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

Short Title: I-ACQUIRE Study
Protocol Number: 2018-8193
National Clinical Trial (NCT) Identified Number: NCT03910075
Principal Investigator: Sharon Ramey, PhD
Sponsor: Not Applicable
Funded by: National Institute of Neurological Disorders and Stroke
Version Number: 4.0

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I-ACQUIRE

AGREEMENT ON THE PROTOCOL

By signing below, I confirm that:

1. I have read this protocol and it contains all necessary details for conducting this study

AND

2. I agree to conduct the trial in compliance with this protocol and to adhere to all regulations that govern the conduct of the study.

_____

Principal Investigator's Printed Name

_____ _____

Principal Investigator's Signature Date

_____

Clinical Performance Site Name

STATEMENT OF COMPLIANCE

The I-ACQUIRE trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

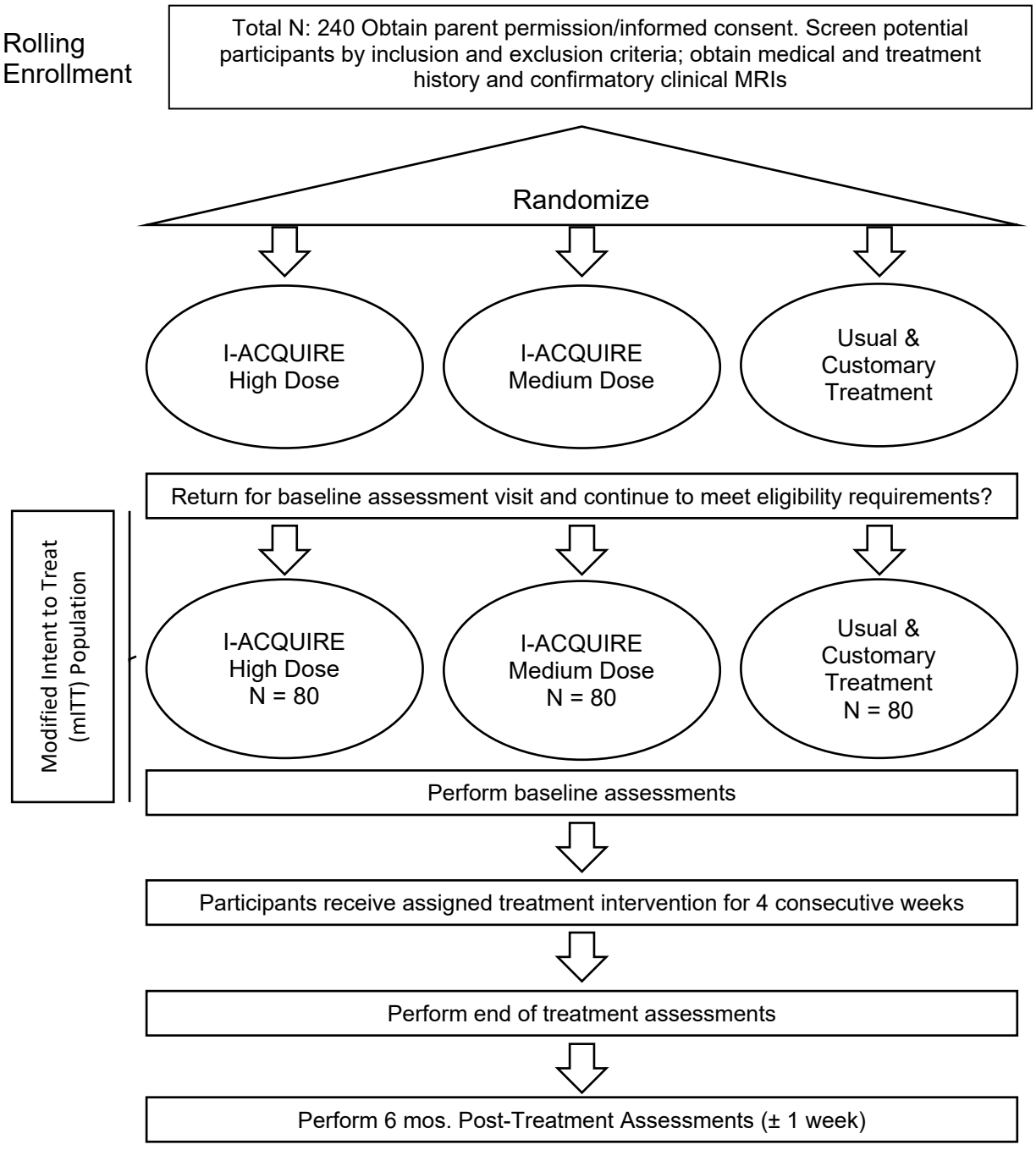
The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the common (single) Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Perinatal Arterial Stroke: A Multi-site RCT of Intensive Infant Rehabilitation (I-ACQUIRE)
Study Description:	This is a Phase III clinical trial to compare the efficacy of two dosages of a new infant rehabilitation protocol - I-ACQUIRE - to usual and customary forms of infant rehabilitation in infants who experienced Perinatal Arterial Ischemic Stroke (PAIS).
Objectives:	1) 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. 2) To 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. 3) To 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)
Endpoints:	End of Treatment and 6 mos. Post-Treatment
Study Population:	Infants with Perinatal Arterial Ischemic Stroke between 8 and 36 mos. of age.
Phase:	Phase III Clinical Trial
Description of Sites/Facilities Enrolling Participants:	10 are NINDS StrokeNet sites, 2 are outside clinical sites
Description of Study Intervention:	I-ACQUIRE is an innovative form of intensive pediatric rehabilitation that includes core elements of pediatric Constraint-Induced Movement Therapy with supplement components of bimanual and whole body motor activities and a parent home program, delivered in natural settings. Previous smaller-scale trials showed high safety, acceptability, treatment compliance, and both statistically and clinically significant benefits.
Study Duration:	Study period is 5 years with enrollment open approximately 6 months into Year 1 through Year 5.
Participant Duration:	Participants will be involved for a minimum of 7 months and up to 13 months (depending on scheduling of the treatment month).

1.2 SCHEMA


Rolling Enrollment
Total N: 240 Obtain parent permission/informed consent. Screen potential participants by inclusion and exclusion criteria; obtain medical and treatment history and confirmatory clinical MRIs
Randomize
I-ACQUIRE High Dose
I-ACQUIRE Medium Dose
Usual & Customary Treatment
Return for baseline assessment visit and continue to meet eligibility requirements?
Modified Intent to Treat (mITT) Population
I-ACQUIRE High Dose N = 80
I-ACQUIRE Medium Dose N = 80
Usual & Customary Treatment N = 80
Perform baseline assessments
Participants receive assigned treatment intervention for 4 consecutive weeks
Perform end of treatment assessments
Perform 6 mos. Post-Treatment Assessments (± 1 week)

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening	Baseline Assessment	One-month of Assigned Treatment	End of Treatment Assessment	6 mos Post-Treatment Assessment
Informed Consent	X				
Demographics and eligibility criteria	X				
Clinic MRI requested	X				
Randomization to Tx groups	X				
Neurology Exam - Medical & Tx History - Pediatric Stroke Outcome Measure		 X X			
Gross Motor Functional Classification Scale		X			
Mini-MACS Rating[1]		X			
Emerging Behaviors Scale (EBS)		X		X	X
Mini-AHA		X		X	X
Bayley-4		X		X	X
GMFM-66		X		X	X
I-MAL		X		X	X
MacArthur-Bates Communicative Development Inventories		X		X	X
Perceived Stress Scale -14		X		X	X
Parent Report of Other Life and Treatment Stressors		X		X	X
Parent Report of Therapy		X		X	X
Parent-Therapist Relationship Tool (Information Exchange)				X	
Treatment Delivered and Fidelity Measured			X		
Parent Council Survey about Study Participation					X
Corona Virus Pandemic: Impact on families enrolled in I-ACQUIRE				X	X
DNA sample collection				X	X[2]
Adverse Event Review and Evaluation	X>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>X				

[1]If subject is less than 12 months, the Mini-MACS rating will be completed at the End of Treatment Assessment or 6 mos. Post-Treatment Assessment when the child becomes age-eligible for this rating scale.
[2]Repeat DNA sample can be collected if first DNA sample quality was not sufficient.

2 INTRODUCTION

2.1 STUDY RATIONALE

Perinatal Arterial Ischemic Stroke (PAIS) and the need for efficacious rehabilitation for infants. Perinatal Arterial Ischemic Stroke (PAIS) involves cerebral infarction caused by arterial thrombosis or embolism. PAIS diagnosis can occur in the first 28 days of life (Neonatal Arterial Ischemic Stroke [NAIS]) or in utero (Presumed Prenatal Arterial Ischemic Stroke [PPAIS]).[1-5] In the neonatal period, common signs of a stroke are seizures, encephalopathy, and/or hypotonia.[5] Since these signs can occur in CNS infection, hypoxic-ischemic encephalopathy, and inborn errors of metabolism, neuroimaging is critical to verify stroke.[1] MRI brain scanning is the most valid method to confirm acute ischemic stroke (ultrasound and CT scan are not sensitive to acute ischemic change).[1] In older infants, delayed development or noticeable problems with voluntary movement can lead to a diagnosis of PPAIS which also requires a confirmatory MRI. PAIS is a serious event that can produce lifelong severe impairments: hemiparesis is the most prevalent.[30-33] Incidence of PAIS is surprisingly high: about 1 in 1150[11,8] live births, even higher than adult large vessel ischemic stroke incidence.[5,12]

There is no or only weak evidence of efficacy for the disparate rehabilitation approaches widely used to treat infants with PAIS.[9,13-15] Most commonly, infants with hemiparetic PAIS receive 1 – 3 hrs per week of individualized occupational and/or physical therapy, often not further specified[13,14,21,34] A comprehensive review[35] of treatments in cerebral palsy (CP) concluded that "the lack of certain efficacy evidence for large proportions of the interventions in use within standard care is a problem" and "alarmingly, another 20% are ineffectual, unnecessary, or harmful." (Note: children with PAIS and hemiparesis meet diagnostic criteria for CP.[36]) Further, Novak et al[35] identified constraint-induced movement therapy (CIMT) as the treatment with the strongest scientific evidence and largest effect sizes in improving motor skills and function. Accordingly, many therapists and parents now try to implement some form of CIMT, often with doses 50% – 80% lower than those shown to produce benefits for older children with CP[38-43] and little evidence that essential operant conditioning techniques are used systematically to elicit and shape new upper extremity (UE) skills (see **Box A**). Of urgent concern is the absence of findings from adequately powered randomized controlled trials (RCTs) about the efficacy of CIMT for infants under 2 yrs old. (Three RCTs for infants with hemiplegic CP are underway; two outside the U.S. involve very low therapy doses; Baby CHAMP, funded by NIH, uses ACQUIRE.) Independent review[13] of other forms of infant interventions concluded that most are ineffective, although some yield small magnitude short-term benefits. Additionally, no RCT of CIMT has focused on patients with a diagnosis of PAIS. These knowledge gaps matter: i) infants, *compared to older children,* differ in attention span, motor development, and learning modes and may require age-adapted techniques and different dosages of CIMT; and ii) infants with PAIS likely differ from a heterogeneous CP population in terms of underlying CNS injury and potential for functional brain plasticity.[44-49]

Box A: Overview of Operant Conditioning (core feature of CIMT and I-ACQUIRE): Operant conditioning (or instrumental learning) refers to learning promoted by specific behavioral techniques informed by a century of empirical research.[50-55]To promote and maintain learning, response-contingent feedback is essential – i.e., showing that a behavior results in clear consequences. Operant conditioning in rehabilitation uses varied reinforcers and reinforcement schedules; shapes targeted behaviors through a process known as successive approximations; creates opportunities for massed and distributed practice of new skills; and employs methods to increase generalization and maintenance of new skills in different settings and activities. Extensive research has identified many effective operant conditioning parameters unique to infants (e.g., reward timing, spacing, specificity).[14,16,53] I-ACQUIRE explicitly uses these.

Biological relevance of the proposed clinical trial. Converging evidence from studies on animals, adult stroke patients, and older children with CP affirms that CIMT approaches can produce significant and enduring gains in upper extremity (UE) skills used in uni- and bimanual activities.[35,56-58] Further, CIMT has produced evidence of altered brain structure and function (i.e., treatment-induced neuroplasticity)[43,48,59-63]

Infants and adults with stroke differ in many ways.[64] To begin, infants do not yet have a full repertoire of UE skills, so after stroke they are not "recovering" lost skills. Although healthy infants and those with hemiparesis learn through daily trial-and-error learning, those with hemiparesis must exert greater effort in voluntary use of

their hemiparetic UE.[65] Even with effort, they often experience frustration and failure due to poorly controlled, ineffective movements. Over time, they are likely to neglect their hemiparetic UE.[21,66] Finally, families struggle about how best to help their infants.[67-69] Clinicians describe the stroke brain damage *as "*permanent and static" and often tell parents to expect delays in motor milestones (e.g., crawling, standing, walking), self-help skills, language, and cognitive competence. This clinical portrayal of PAIS can become self-fulfilling if adults do not expect a child to show major improvement in neuromotor (or other) skills.

