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

MANUAL OF PROCEDURES

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Protocol Principal Investigators
Sharon Landesman Ramey, Ph.D. (Lead PI)
Warren Lo, M.D. (Co-PI)

Supported by
The National Institute of Neurological Disorders and Stroke (NINDS)
National Institute of Health

Table of Contents

A. PROTOCOL SYNOPSIS

I-ACQUIRE protocol available in WebDCU™ (Toolbox→ Project Documents)

Protocol Title	**Phase III Multi-site RCT of Intensive Infant Rehabilitation – I-ACQUIRE**
Sponsor and Trial Information	National Trial Principal Investigators: Sharon Ramey, PhD and Warren Lo, MD Registered with ClinicalTrials.gov: NCT03910075 Sponsor: National Institute of Neurological Disorders and Stroke (NINDS)
Study Design	Phase III trial powered to determine efficacy of two different doses of I-ACQUIRE for children 8 to 24 months old with Perinatal Arterial Stroke (PAS) and hemiparesis.
Investigational Agents	3 treatment groups (N=80 per group): 1) Moderate Dose I-ACQUIRE (3 hrs/day, 5 day/week X 4 weeks), 2) High Dose I-ACQUIRE (6hrs/day, 5 days/week X 4 weeks), or 3) Usual and Customary Treatment (U&CT) for 4 weeks
Primary and Secondary Objective	1) To determine the efficacy of I-ACQUIRE at 2 dosage levels compared to 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, and 3) To explore the association between I-ACQUIRE treatment at Moderate and High Doses and gross motor development, cognition, and language (i.e., cross-domain effects of treatment).
Primary Safety Objective(s)	The primary safety objective is that children show no harm to either the casted upper extremity or the hemiparetic upper extremity in terms of loss of function, injury, or other damage and that caregivers and children show no signs of undue stress due to casting or the I-ACQUIRE treatment.
Primary and Secondary Safety Outcome	*Primary safety outcomes*: No adverse events linked to treatment. *No loss of function to casted upper extremity, based on systematic weekly exam when cast is removed. No report of injury or harm to the hemiparetic upper extremity - the central focus of the I-ACQUIRE treatment. Secondary safety outcomes*: No undue parent or child stress leading to ending treatment early.
Primary and Secondary Efficacy Outcome	Primary Efficacy Outcome: Significant gains in upper extremity (UE) skills on the hemiparetic side at end of treatment and 6 months later. Secondary Efficacy Outcome: Significant improvement in bilateral UE skills at the end of treatment and 6 months later
Study Duration	Study period is 5 years with enrollment open in the second 6 months of Year 1 through Year 5.
Follow-up Schedule	After receiving the 4 weeks of treatment, children will be assessed at end of treatment and 6 months later. (For those assigned to Usual and Customary Treatment, an option to enroll in a second phase and receive treatment will be offered. The second phase will require a new consenting process.)

Clinical Inclusion and Exclusion Criteria	Inclusion Criteria: 1. Child will be 8 - 24 months old when receiving study treatment during Phase 1; 2. Child will have a diagnosis of PAS with parent permission to provide the child's clinical Magnetic Resonance Imaging (MRI) to the study; 3. Child has hemiparesis; 4. Parent(s) willing to participate in the home therapy component; and 5. At least one parent who is English language proficient and will take a lead in interacting with study staff and completing self-administered tools and interviews in English. Note: for Phase 2, children who participated in Phase 1 in Group 3, Usual & Customary Treatment (U&CT), may be older than 24 months when they receive I-ACQUIRE treatment. Exclusion Criteria: 1. Child has a medical or sensory condition(s) that prevent(s) full therapy participation (e.g., frequent uncontrolled seizures, fragile health); 2. Child received a prior form of Constraint-Induced Movement Therapy (CIMT) with a dose of at least 2 hrs/day for ≥10 days; 3. Child has received botulinum toxin in the past 3 months; and 4. Child is a ward of the state or other agency. Note: botulinum toxin or another form of CIMT cannot be administered until after the 6-month post-treatment assessment has occurred.

B. STAFF ROSTER

TITLE / ROLE	NAME	CONTACT INFORMATION	WHEN TO CONTACT
Virginia Tech - Awarded Primary Project Site (PPS)			
PRIME Principal Investigator (PI) - Virginia Tech	**Sharon Ramey, PhD**	Email: slramey@vt.edu Phone: 1-540-526-2033	· Urgent questions arising during subject recruitment, enrollment, treatment, and assessment.
Multiple Principal Investigator (MPI) – The Ohio State University	**Warren Lo, MD**	Email: Warren.Lo@nationwidechildrens.org Phone: 1-614-722-4639	· Urgent questions arising during subject recruitment, enrollment, treatment, and assessment.
Responsibility: Will function as the administrative Lead PIs. Overall responsibility for the preparation, training, and conduct of the clinical trial. Leads monthly site PI/SC call. Share duties for responding to email questions related to I-ACQUIRE study subjects (I-ACQUIRE Clinical Email).			
PRIME Study Coordinator (SC) – Virginia Tech	**Laura Bateman**	Email: laurapb2@vt.edu Phone: 1-540-526-2033	· Site Training/Initiation · Coordinator protocol related questions
PRIME Study Coordinator (SC) – The Ohio State University	**Hannah James**	Email: Hannah.James@nationwidechildrens.org Phone: 1-614-722-4641	· Site Training/Initiation · Coordinator protocol related questions
Responsibility: Coordination and implementation of trial updates and site visits. Assist the Protocol PIs with preparation, submissions, and maintaining any and all appropriate correspondence. Assist with the updating of clinicaltrials.gov information.			
NAME		**CONTACT INFORMATION**	
Treatment Implementation Center at Virginia Tech			
Stephanie DeLuca, PhD		Email: stephdeluca@vt.edu Phone: 1-540-526-2098 Co-I and Co-Director; **Treatment Implementation Center at Virginia Tech**	
Craig Ramey, PhD		Email: ctramey@vt.edu Phone: 1-540-526-2033 Co-I and Co-Director; **Treatment Implementation Center at Virginia Tech**	
Responsibility: Directing the I-ACQUIRE Treatment Implementation Center to include conducting cross-site training for therapists and assessors, providing study certification for I-ACQUIRE therapists, monitoring therapist daily log data submitted from clinical performing sites (CPSs), overseeing the scoring of weekly videotapes for Fidelity of Treatment Implementation and providing feedback to site therapists; letting PIs know when site concerns arise about treatment implementation; making recommendations for re-training and corrective site visits in a timely manner; entering data into WebDCU™ about Fidelity of Implementation.. Work with PRIME PIs to help prepare major study presentations and papers.			
Mary Rebekah Trucks, MS, OTR/L		Email: mrebekah@vt.edu Phone: 1-540-526-2171 Master Therapist; **Treatment Implementation Center at Virginia Tech**	
Dory Wallace, MS, OTR/L		Email: wdorian6@vtc.vt.edu Phone: 1-504-526-2176 Master Therapist; **Treatment Implementation Center at Virginia Tech**	
Responsibility: Lead role in providing training on I-ACQUIRE therapy to all Treating Therapists. Monitor treatment fidelity at all CPSs under direction of Stephanie DeLuca. Review and code documentation and treatment for all CPSs.			

