patient advocates (parents) in the trial through a Parent Council
- Designed to set the stage for Implementation Research. Important because I-ACQUIRE protocol is complex, intensive, and requires training to ensure high fidelity – thus challenging traditional clinical treatment of this patient population.
- Well-suited to advancing knowledge about differential responses to treatment and theories re: neuroplasticity in young children after stroke, including potential biomarkers for individualizing treatment choices.
- Explicit shared goal to begin to create an even stronger multidisciplinary network of pediatric neurology and rehabilitation scientists – to exchange ideas and propose other studies in the near future.

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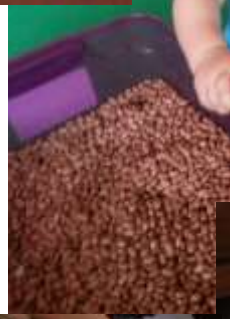
Stephanie C. DeLuca, PhD



VTC | Fralin Biomedical Research Institute

NEUROMOTOR RESEARCH CLINIC

The EIGHT I-ACQUIRE Treatment Components

1. Constraint of the infant's less-impaired upper extremity for first 17 days of treatment; cast is worn contir wear a removable, full-arm lightweight cast for the first 17 of 20 therapy sessions. On the last 3 treatment days, after c focus on integrating new skills of the hemiparetic UE into bimanual activities.

2. High dosage of treatment – either 3 or 6 hrs/day, 5 days/wk for 4 weeks. (*see B4.9.3 for rationale for dos* premised on evidence that concentrated high amounts of operant conditioning (shaping) and varied practice of ne rapid and enduring improvements. Note: if an infant takes a nap, both the therapist and parent(s) know that the therap extended, so that the infant receives the full active treatment dosage. (The therapist's time is covered for these occ affirm that infants and parents have tolerated both dosage levels well, largely because therapists are trained to mal interesting, and rewarding for infants and parents.

3. Operant conditioning techniques to shape and improve upper extremity (UE) skills; combined with pra Operant conditioning is applied across a wide range of activities to elicit new UE skills and then progress to volunta **Box A above for operant conditioning definition**.) The methods for setting behavioral goals, providing rewards, and levels of consistent performance required to earn continued reinforcement are described in detail in the ACQUIRE manual[16] and training materials. We term this the MR3 Cycle (**m**ovement, **r**einforcement, **r**epetition, and **r**efinement) varied, game-like, and enjoyable for the infant and include many self-help activities (eating, dressing, hand washing).

4. Provision of therapy in natural settings. We provide therapy in natural environments, because this promotes ge maintenance of skills. For infants, this can include the home or a childcare or early intervention setting. Some clinic set-up to be similar to home or childcare settings. Parents and family members often are present and join in some the