Our team has been instrumental in developing and testing pediatric CIMT since 1998. We have new findings about CIMT that inform this proposed Phase III trial of a "signature form" of CIMT known as Infant ACQUIRE (I-ACQUIRE). Extrapolating from results of CIMT-induced CNS change in older children and adults,[43,59-62] we reason that I-ACQUIRE may exert biological effects by: 1) applying continuous constraint to the non-hemiparetic UE which helps direct attention to the hemiparetic side and may lower competing sensory-motor input from the non-hemiparetic UE; 2) reducing frustration and fatigue that can compete with success in voluntary control. As the infant acquires new skills and ease in controlling the hemiparetic side, he/she experiences less of the negativity that previously impeded voluntary control; and 3) increasing the number of new and practical UE skills (both uni- and bimanual) which may stimulate synaptic growth and efficient neuronal pruning to help improve brain laterality and maturation in the primary and secondary motor cortices and corticospinal tracts.[70-75] Emerging new UE skills foster successes the infant had not previously experienced; in turn, the infant becomes more likely to attempt new and more complex UE skills. UE skills also are integral to balance, postural changes, and mobility (rolling, sitting, crawling, scooting, walking) and facilitate bimanual activities used in object manipulation and self-help. In theory, without efficacious rehabilitation, an infant with PAIS and hemiparesis is likely to display major deficiencies in basic UE skills which may impede development of competencies in other domains of development, such as gross motor and cognitive development.

Potential Impact. Findings from this Phase III trial have the potential to transform clinical rehabilitation for an estimated >3000 infants/year with PAIS in the U.S and >64,500/year worldwide. Many infants with PAIS experience multi-domain impairment.[9,76,77] For infants with NAIS, 64% later have intellectual disabilities, delayed language, and/or social-emotional problems.[4] This leads to high lifelong costs related to their rehabilitation, special education, health care, and lack of adult self-sufficiency.[29,78] If I-ACQUIRE proves efficacious in producing significant and enduring gains in UE skills on the hemiparetic side (primary efficacy outcome) and improving bimanual UE skills (secondary efficacy outcome), then these infants are more likely to engage in age-typical activities that promote development of greater independence and success in a wide array of daily activities. Further, I-ACQUIRE benefits have the potential to prevent common secondary conditions – particularly musculoskeletal contractures, pain, and social stigma as children become older.[79] If efficacious, I-ACQUIRE may result in large cost savings and physical and psychological burden on families. In fact, the apparent high cost of 60 hrs or 120 hrs of I-ACQUIRE over 4 wks is less than current costs for a year of most forms of Usual and *Customary Treatment (U&CT) provided at low weekly dosages all year* (without evidence of benefits).[35] Data generated by this trial will be well-suited to support future cost:benefit analyses if the treatment is successful. Because of the potential high impact on families, we propose to actively engage parents and advocacy organizations in the trial.[80,81] This supports the NIH and IOM goal of including patient and stakeholder perspectives in conducting "rapid, responsive, relevant" clinical research."[19,20]

2.2 BACKGROUND

Early protocol development and differences from adult CIMT. We developed our treatment protocol via multiple RCTs and clinical studies, starting with an infant with severe asymmetrical CP (Phase I trial).[82] Results showed high safety, feasibility, and evidence of large gains in fine and gross motor skills. The treatment protocol was informed by Stephanie DeLuca's decade of research experience with adult CIMT (including launch of the EXCITE trial[57,83,84], Sharon and Craig Ramey's 40+ years of developing and testing interventions for children with developmental disabilities and biosocial risk conditions, and research and clinical insights from other colleagues. Our new pediatric CIMT protocol (later named ACQUIREc) included the 3 required core elements of CIMT:[16-18] 1) constraint of the non-hemiparetic UE, 2) high therapy dosage, and 3) operant conditioning (see **Box A, above**). We also innovated many CIMT protocol changes for a pediatric patient population:

1) Type of constraint: we constrain the non-hemiparetic UE via a full-arm, lightweight cast worn continuously for 3.5 of 4 treatment weeks (in contrast to a hand mitt or splint that provides only partial constraint). We reasoned that very young children, unlike adults, would benefit from continuous

constraint that limits use of their non-hemiparetic UE, theoretically reduces competing sensory-motor input, and may promote shifting their attention to use of the hemiparetic UE. We coined the term "developmental disregard"[21,66] to characterize neglect of the hemiparetic UE that many (but not all) infants with hemiparesis show. Overcoming this developmental disregard is similar to adults with stroke overcoming "learned non-use"[85] of the hemiparetic UE. Initially, we did not know if the cast would create safety problems (e.g., falling, skin damage), high stress for children or parents, or loss of skills in the casted UE; thus, we closely monitored for safety effects (and still do so). Findings consistently show high safety, minimal or no short-term stress, and no functional loss to the casted UE (which sometimes shows unexpected improvement).[26,66,86]

2) Treatment activities and reinforcers are individualized. Rather than administer a standard set of treatment activities (as in most forms of adult CIMT), we select activities and reinforcers tailored to each child. These become the basis for motivating, eliciting, then shaping new and improved UE skills and general body movements. Very young children learn and remember best when they self-initiate and engage in enjoyable, useful activities (cf. classic research by Vygotsky, Piaget, Bijou, and Baer, among others[51,55,87]).

3) Treatment goals go beyond improving isolated upper extremity (UE) skills, *including bimanual and total body skills*. For infants and toddlers, voluntary control of both UEs affects weight bearing, changing positions, balance, sitting, standing, and mobility.[14,88] Accordingly, I-ACQUIRE explicitly addresses bimanual behaviors and total body behaviors, in contrast to CIMT for adults and older children that focuses primarily on wrist, hand, and finger movements.

4) Parents are included in treatment planning and home-based practice during non-therapy hours. Parents naturally want to encourage and teach their children; however, parents of infants with PAIS may lack the specialized knowledge needed to induce new UE skills in their child with PAIS. Because parents can be successful "therapy-extenders," we developed and include a formal parent "home" component that improves parental knowledge, skills, and confidence, while minimizing frustration, ineffective approaches, or potential harm.

5) Treatment occurs in a natural setting (e.g., home, childcare, early intervention setting). This is based on extensive findings that children are more likely to transfer and maintain new skills when they learn these in their home or natural settings. One RCT of CIMT showed significant benefits of a home vs clinic setting.[89]

6) Sessions are designed to be interesting and enjoyable, an essential for high-dose therapy sessions. Adults who lose UE skills after stroke are highly motivated to regain skills. In contrast, a very young child cannot know the value of new UE skills, so the therapist must motivate the child to try new behaviors. Because learning new skills with the hemiparetic UE requires high effort and often produces frustration and fatigue (at least initially), the I-ACQUIRE sessions are designed to be play-like, interesting, and highly rewarding to the child.[14]

Findings from clinical trials of ACQUIREc and new evidence about I-ACQUIRE.

STUDY 1A.[21] In 1999, we launched the first RCT of pediatric CIMT (Phase II) with 18 children (2 - 8 yrs old) with hemiparetic CP. *We developed the **Emerging Behaviors Scale (EBS)**[21] to provide a valid, reliable measure of a child's repertoire of skills with the hemiparetic UE. We identified a core set of 30 UE "essential skills" by reviewing i) standardized tools for assessing fine and gross motor function in typically developing children and those with neuromotor impairment and ii) research findings about the developmental emergence of UE skills in the first 2 yrs of life.* We adapted the Motor Activity Log[85] from adult stroke CIMT research to create a Pediatric Motor Activity Motor Log (PMAL).[21] FINDINGS: Parents of all eligible patients agreed to participate (100% acceptance). There were no adverse events. All children completed treatment as planned: there was 100% compliance with the 6 hrs/day High Dose of CIMT for 21 consecutive days. (Later, we shifted to 5 days/wk X 4 wks based on preferences of both parents and therapists.) During weekly cast removal, we detected minor skin irritations in 4 children - all readily treated with topical medicine and cast adjustment. The casted UE had no functional loss. The primary outcome (blinded assessment) showed CIMT led to a mean increase on the EBS of 9.3 new skills (ranging from 7 to 12), compared to only 2.3 new skills for controls (**Figure 1, next page**). Parent PMAL ratings of treated children for Amount of Use had a baseline mean of 0.8 and post-treatment mean of 2.8 (0 – 5 scale); for Quality of Movement, baseline mean was .9 and post-treatment mean was 2.7 (0 – 5 scale).

STUDY 1B.[66] Next, we conducted a crossover study in which the U&CT subjects received the identical CIMT protocol to test for replicability. FINDINGS: Crossover treatment produced similar results about safety, treatment acceptability, compliance, and outcomes (**Figure 1**). At 6 mos. post-treatment, subjects maintained or improved both their EBS scores and PMAL gains. Finally, some children showed "spillover effects" (i.e., changes in domains *not* designated as treatment goals): some began speaking and/or walking, improved their social skills,

and/or had fewer behavior problems. This strongly stimulated our interest in cross-domain effects.[26, 88, 90-92]

STUDY 2.[93,94] Next, we created a 3-site research network to determine whether we could train therapists at multiple sites to deliver ACQUIREc in a standardized way; if so, would we replicate treatment effects? We also explored whether a lower dose could produce significant gains. Children (2 – 8 yrs) with hemiparetic CP were randomly assigned (6 per site) to receive either 3 hrs or 6 hrs/day of ACQUIREc for 5 days/wk X 4 wks. FINDINGS: *We were able to train therapists to deliver ACQUIREc with high treatment fidelity in diverse clinical sites*. (NB: One site created a homelike treatment setting in the clinic.) All children quickly adjusted to the cast and received their full treatment dose. The 3 and 6 hr doses produced highly comparable benefits, although the small sample size precluded a statistically reliable conclusion. These results justify further testing of the 3-hr Moderate Dose as a promising alternative to the 6-hr High Dose. In Study 2, we used the newly available Assisting Hand Assessment (AHA)[22] to measure use of the hemiparetic UE as a "helping hand" in bimanual activities. AHA scores showed a mean treatment effect size of 0.63. Parent PMAL ratings had a mean effect size of 0.71. Only one child (severely dystonic) showed no benefits.

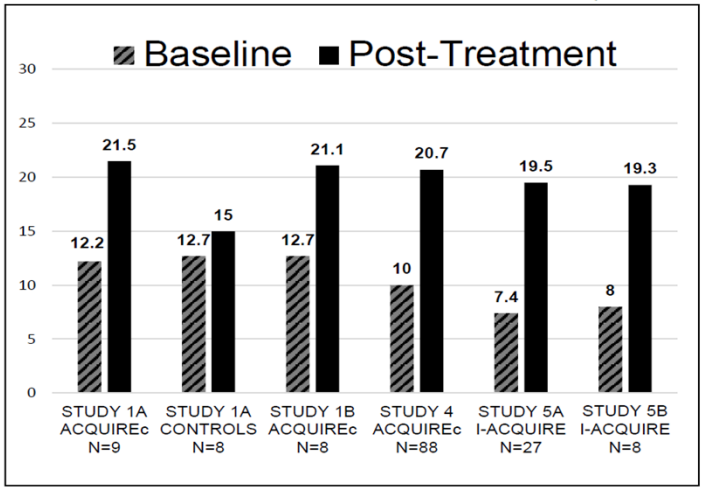
STUDY 3.[26] Our colleagues then adapted a Moderate Dose ACQUIREc (3-hr daily sessions X 20 days) to test safety, feasibility, and outcome effects in infants and toddlers (7 – 18 mos) with hemiparetic CP. Primary outcomes were Bayley-III Fine Motor and Gross Motor scores and the Infant Motor Activity Log (IMAL), an infant version of PMAL. FINDINGS: All 5 treated infants adjusted well to the cast; 1 developed a minor blister; none lost function in the casted UE. Unexpectedly, the casted UE showed improvement – reported also by others**.** Treated infants had significant gains on both the Fine Motor and Gross Motor subtests at end of treatment, and had increased gains one month later. The parent IMAL ratings show increases for 4 of 5 infants; the one infant with no IMAL gains had severe cognitive delay.

STUDY 4.[95] This Phase II study was a clinic-based cohort study of 88 children (2 - 8 yrs) with asymmetrical CP (significantly greater weakness or impairment on one side of the body; most children were diagnosed as hemiparetic, others as tri- or quadriplegic) who received the 6-hr High Dose of ACQUIREc at 2 university research clinics (UAB, Virginia Tech). FINDINGS: Results showed high safety, 100% treatment compliance, and no adverse events. ACQUIREc produced significant baseline to post-treatment changes comparable to (and sometimes >) similar age children in Studies 1A/B and 2. On the EBS (**Figure 1),** children increased a mean of 10.7 new skills after ACQUIREc treatment.

STUDY 5A.[96] This Phase II study was a clinic-based cohort series of 27 infants and toddlers (7 - 24 mos) treated with the I-ACQUIRE High Dose and assessed with the EBS, PMAL, and other tools. (NB: the Mini AHA and Bayley-III, proposed for the Phase III I-ACQUIRE study, were not yet available). FINDINGS: All children received the full treatment dose; 27% had minor, easily treated skin irritations; none lost function in the casted UE. Infants showed a mean gain of 12.1 EBS skills ($p<.0001$), somewhat higher than Study 1A/B. Further, 25 of the 27 infants gained at least 7 new skills, representing what we propose comprises a clinically significant change in the infant's abilities (**Figure 1).** These large EBS gains predicted infants becoming more active in object exploration, self-help skills, and mobility. Mean increases were 2.1 for PMAL Quality of Movement and 1.8 for PMAL Amount of Use. Examples of clinically meaningful changes that emerged after 4 wks of I-ACQUIRE and were highly valued by parents included 7 infants who began crawling, 5 who learned to pull to stand, 5 who started walking, and 2 who began to climb stairs.