TITLE / ROLE	NAME	CONTACT INFORMATION	WHEN TO CONTACT
Assessment Center at The Ohio State University			
Amy Darragh, PhD, OTR/L		Email: Amy.darragh@osumc.edu Phone: 1-614-293-3760 Co-I and Co-Director; **Assessment Center at The Ohio State University**	
Jill Heathcock, PhD, MPT		Email: Jill.heathcock@osumc.edu Phone: 1-614-292-2397 Co-I and Director; **Assessment Center at The Ohio State University**	
Responsibility: Provide training to Assessors at CPSs, provide study certification to the blinded assessors; overseeing the scoring of the Emerging Behaviors Scale and the structured play session (including bimanual assessment outcome), ongoing monitoring of inter-rater reliability and standardized administration of assessment tools. Work with PRIME PIs to help prepare major study presentation and papers.			
Thais Cabral, OT, PhD		Email: Thais.InvencaoCabral@osumc.edu Phone: Post-Doctoral Research Fellow; **Assessment Center at The Ohio State University**	
Responsibility: Lead role in providing training on I-ACQUIRE to Blinded Assessors. Monitor reliability of assessment tools under the direction of Jill Heathcock and Amy Darragh. Review and score EBS and bilateral assessments. Work with Assessment Center and Prime PIs to help prepare study presentations and papers..			
I-ACQUIRE Clinical Email: I-Acquire@vtc.vt.edu ***** Questions regarding eligibility or protocol implementation**			
Study Centers			
Independent Medical Safety Monitor (IMSM)	**Jilda Vargus-Adams, MD**		
Responsibility: Review Serious Adverse Events (SAEs) to determine seriousness, relatedness, and expectedness.			
Clinical Imaging Center	**Max Wintermark, MD**	Stanford University Medical Center	
Responsibility: Review clinical MRI scans to ascertain study eligibility (in coordination with Warren Lo); review and score MRI scans for volume and location of infarcts. Work closely with the PRIME MPIs to interpret the data with regard to treatment responses of the two I-ACQUIRE dosages in comparison to Usual & Customary Treatment (U&CT). Work with PRIME PIs to help prepare major study presentations and papers.			
NIH StrokeNet National Coordinating Center (NCC) - University of Cincinnati			
TITLE / ROLE	**NAME**	**CONTACT INFORMATION**	**WHEN TO CONTACT**
NCC I-ACQUIRE Project Manager (PM)	**Kim Bernstein, BS, CCRP**	Email: gammk@ucmail.uc.edu Phone: 1-513-558-3970	Questions about the NCC responsibilities for trial.
Responsibility: Works closely with the PRIME MPIs and Study Coordinator to determine CPS readiness. Regulatory and performance tracking. Liaison between CPS & IMSM in collection of pertinent clinical information for SAE review. General interaction with NCC, Awarded PRIME Clinical Coordinating Center, NDMC, and CPSs.			
NCC Central Institutional Review Board (CIRB) Liaison	**Susan Roll, RN, BSN, CCRP**	Email: rollsn@ucmail.uc.edu Phone: 1-513-558-6061	Questions or concerns relating to CIRB.
Responsibility: Processing of CIRB submissions, annual reviews, and clinical performing site amendments.			
NCC Regulatory Compliance Specialist	**Emily Stinson, MS**	Email: stinsoey@ucmail.uc.edu Phone: 1-513-558-3979	Questions about regulatory concerns.

NCC Regulatory Compliance Specialist	**Jennifer Golan, MS**	Email: golanjl@ucmail.uc.edu Phone: 1-513-558-3976	Questions about regulatory concerns.
Responsibility: Regulatory review of CPS documents prior to CIRB submissions. Works closely with the NCC CIRB Liaison, NCC Project Manager, PRIME Study Coordinator, and CPS study coordinators.			
NCC Contracts Manager / Legal Liaison	**Diane Sparks, RN, BS**	Email: diane.sparks@uc.edu Phone: 1-513-558-3924	Questions and concerns about the CTA.
Responsibility: StrokeNet legal agreements and compliance documentation needed for the StrokeNet network and the various clinical trials. Responsible for coordination with the University of Cincinnati Office of the General Counsel.			
TITLE / ROLE	**NAME**	**CONTACT INFORMATION**	**WHEN TO CONTACT**
NCC Contract Specialist	**Wren Hanson**	Email: hansonwm@ucmail.uc.edu Phone: 1-513-558-6566	
Responsibility: Assist the Contract Manager with the StrokeNet legal agreements and compliance documentation needed for the StrokeNet network and the various clinical trials.			
NCC Financial Management		Email: strokenettrialpymts@ucmail.uc.edu	Reporting, budgeting, per-subject payment questions or remittance instructions.
Responsibility: Budgeting, grant expense monitoring, and reporting. Initiate invoices for payment using WebDCU™ payment module.			
NIH StrokeNet National Data Management Center (NDMC)			
WebDCU™ Emergency Randomization Hotline at 1.866.450.2016 *****Call if experiencing problems with performing randomization**			
TITLE / ROLE	**NAME**	**CONTACT INFORMATION**	**WHEN TO CONTACT**
NDMC Data Manager	**Catherine Dillon, MS**	Email: rileycp@musc.edu Phone: 1-843-876-1942	· Data management questions
NDMC Data Manager	**Sara Butler**	Email: butlers@musc.edu Phone: 1-843-792-1599	· WebDCU™ user account set-up · Data management questions
NDMC Monitoring Manager	**TBD**	TBD	- Site monitoring questions
NDMC PI and Statistician (unblinded)	**Caitlyn Ellerbe Meinzer, PhD**	Email: ellerbcn@musc.edu Phone: 1-843-792-6588	
NDMC Co-I and Statistician (blinded)	**Renee' Martin, PhD**	Email: hebertrl@musc.edu Phone: 1-843-876-1913	