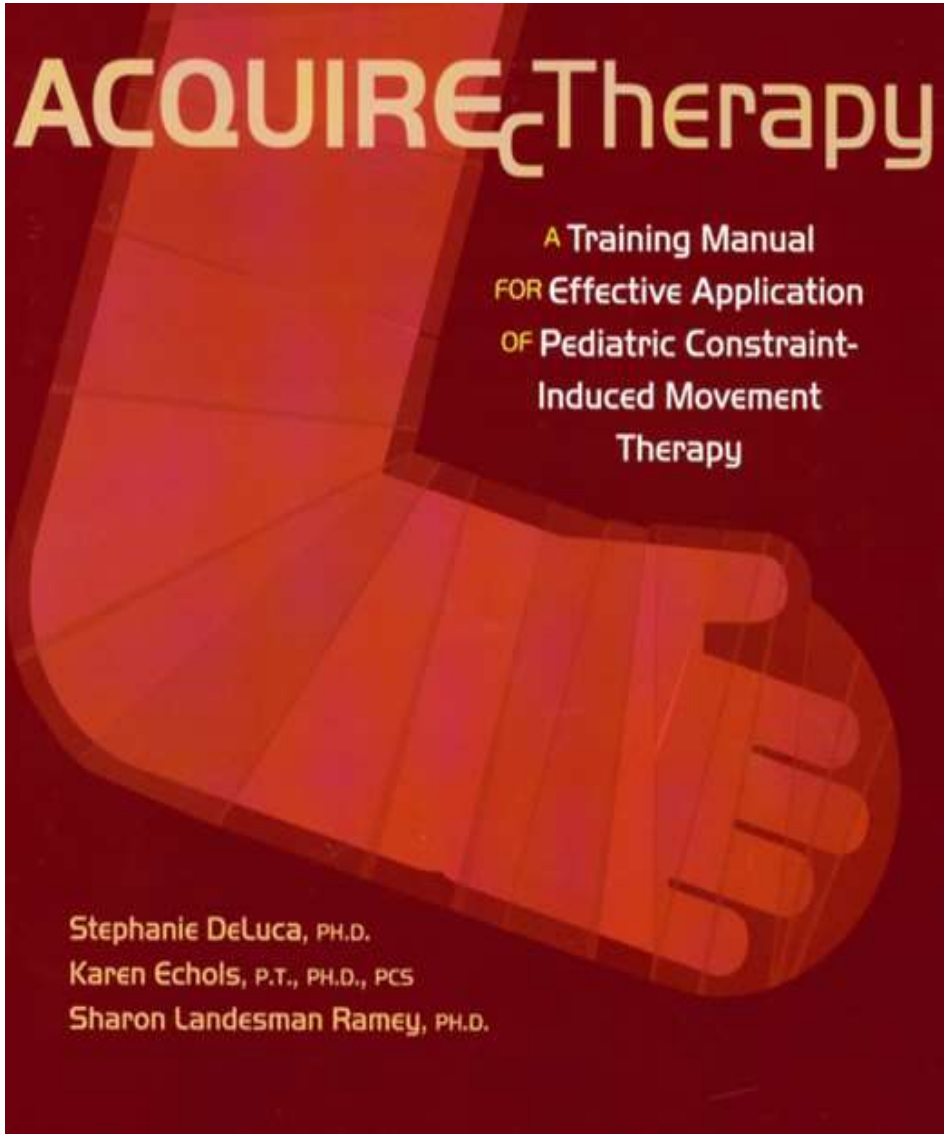
5. Emphasis on total body and bimanual activities (as well as traditional arm/hand therapy activities) Treatment to total body and gross motor activities that use the hemiparetic UE, such as sitting, weight bearing, rolling, crawling, st Even with the cast, many gross motor bimanual activities can occur, such as carrying, pushing, pulling, or catching a