STUDY 5B. This is a *post hoc* subgroup analysis of the 8 infants in Study 5A who had a primary diagnosis of early infant stroke. On the EBS, their mean improvement was a gain of 11.3 new EBS skills by the end of 4 wks of I-ACQUIRE treatment (**Figure 1.**)

Figure 1: Emerging Behaviors Scale (EBS): Mean Gain Scores across Studies of ACQUIRE



Cross-study comparison of changes on the Emerging Behaviors Scale in Figure 1. EBS outcomes combined across studies show statistically significant mean EBS gains of 9.9 new UE skills. For Study 1A, the mean EBS gain of 9.3 skills for treated subjects was >4 times the U&CT mean gain of 2.3 new skills. After the U&CT subjects received ACQUIREc, their EBS scores showed a gain of 8.4 skills.

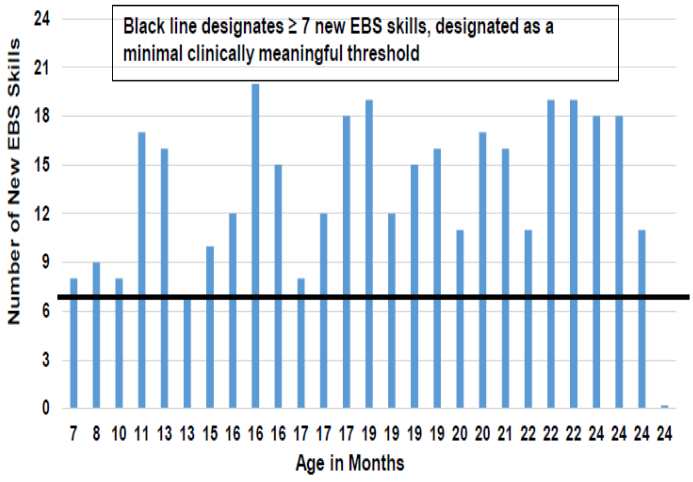
What comprises U&CT? In our studies, all patients were receiving U&CT when enrolled. The

mean U&CT dosage has been fairly stable for 2 decades – about 2. 2 hrs/wk (range of 1 to 3 hrs/wk) of OT/PT. The U&CT content was remarkably similar across patients, often described as an individualized therapy that combines motor learning, sensory integration therapy, neurodevelopmental therapy (NDT), and play techniques. More recently, up to 25% of the patients enrolled in our ongoing RCTs had some form of modified CIMT previously; this seldom met minimal criteria to qualify as evidence-based CIMT – that is, having the 3 CIMT core elements of i) high dosage (>2 hrs/day for at least 10 days within 2 wks), ii) active shaping and repetitive practice of UE skills, and iii) use of constraint. Examples of non-evidence-based or insufficient forms of CIMT are: 1 hr of therapy/wk with constraint and parent practice of 15 – 30 min/ day; 2 90-min sessions/wk for 6 wks using a hand mitt; and parents applying their own constraint. For this revised application, we asked clinical sites about the forms and dosages of typical U&CT: mostly, infants receive one or two 60-min sessions of OT and/or PT/wk in a community or hospital clinic or during a home visit. The U&CT therapy is described as a combination of techniques and the goals are individualized. Almost never is the content or therapeutic approach documented in detail. Many also receive speech therapy. Thus, the range in U&CT is relatively modest in dosage and content (therapy approach) with the caveat that some sites provide "modified CIMT."

Establishing a valid and reliable threshold for clinically meaningful benefits of treatment. Recently, our team proposed a systematic approach to estimate clinically meaningful gains, a relatively new endeavor in pediatric rehabilitation. First, we looked at approaches used in other rehabilitation trials (mostly adults).[97-99] Next, we studied available EBS data for individual subjects in Phase I and II trials and our clinical database, along with other outcome measures, including therapist and parent ratings and observations. We examined a variety of thresholds, to understand whether there was an amount of gain (either an absolute number of new skills or a percent improvement score) that correctly differentiated patients whose parents and therapists did or did not consider their outcomes clinically meaningful. Consistently across studies and in the clinical database, a gain of 7 new EBS skills better coincided with parent impressions of substantial benefits compared to a % gain (even attempting % gain thresholds adjusted for age or baseline scores) Our process included discussions with rehabilitation experts and compiling validity (face validity, cross-tool validity, and predictive validity) and reliability (inter- and intra-rater >85%) data for EBS items (from multiple standardized tools). Other corroborating evidence for the EBS threshold was that children who met the criterion used their hemiparetic UE more often daily and in a wider array of age-normative activities (e.g., self-help, games, social interactions, and object manipulation).

The proposed threshold for clinically meaningful gain at the individual level has support from our prior trials and clinical database since the mean gain scores exceeded this in all prior studies. Face validity derives from considering that gaining at least 7 new core UE skills in just 4 wks, and maintaining at least this many at a later timepoint, represents about one-fourth (23.3% precisely) of the 30 item EBS total. This magnitude gain occurred for subjects with baseline EBS scores as low as 0 and as high as 23 (higher scores are rare for patients seeking CIMT). As **Figure 2** shows, 25 of 27 treated infants had EBS gains ≥7.

Figure 2: Number of New Skills Gained on the Emerging Behaviors Scale (EBS) for 27 Infants with Hemiparesis after Receiving High Dose I-ACQUIRE



Ongoing multi-site RCT of I-ACQUIRE for infants with hemiparetic CP: Baby CHAMP (Study 6). We are completing an NIH Phase II comparative efficacy trial of 3 types of infant rehabilitation: 1) I-ACQUIRE with a continuous cast, 2) I-ACQUIRE with part-time splint (used only in therapy sessions), and 3) Bimanual Therapy with no constraint (HABIT)[101-103] (Andrew Gordon is trial consultant for HABIT.) Blinded outcomes include the Mini AHA,[22] the Bayley-III[9] Fine and Gross Motor Subscales, the EBS, and a novel Reach-and-Grasp Kinematics Tool.[104] To date, we have recruited 60 of 72 infants (8 – 24 mos old) with spastic hemiparetic CP. PRELIMINARY FINDINGS (embargoed): Thus far, infants in the I-ACQUIRE with the continuous cast group show the largest mean gain (15.7) in Mini AHA scores compared to those in the part-time splint group (8.0 pts) or the HABIT bimanual group (5.0 pts). For the EBS, the infants in the I-ACQUIRE continuous cast group exceed the proposed clinically meaningful gain of ≥7 new skills by the end of 4-wk treatment (6 mos follow-up scores not yet available). Finally, using a novel fNIRS paradigm, we have evidence

that I-ACQUIRE with continuous casting can lead to changes in brain laterality, based on resting state and movement-induced recordings.[105] (NB: we decided not to propose repeated neuroimaging for this Phase III trial, due to multiple methodological concerns and cost.)

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

In general, the potential risks are considered minimal. These potential risks include:

Potential risks of casting/splinting: While a child's less impaired arm is constrained, she/he may have some initial negative feelings and may require a period of adjustment (usually <24 hr) to the constraint. These may include feelings of anxiety or fear because the cast is something that is new and perhaps unknown to the child; frustration or anger about having the "good arm and hand" restrained and thus limiting the child from some typical activities using this upper extremity; and possible swelling (if the constraint were not properly applied) or skin irritation or an allergic reaction to the casting or splinting material. Parents will be informed about all potential risks. Any casting-related problems would be corrected within 24 hrs.

A child's initial reaction during the first 24 - 48 hours of being casted may include mild distress; for most children, however, their reaction is one of rapid adjustment, curiosity, and then within a day or two, they seem to ignore the cast. The casting procedure is usually constructed while the child interacts with the parent or watches a fun videotape. It is made with a very lightweight material known as Focused Rigidity casting that allows one side of the cast to be fairly rigid while allowing the other side of the cast to maintain some flexibility. This material allows for a very lightweight cast which immobilizes and restricts use but is not as restrictive as a more traditional and heavier casting material designed to fully immobilize joint and bone placement (e.g., for a broken bone). The cast is constructed so that it can be readily removed, and parents are told how to remove this if an urgent situation arises. We ask parents not to remove the cast, however, without calling the local treatment team. Parents are given the therapist's name and 24-hour (mobile) telephone number, and at least one additional name and phone number of another clinician on the research team; they are strongly encouraged to call *at any time* during the course of treatment with any concerns about the cast or any other aspects of treatment and their child's well-being. If needed, we send someone to the child's home as soon as possible.

We will systematically remove the cast (that is univalved when fabricated) once a week to check on skin integrity. If any irritation or cuts appear, we treat these and, as needed, provide additional padding or adjustment of the cast before returning it. During this weekly check, we also wash the child's arm and hand, test range-of-motion, and spend about 10-15 minutes having the infant use the arm and hand in typical ways, such as manipulating a toy or object. If any loss of function is detected or suspected, this would be reported as an Adverse Event or Serious Adverse Event complying with the University of Cincinnati Human Research Protection Program Policy 11.02. (To date, this has never happened.)

Potential risks of intensive treatment: We anticipate that all of the children enrolled in this RCT will have had some prior experience with occupational and/or physical therapy that is focused on trying to improve their use of the hemiparetic side of the body. We consider the risks involved with this study to be minimal, but they may include the following: a possible period of adjustment to a new therapist, because some children are naturally shy or slow-to-warm-up; and experiencing fatigue or frustration because many of the tasks that the therapist will be using to engage the child necessitate that the child be an active partner in making effort and repeatedly practicing certain new movements and skills. For most children, the U&CT therapy they typically receive occurs in a session that lasts about 50-60 minutes, although some may have had sessions that last as long as 90-120 minutes. The I-ACQUIRE treatment we have developed and will administer in this RCT emphasizes that the tasks used in therapy should primarily be ones which are fun, interesting, and practically useful for the child. For almost all young children, parents can identify favorite toys, objects, or activities to include in the therapy goals. Examples of objects and activities that have wide appeal are using bubble wands to blow bubbles, activity boxes with fun and surprising results from pressing and pulling, books, puzzles, different sizes and types of balls, and games that involve reaching and targeting a goal. In addition, everyday self-help skills of eating, drinking, and

dressing are natural activities ideal for implementing the therapy cycles that have the child initiate a movement, receive reinforcement and feedback, and then repeat and eventually refine their upper extremity skills. The therapists are trained and instructed to end or change activities when a child shows high or sometimes even moderate levels of fatigue or frustration – usually lasting more than 2 or 3 minutes. However, it is undeniable that there are some periods of openly expressed frustration and fatigue that infants show while they are "trying so hard" to do something that does not happen easily. Because the therapist can shift activities throughout the course of a treatment session, such as returning to earlier (more successful) activities, and can provide periods of reassurance with soothing interactions that help infants to calm negative emotions and redirect attention, the I-ACQUIRE therapy sessions are most often interesting, pleasant, and productive. Whenever needed, as observed and suggested by the therapist or parent, the child may take a nap. When naps occur, the therapy session is adjusted to make up for any lost active therapy time.

We actively monitor the progress of each child in therapy. The therapists maintain daily detailed logs on a standardized form, and these are reviewed by the Treatment Implementation Center weekly, with feedback provided to the therapist. Parents are encouraged to contact the local site study coordinator or the PI with any concerns, questions, or suggestions.

Potential risks of treatment in naturalistic settings: Because I-ACQUIRE is delivered in naturalistic environments with families often involved, therapists may sometimes be exposed to family dynamics that do not occur as much in traditional hospital or clinical settings. The family thus may sense intrusion or a loss of privacy; sometimes families may feel embarrassment or shame related to something highly sensitive that may occur when the therapist is in their home.

Therapists will be instructed to report all instances of unusual circumstances that may be a cause for concern about the health, safety, or well-being of the treated child (or any other child on this premise). This report will comply with the reporting requirements of the University of Cincinnati Human Research Protection Program Policy 11.02 for reporting unanticipated problems involving risk to human subjects or others, adverse events, and other problems. We will provide formal training to all project personnel about local guidelines at all clinical sites for reporting suspected child neglect and abuse. Parents also are informed -- verbally and in writing -- when they volunteer to be in the study that we must adhere to local policies about reporting observed or suspected child maltreatment.

Behavioral Assessments: All children in this trial will have likely been seen for clinical assessments that are similar to what children will be asked to do during our outcome assessment battery. The standardized assessments primarily involve having the child manipulate small objects and toys, demonstrate gross motor skills, and show their abilities related to age-typical self-help activities, problem-solving, or knowledge about language and social interactions. The primary risks are slight fatigue and frustration at not being able to complete a task. The administration procedures for the tools selected are ones that take into account the needs and interests of children. The assessment session is play-like in its structure and there are no negative judgments or expressions of disappointment about the child's performance. All of these standardized tools have explicit protocols for the non-completion of items and stopping rules for more difficult items. These protocols will be followed and if signs of undue stress occur, the assessor will offer the child a break, a snack (with parent approval), or may choose to end the session. (Many of the assessments are included in NINDS recommendations for Common Data Elements for Stroke or for Cerebral Palsy and/or the NIH toolbox.)

Parental Reporting: A potential risk associated with the standardized parental reporting about their child involves the possibility that a parent becomes more aware of limits the child may demonstrate due to the targeted and specified questions about their child's developmental progress and arm and hand use. Parents will be encouraged to ask questions brought up by the reporting and they will receive appropriate information in response to their questions and/or directed to reliable sources to obtain information.