C. STUDY ORGANIZATION AND RESPONSIBILITIES

1. National Institute of Health (NIH) StrokeNet National Coordinating Center (NCC) - University of Cincinnati

The NIH has created the NIH StrokeNet NCC to conduct small and large clinical trials and research studies to advance acute stroke treatment, stroke prevention, and recovery and rehabilitation following stroke. This network of 24 regional centers plus 5 legacy regional centers across the U.S., which involves more than 300 hospitals, is designed to serve as the infrastructure and pipeline for exciting new potential treatments for patients with stroke and those at risk for stroke. In addition, NIH StrokeNet provides an educational platform for stroke physicians and clinical trial coordinators. The NCC is responsible for the network infrastructure, initiation of collaborative relationships, facilitation of the study design, oversight, and management of network studies. Operationally, the NCC is the home for the Central Institutional Review Board (CIRB) for the NIH StrokeNet. The NCC works with the Protocol Principal Investigator (PPI) and his/her team to manage trials within the NIH StrokeNet.

I-ACQUIRE study specific information is posted on the NIH StrokeNet website with information for study personnel, patients, and other interested parties.

1.1 NCC Project Manager

Overseeing the I-ACQUIRE team is the Project Manager (PM) who coordinates with the Trial PPIs and PRIME Study Coordinator (SC) as well as the CIRB and National Data Management Center (NDMC). The responsibilities include but are not limited to the following services: provides review via WebDCU™ of all clinical performing site (CPS) study staff credentials and essential documents; performs initial review of acuity and completeness of reported serious adverse events (SAE) requiring Independent Medical Safety Monitor (IMSM) review; verifies that contractual and regulatory requirements are finalized prior to NCC authorization of the CPS to begin active recruitment; maintains communication with NCC, Prime Awarded PPI and SC, NDMC and participating CPSs; and, verifies study site payments with NCC financial manager.

1.2 NCC Contracts Manager/Legal Liaison

The NCC Contracts Manager prepares and executes the I-ACQUIRE Clinical Trial Agreement (CTA) for both the network and non-network CPSs. The CTA contains a fixed cost per study site payment schedule (noted via a link to the Manual of Procedures (MOP) found on the NIH StrokeNet Website), a special National Institute of Neurological Disorders and Stroke (NINDS) approved Financial & Administrative (F&A) rate, a Standard of Care (SOC) document and any special terms and conditions associated with trial recruitment and payment. Each participating network hospital signs a Reliance Agreement (RA) with the University of Cincinnati (UC) that delegates the responsibility of human subject protection review to the StrokeNet CIRB at UC.

1.3 NCC Financial Management

Study sites will not submit invoices to pass-through entity for study activities completed. The NCC Financial Management team will issue startup payments and subject enrollment reimbursements based on data entry and imaging transmission flags within the NDMC WebDCU™ payment module. Payments for startup, subject enrollment and interval/milestone achievements, as outlined in the Payment Schedule (Appendix 1 of the MOP), will be made no less than quarterly for all tasks confirmed as completed by NCC Contracting (startup funds inclusive of full execution of the CTA and CIRB approval, travel to and attendance at the Investigator Meeting, and satisfactory completion of all activities for Training/Travel for Treating Therapist and Training for Blinded Assessors), or by NDMC (study-related reimbursements). Subject reimbursements are inclusive of F&A costs. Payments are to be made via electronic funds transfer. Payments will be sent only after remittance instructions have been received and accepted by Accounts Payable. For information about electronic funds transfer please contact the Financial Management team.

1.4 NCC Central Investigational Review Board (CIRB) Liaison – University of Cincinnati

The StrokeNet CIRB at UC is the trial protocol CIRB of record for all participating CPSs. Each CPS is required to have an active current Federalwide Assurance (FWA) and executed RA in place. The CIRB liaison works with the PRIME SC, NCC PM, NCC Regulatory Compliance Specialist, CPSs and WebDCU™ on regulatory document compliance, developing and approving the informed consent (IC), Health Insurance Portability and Accountability Act (HIPAA) authorization, protocol amendments, unanticipated event reports, approval of study related documents, and annual/continuing review (CR). The CPS Investigational Review Board (IRBs) remain in close communication with the CIRB to provide knowledge of the local research context.

1.4.1 NCC Regulatory Compliance Specialist

Provides regulatory review via WebDCU™ of all regulatory documents; compiles CIRB submission materials and CR documents from CPSs, and when complete, provides submission documents to the CIRB for review/approval; processes CIRB queries and/or approvals to CPSs.

2. PRIME Project Sites

The NIH Awarded Principal Investigators are Sharon L. Ramey, PhD, at the Fralin Biomedical Research Institute at Virginia Tech (Lead PI) and Warren Lo, MD, Nationwide Children's Hospital and The Ohio State University. Responsibilities of the primary project sites include but are not limited to identification of CPSs, CPS training, overall trial recruitment, serving as a resource to the CPSs for questions regarding inclusion/exclusion criteria, protocol implementation and compliance with all study procedures.

2.1 Lead Principal Investigators (LPI)

The I-ACQUIRE Trial Protocol was developed and will be maintained by Sharon L. Ramey, PhD at Virginia Tech and Warren Lo, MD at Nationwide Children's Hospital. The Lead PIs are responsible for the scientific and intellectual leadership for the study protocol, overall conduct of the trial, and protection of participant safety. They will maintain compliance with applicable laws and regulations, and serve as the overall directors of trial operations.

2.2 PRIME Study Coordinators (SCs)

Overseeing the Virginia Tech and The Ohio State University I-ACQUIRE teams are the protocol sponsor SCs who coordinate with the NCC PM as well as the CIRB and NDMC. Responsibilities include but are not limited to the following services: acting as the primary point person(s) for all Data and Safety Monitoring Board (DSMB) correspondence; sending trial updates and urgent notifications to sites; maintaining ongoing communication between Virginia Tech, Nationwide Children's Hospital, The Ohio State University, Stanford University, the NCC, and the NDMC; documenting and managing site training at participating CPSs; and coordinating communication on behalf of the trial. Assists the PPIs with preparation, submission, and maintaining any and all appropriate correspondence.