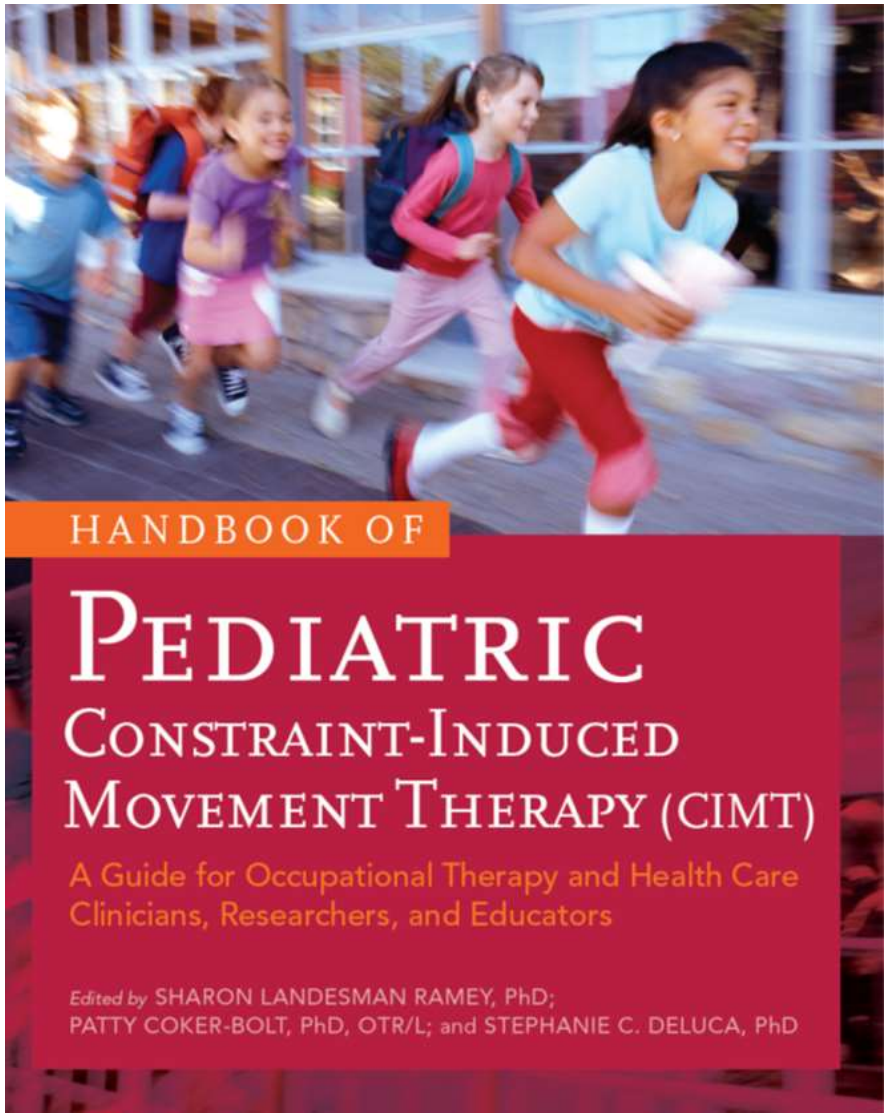
6. Home Treatment Module developed as an active Parent-Therapist Partnership. We use a parent-home traini supportive written materials and photo/videotapes). The therapist and parent(s) meet when treatment begins. The th the parent in I-ACQUIRE methods, particularly concerning effective and ineffective use of operant conditioning. Pare goals, introduce new activities, and adjust therapy activities to encourage the infant's practice of new skills. Parents are about 45 min/day helping their infant practice new skills for 5 of 7 days. (This can occur in shorter bursts throughout th report time spent on this to the treating therapist.

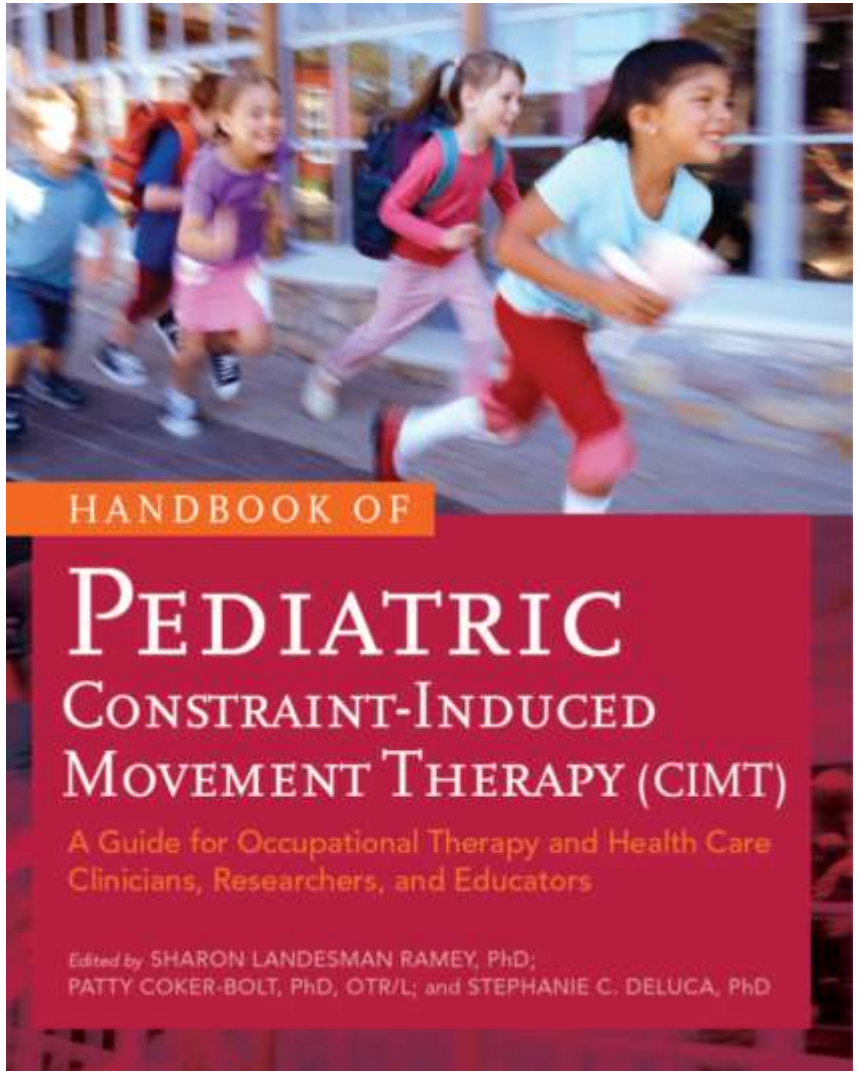
7. Documentation of daily therapy sessions. Each therapist documents treatment with standardized daily logs that r goals worked on, activities completed, and infant behavior (interest level, signs of frustration or fatigue) and any progr