2.3.2 KNOWN POTENTIAL BENEFITS

There is the potential for many or even all of the children participating in this proposal to receive substantial benefits that are detectable during and soon after therapy is provided, and these benefits may endure (and even

increase) for many months after therapy ends. The benefits of participation are anticipated based on the published results from previous RCTs, published clinical cases, and data analyses of two large clinical research cohorts. These likely benefits include but are not limited to increased movements in the hemiparetic arm and hand, increased bimanual skills, and increased coordination and functional skills with the hemiparetic arm and hand. These improvements have been associated later with children participating more in daily activities and attempting an increased number of new tasks. Since the children will be very young, there is also a possible benefit that increased awareness and abilities with the hemiparetic arm and hand will produce a base of functional abilities that will naturally allow them to continue and build new skills in other domains of functioning as they become older.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

At the present time, there is insufficient knowledge about the efficacy of I-ACQUIRE for children with PAIS. The results from this adequately powered RCT will help to resolve clinically and theoretically important issues by providing much needed information to inform treatment recommendations and insurance coverage. Because there are minimal risks and many potential benefits to the children, we think the benefits outweigh the associated risks.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary (Aim 1)		
Determine the efficacy of I-ACQUIRE at 2 dosage levels compared to U&CT to increase upper extremity skills on the hemiparetic side both at End of Treatment and 6 mos Post-Treatment.	The primary efficacy outcome is measured by the Emerging Behaviors Scale (EBS). A favorable outcome is defined as a gain of ≥7 new EBS skills above baseline both at the End of Treatment and 6 mos. Post-Treatment Assessment.	Because I-ACQUIRE is a highly intensive and expensive treatment, we think the primary outcome must be large and sustainable – i.e., lasting at least 6 mos post-treatment. Although short-term gains may have some clinical benefit, we deem these insufficient to recommend adopting I-ACQUIRE as standard-of-care for children in this age range with PAIS.
Secondary (Aim 2)		
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.	The secondary efficacy outcome is assessed by mean increases in Mini AHA scores in the 3 treatment groups at both the End of Treatment and 6 mos. Post-Treatment Assessment taking into account their baseline scores.	The Mini AHA assesses how well a child uses the hemiparetic upper extremity as a "helper arm and hand" in a range of age-typical bimanual activities, recognizing that the function of being a "helper arm and hand" is of clinical and practical value.
Exploratory (Aim 3)		
Explore the association between I-ACQUIRE treatment at Moderate and High Doses and gross motor development and cognition (i.e., examples of cross-domain effects of treatment).	If and only if I-ACQUIRE shows efficacy for primary and/or secondary outcomes, we will conduct exploratory analyses about cross-domain effects assessed by the Gross Motor Function Measure-66 and the Bayley-4 Cognition subtest at baseline, post-treatment, and 6 mos. post-treatment. (Other cross-domain changes amenable to exploratory analyses include Language as measured by Bayley-4 and the MacArthur-Bates Scales of Communicative Competence).	Prior small-scale trials reported cross-domain effects after treatment. Here we posit that improved upper extremity competency will increase child exploration and learning, with detectable benefits for at least some children in gross motor, language, and cognitive domains.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The proposed study is a Phase III trial powered to determine efficacy of two different doses of I-ACQUIRE for children 8 to 24 months old with PAIS and hemiparesis. The design is a prospective RCT in which 240 children will be randomly assigned to one of 3 treatment groups (N=80 per group): 1) Moderate Dose I-ACQUIRE (3 hrs/day, 5 day/wk X 4 wks), 2) High Dose I-ACQUIRE (6hrs/day, 5 days/wk X 4 wks), or 3) Usual and Customary Treatment (U&CT). I-ACQUIRE will be delivered by protocol-trained therapists and monitored weekly for dosage and treatment fidelity; U&CT will be provided by community therapists with dosage and approaches documented weekly. All primary and secondary efficacy outcomes rely on blinded assessments at baseline, end of treatment, and 6 mos post-treatment. Exploratory outcomes and supplemental clinical measures may provide valuable additional data about development and health in this sample of children with PAIS.

There will be a second phase of the I-ACQUIRE Study for the children who had been randomly assigned to Group 3 (Usual and Customary Treatment). Their parent(s) may choose to enroll (via a new IRB-approved consent process) to have their child randomly assigned to receive either the Moderate or High Dose I-ACQUIRE treatment. This will occur after the 6-mos Post-Treatment Assessment from the primary phase. Outcome data from this second or crossover phase of the study will not be used in the primary data analysis for this trial but will be available for exploratory and post hoc data analyses.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

PAIS is a serious event that can produce lifelong severe impairments: the most prevalent impairment is hemiparesis. Of high significance is that there have been *no* randomized controlled trials (RCTs) of CIMT protocols for this clinical population of children and no reported trials of CIMT for children under 2 yrs old. Multiple independent reviews of other therapy interventions for infants and toddlers conclude most are ineffective, some yield small magnitude benefits, few show enduring benefits. Similarly, no RCT of CIMT has focused on children with a diagnosis of PAIS. This matters because i) children under 3 yrs old differ in attention span, motor development, and learning modes from older children; ii) children with PAIS may differ clinically from the general hemiparetic CP population; and iii) plasticity of brain function after injury may relate inversely or differently to the child's age or stage of development.

Justification for age range of children in this trial: Typical UE development is rapid in the first 3 years. Bimanual skills emerge at 6 - 8 mos when a child holds an object with both hands and easily transfers it from hand to hand. The infant practices these bimanual skills so by ≈10 mos. the infant shows symmetrical movements (e.g., banging objects together, clapping). From 12 - 24 mos., the child acquires differentiated bimanual skills that permit one hand to hold an object while the other manipulates it. This milestone affects acquiring many other skills (e.g., holding a bowl and scooping food, stabilizing a bottom block while stacking others, placing marks on a paper held by one hand). Soon after, the child discovers that simultaneous hand movements can be separated and coordinated to achieve a wide array of functions from advanced toy play to self-feeding, turning pages of a book, dressing/undressing, and moving through space. With increasing age and opportunities, the child combines and refines upper extremity skills to engage in more complex and challenging activities in a variety of play, exploration, and self-help areas. Accordingly, 8 to 36 mos represents an ideal age window for I-ACQUIRE. (We found that 6 and 7 mos olds are a bit young for intensive shaping of UE skills.) Note: An additional benefit of focusing on this young age range is that this corresponds with the federal and state legal definition for "early intervention" defined as "birth to 2" that goes up to the child's third birthday and entitles to the child to provision of appropriate services for developmental delays and disabilities (under the federal and state IDEA regulations).

4.3 JUSTIFICATION FOR DOSES

We originally selected a 6-hr daily session because this comprises a large portion of the waking day, similar to the time infants and toddlers spend in childcare, early intervention programs, or school. This is the most tested

dosage for a "signature form" of pediatric CIMT[17] and we know infants and toddlers tolerate (and often enjoy) this 6-hr dose (see Prior Studies). We selected other dose - the 3-hr dose – because it is similar to a half-day session in childcare, early intervention, or school. Both practically and clinically, the difference between 3 and 6 hr is large in terms of therapy cost and time demands on therapists and families. We did not select an even lower dose because we know of no evidence that this can produce benefits that are comparable to the large effect sizes reported in Prior Studies (many are much smaller or non-existent).[37-39,41,43,125] Theoretically, the 6-hr dose may promote a stronger habit pattern of using the hemiparetic UE and, resultantly, produce larger and more enduring effects by 6 mos post-treatment than the 3-hr dose. Alternatively, if the 3-hr dose can produce significant, large, and enduring benefits, this would be important new information to inform the vigorous debate about the different high-dosage levels and reduce the cost of delivering I-ACQUIRE to eligible infants.

4.4 END OF STUDY DEFINITION

End of Study for the Primary Phase 1 is defined as after completing the 6 mos. Post-Treatment Assessment after the child received one of two dosages of I-ACQUIRE treatment or U&CT. In the second Crossover Phase, for those children who were in Group 3, Usual and Customary Treatment, the end of study will be after completing the 6 mos. Post-Treatment Assessment after receiving I-ACQUIRE.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Inclusion Criteria: child will be 8 - 36 mos. old at time when study treatment during the primary Phase 1 will be delivered; have a diagnosis of Perinatal Arterial Ischemic Stroke (PAIS) with parent permission to provide the child's clinical MRI to the study; hemiparesis; and parent(s) willing to participate in the home therapy component. At least one parent must be English-language proficient and be the parent who will take a lead in interacting with study staff and completing self-administered forms and interviews in English. (Note: for the crossover second phase, children from the U&CT group may be older than 36 mos. when they receive one of the two doses of I-ACQUIRE treatment.)

5.2 EXCLUSION CRITERIA

Exclusion Criteria: medical or sensory condition(s) that prevent(s) full therapy participation (e.g., frequent uncontrolled seizures, fragile health); received modified CIMT with a dose of at least 2 hrs/day for ≥10 days Lower modified CIMT doses are permitted.); received botulinum toxin in past 3 mos, or baseline EBS score >24 points. If a child is a ward of the state or other agency, the child will not be eligible. NB: botulinum toxin or another form of CIMT cannot be administered until after the 6 mos Post-Treatment Assessment has occurred. (Note: an EBS score >24 points would be extremely rare in this age group and clinical population. It is an exclusion criterion because a child would be precluded from reaching the study primary outcome threshold of a gain of 7 or more EBS points. However, the EBS baseline score is not known until the Baseline Assessment is completed and scored centrally at the I-ACQUIRE Assessment Center at OSU.)

5.3 LIFESTYLE CONSIDERATIONS

There are no known normal range lifestyle considerations that could impact treatment efficacy of I-ACQUIRE other than non-compliance with the treatment protocol. This will be monitored daily during the month of treatment.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened at a time when they may meet enrollment criteria (e.g., infant had become ill at time when treatment was scheduled or an unexpected event prevented parents from fulfilling their role in the parent training component). Infant can be rescreened when he or she recovers, or family can fulfill inclusion criteria for participation. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

We will recruit 240 families who complete baseline assessments from 12 or more sites. Eligible children will include those known to the sites (from clinical databases, direct care, and satellite sites) and those recruited from other hospitals, clinics, and early intervention programs. Each site will compile an inventory of regional sources to distribute recruitment materials, using locally-adapted print materials, posters, media announcements, and web-based study information. Also, we will use 2 approaches that have successfully recruited subjects in our other multi-site studies - social media and advocacy groups. Finally, we will list the trial on *ClinicalTrials.gov,* which has generated volunteers who re-locate temporarily for treatment and agree to travel for all scheduled assessments. We will assist these families in finding low- or no-cost housing options, if requested. The I-ACQUIRE Clinical Trial website will have recruitment materials for families and clinicians in English (with a notation that at least one parent must be proficient in English). Recruitment materials and methods will be finalized jointly with the Parent Council (see below) with a clear goal of recruiting a representative and racially/ethnically diverse sample.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

OVERVIEW OF CORE TREATMENT COMPONENTS FOR I-ACQUIRE (BOTH DOSES)

1. Constraint of the child's less-impaired upper extremity for first 17 days of treatment; cast is worn 24/7. Children will continuously wear a full-arm lightweight cast for the first 17 of 20 therapy sessions. The cast is made from focus rigidity casting material with arm and hand positions specified and uni-valved for easy removal weekly for safety checks. For the last 3 treatment days, the therapist removes the cast and focuses on integrating the new skills of the hemiparetic UE into bimanual activities. Constraint is designed to reduce competing sensory-motor input and consistently help direct the child's attention to use of the hemiparetic arm/hand.
2. High dosage of treatment – either 3 or 6 hrs/day, 5 days/wk for 4 weeks. (see above for rationale in choosing these dosages). CIMT is premised on evidence that concentrated high amounts of shaping and varied practice of new skills can produce rapid and enduring improvements in UE skills and functional use. A protocol-trained therapist provides 20 treatment sessions of either 3 or 6 hrs/day, 5 days/wk X 4 wks. Therapists are scheduled to have an extra hour each day to cover child naps and breaks (which are not included in daily documentation of time spent in active therapy). We re-affirm that young children have tolerated both dose levels well, largely because of therapists' skills in maintaining high infant interest and enjoyment and frequent shifts in the therapy activities. (See Prior Studies.)
3. Operant conditioning techniques to shape and improve upper extremity (UE) skills; combined with practice variation. Operant conditioning is applied across a wide range of activities with the goal of eliciting new UE skills and then improving voluntary motor control by progressing through a cycle in which specific verbal, visual, and/or physical requests for a movement or behavior are made, often with the therapist modeling and prompting, particularly at early stages. The methods for setting behavioral goal standards, providing rewards, and then increasing levels of consistent performance required to earn continued reinforcement are

described in detail in the ACQUIREc administration manual[16] and training materials. We term this the MR3 Cycle (**m**ovement, **r**einforcement, **r**epetition, and **r**efinement).[16] Activities are varied, game-like, and enjoyable for the infant; self-help activities provide frequent natural opportunities for the MR3 cycle.

4. Provision of therapy in natural settings. We provide therapy in natural environments, because this promotes generalization and maintenance of skills. For young children, this can include varied environments such as the home, childcare, or early intervention settings. Sometimes clinic settings can be set-up to be similar to home or childcare settings. Parents and family members often are present and join in some therapy activities.

5. Emphasis on total body and bimanual activities (as well as traditional arm/hand therapy activities) Treatment activities extend to total body and gross motor activities that use the hemiparetic UE, e.g., sitting with stability, weight bearing, rolling, scooting, standing, crawling, and walking. Even with the cast, many gross motor bimanual activities can occur during treatment, e.g., crawling, rolling, carrying, pushing, or pulling large object).