3. StrokeNet National Data Management Center (NDMC) – Medical University of South Carolina (MUSC)

The NDMC is the centralized data management center for NIH StrokeNet. I-ACQUIRE data management, site monitoring, interim data analysis and statistical reports, and unblinded interactions with the DSMB are conducted by the NDMC at the MUSC. The NDMC has created the I-ACQUIRE database and developed the interface to the web-based clinical trials management system (CTMS), WebDCU™ (https://webdcu.musc.edu/login.asp), where CPSs personnel randomize patients and enter data into the electronic case report forms (eCRFs). I-ACQUIRE data will be shared in accordance with the StrokeNet data sharing policies and in compliance with federal requirements.

4. Clinical Performing Sites (CPSs)

Up to 12 CPSs are proposed in the I-ACQUIRE protocol. StrokeNet CPS selection is based on feasibility surveys and factoring in the clinical trial experience of the site teams, the availability of eligible patients based on records review, ability to recruit qualified therapists and assessors, prior history and knowledge related to Constraint-Induced Movement Therapy, and diversity of patient population.

Study leadership at participating CPSs is comprised of one Site PI who is responsible for the overall conduct and performance at their site. In addition, I-ACQUIRE study team members may include co-PIs and/or sub-investigator(s) (SubI), Primary Study Coordinator (PSC), SCs, Treating Therapists (TTs), Blinded Assessors (BAs), and other qualified study staff.

5. Study Committees / Centers

5.1 I-ACQUIRE Executive Committee (EC)

The EC will provide overall clinical guidance and leadership for the execution of the I-ACQUIRE Trial. The EC will oversee study conduct, protocol compliance and modifications, and basic reports generated to monitor and guide the study. Responsibilities include oversight of the overall conduct of the study with regard to protocol compliance and modifications/amendments, study progress, and problem solving. This committee will provide a means of partnership between the investigators, NINDS, and the sponsors. The EC, comprised of the Multiple Principal Investigators (MPIs) and the Directors of the study-specific centers (Treatment Implementation Center, Assessment Center, and Clinical Imaging Center), NCC PM and Administrative Leadership, and the NDMC study statisticians.

We anticipate we will have weekly planning calls throughout the first part of Year 1, and then shift to twice a month and continue bimonthly in Years 2 - 4, with a likely return to weekly calls again in Year 5 when study outcome data analyses, major trial outcome papers, and presentations are being finalized. The EC will be co-chaired by the LPIs, Dr. Sharon Ramey and Dr. Warren Lo.

After the database is locked, this committee will become the I-ACQUIRE Trial Publications Committee. The Publications Committee will participate in the review and approval of all requests for data analysis, abstract and manuscript preparation and submission.

5.1.1 Treatment Implementation Center

The Treatment Implementation Center located at Virginia Tech in Roanoke, VA, will be co-directed by Stephanie DeLuca (unblinded director) and Craig Ramey (blinded director) with primary responsibility for training and monitoring of all local site therapists who will provide ongoing I-ACQUIRE treatment; conducting weekly monitoring of Fidelity of Treatment Implementation via review and coding of videotaped therapy sessions and study of therapist logs; taking corrective actions when deviations are detected; providing 24-hr availability to local therapists about treatment-related questions; and- planning and leading the telecommunication meetings with therapists over the course of the trial.

5.1.2 Assessment Center

The Assessment Center located at The Ohio State University in Columbus, OH, will be co-directed by Amy Darragh (unblinded director) and Jill Heathcock (blinded director) with primary responsibility for training and monitoring of the assessment sessions administered at baseline, post-treatment, and 6 mos later at each site by blinded assessors as well as training, supervising, and monitoring the core research team (also blinded) at The Ohio State University that will code the videotaped assessment sessions to yield the primary and secondary efficacy outcomes.

5.1.3 Clinical Imaging Center

Max Wintermark, MD, Director of the Clinical Imaging Center at Stanford University, is a clinical neuroradiologist and a leader in brain perfusion imaging. He is the chair of the imaging working group of StrokeNet. In this study, he will serve as the Director of the Clinical MRI Center for the central review of images obtained at CPSs. He will review the clinical MRI scans for affirming study eligibility (in coordination with Dr. Lo) the volume and location of the infarcts. Dr. Wintermark will work closely with Drs. Ramey and Lo to consider the imaging results as they may or may not help interpret the other functional data with regard to possible treatment responses as a result of the two I-ACQUIRE dosages in comparison to Usual & Customary Treatment (U&CT).

6. Independent Medical Safety Monitor (IMSM)

The IMSM and DSMB will receive periodic safety reports of all adverse events (AEs) including SAEs if any occur following the reporting requirements of the UC Human Research Protection Program (HRPP) Policy 11.02. All clinical safety endpoints and SAEs will be summarized by AE code (as provided on the AE Case Report Form (CRF)) 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 group with two-sided 95% Confidence Intervals (CIs) and unadjusted relative risks.

The blinded IMSM will review all SAE reports submitted by the CPSs throughout the trial. The IMSM may suggest protocol modifications to prevent the occurrence of particular AEs. To minimize bias, he/she will evaluate SAEs blinded to treatment assignment, unless the DSMB approves partial or complete unblinding. In the event of unexpected SAEs or an unduly high rate of SAEs, the IMSM will promptly contact the LPI and the NINDS Program Official who will notify the DSMB Chair. The IMSM will also have final say in adjudicating all other safety outcomes.

7. Data and Safety Monitoring Board (DSMB)

This independent committee will determine at study initiation whether to review blinded or unblinded data, will perform data reviews and analyses at regularly scheduled intervals, will be responsible for final determinations of safety and ethical concerns, recommendations about whether the study should continue, and other related issues. The DSMB will also have access to the IMSM who will review AEs on an ongoing basis. The members of the DSMB have been chosen by the program staff at NINDS and will not include any of the PIs or members of the study team.

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% CIs 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 measured using a standardized exam to score skin integrity, active range-of-motion, and use of the casted upper extremity during 15-30 minutes of play
- Stress in parents and infants related to the treatment or study participation as measured using the Perceived Stress Scale.

8. Parent Council

The Parent Council will have 1 to 2 parents from each CPS serve (with compensation and travel expenses covered). The Parent Council will be co-chaired by Nicole Dodds (from Gainesville, FL) and Kim Hindery (from Hamilton, OH). The Co-chairs have children with hemiparesis, have participated in NIH clinical trials, and have firsthand knowledge about high-intensity ACQUIRE forms of infant and toddler rehabilitation.