8. Transfer Package to promote future progress. Therapist and parents develop a written plan with supportive mate infant maintain and improve skills post-treatment. This plan targets daily and special activities, informed by the o process, how well the infant has progressed across various skill levels, and next steps towards higher-level functional

Video of Weekly Progress of Infant over 4 week treatment


ACQUIRE Therapy
A Training Manual
FOR Effective Application
OF Pediatric Constraint-
Induced Movement
Therapy
Stephanie DeLuca, PH.D.
Karen Echols, P.T., PH.D., PCS
Sharon Landesman Ramey, PH.D.


HANDBOOK OF
PEDIATRIC
CONSTRAINT-INDUCED
MOVEMENT THERAPY (CIMT)
A Guide for Occupational Therapy and Health Care
Clinicians, Researchers, and Educators
Edited by SHARON LANDESMAN RAMEY, PhD;
PATTY COKER-BOLT, PhD, OTR/L; and STEPHANIE C. DELUCA, PhD



Five Essential Components of P–CIMT	*Signature or Traditional P–CIMT	Modified P–CIMT
1. Constraint of the less or unimpaired upper extremity	Constraint of the less or unimpaired upper extremity for majority of waking hours and during active treatment	Constraint of the less or unimpaired upper extremity at least during active treatment
2. High dosage (likely minimum threshold: 2-hr sessions per day for 5 days/wk)	High dosage of therapy in a concentrated period of time involving active treatment for a minimum of 3 hrs/day for 5 days/wk for multiple weeks	High dosage of therapy in a concentrated period of time with a minimum of 2 hrs/day for 5 days/wk for multiple weeks
3. Use of shaping techniques and repetitive practice with task variation	Use of shaping techniques to review, extend, practice, and refine skills that use formal operant learning techniques with immediate feedback and reinforcement in all treatment sessions	Use of shaping techniques to review, extend, practice, and refine skills as an active component of treatment
4. Learning functional skills in natural and diverse settings	Learning functional skills in natural and diverse settings (i.e., treatment is in these settings)	Treatment may occur in clinics, although emphasis is on functional skills for use in natural and diverse settings
5. Transition (post-therapy) planning for maintenance of gains	Post-therapy planning to promote functional bilateral and unilateral upper extremity development and continued practice of new skills with more-impaired upper extremity	Post-therapy planning to promote functional bilateral and unilateral upper extremity development and continued practice of new skills with more-impaired upper extremity

Differences with Infants

I-ACQUIRE

1. Constraint of the infant's less-impaired upper extremity.
2. High dosage of treatment – either 3 or 6 hrs/day, 5 days/wk for 4 weeks.
3. Operant conditioning techniques to shape and improve upper extremity (UE) skills;.
4. Provision of therapy in natural settings.
5. ***Emphasis on total body and bimanual activities***
6. ***Home Treatment Module developed as an active Parent-Therapist Partnership.***
7. ***Documentation of daily therapy sessions.***
8. Transfer Package to promote future progress.