6. Home Treatment Module developed as an active Parent-Therapist Partnership. We developed and use a parent-home training module (with supportive written materials and photo/videotapes). The therapist and parents meet at the beginning of treatment and at least weekly for 4 weeks. Initially, the therapist coaches the parent in the I-ACQUIRE processes, particularly concerning effective and ineffective use of operant conditioning. Parents help identify goals, introduce new activities, and help tailor therapy activities to promote the use of newly acquired skills in many different situations. Expectations are that parents enact their component for about 45 min per day on 5 of 7 days. (This can be divided into shorter times and include mother and/or father engagement. It is acceptable if only one parent provides the home program.) Daily review by therapists and parents of individualized home-based activities includes child responses and time spent and promotes two-way benefits for the child's treatment. Parents and therapists complete the Parent-Therapist Relationship Tool at the end of treatment week 4.

7. Documentation of daily therapy sessions. Each therapist documents treatment with standardized daily logs that record treatment goals worked on, activities completed (divided into discrete skills and levels), infant behavior (interest level, signs of frustration or fatigue), and any progress or decline. I-ACQUIRE protocol recommends that the therapist vary the therapy activities or stop therapy (within a session or overall) if unexpected problems occur, such as high levels of infant distress (lasting more than 3 minutes). If needed, the therapist may obtain consultation from senior I-ACQUIRE therapists at the Treatment Implementation Core about the course of treatment.

8. Transfer Package to promote future progress. Therapist and parents develop a written plan with extensive supportive materials to help the child maintain and improve skills post-treatment. This plan targets every day and special activities, informed by the overall treatment process, how the child has progressed across various skill levels, and next steps towards higher level functional use.

6.1.2 DOSING AND ADMINISTRATION

In the primary Phase 1, all participants will be randomly assigned to one of the 3 groups. Two pre-determined dosages of I-ACQUIRE are implemented as part of the study design. In the crossover Phase 2, for children assigned initially to Group 3, Usual and Customary Treatment, their parent(s) may consent for the child to be randomized to Moderate or High Dose I-ACQUIRE and then be assessed at the end of treatment and 6 mos post-treatment. Note: the crossover Phase 2 data will not be used to test the primary trial hypotheses about efficacy of the two dosages of I-ACQCUIRE compared to Usual and Customary Treatment and to each other.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

At the Post-Treatment Assessment visit, after obtaining parental consent for DNA collection, the blinded assessor will collect a DNA sample from the child by gently rubbing the inside of the child's cheeks with two small, soft tipped, Oragene brushes. These have been successfully used by our collaborators in other genetic studies. In 1 out of 4 children we will likely need to collect a second sample, because of insufficient saliva or other problems with the quality of biological material collected. This repeat data collection will occur at the 6 mos. Post-Treatment Assessment.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Not Applicable

6.2.3 PRODUCT STORAGE AND STABILITY

Not Applicable

6.2.4 PREPARATION

The two swabs will be sent to a central Yale University laboratory where the DNA will be stored, extracted, and analyzed for single nucleotide polymorphism expression.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Subjects will be randomized in a 1:1:1 fashion to U&CT, Moderate Dose I-ACQUIRE, or High Dose I-ACQUIRE using a restricted randomization algorithm which controls for within site treatment imbalances. If no imbalances exceed the tolerated threshold, the patient is randomized according to the specified allocation ratio (1:1:1) using a block urn design. If an unacceptable level of imbalance exists, the algorithm will determine whether the current allocation ratio improves or exacerbates the current imbalance and adjust the ratio accordingly. The detailed randomization scheme and source codes will be provided in the Randomization Plan document. Note: for general understanding, the randomization process will be described in the consent document for parents as having an equally fair chance of being assigned to one of the 3 treatment groups.

Upon confirmation of eligibility and obtaining parental permission to participate, study coordinators will log into the WebDCU™ study database and receive the computer-generated randomization assignment. Local Site Coordinators will notify families promptly to schedule baseline assessments and designate the treatment month.

It is not possible to blind the family or the treatment team; however, no treating therapist will conduct assessments for primary and secondary outcomes, and none of the blinded assessors will work in the same setting as treatment staff. In addition, the primary and secondary outcomes will be coded by staff at the Central Assessment Core at The Ohio State University, remote from the clinical site and treatment implementation core. Assessment Core research staff will be blinded to treatment and the videos will be randomly sorted so that central coders cannot know whether a video is the baseline or one of the follow-up assessments. Parents also are reminded before each assessment session not to discuss their child's treatment with the assessor.

For assessments completed by the local blinded assessor, a second blinded scoring will be calculated by the central blinded assessment team if the local assessor has indicated that he or she possibly has become unblinded. Only blinded scores will be used in the primary analysis, but sensitivity analyses will compare the local and central scores to assess for any potential differences due to the unblinding.

6.4 STUDY INTERVENTION COMPLIANCE

We will define I-ACQUIRE treatment compliance as: (1) receiving therapy on at least 17 of the 20 intended days; (2) receiving the full daily dosage ± 30 minutes on at least 15 treatment days; (3) wearing the cast continuously on at least 15 treatment days and over the weekends (NB: the cast is removed for the final 3 days of therapy intentionally to provide 3 sessions focused on bimanual activities); (4) the parent received training in the home-based component and provided evidence that this occurred on at least 12 days over the 4 wk treatment period; (5) completion of treatment occurs within 5 weeks of the first treatment session (this allows for a brief extension in the 4-wk treatment in the event of a short disruption, such as an illness, minor injury (not treatment-related), or family problem). We will examine the proportion of subjects in each I-ACQUIRE treatment group who did not receive this minimum level of treatment (i.e., met these criteria for treatment compliance) and seek to understand the likely reasons for non-compliance.

Whenever we restrict the analytic sample to the as-treated sample, we will report the number and characteristics of subjects who differ in treatment compliance (Moderate and High Dose I-ACQUIRE) or in distinct U&CT care subtypes (e.g. type of therapy, categorized treatment durations), and will consider if the final as-treated and Modified ITT samples differ in their sociodemographic or clinical characteristics. This is important so that study findings obtained from any as treated sample analyses can specify whether the results apply to the entire patient population or only to certain subgroups.

6.5 CONCOMITANT THERAPY

Not Applicable

6.5.1 RESCUE MEDICINE

Not Applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Study intervention would be discontinued for an individual subject if a serious adverse event (SAE) related to the trial occurs, if an SAE unrelated to the trial occurs that in the opinion of the site investigator will preclude safe participation in the rest of the trial, or if the futility analysis (see full statistical plan for details) deems the treatment highly unlikely to be worthy of continued study.

Note: a short-term disruption or discontinuation of the study intervention could occur due to unforeseen health, safety, or family issues. If these occur, we would discuss this with parents and seek a resolution to the problem. If these necessitate any change to the overall study protocol or procedures, we would notify the CIRB to discuss and consider any options. (In the past, for example, a family emergency could arise and cause a re-scheduling of a treatment session on the weekend, or a sudden onset of a short-term illness in the child, parent, or even therapist could lead to a re-scheduling of an assessment session that has begun, or a treatment session. Typically, these lead to a minor schedule adjustment. This does not lead to dropping a participant form the study or future follow-up assessments.)

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

- The reason(s) for participant discontinuation or withdrawal from the study will be recorded.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for scheduled post-treatment assessments, and/or is unable to be contacted by the study staff.

The following actions must be taken if a participant fails to return for a required study visit:

- The study team will attempt to contact the participant‘s parent(s) and reschedule the missed visit and counsel the parent on the importance of maintaining the assigned visit schedule.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the parent(s) of the participant (when possible, 3 telephone calls and email communications and, if necessary, a certified letter to the participant’s last known mailing address or local equivalent methods). These contact attempts should be documented in the participant’s study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Primary Outcome MEASURE: The Emerging Behaviors Scale (EBS). The EBS is a standardized tool developed for pediatric rehabilitation research in hemiparesis. The rationale for this tool is that all young children, including those with hemiparesis, need to acquire a repertoire of essential upper extremity (UE) skills that are used frequently every day during play, self-help, object manipulation, and social communication. Without a sufficient number of these critically important UE skills, a child’s future progress will be delayed and will lead to increasing impairment over time. The EBS thus represents a foundational base of core UE skills that extend into later ages. The EBS tallies the number of core skills (0 to 30) with the hemiparetic UE. (Note: once an infant acquires an early version of each skill, therapy focuses on improving that skill – e.g., ease, accuracy, speed, and integration with other skills into complex sequences). Items on the EBS appear as part of standardized tools (e.g., Bayley-4, Peabody Scales of Motor Development-2, the QUEST, NIH Toolbox). A unique feature of the EBS is the requirement that the child display each skill at least twice. Coding is completed by the blinded Central Assessment Core staff based on the videotaped session that includes the full Bayley-4, the Mini AHA, a snack break, and interactions with the assessor and parent at the start and close of the session. The parent ratings on the IMAL can be used as a source of one of the two times the skill was documented. All EBS items have high face and content validity and inter-rater reliability established on at least 3 standardized tools. Most have high predictive validity for the child’s future performance on the same or similar items.

The primary efficacy outcome is defined as gaining and retaining ≥7 new EBS skills above baseline EBS score at the End of Treatment and 6 mos Post-Treatment Assessments. Rationale and supportive evidence for the proposed criteria for a minimal clinically important outcome: For the past several years, we have engaged in efforts to identify a minimal clinically meaningful improvement on the EBS. We have reviewed outcomes for subjects in prior trials and our clinical database; studied clinical thresholds in other rehabilitation trials and goal-setting in therapy (often 5 – 10% gains); obtained input from pediatric OTs, PTs, and physiatrists; compared several thresholds that vary for subject age or baseline score; and cross-checked EBS scores with parent ratings, observations, and therapist logs of child progress

We recognize that a single dichotomous primary outcome has limits – notably, reduced detail about the precise magnitude of change and its slope over time. Finally, we selected the dichotomous outcome because: i) we think establishing pre-specified minimum high expectation for gaining and then maintaining a large number of new skills is justified, given the high cost of this time-intensive treatment. That is, if the gains were only short-term, parents and clinicians would likely be disappointed that benefits are merely transitory; and ii) we think the dichotomous outcome is easier for clinicians and parents to understand than a distribution-based or individualized outcome that is difficult to understand (because the EBS tool itself and the meaning of the range of scores are not widely known). The threshold of gaining ≥7 new EBS skills can be equated with about one-fourth of the entire EBS repertoire; further, all infants in the I-ACQUIRE trial and most infants with PAIS will have baseline EBS scores that allow them to acquire this many new skills. Our analyses affirm that this simple,

dichotomous outcome works well across the entire EBS continuum to classify those with and without a favorable treatment outcome. In our earlier studies, patients with divergent EBS baselines showed mean EBS gains ≥7 new skills. We are not certain, however, that a gain of only 6 EBS skills has no clinical meaning to an infant or parents.

We further note that children with a baseline EBS of 24 or higher are excluded from the trial in terms of testing the primary efficacy outcome, because this would preclude achieving the study threshold. (Based on prior clinical trials and clinical research, a baseline EBS score of 24 or higher would be extremely rare. We further note, however, that we think the I-ACQUIRE treatment could possibly result in meaningful improvement for such a high functioning child, although the choice of the EBS as the primary outcome measure does not allow for fully capturing such potential benefits.)

Secondary Outcome MEASURE: The Mini-Assisting Hand Assessment (Mini AHA). The Mini AHA is a new tool that rates how well a child engages the hemiparetic UE as a "helper" in bimanual activities, recognizing that children with hemiparesis are unlikely to use their hemiparetic UE as their dominant E. The Mini AHA has high inter-rater reliability. A Rasch measurement analysis supports inter-scale validity, showing items fit well with underlying constructs and a developmental model. A Pearson Separation ratio of 9.67 affirms children can be reliably separated into functional levels based on scores. Note: Test developers require formal training and certification to use this tool. We sponsored the first training session in the U.S. Certified assessors score 20 items on a 4-pt scale from videotaped sessions. Raw scores are converted into unit (or logit) scores (0 to 100). Presently, there is no basis for establishing a minimal clinically meaningful threshold, thus we will use the total Mini AHA unit score.

8.2 SAFETY AND OTHER ASSESSMENTS

The Independent Medical Safety Monitor (IMSM) and the Data and Safety Monitoring Board (DSMB) will receive periodic safety reports of Adverse Events including Serious Adverse Events serious adverse events (SAEs) that have a reasonable possibility of being related to the study intervention following the reporting requirements of the University of Cincinnati Human Research Protection Program Policy 11.02. All reportable AEs will be summarized in terms of type of AE (AE code), when the AE occurred, frequency of the AE, number of subjects having the AE, severity of the AE, and relatedness to the study treatment. The proportion of subjects experiencing AEs will be provided in the closed report by treatment group arm with two-sided 95% CIs and unadjusted relative risks.

Safety analyses. Safety will be assessed by monitoring the rate of all clinical safety endpoints and SAEs throughout the treatment period. The proportion of children experiencing each of these events will be provided to the DSMB as unadjusted relative risks and 95% confidence intervals at regular intervals to facilitate decision making, but the trial does not provide binding statistical guidance on safety stopping.

In addition, the following measures of safety and tolerability will be assessed:

- Effects of continuous casting as noted in the daily logs by therapists, including recorded notes about the casted upper extremity during weekly cast removal to check for skin integrity, range-of-motion, and use of the casted upper extremity during 15-30 minutes of play (this is scored by the treating therapist).
- Stress in parents and infants related to the treatment or study participation as measured using the Perceived Stress Scale (for parents) and supplemental stress questions answered by parents about their child's stress levels

We also include a set of measures for Exploratory Analyses.

Measures of child development for Exploratory Aim 3: Gross Motor Function Measure (GMFM-66) and the Bayley-4 Cognitive subtest. The GMFM-66[7] measures gross motor function in children with cerebral palsy (5 mos - 16 yrs). 66 items are scored each on a 4-point scale and grouped into 5 domains (lying and rolling; sitting; crawling and kneeling; standing; and walking, running, and jumping); an overall GMFM Total Score also is computed. The GMFM-66 is considered valid and sensitive to changes in children with neuromotor impairment. We will use the Total Score in the exploratory analyses relating treatment group to gross motor development.