D. TRAINING PLAN

The goal of training is to ensure human subjects protection and a full understanding of the I-ACQUIRE treatment protocol, as well as to standardize the methods of data collection to help ensure comparability of data across sites. Prior to the activation of any CPS, the training requirements outlined in this section must be completed and uploaded to the regulatory documents tab in WebDCU™. When new study personnel join during the trial, they must complete the on-line training via the WebDCU™ training site (https://webdcu.musc.edu/campus/) and upload all required training documentation prior to participating in any study related activities.

1. WebDCU™ Navigation

In order to set up initial personal WebDCU™ login credentials, contact Catherine Dillon at rileycp@musc.edu or Sara Butler at butlers@musc.edu. All I-ACQUIRE study personnel will be provided with a username and temporary password for the purpose of accessing WebDCU™. The link to the WebDCU™ database is: https://webdcu.musc.edu/login.asp. You will be prompted to change your temporary password the first time you log on to WebDCU™. WebDCU™ will be the CTMS that will house all study specific documents, data entry and regulatory maintenance.

Project Documents can be accessed by going to https://webdcu.musc.edu/login.asp, "I-ACQUIRE → Toolbox → Project Documents" and includes but is not limited to:

- StrokeNet WebDCU™ User Manual
  - Contains step-by-step instructions for logging in to WebDCU™ and navigating the system for study specific tasks
- I-ACQUIRE Regulatory Document Parameter Guidelines for WebDCU™
  - Contains instructions specific for posting study required documents
- I-ACQUIRE Study Book
  - Study CRFs
- I-ACQUIRE Data Collection Guidelines
  - Contains general and specific guidelines for completion of I-ACQUIRE CRFs
- I-ACQUIRE Randomization Instructions
- I-ACQUIRE Manual of Procedures (MOP)
- I-ACQUIRE Participant Correspondence Letters, as applicable

I-ACQUIRE-specific training modules are located at (https://webdcu.musc.edu/campus/ - Project Specific Training -> I-ACQUIRE Project). Another way to access the project specific training for I-ACQUIRE is located on the WebDCU™ login page located at https://webdcu.musc.edu/login.asp. At the bottom of the page is a link for WebDCU™ Training Center. By clicking on this link, you will be routed to the WebDCU™ Training Center page. See sections 5-7 below for details on required training modules.

2. Human Subjects Protection (HSP) and Good Clinical Practice (GCP) Training

It is the expectation that all investigators and staff involved in the conduct, oversight, or management of this NIH funded trial must be trained in and comply with all local, and US federal requirements for the initiation and ongoing performance of a clinical trial per the principles of GCP as defined in International Council for Harmonization Consolidated Guidance (ICH E6) and Title 45 and part 46 Federal Policy for the Protections of Human Subjects "Common Rule". Acceptable documentation of GCP and HSP will be a training module from an accredited institution that describes the investigational nature of the I-ACQUIRE Trial.

Participating institutions may require a particular program (e.g. Collaborative Institutional Training Initiative [CITI] Training) or may choose to develop a program to meet these requirements. Frequency of HSP and GCP training is institution specific and will be driven by the expiration date stated on the certificate. If no

expiration date is listed and if not in conflict with local institutional policy, the expiration date is 3 years from the certification date. All study staff members are required to have undergone HSP and GCP Training, as determined appropriate by your institution for fulfilling this education requirement, prior to participating in the I-ACQUIRE study. Documentation of training must be uploaded to WebDCU™ and verified initially by the NCC Project Manager and then by the StrokeNet CIRB prior to initial site approval and when adding new study personnel.

3. CIRB

All Regional Coordinating Centers (RCCs) and Satellites, which includes CPSs, have signed a StrokeNet CIRB Reliance Agreement prior to being trial eligible. Use of the StrokeNet CIRB is NIH mandated.
Process Overview:

1) Prime Award Site PI will submit the protocol and Informed Consent Document (ICD) template (along with any other study-wide documents that need CIRB approval) to the NCC PM who will submit the appropriate documents to the CIRB Inbox for submission to the CIRB. All approved documents will then be available for distribution to the performance sites.
2) The NCC Project Manager and NCC Regulatory Compliance Specialist will work together to distribute to the CPS the following documents:
    a. Prime Protocol Approval Letter
    b. Approved Prime Protocol
    c. Any approved Study-Wide Documents
    d. ICD Template
    e. ICD Instructions
    f. Stand-alone HIPAA Authorization Form
    g. Performance Site Application Form
    h. CIRB Assurance Form (to be completed by only Site PI)
    i. Local Site Context Form (to be completed in conjunction with the performance site's local Human Subjects Protection Program or equivalent office)
    j. Partial HIPAA Waiver Request for screening purposes
    k. Financial Conflict of Interest (fCOI) Form
3) The CPS CIRB Application Packet (inclusive of the documents noted above) will be reviewed by the NCC Regulatory Compliance Specialist for completeness prior to submission to the CIRB.
4) Upon receipt of CIRB approval, the NCC Regulatory Compliance Specialist will upload to WebDCU™ the approval letter, and approved documents (ICD, Stand-alone HIPAA Authorization Form) before distributing all approved documents to the CPS.

For CIRB submissions, follow the study specific directions provided by the NCC PM and NCC Regulatory Compliance Specialist in the I-ACQUIRE Study Start-Up email. A resource guide for getting ready to enroll for the I-ACQUIRE Trial can be found in WebDCU™ (Toolbox → Project Documents → NIH StrokeNet Study Start-Up Checklist).

Following is a chart that breaks down CIRB Responsibility versus Local Site Responsibility:

CIRB Responsibility	Local Site Responsibility
IRB review tasks ➢ Initial review ➢ Continuing review ➢ Amendments, deviations, etc. ➢ COI	**Site specific context** ➢ Local laws ➢ Institutional policies ➢ Local context ➢ COI
HIPAA determinations of: ➢ Authorization forms and any accompanying request for alterations when authorization is combined with informed consent ➢ Requests for waivers of authorization	**Ancillary reviews** ➢ Nursing ➢ Radiation ➢ Safety
Local context review ➢ Collect local information required for IRB review ➢ Distribute a high-level protocol synopsis and highlights sheet	**Other compliance areas** ➢ HIPAA requirements outside those expressly covered by CIRB ➢ Oversight of research conduct ➢ Other required reporting and actions under federal, local, or institutional laws, regulations or policies

4. I-ACQUIRE Required Training

PIs, sub-investigators, study coordinators, and other study personnel must show evidence of training in the protocol and study procedures, eligibility requirements, CRF completion, and WebDCU™ procedures, as applicable. Protocol training will be conducted by the I-ACQUIRE PRIME PIs at Virginia Tech and The Ohio State University in any of the following manners: Investigator Meeting, Protocol Specific Webinar(s), In-person training meetings, or other. Training will be verified by a meeting sign-in sheet, or attestation form, which will serve as the documentation of training for posting in WebDCU™.