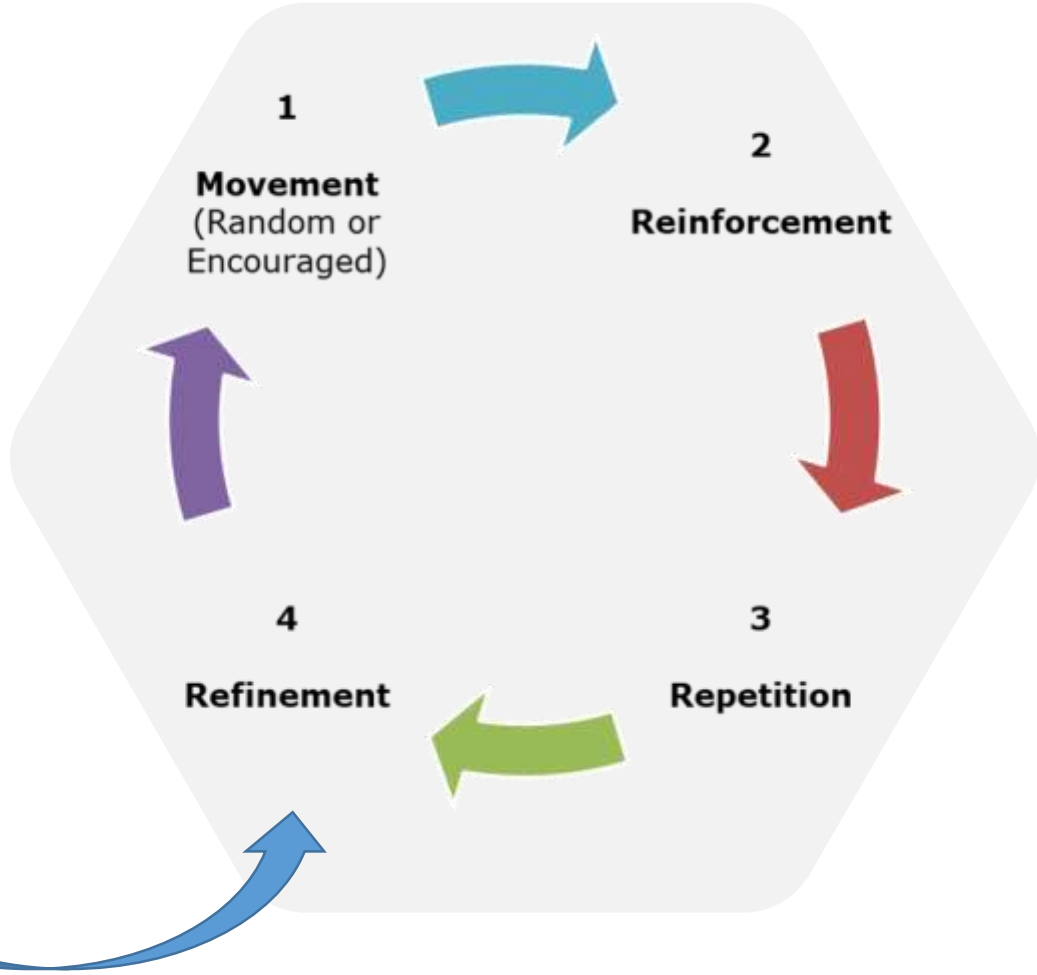
ACQUIRE

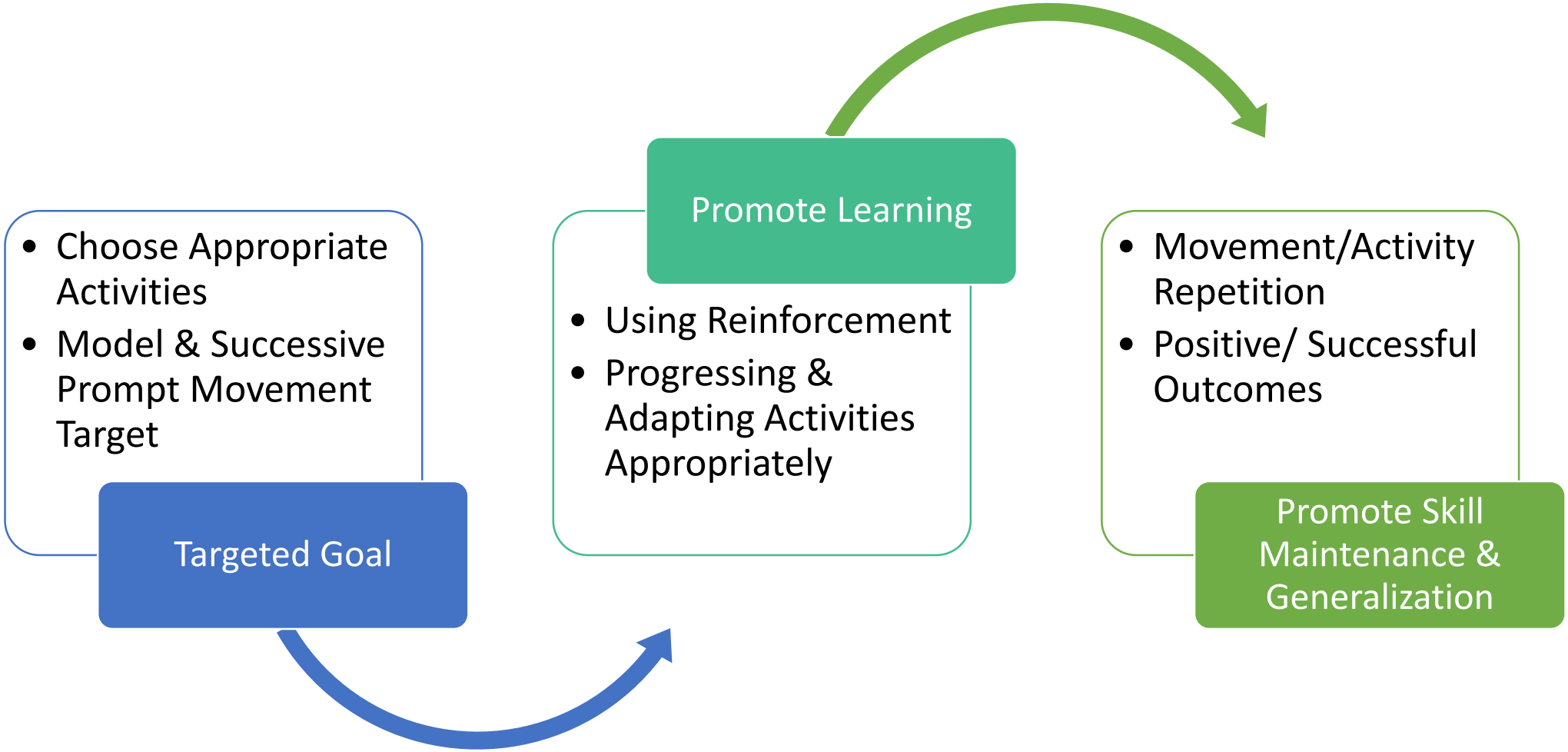
1. Constraint of the less or unimpaired upper extremity
2. High dosage (likely minimum threshold: 2-hr sessions per day for 5 days/wk)
3. Use of shaping techniques and repetitive practice with task variation
4. Learning functional skills in natural and diverse settings
5. Transition (post-therapy) planning for maintenance of gains

Operant Conditioning

Operant conditioning (or instrumental learning) refers to learning promoted by specific behavioral techniques.

Designed to promote and maintain learning, through response-contingent feedback.




Choose Appropriate Activities
Model & Successive Prompt Movement Target
Targeted Goal
Promote Learning
Using Reinforcement
Progressing & Adapting Activities Appropriately
Movement/Activity Repetition
Positive/ Successful Outcomes
Promote Skill Maintenance & Generalization

Video of parent training and showing technique of I-ACQUIRE

What makes I-ACQUIRE Different from Traditional (PT/OT) Therapy?