(One surgical intervention study[127] established a minimal clinically meaningful outcome on the GMFM-66 for older children as a gain of 2.7 points, although a gain of only 0.7 was deemed clinically useful for some patients. We will work with the Parent Council and clinicians to determine whether these (or other) thresholds might be suitable to consider for interpreting findings about GMFM-66 for children with PAIS.)

The Bayley Scales of Infant and Toddler Development-4 (Bayley-4) is the most widely used tool to assess infants (3 - 42 mos). It underwent major revision and re-norming in 2019, including children with disabiltiies.[107] It yields subtest scores for Fine Motor, Gross Motor, Language, Self-help, and Cognition and an overall Developmental Quotient (DQ). For Exploratory Aim 3, we primarily plan to use the Cognitive subtest (scores from 0 – 19, mean of 10, SD=3 pts) to consider whether one or both doses of I-ACQUIRE, compared to U&CT, are associated with significant gains in Cognition. We predict, based on theory, that the High Dose group will show larger mean cognitive gains than the children in the Moderate Dose or U&CT groups, and that likely these become detectable by the 6 mos. Post-Treatment Assessment. Our reasoning is if I-ACQUIRE produces large gains in UE skills (the primary and secondary efficacy outcomes), then treated children will be able to increase their successful interactions with their environment which, in turn, could improve their learning and problem-solving skills and lead to higher Bayley-4 Cognitive scores. Other subtests may also show benefits that will be considered in exploratory analyses.

Additional descriptive measures (not blinded) and rationale for collecting. We value the perspectives of parents about their children's response to treatment and their observations of their child's development. Parents have the greatest amount of experience with their child. They uniquely can provide ratings about what they observe in terms of their child's use of the hemiparetic UE in everyday settings and their participation in a wide variety of age-appropriate activities. Accordingly, parents will complete the Infant Motor Activity Log (IMAL),[26] a standardized tool about "how well" and "how often" their child uses the hemiparetic UE in 20 everyday behaviors (e.g., holding bottle/cup, eating finger foods, pushing a button, reaching to be picked up). The scale is 0 to 5 with behavioral anchoring provided. The IMAL will provide useful descriptive information to accompany the findings about primary and secondary efficacy. Parents also will complete the MacArthur-Bates Communicative Development Inventories (CDI),[130] a standardized reliable tool to assess the child's communicative competence. There is an infant version for 8 to 18 mos and a toddler version for 18 to 30 mos which can be used for older children who have shown language delay. Previous clinical observations of children treated with I-ACQUIRE indicate that children's language abilities may be improved by the treatment. Theoretically, this is important to understanding neuroplasticity and cross-domain changes after treatment. Parents also complete the Perceived Stress Scale at each assessment to monitor for parent response to treatment group and answer questions about their perceptions of their child's stress levels.

Clinical data about the infants: A Pediatric Neurology Exam will occur at each site at baseline by a trial-affiliated pediatric neurologist or physiatrist. It will include the Pediatric Stroke Outcome Measure (PSOM) (severity scores from 0 to 10), and information about co-morbidities, general health and health history, and the child's current and past treatments. These data will be used to describe the clinical sample and to compare subjects across treatment conditions and clinical sites.

NEUROIMAGING ANALYSIS: We will examine and code clinical MRI scans to yield a potentially useful set of imaging biomarkers that may predict differential responses to treatment (with implied underlying CNS mechanisms). The sites have agreed to use uniform imaging protocols for diagnosis of PAIS[1] (many already do this) to ensure that almost all MRI images will be consistently high quality. MRI scans will be reviewed by a pediatric neuroradiologist blinded to the subject's treatment at the Clinical MRI Core at Stanford. Coding will include summary measures about involvement of the hemispheres, basal ganglia (BG), posterior limb of the internal capsule (PLIC), and cerebral peduncle (CP). We will apply a previously described approach[7] in which the path of the corticospinal tracts, including the posterior limb of the PLIC and the CP will be graded as "involved" or "not involved." In addition, we will classify brain regions as being (0) non-affected by the infarct, (1) <50% affected, (2) >50% affected, or (3) completely infarcted. Finally, we will calculate infarct volume by delineating the infarct on each MRI slice, measuring the areas corresponding to these delineations, and then multiplying these areas by the slice thickness (plus the gap if any). Major regions of interest for exploratory analyses include the corticospinal tracts in relationship to UE skills (EBS and Mini AHA) at baseline and at 2 endpoints after

treatment; association with gross motor development (GMFM-66) at all 3 timepoints; and infarct volume of discrete brain regions in relationship to Bayley-4 Cognition at all 3 timepoints. Also, we will have the ability to explore, for example, whether patterns of these MRI measures (e.g., reliable clusters of scores from the above coding) show a predictive association with which subjects show higher or lower change scores for the primary and secondary efficacy outcomes. The results of these biomarker analyses could be clinically useful in treatment recommendations for individual patients.

Parents will be given a questionnaire at the 6 mos Post-Treatment Assessment that has been designed by the I-ACQUIRE Parent Council to learn about parents' experiences with the I-ACQUIRE trial, and to help inform future clinical trials research about important aspects of family preferences, needs, and values.

A 36-item survey was developed that covers three topics: experience with the I-ACQUIRE trial; parents' values and preferences concerning child activities and participation in life situations; parents' experience in general with clinical trials. Participant ID will be the only identifier; no PHI is included on the survey.

The parent survey will be provided to parents with a cover letter from the Parent Council and envelope for returning the survey. Families will complete the survey just prior to and at the 6 mos Post-Treatment Assessment.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse events (AEs) are considered to be any undesirable sign, symptom, or medical condition occurring during the study, whether or not related to the intervention. AEs include new events not present prior to intervention (i.e., at screening AEs), can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject

(See below for additional information about coding the type, severity, and relationship of an AE to study intervention for this trial.)

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An SAE is any untoward medical occurrence that:

- results in death;
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires inpatient hospitalization or causes prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.)

The definition of SAE excludes the following hospitalizations:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event);
- Elective surgery, planned prior to signing consent;
- Admissions as per protocol for a planned medical/surgical procedure;

- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy);
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study (appropriate documentation is required in these cases);
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The severity of adverse events will be reported using the grading system outlined in the NCI Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE). The CTCAE provides a grading (severity) scale for each AE term and AEs are listed alphabetically within categories based on anatomy or pathophysiology. The CTCAE (v4.03) displays Grades 1-5 with unique clinical descriptions of severity for each AE based on this general guidance:

CTCAE Severity Grading Summary	
Grade 1:	Mild AE
Grade 2:	Moderate AE
Grade 3:	Severe or Disabling AE
Grade 4:	Life-Threatening AE
Grade 5:	Death related to AE

The complete definitions of these grades are:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated AE.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

One of the most important components of AE reporting is determining the cause of the AE. It is imperative that the site investigator assess AE causality in terms of overall study participation and make an independent determination as to whether the AE was thought to be related to any study-related activity (i.e., study intervention, test article administration, study-related tests or procedures). For the subjects in U&CT, AEs that occur cannot be considered to be related to study participation, since the child previously was receiving this form of treatment (i.e., parents agree not to change the child's U&CT during the study period). Further, the study has no authority to obtain data from the child's community therapist(s) and thus cannot infer likely relationship to the U&CT intervention. For each Adverse Event, the relationship to the study treatment must be recorded as one of the choices on the following scale:

NOT RELATED (MUST HAVE 1)

- Unreasonable or incompatible temporal relationship to the intervention
- Event is clearly due to extraneous causes (e.g., underlying disease, environment)

-

UNLIKELY (MUST HAVE 2)

- Reasonable or tenuous temporal relationship to intervention
- Could readily have been produced by the subject's clinical state, or environmental or other interventions
- Does not follow known pattern of response to intervention
- Does not reappear or worsen with reintroduction of intervention

-

REASONABLE POSSIBILITY (MUST HAVE 2)

- Reasonable temporal relationship to intervention
- Could not readily have been produced by the subject's clinical state or environmental or other interventions
- Follows a known pattern of response to intervention

-

DEFINITELY (MUST HAVE 4)

- Reasonable temporal relationship to intervention
- Could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions
- Follows a known pattern of response to intervention
- Disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure

8.3.3.3 EXPECTEDNESS

The IMSM is typically responsible for determining whether an SAE is **expected** or **unexpected**. An SAE is considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study treatment or based on the underlying disease.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. The following AEs will be reported in the study database: 1) Any serious AE (SAE) possibly related to study participation occurring from the Baseline assessment through the participant's end of study; 2) Any AE occurring from the Baseline Assessment through the participant's end of study that has a reasonable possibility of being related to study participation. All such events are captured on the appropriate CRF and entered into WebDCU™. Information to be collected for reportable adverse events includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event.

Any medical condition that is present prior to Baseline Assessment will be considered as pre-existing or baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, and is possibly related to study intervention, it will be recorded as an AE.

Changes in the severity of an AE possibly related to study intervention will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Site PIs will record all reportable events consistent with the University of Cincinnati Human Research Protection Program Policy 11.02.

8.3.5 ADVERSE EVENT REPORTING

All reporting is done in accordance with StrokeNet Standard Operating Procedures for Safety Monitoring and Reporting as outlined in the administrative documents available on the website (https://www.nihstrokenet.org/docs/default-source/default-document-library/adm13-safety-monitoring-and-

reporting-12-19-16.pdf?sfvrsn=0). Clinical sites report all SAEs and any AEs that have a reasonable possibility of being related to the intervention into WebDCU™. These events are coded using MedDRA. Sites are required to report SAEs within 24 hours and non-serious AEs within 5 days of their awareness of the event.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

All SAEs are required to be reported in WebDCU™ within 24 hours of the study site being made aware of the occurrence of the SAE. The local site investigators are required to provide relevant information such as description of the SAE, date/time of onset and resolution, severity and seriousness, action taken, and suspected relationship to the study intervention. Reporting of SAEs will trigger notification of the event to the Project Manager (PM). After reviewing the SAE for completeness and accuracy, the PM will forward the SAE to the IMSM who will conduct an independent review of each SAE to determine its relationship to the study intervention along with other elements. The IMSM will then enter an opinion into WebDCU™ as to whether the SAE is, in fact, serious, unexpected, and related to the study intervention. After the submission of the initial SAE Report, the site investigator at the corresponding clinical site will be responsible for obtaining follow-up information about the event and reporting it in WebDCU™.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

As part of the consent process we commit to informing parents if there are incidental findings from previous participants (including from other clinical sites) or findings that occur as a result of interim data analyses if these findings might have an impact upon allowing their child to participate. We will not and cannot ethically discuss specific events regarding any one participant but will indicate to any enrolled parents or future parents considering providing permission to participate that there have been one or some events beyond those currently identified as risks in the consent document approved by the CIRB. If this occurred, we would notify the CIRB about the method and wording of such notification to parents.

8.3.8 REPORTING OF PREGNANCY AND EVENTS OF SPECIAL INTEREST

Not Applicable

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the CIRB complying with the University of Cincinnati Human Research Protection Program Policy 11.01. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;

- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 5-days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 7 days in accordance when the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 7 days of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

All unanticipated problems will be reported as soon as possible (usually within 24-48 hours) to the child's parents in the event that the parents were not already of this. This may include a written description of the event and how the event will be followed up on. We will invite questions by parents and view this as an opportunity for discussion about any unanticipated events. The reporting and the resolution associated with the event will be documented in the study's history and, when applicable, in the individual subject's file.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

1. 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. The primary efficacy outcome is a gain and retention of ≥7 new skills on the Emerging Behaviors Scale (EBS) at the end of the 4-wk treatment and 6 mos. later.

Hypothesis 1A: The 3 groups will differ significantly in the proportion of infants meeting primary efficacy criteria.
Hypothesis 1B: Both the Moderate Dose and High Dose I-ACQUIRE groups will have significantly higher proportions of infants meeting the primary efficacy criteria compared to U&CT.
Hypothesis 1C: The High Dose compared to Moderate Dose I-ACQUIRE group will have a significantly higher proportion of infants meeting the primary efficacy criteria.
Additional sensitivity analyses using repeated EBS scores (from 0 – 30) will explore specific aspects of treatment outcome and maintenance (e.g., differential magnitude of EBS changes across treatment groups) in relationship to predictor variables (e.g., stroke CNS damage coded from MRI scans, family engagement levels).

2. 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. The secondary efficacy outcome is the Mini Assisting Hand Assessment score at the end of 4-wk treatment and 6 mos. later.
Hypothesis 2A: The 3 groups will differ significantly in mean Mini AHAs at end of treatment and 6 mos later.
Hypothesis 2B: Both the Moderate Dose and High Dose I-ACQUIRE groups will have significantly higher mean Mini AHAs compared to U&CT at the end of treatment and 6 mos later.
Hypothesis 2C: High Dose compared to Moderate Dose I-ACQUIRE will have significantly higher Mini AHAs at end of treatment and 6 mos later.

3. 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).
3A. Evidence-informed prediction for motor development: Both Moderate and High Doses of I-ACQUIRE will have higher mean gains in Gross Motor skills compared to U&CT at end of treatment and 6 mos later.

3B. Theory-informed prediction about cognition: High Dose I-ACQUIRE will be associated with larger mean gains in Cognition (Bayley-4) than Moderate Dose I-ACQUIRE and U&CT at 6 mos post-treatment.