For those not able to attend any of the protocol training venues, there will be I-ACQUIRE web based training modules located on the MUSC-supported training WebDCU™ at https://webdcu.musc.edu/campus/ to be completed instead. Upon completion of the web based training modules, attestation forms corresponding to the training must be completed and posted in the CPS regulatory file in WebDCU™ prior to an individual's approval to participate in study activities. The addition of any newly added study personnel will need to follow the same training procedures prior to conducting any study related activities.

4.1 Informed Consent Requirements

All study personnel designated on the Delegation of Authority (DOA) Log with the responsibility of obtaining informed consent on behalf of the trial must document acceptable GCP and HSP Training. Only study personnel who have been approved as delegated and trained may obtain informed consent for I-ACQUIRE.

5. On-going Training Efforts

Annual Investigator meetings and/or other study identified meetings, will offer further opportunities for protocol training, to give trial updates, re-train and educate, address problems or concerns, and generate continued enthusiasm for the trial. I-ACQUIRE protocol retraining will occur if a CPS has greater than or

equal to 6 months with no randomizations. Personnel from the PRIME, NCC and the NDMC will be available to provide any assistance or training that may be required or requested. The Protocol, Manual of Procedures (MOP), Regulatory Document Parameters Guidelines and other study-specific documents are available on the I-ACQUIRE WebDCU™ website under "ToolBox"→"Project Documents".

5.1 6-Month Protocol Retraining

If a site goes without any randomizations for a 6-month time period, the I-ACQUIRE Leadership team will schedule a conference call with the site PI and lead study coordinator to discuss site-specific barriers to enrollment and create solutions. In addition, site personnel are encouraged to review the protocol, MOP and Frequently Asked Questions (FAQ) when lapses in site activity occurs.

6. Required Training Chart

Please see the chart below for an outline of site-wide and individual study team member training requirements that should be uploaded to the regulatory documents tab on the I-ACQUIRE WebDCU™ Website:

Site	**Required Documents**	
Clinical Performing Site	• CIRB Approval Letter • CIRB Approved ICD • CIRB Approved HIPAA Waiver of Authorization for Screening • CIRB Approved Administrative Amendments • Protocol Signature Page • Local IRB Acknowledgement • CIRB Assurance Statement • CIRB Protocol Site Application Form	• Local Site Context Form • CIRB Reliance Agreement • Site Specific Stand-alone HIPAA Authorization Form • Site Specific Stand-alone Bill of Rights
Person	**Required Documents**	
Principal Investigator	• Curriculum Vitae • Medical license • NIH StrokeNet Financial Conflict of Interest (fCOI) • Human Subjects Protection Training	• Good Clinical Practice Training • Protocol Training
Sub-Investigator	• Curriculum Vitae • Medical license • NIH StrokeNet Financial Conflict of Interest (fCOI) • Human Subjects Protection Training	• Good Clinical Practice Training • Protocol Training
Treating Therapist	• Curriculum Vitae • Professional license (if applicable) • NIH StrokeNet Financial Conflict of Interest (fCOI) • Human Subjects Protection	• Good Clinical Practice Training • Protocol Training

	Training	
Person	**Required Documents**	
Blinded Assessors	• Curriculum Vitae • Professional license (if applicable) • NIH StrokeNet Financial Conflict of Interest (fCOI) • Human Subjects Protection Training	• Good Clinical Practice Training • Protocol Training
Primary Study Coordinator	• Curriculum Vitae • Professional license (if applicable) • NIH StrokeNet Financial Conflict of Interest (fCOI) • Human Subjects Protection Training	• Good Clinical Practice Training • Protocol Training • Study Coordinator Training
Secondary Study Coordinator	• Curriculum Vitae • Professional license (if applicable) • NIH StrokeNet Financial Conflict of Interest (fCOI) • Human Subjects Protection Training	• Good Clinical Practice Training • Protocol Training • Study Coordinator Training
Regulatory Document Coordinator	• Curriculum Vitae	
Administrator	• n/a	

E. COMMUNICATIONS PLAN

Ongoing study communication will be maintained through, but not limited to, the following mechanisms for the duration of the trial:

1. I-ACQUIRE Clinical Email: I-Acquire@vtc.vt.edu

The I-ACQUIRE Clinical Email should be used for consultation on screening, eligibility, and non-emergency randomization questions. This email will be supervised by one of the I-ACQUIRE Trial PIs in order to provide real-time answers to study related questions and concerns.

2. WebDCU™ Emergency Randomization Hotline: 1-866-450-2016

The WebDCU™ Emergency Randomization Hotline is a toll free number that is available 24/7 to investigators experiencing problems with performing randomization. This hotline should only be used for randomization emergencies.

3. DSMB Meetings

The I-ACQUIRE DSMB met prior to final study approval and study initiation and will continue to meet semi-annually or on an as needed basis dependent on enrollment and safety findings throughout the duration of the trial. Participant organization for these meetings is in coordination with NIH/NINDS staff.

4. Investigator Meeting

The I-ACQUIRE trial will include up to 12 sites. There will be an Investigator Meeting held at the beginning of the study that will include a PI and SC from each CPS. This meeting will serve as the initiation and protocol training for all CPS investigators and SCs who are able to attend.

At least one additional investigator meeting will be held during the course of the study and is usually held at the time of study closeout. Shorter investigator meetings, or other study-identified meetings, will be held annually to coincide with the International Stroke Conference (ISC) to offer further opportunities for protocol training and to give trial updates. These brief meetings will provide another opportunity to convey study updates, address problems or concerns, generate continued enthusiasm for the trial and provide focused training to investigators and study coordinators. Personnel from Virginia Tech, The Ohio State University, NCC, and NDMC will be available to provide updated study information and training that may be required or requested.

5. StrokeNet Website and ClinicalTrial.gov

I-ACQUIRE has a dedicated website that can be accessed directly at https://www.nihstrokenet.org/clinical-trials/acute-interventional-trials or via a link from the NIH StrokeNet website (https://nihstrokenet.org/). The NIH StrokeNet website contains information for both healthcare professionals and laypeople and is maintained by the StrokeNet NCC. The I-ACQUIRE trial is listed on ClinicalTrials.gov**,** NCT03910075. Any changes, updates and results for ClinicalTrials.gov are maintained by the PRIME Trial Sponsors, or the PRIME Study Coordinator. For any changes, updates to the NIH StrokeNet website will go through the NCC PM.