Traditional Therapy

- Less operationalized definitions of learning principles
- ***Good Therapists do much of the same learning principle techniques in their treatment sessions***
  - Less opportunity to see progression
  - Success becomes harder for both the child and the therapist across time

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- Focus on Learning Principles
- Progression expected both within each session and across sessions
  - Small Incremental Steps (as dictated by learning principles)
  - Specificity of
    - Prompts & Reinforcements
  - Success oriented
- **Intensity**
  - **There is Greater Number of Repetitions**
  - **Affords Greater Opportunity for Refinement, Solidification (skill and neural representation), & Generalization**

Assessment Core

Jill Heathcock PT, PhD – Associate Professor
Amy Darragh OTR/L, PhD – Associate Professor
Thais Cabral OT, PhD – Post Doctoral Fellow

The Ohio State University

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Outcome measure

- Emerging Behaviors Scale
  - Bayley Scales of Infant Development (Bayley-III)
  - Gross Motor Function Measure-66 (GMFM-66)
  - Mini Assisting Hand Assessment (mini-AHA)

  - Time points
    - Pre-treatment, Post treatment 1 month, Post-treatment 6 months

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Blinded Assessors

- Complete the outcome measures
    - Emerging Behaviors Scale – partial, confirmed centrally
    - Bayley Scales of Infant Development (Bayley-III) – full, with modifications for R + L on FM subscale
    - Gross Motor Function Measure-66 (GMFM-66) – full
    - Mini Assisting Hand Assessment (mini-AHA) – administer the play session, scored centrally.
        - All sessions are videotaped and transfer to the OSU
        - IACQUIRE computer, tripod

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Blinded Assessors

- PT, OT, developmental psychology, psychologists, person with experience conducting evaluation with children
- Preferably with age range or some assessment
- ***not** the treating therapist or study coordinator* (maintain blinding is the goal)
- Each site = 2 blinded assessors
- Attend training, achieve and maintain >85% reliability on tools
    - Prior Study (June)
    - Web-based training with Assessment Core (July)
    - Score videos for reliability
    - Send back to assessment core a child/assessor interaction + score
        - Administration and score (hemiparesis preferred)
    - Yearly reliability checks to avoid and correct drift

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Parent Outcome Measures

Parent Measures

Parent Report

- Infant Motor Activity Log
- MacArthur Bates Communicative Development Inventories (CDI-III)

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I-MAL

Evaluates the infant's frequency and quality of affected UE movement in everyday tasks.

Collected at Pre, Post, 6 mos

Parent rates how often (never-always) & how well (poor-normal) child uses affected-UE for 20 infant arm/hand tasks.

Sample items: Hold a bottle/cup, Eat finger foods, Pick up a cylindrical object (e.g., crayon, marker, bottle, cup, or rattle).

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MacArthur Bates
Communicative Development Inventories (CDI-III)

Assesses early language skills in infants & toddlers:

(Comprehension, Vocabulary, Grammatical Skills, Nonverbal Gestures and Actions)

Collected at Pre, Post, 6-mos

Available for Infants and Toddlers 8 – 30 months

Forms can be completed in 20 – 45 minutes

Parents can complete at home

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Parent Measures

Parent Experiences and Background

- Demographics
- Perceived Stress Scale plus stress schedule
- Pre-treatment and Post-treatment Questionnaire
- Report of Therapy Experiences
- Report of Parent-Therapist Information Exchange

Physician Administered

- Neurological Exam: Medical History and PSOM (pre-only)

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Perceived Stress

Assesses perceptions of stress; specifically, the extent to which situations are perceived as stressful

Parent's self-reported perceptions of stress are assessed at baseline, post-treatment 1-month, and at post-treatment 6-month.

Includes Perceived Stress Scale and Self-reported perceptions of stress

Parents can complete at home

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Pre and Post-Questionnaire

General information about therapy and therapist

Parent Measures

Report of Therapy Experiences

Information about the therapies that the children in the study have participated in

Parent Measures

Physician Administered

Neurological Exam: Medical History and PSOM

Parent – Therapist Information Exchange

Assesses process of goal setting; preparation and training; role of parent in therapy

Completed by both parent and therapist post-treatment

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