9.2 SAMPLE SIZE DETERMINATION

The proposed minimal clinically meaningful threshold on the primary efficacy is a gain of 7 points after receiving High Dose I-ACQUIRE. We estimate 70% of children in the High Dose group will meet the primary efficacy outcome of ≥7 new EBS skills threshold at both post-treatment assessments. We further project that only 40% of the children in the Moderate Dose group will show primary efficacy, because we anticipate higher levels of decline over the 6-mth post-treatment period compared to those in the High Dose group. That is, we predict the new EBS skills at end of treatment will be less permanently established for subjects in the Moderate compared to High Dose group. Thus, to detect a minimal clinically meaningful difference in the primary efficacy outcome between the High and Moderate Dose groups with a two-sided type I error rate of 5% and 90% power, we would need a final randomized sample of N=57 subjects in each of the 3 groups. The sample size further inflates the required sample size to ensure adequate power after accounting for up to 15% of subjects lost to follow-up or missing outcome data using an inflation rate of 1.39 [109].

We have limited data about precise EBS changes in children with PAIS receiving U&CT; thus, we relied on U&CT changes from 2 – 6 yr olds and from our clinical database. We estimate up to 15% of U&CT children may meet criteria for the primary outcome, because more families and therapists know about evidence supporting high therapy dosages and CIMT, and thus more U&CT children may be obtaining more effective therapy than in the past (when systematic reviews were conducted and published about many forms of U&CT). We have >80% power to detect a clinically significant treatment difference between either the Moderate Dose or High Dose I-ACQUIRE group and U&CT for any active treatment effect with ≥ 40% of children with favorable outcomes. Finally, although the trial is specifically powered to detect differences in the primary outcome, given the total sample size of N=240 and a 5% type I error rate, the secondary and exploratory endpoints have ≥ 80% power to detect pairwise differences in mean change as small as 5 units when the standard deviation is 10. Further note that power and sample size calculations use the conservative assumption of single-time point models and unadjusted analyses; in general, covariate-adjusted repeated measures models will have increased power to detect differences.

9.3 POPULATIONS FOR ANALYSES

Modified Intent to Treat (mITT) Sample
All efficacy analyses (primary, secondary, and exploratory) will be conducted using a modified ITT (mITT) sample. That is, the evaluable sample includes all randomized subjects who continue to meet the inclusion/exclusion criteria at the time of Baseline Assessment and who complete the Baseline Assessments prior to treatment initiation, notwithstanding whether or not the subjects completed the study treatment protocol for their group. A sensitivity analysis will consider differences between the mITT sample and a traditional ITT sample, which is inclusive of the mITT sample but also analyzes all subjects who are randomized but withdraw, are lost to follow-up, or no longer meet inclusion criteria prior to the time when a baseline assessment would have occurred.

As Treated Sample.
Sensitivity analyses will use the as treated sample when specified. That is, the evaluable sample includes all randomized subjects, regardless of whether or not the subjects completed the treatment as planned. In contrast to the mITT sample which categorizes treatment by randomly assigned group, the As Treated Sample analyses will consider the dose of treatment defined as the actual number of treatment sessions as well as total hours received (e.g., a child who is perfectly compliant in the Moderate Dose or High Dose I-ACQUIRE is expected to get 60 or and 120 hours of I-ACQUIRE treatment respectively).

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Randomization. Randomization will take place centrally via a web-based central randomization system (described above) developed by the National Data Management Center (NDMC).

Multiplicity and Control of Type I Error. Inflation of the type-I error through multiple hypothesis testing is controlled using a sequentially rejective multiple test procedures approach to address repeated testing of pairwise comparison and hypothesis tests of multiple primary, secondary, and exploratory endpoints. This method, which generalizes the approach for closed testing procedures including Bonferroni-Holm, fixed sequence, fallback, and gatekeeping procedures, defines the sequence in which hypotheses and families of hypotheses are tested and sequentially allocates the local type I error rate to guarantee strong control of the familywise error rate (i.e. the probability of incorrectly rejecting at least one true null hypothesis given any configuration of true or false null hypotheses). This approach also provides corresponding methods for correctly specifying the adjusted p-values and confidence intervals with a minimum of 1-α coverage. The primary and secondary aims will each test a sequence of null hypotheses comparing 1) whether a difference exists among the three treatment groups, 2) whether Moderate and High Dose I-ACQUIRE each differ from U&CT, and 3) whether Moderate Dose I-ACQUIRE is different from High Dose I-ACQUIRE at a local familywise two-sided type I error rate of 5%. A given hypothesis may only be tested if the previous hypothesis has been rejected.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary analysis (Aim 1) will use a modified intent-to-treat (mITT) study sample defined as those subjects who attend the baseline visit and continue to meet eligibility. This approach will permit exclusion of subjects who are randomized, but then drop out prior to any baseline data being collected, due to changes in eligibility or family circumstances that preclude any study participation. The sample size for analysis will be 240 subjects who meet the mITT definition.

Missing outcomes will be imputed as unfavorable, which is a conservative but reasonable approach given minimal (<5%) missing data. If the amount of missingness is unexpectedly high, e.g. >5%, then missing primary outcome data will be imputed via standard multiple imputation methods (i.e., via logistic regression model predicting outcome based on pertinent baseline and treatment data). The primary analysis will test the sequence of null hypotheses using fitted estimates from a logistic regression model, where the dependent variable is the dichotomized indicator of a favorable outcome, ≥ 7 new EBS skills above baseline at the end of 4-wk treatment and 6 mos post-treatment. An interim analysis for futility is planned after N=120 (N= approximately 40/group) subjects complete the 6-month post-treatment visit using a non-binding O'Brien and Flemming type stopping boundary. Sensitivity analyses of the primary analysis will also consider the impact of distribution-based methods, using a generalized linear mixed-effects repeated measures model where change in EBS is modeled as continuous and the model is adjusted for baseline EBS score, treatment group, study visit (4 weeks or 6 months), and an interaction for treatment group and visit. Subgroup analyses will evaluate the impact of race/ethnicity, gender, neuroimaging biomarkers of injury, therapy fidelity, and parental involvement. The impact of U&CT dose variability will also be assessed in a model where the categorical indicator for treatment group will be replaced by a continuous covariate measuring total hours of therapy received and a categorical indicator for type of therapy.

Data analysis and management. The NDMC will be performing all the primary data analysis and management. All activities will be conducted in coordination with the participating clinical sites, Executive Committee, and the IOC. Case report forms will be developed and distributed to clinical sites prior to study initiation.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary analysis (Aim 2) comparing changes in Mini-AHA among the three treatment groups will use a generalized linear mixed model with repeated measures to model the change in Mini-AHA at the End of Treatment and 6 mos. Post-Treatment; the same set of subgroup analyses are proposed for this endpoint. For the secondary analysis, the sequentially rejective hypothesis testing procedure must first reject the series of null hypotheses of no difference at 6 months post-treatment before testing for differences at 4 weeks post-treatment.

9.4.4 EXPLORATORY ANALYSES

The exploratory analyses (Aim 3) for GMFM-66 and Bayley-4 Cognitive subtests will follow the model and sequence of hypothesis tests described for the secondary endpoint. For missing secondary and exploratory endpoints, the mixed effects model naturally accounts for missing data and has been shown to be more powerful than either the last observation carried forward of multiple imputation approaches.

9.4.5 SAFETY ANALYSES

All reportable AEs and SAEs will be summarized by Medra term and body system in terms of frequency of the event, number of subjects having the event, severity, and relatedness to the study treatment. The proportion of subjects experiencing each of these events will be provided in the closed report by treatment arm with two-sided 95% CIs and unadjusted relative risks. Fisher's exact tests will be used to assess treatment group differences in the rates of serious adverse events.

9.4.6 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Coded individual participant data will be examined and presented in data presentations in ways that fully protect privacy and anonymity.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT/ PARENTAL PERMISSION PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the parent of the participant and written documentation of informed consent/ parental permission is required prior to starting intervention. The following consent materials are submitted with this protocol:

Informed Consent Document/ Parental Permission

In accordance with ICH-GCP Consolidated Guidelines, a CIRB-approved informed consent is required for all participants prior to participating in this study. The informed consent is obtained by either the clinical site PI or other members of the study team who are qualified to perform this task and are designated to do so on the Delegation of Authority Log (DOA).

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent/ parental permission for each child to participate is a process that is initiated prior to the child participating in any study procedures. Consent (permission) forms will be approved by StrokeNet's Central Institutional Review Board (CIRB). The participant's parent/guardian will be asked to read and review the document at the first study visit. The investigator will explain the research study to the parent/guardian and answer any questions that may arise. This verbal explanation will be provided in terms suited to the parent/guardian's comprehension and explain the purposes, procedures, and potential risks of the study and their rights as parents of a research participant. Participant's parents/guardians will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participant's parents/guardians will have the opportunity to discuss the study with their family or surrogates and have a minimum of 24 hours prior to the implementation of any study procedures after enrollment to think about all study processes. The participants in this study will be children below the age of eight, so their assent is not required. Consent is considered to be ongoing throughout the study period.

While the participant's parent/guardian will sign the informed consent/parental permission document at enrollment, they will verbally be reminded of all planned study processes at the first Baseline Assessment and be asked to confirm their willingness to participate prior to any study procedures starting. Parents and guardians will be informed at enrollment and at this second point of consent validation that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent/parental permission document will be given to the parents/guardians for their records. The informed consent process/ parental permission will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. A phone/fax alternative for the consent procedures and documentation will be available if the participant's parents/guardians cannot come in person to a recruitment site office. (see description of procedure in I-ACQUIRE Manual of Procedures (MOP)) The participant's rights and welfare will be protected by emphasizing to parents that the quality of their child's medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, and funding agency. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the CIRB, or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Data Coordinating Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data will be stored for possible future use, such as a longitudinal follow-up of the participating children and their families or for new coding methodologies of the stored assessment data or for new exploratory data analyses. In the event that there would be future use, we would contact parents who indicated they would be willing to be contacted when they signed the original consent document. Any future use would be subject to CIRB review and approval in advance of proceeding.

Samples collected for genetic study will be stored if consent is granted for the future study of the samples. Any future use would be subject to CIRB review and approval in advance of proceeding.

The I-ACQUIRE principal investigators (Drs. Sharon Landesman Ramey and Warren Lo) have responsibility for ensuring protection of data confidentiality. All of the protections in place for The I-ACQUIRE Study extend to the addition of the new biomarker data. The lab at Yale University will produce the DNA polymorphism results, associated only with subject I.D. codes. The lab team sends these results to the Assessment Center for entry into the I-ACQUIRE centralized database that adheres to strict guidelines protecting subject confidentiality. If a sample is deemed inadequate by the lab, then the Assessment Center will notify the local site so that a second set of swabs can be obtained during the next assessment visit and re-submitted for that study participant. (Only the local sites maintain the names and contact information associated with subject I.D. code.) Any new investigators joining the study must be approved and adhere to all local and central IRB guidelines.

Only the collaborating lab at Yale has access to the samples directly after these are mailed to the lab by the local site. In the event that something happens that requires the samples to transfer to another lab setting, the Multiple PIs and Executive Steering Committee of the I-ACQUIRE Study will vet the location and provide supportive data that standards for patient confidentiality, high lab standards, and safe and secure storage are met. We will immediately notify the CIRB and provide needed information if there is a need for a change in plans related to access, lab analysis, and storage.

Patient samples will be stored by study I.D. code, complaint with HIPAA regulations.

Specimen and Data Storage

The I-ACQUIRE principal investigators (Drs. Sharon Landesman Ramey and Warren Lo and Local Site PIs) have access to subject identities. All proposed data analyses linking biological markers to other aspects of a subject's dataset do not require having subject identities.

The DNA samples will be stored at the research laboratory at Yale University.

Samples will be stored in locked freezers that are in a locked laboratory accessible only to authorized personnel. Lab personnel adhere to strict guidelines about who can assess secured specimens linked to the parent I-ACQUIRE Study.

The samples will be destroyed 10 years after the completion of the primary planned data analyses for the I-ACQUIRE Study.

We have requested separate parent permission to store any unused DNA for future studies. We advise parents that deidentified DNA samples may be shared with NIH biorepositories for future research uses that go beyond the original purposes for the biomarker study linked to the parent I-ACQUIRE Study.

Specimen and Data Distribution

An agreement will require the investigators state the purpose of the proposed research, show that the research has been approved by the appropriate IRB, affirm that the investigators guarantee that they will not attempt to de-identify the data by any means, and understand that there will be no secondary distribution of the samples. We also will require investigators outside of the protocol to acknowledge in any publications and presentation that the I-ACQUIRE Study was the source of the samples.

No specimens be made available to commercial organizations.

Associated data will be provided with the specimen that the child sustained a perinatal arterial ischemic stroke.

Policy on Withdrawal of Specimens/Data

We allow parents granting permission for collecting the DNA samples from their child to withdraw and ask that no biomarker data about their child be used or stored. We do inform parents, however, that if they choose to withdraw permission after excess DNA from their child already was transferred to the deidentified storage, this will not be possible. We do let parents know that we would be able to delete the biomarker data in the dataset for their own child. We tell parents there will no negative consequences if they change their mind to have their participate.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor.

Principal Investigator	**Medical Monitor**
Sharon Ramey, PhD	Jilda Vargus-Adams, MD
Fralin Biomedical Research Institute at Virginia Tech (formerly the Virginia Tech Carilion Research Institute)	Cincinnati Children's Hospital Medical Center
2 Riverside Circle Roanoke, VA 24016	
(540)526-2081	
slramey@vt.edu	Jilda.Vargus-Adams@cchmc.org

We propose a Steering Committee of Multiple PIs, Core directors, a lead team member from the National Coordinating Center (NCC) and NDMC, local site PIs/directors, and 2 parents from the Parent Council. We provide additional details about study planning, communicating, and operations in the Multiple Principal Investigators (MPIs) Plan, Clinical Protocol, and the Milestone Plan.