6. Study Coordinator Meetings / Webinars

Study coordinator meetings occur quarterly or as needed via teleconference on pertinent topics of interest or identified need. The PRIME personnel at Virginia Tech, Nationwide Children's Hospital, The Ohio State University and the NCC Project Manager jointly organize and facilitate these calls. The content for topics presented is available at https://nihstrokenet.org/education.

7. I-ACQUIRE Steering Committee Calls

The I-ACQUIRE Steering Committee will form by the end of the first year that the study is open for enrollment. This group of site PIs and/or designees will typically meet quarterly or as needed by phone for the full duration of the study to discuss the overall conduct of the study with regard to protocol compliance,

modifications/amendments, study progress, problem-solving and other issues pertinent to ensure the ongoing success of the study.

8. I-ACQUIRE Trial Operations Calls

Weekly trial operations updates are provided to the NIH StrokeNet Operations Committee with meeting agenda and minutes distributed by the NCC.

9. Webinars / Teleconferencing

The NCC Education Coordinator organizes monthly webinars and agendas are sent in advance to all RCC and CPS coordinators.

10. Site Directory

The I-ACQUIRE site directory is maintained within WebDCU™. Each CPS is responsible for notifying the NCC Project Manager whenever there is a change to key site personnel (e.g., PI, primary study coordinator) and updating the DOA Log in WebDCU™ as appropriate.

11. Newsletters

PRIME will issue monthly newsletters starting at time of subject recruitment. These trial newsletters will contain enrollment updates, identified common problems and potential solutions, important reminders, and information on upcoming events (webinars and training).

12. Additional Communications

Additional communications will be conducted on an as-needed basis for team building, sharing success strategies, training and discussion of any pertinent issue or identified need. For study team contact information and who to contact for specific questions, please see the Staff Roster, MOP Section A.

F. RECRUITMENT PLAN

Recruitment is the dialogue which takes place between an investigator and a potential participant/ Legally Authorized Representative (LAR) prior to the initiation of the consent process. It begins with the identification, targeting and enlistment of participants for the research study. 240 families from 12 or more sites over 3.5 years will be recruited. Eligible children will include those known to the sites (from clinical databases, direct care, and satellite sites); those recruited from other hospitals, clinics, and early intervention programs; and those who learn about the trial from clinicaltrials.gov or contact with other parents, advocacy groups, and/or social media. 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. We will assist these families in finding low- or no-cost housing options. 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. We have a StrokeNet Recruitment and Retention Plan to Enhance Diversity that builds on local knowledge and relationships and incorporates racially and ethnically diverse images, personal stories, and cultural practices.

Enrollment will be tracked using the study progress module in the WebDCU™. Overall randomization will be tracked by site and month for comparison to the NINDS recruitment plan. Trial and site recruitment data is regularly provided to NINDS by the NDMC.

G. RETENTION PLAN

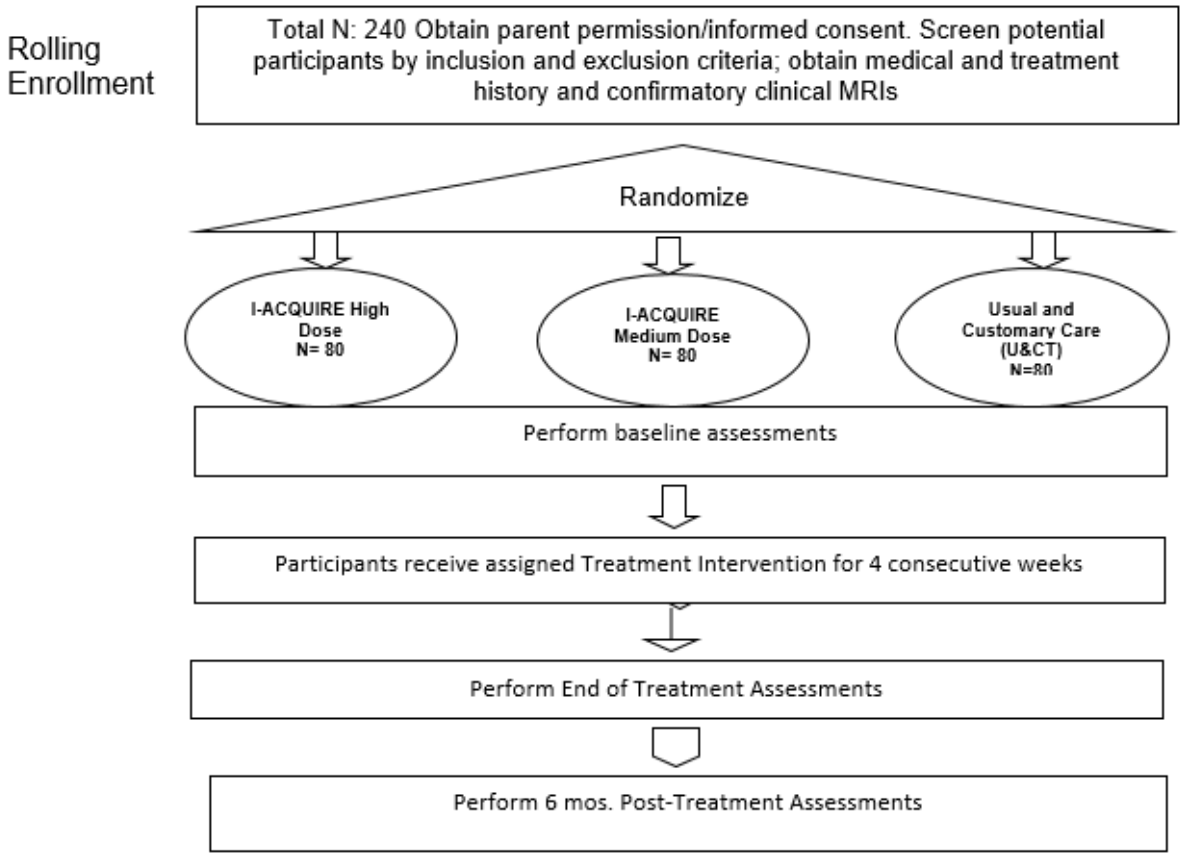
We have a StrokeNet Recruitment and Retention Plan to Enhance Diversity that builds on local knowledge and relationships and incorporates racially and ethnically diverse images, personal stories, and cultural practices.