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to NINDS.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected; that the reported trial data are accurate, complete, and verifiable; and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP).

- Monitoring for this study will be performed by the NDMC centrally, on site, and remotely.
- Per the study's monitoring plan, monitoring will include a combination of on-site monitoring strategies to verify data entered into the WebDCU™ database against source documents and query inaccuracies between the source documents and WebDCU™ database and to verify source documents, such as written consent, electronic medical records, and central monitoring (using web-based data validation rules, data manager review of entered data, statistical analysis, and on-going review of site metrics).
- The NDMC, study PIs, and the appropriate site PIs will be provided copies of monitoring reports within 30 days of site visits.

In an effort to review informed consent forms in a timely manner, enrolling sites will upload a PDF of the signed informed consent form, into the password protected clinical trial management system, WebDCU™. The PDF file will be linked to the subject ID but will be stored on a secure server separate from the study's CRF data. The secure server on which these files are stored is not backed up to prevent copies of files containing Individually identifiable health information from being copied and stored on non-NDMC back up servers. The files on these servers can only be accessed by designated study personnel upon entry of a second password. NDMC staff will remotely monitor the informed consent forms and issues identified will be relayed to the clinical site for corrective and preventative action. After remote monitoring is complete, the PDF file containing the informed consent form will be permanently deleted from the secure server. If a subject must be re-consented, the process will repeat itself.

Further details of clinical site monitoring are documented in the study's Monitoring Plan. The Monitoring Plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

Some of the monitoring for this study will also be performed by site supervisors on a 100% basis and will be entered into a database maintained and monitored by the Treatment Implementation Center with corrective action by sites as needed.

Independent audits will be conducted by the Treatment Implementation Center to ensure monitoring practices are performed consistently across all participating sites.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical site trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Copies of the electronic CRF (eCRF) are provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data are entered into WebDCU™. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data are entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

Study documents should be retained for the duration specified by the StrokeNet SOP or for a longer period if required by local regulations.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), or MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 24 hours of identification of a protocol deviation meeting criteria for prompt reporting, or within 5 days otherwise. These deviations must be addressed in study source documents and reported via WebDCU™ for initial review by the I-ACQUIRE project manager. All other protocol deviations must be reported to the CIRB at the time of annual scheduled continuation review and listed in DSMB reports. The site investigator is responsible for knowing and adhering to the CIRB requirements. Further details about the handling of protocol deviations are included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested by other researchers 2 years after the completion of analysis and reporting about the primary study hypotheses by contacting Sharon Ramey.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NINDS has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

None

10.3 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DOA	Delegation of Authority
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee

eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IMSM	Independent Medical Safety Monitor
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MPI	Multiple Principal Investigator
MSDS	Material Safety Data Sheet
NCC	National Coordinating Center
NCT	National Clinical Trial
NDMC	National Data Management Center
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
2.0	03-03-18	Changes in all aspects of Trial.	Updates to match changes suggested by reviewers in grant application
3.0	04-22-19	Updates primarily for clarification and to be consistent with terminology in other StrokeNet trials. Some minor changes in randomization and statistical analytic issues and terms used for reporting AEs.	With multiple individuals added to our team, a number of omissions or minor inconsistencies were detected. We are not proposing any major

			substantive changes to the treatment protocol.
4.0	03-12-20	Update for collection of a salivary DNA sample in Section 6.2. Update Section 10.1.4 for future use of genetic specimens if permission has been granted.	The protocol was modified to include DNA collection from saliva for all patients. The Study Design was changed to explain why the DNA sample is being collected. The Study procedures were modified to explain how the DNA sample will be collected. This is a one-time collection that will occur after the treatment month. The DNA collection is very brief, poses no risk to the patient, and potentially may provide a new biomarker for the study.
4.0	3-12-20	Update to change what adverse events need to be reported in Section 8.3.4.	The following AEs will be reported in the study database: 1) Any serious AE (SAE) occurring from Baseline Assessment though end of study; 2) Any AE occurring from Baseline Assessment though end of study that has a reasonable possibility of being related to the study intervention.
4.0	3-18-2020	A further addendum to the protocol was inserted at Section 11.1	On 16 MARCH 2020, ALL IN-PERSON HUMAN SUBJECTS ACTIVITIES AND ALL STUDY-RELATED IN-PERSON MEETINGS WERE TO BE SUSPENDED. This was due to the Coronavirus Pandemic. Specific recommendations were provided to local site PIs and Study Coordinators as to the management of subjects enrolled in the study and communicating with parents.
4.0	3-25-20	The Schema of the study in section 1.2	The flow diagram was modified to reflect the

			influence of a modified Intent to Treat analysis on study design as well as the re-evaluation about study eligibility at time of conducting the Baseline Assessment.
4.0	3-25-20	Section 6.3; Measures to minimize bias	Two paragraphs pertaining to assessing the success of blinding were deleted to reflect actual study practice. The study team decided to remove the method in these paragraphs. Instead we currently only capture whether central reading occurred as a result of study team unblinding and indicate these data are used instead for conducting the primary data analysis.
4.0	3-25-20	Section 7.1 Discontinuation of study intervention.	This section was modified to only refer to SAEs related to the trial or SAEs that in the opinion of the site principal investigator will preclude the safe participation in the rest of the trial.
4.0	4-15-2020	Update to Section 8.2 that will include a survey of parents performed at the 6-mos. Post-Treatment Assessment.	Parents will be surveyed at the 6-mos. Post-Treatment Assessment about their experience with the I-ACQUIRE trial, and to inform future scientists about integrating family preferences, needs, and values into their clinical trials. Specific questions will evaluate and address procedural challenges that families identify. This 36-item survey was developed by The Parent Council. Participant ID will be the only identifier; no PHI is included on the survey.
4.0	04-15-20	Updates for analysis using a modified intent-to-treat analysis in Section 9.3 and 9.4.2.	This approach will permit exclusion of subjects who are randomized, but then drop out prior to any baseline data

			being collected, due to changes in eligibility or family circumstances that preclude any study participation.

11 ADDENDUM TO PROTOCOL – PILOT-TESTING PHASE

We plan to have a pilot-testing or practice phase to allow our clinical research team to check if our research protocol and procedures are working as intended. This testing will occur at either the Treatment Implementation Center (Virginia Tech, Roanoke, VA) or The Assessment Center (The Ohio State University, Columbus, OH). We plan to enroll a small number of children (between 1 and 5) and provide the I-ACQUIRE intervention and assessments proposed in the Phase III clinical trial.

We will not store data on individual children or families who participate in the pilot-testing phase. We do, however, include a statement in the consent document that allows parents to grant permission for us to use videotaped materials and or parent responses in conducting training and communication about the Phase III trial.

11.1 ADDENDUM TO PROTOCOL IN RESPONSE TO THE CORONAVIRUS PANDEMIC AND COVID-19 EMERGENCY

From March 10 through March 19 the I-ACQUIRE Study team communicated with all Clinical Site PIs/CoIs and Study Coordinators about evolving responses to the threat of the COVID-19 to the health and well-being of study participants and I-ACQUIRE staff. The major recommendation on 16 MARCH 2020 was for all in-person human subjects' in-person activities and all study-related in-person meetings to be suspended immediately.

The I-ACQUIRE Study team recognized that the COVID-19 situation was likely to worsen. The team anticipated there will likely be future changes as new information emerged regarding the COVID-19 virus so that the following specific recommendations would likely be modified. The primary objective of these emergency modifications is to protect the health and safety of all connected to the I-AQCUIRE Study. Secondary to that, we seek to adhere to the original I-ACQUIRE Protocol to the greatest extent possible. We try to provide our rationale for decisions that may lead to modifications.

Table 1: Re-scheduling guidelines for COVID-19 disruptions

TIME WHEN ACTIVITIES ARE DISPRUPTED	RE-SCHEDULING PARAMETERS AND IMPACT
When a new family contacts us seeking to be consented and enrolled (randomized)	Wait to consent and enroll after trial resumes. IMPACT: This will delay overall recruitment and trial progress but does not change any aspect of the study protocol. Note: speaking with parents whose child may be eligible and who seek to find out more about the study is acceptable. Let them know that you will get back as soon as the trial becomes active again. During the study suspension, sites are free to stay in touch with parents who have a potentially eligible child and who want to learn about the trial. When the trial resumes, we will accept children who would have been age-eligible (if the study had not been paused) and who will be no older than 36 months when they begin treatment (after the

	study resumes). If need be, we can consider this age variable in post hoc data analyses.
Pre-treatment (Baseline) through Casting and Day 1 of Treatment	Do not proceed. Re-schedule when trial resumes. IMPACT: Some children may be older than the original designation of 24 months when their treatment begins. If need be, we can consider this age variable in post hoc data analyses.
During the 4 weeks of I-ACQUIRE Treatment (Tx) but prior to Day 17	Stop Tx immediately. Re-schedule when the trial resumes. IMPACT: #1. For a child who has completed 10 or more days, the child would meet the original study exclusion criterion of having had a prior high-dose CIMT treatment. Despite this protocol deviation, we will offer the fully planned I-AQCUIRE treatment when the trial becomes active again. (In other words, we will have a waiver of this exclusion criterion.) We will be able to look at this post hoc when we conduct data analyses. #2. The child can be re-scheduled when the trial resumes, even if the child is older than 24 months. *The re-scheduling will necessitate collecting a new pre-treatment (baseline) assessment as well as implementing the full I-ACQUIRE treatment.* **#3.** We anticipate that parents who already have been providing the home component of the I-ACQUIRE treatment will, understandably and ethically, continue to implement their own best version of being supportive of their child's continued positive development. We should not instruct parents to "stop" this –we do not think it could be harmful, nor do we think the coronavirus risk would be affected by this. **#4.** Almost certainly, the disruption will extend to the Post-Treatment 1 assessment. See below about how this will be handled. (In other words, most children will have both Treatment and Assessment disrupted and guidelines for each will be followed, if feasible.) NOTE: ONLY 1 CHILD HAD THIS OCCUR.
Between Day 17 and Day 20 of I-ACQUIRE treatment.	Stop Tx. At this particular time, the child will have qualified for receiving what was a priori defined as a sufficiently "full dose" of the treatment. However, we realize that Days 17 – 20 are distinctive because: i) we remove the cast; ii) we concentrate our focus on promoting bilateral activities – during formal therapy session and during parent-enacted home treatment; and iii) at the end, parents and the therapist finalize a post-treatment plan. For children and families who have their study participation disrupted at this timepoint, we propose working distally with the parents to provide bilateral shaping and activities and to develop the Post-treatment plan. We propose documenting these in the Web-DCU system using the Daily Log format we already have. The child and family will not require a new complete (or partial) treatment. IMPACT: #1. Additional time will be needed for the I-ACQUIRE Study central team at the Virginia Tech Treatment Implementation

	center to develop individualized and online modules for Days 17 – 20. #2. The post-treatment assessment 1 likely will not be conducted. (See below for how this will be handled.)
During Usual and Customary treatment (UCT), from start to end of the 4 week period	For children in the UCT group, the local study coordinator or a team member needs to be in contact with a family to determine if there are disruptions in the child's receipt of usual therapy. Note: we will not be advising parents about whether to continue or to stop the UCT that they arrange and for which they are responsible. Any disruption to the child's UCT will result in the need to re-schedule when the trail resumes. As above, this will necessitate scheduling a new pre-treatment (baseline) assessment as well as the treatment month. The child can be > 24 months old when re-scheduled, up to 36 months old.). Finally, it is likely a disrupted UCT period will be associated with a disruption to the Post-treatment Assessment 1 (see below).
At Post-treatment Assessment 1	STOP. This can be re-scheduled when the trial resumes. IMPACT: At this time, we are recommending allowing a protocol deviation for this to extend to 3.49 months after treatment ends (rather than the current recommendation of 2 weeks). We may need to re-consider this proposed endpoint for this assessment depending on duration of study suspension.
At Post-treatment Assessment 2 (6 months later)	STOP. Re-schedule when trial resumes. HOWEVER, COLLECTION OF PARENT RATINGS THAT DO NOT REQUIRE IN-PERSON CONTACT CAN OCCUR. LOCAL SITE STUDY COORDINATORS WILL RECEIVE ISNTRUCTION ABOUT HOW TO COLELCT, STORE, AND SUBMIT THESE DATA. IMPACT: Current protocol allows up to 2 months delay. We hope that this will be adequate for most disruptions. However, we are not certain. We will re-consider whether we will permit obtaining this assessment even later than 8 months post-treatment and notify sites if we propose extending this time window.
For Phase 2, UCT families only: Pre-treatment up to day 1 I-ACQUIRE	DO NOT PROCEED. DO NOT RE-CONSENT UNTIL THE STUDY RESUMES. Okay to re-consent and re-schedule when the trial resumes. All of the above guidelines are the same for the crossover children. If treatment is re-scheduled after the family has re-consented but before Treatment has started, then the child will need to have a new pre-treatment assessment 1 (baseline). (For the UCT children their 6-month assessment serves as their new baseline for the crossover treatment phase.).
During the 4 weeks of Treatment Between Day 17 and Day 20 of Treatment	See above

At Post-treatment Assessment 1	See above
At Post-treatment 2 Assessment (6 months later)	See above

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