Once a child is randomized, we will stay in close touch with the child's parents/caregivers regarding when the baseline assessment will occur and the dates for the 4 weeks of treatment. We will ask parents their preferred methods for staying in contact and find out the best times to talk directly with them to finalize sharing of information prior to assessments and treatment.

At each contact, we will:

- Ensure participant contact information is correctly recorded and the telephone numbers and email contacts are still in use. If the contact information collected is not the participant's, verify the identity of the person and their relationship with the participant. Attempt to get at least two contact numbers/alternative contact information for each parent/caregiver (e.g., home, work, mobile, email address), as one contact number may not be adequate or always in service.
- Call or send reminders for upcoming visits and accommodate participant's schedule as much as possible.

H. STUDY FLOW


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 N= 80
I-ACQUIRE Medium Dose N= 80
Usual and Customary Care (U&CT) 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

I. SCREENING AND ELIGIBILITY CRITERIA

1. Screening

A potential participant's parent or guardian will have an initial contact with a study team member, likely the PI or SC. The team member should provide a comprehensive explanation of the purpose of the study, all study procedures, and all possible risks and potential benefits of the study in language that is understandable to a non-medically trained person. If the parent or guardian indicates further interest the team member should go over all study eligibility criteria and the randomization process. In addition, the team member should discuss the responsibilities of the family during the entire study period, including the scheduling process and the second phase of the study if the child is randomized to the usual and customary care condition. Parents (guardians) should explicitly be made aware that participation is voluntary and that permission for their child to participate may be withdrawn by them at any point during the study without impacting the child's care at the site or elsewhere in any way. The importance of completing all study follow-up assessments should be emphasized to the parent (guardian) because these are the sole basis for judging when the treatment is beneficial to children.

If a child appears to meet all eligibility criteria, parents should be provided the ICD and given ample opportunity to read the consent document, to ask questions and to consider their decision regarding participation. The team member needs to go over each section of the IC to ensure that the parent understands all study aspects. Once informed consent is obtained information about obtaining the child's neuroimaging scans to confirm the diagnosis of Perinatal Arterial Ischemic Stroke (PAS) should be collected. There is a spate form for permission to release the MRI scan to the study team. Once diagnosis is confirmed by independent review, then randomization and final scheduling for the child's 4 weeks of treatment, with corresponding dates for baseline and the two post-treatment assessments, can occur.

1.1 Screen Failure Log

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). A child can be rescreened when he or she recovers or family can fulfill inclusion criteria for participation.

2. Eligibility Criteria

2.1 Clinical Inclusion Criteria

- child will be 8 - 24 mos old at time when study treatment during Phase 1 will be delivered
- child has a diagnosis of Perinatal Arterial Stroke (PAS)
- parent permission to provide the child's clinical MRI to the study
- child has hemiparesis

- parent(s) willing to participate in the home therapy component
- 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 Phase 2, children who participated in Phase 1 in Group 3, U&CT, may be older than 24 mos. when they receive I-AQCUIRE treatment

2.2 Clinical Exclusion Criteria

- child has medical or sensory condition(s) that prevent(s) full therapy participation (e.g., frequent uncontrolled seizures, fragile health)
- child previously received modified CIMT with a dose of at least 2 hrs/day for ≥10 days (lower modified CIMT doses are permitted)
- child received botulinum toxin in past 3 mos.
- child is a ward of the state or other agency

J. INFORMED CONSENT AND HIPAA AUTHORIZATION

In accordance with Food and Drug Administration (FDA) regulations (21 CFR 50) and International Council for Harmonization-GCP Consolidated Guidelines, a witnessed, CIRB-approved, informed consent is required from all patients prior to study participation. All qualified study personnel designated on the DOA log with the responsibility of obtaining informed consent on behalf of the trial must provide documentation of acceptable HSP Training.
The CPS PI is responsible for ensuring that a signed and dated ICD is obtained from each participant ***before*** the participant participates in any study related activity even when this task has been delegated to other individuals on the study team.

1. Informed Consent

The ICD should be the basis for a meaningful exchange about the study between the investigator, or other designated member of the study staff documented on the DOA, and the subject and/or LAR. Please keep the following in mind before you begin the consenting process:

- CPSs are required to use the most **current NIH StrokeNet CIRB approved** ICD provided to their individual CPS.
    - Confirm use of the most current CIRB approved ICD ***prior*** to initiating the informed consent process. If you don't have the most current version, know where to get it.
- Informed consent – in the form of parental permission for I-AQCUIRE - must be obtained before initiating any study related activity - no exceptions.
- In addition to signing the ICD, the parent/LAR should enter the date of signature on the consent document, to permit verification that consent was actually obtained before the subject began participation in the study.
- The original ICD should be retained in the study/subject file in a secure/confidential manner.
- A copy of the ICD must be provided to the parent/LAR.
- ICDs are required to be made available at the request of external site monitoring staff.
- CPSs must adhere to any additional local site requirements for the management and storage of ICDs. This NIH funded trial requires all study files to be retained over the life of the trial award and at a minimum of 5 years beyond the date of trial publication.

1.1 Remote Fax/Phone Consent

If there is no LAR present at the time of screening, consent can be obtained by fax if allowed by the clinical performance site local HSP determination.

An example of such a procedure follows:

- Contact the appropriate LAR by telephone, arrange to provide them with two hard copies of the ICD before the consenting call.
- For faxing, fax the entire consent form to the LAR (if the fax provides a confirmation fax, retain that page in the study files). Provide return fax number.
- Once the appropriate LAR has the full ICD, conduct the consenting call.
- Discuss the study details, including procedures, study drug/device and potential risks. Discuss the ICD, allow time for questions the LAR may have and give instructions about where the LAR needs to sign and date.
- Provide the LAR with a phone number to call you back in the event that s/he has additional questions.
- The LAR should return the entire, signed and dated ICD back by fax, and keep the second copy for themselves.
- Provide the LAR with a return address to mail the original signed ICD to the study team at the

enrolling site.

- The ICD is not valid and you cannot proceed with study enrollment unless all pages are received and appropriately filled out/signed/dated.

2. Informed Consent Process

In accordance with the NIH StrokeNet GCP SOPs, sites should address the following guidelines regarding the basic elements of the informed consent process and documentation required. The process of obtaining consent should be conducted by trained, Central Institutional Review Board (CIRB) approved study personnel listed on the delegation of authority log as having been delegated the task of obtaining consent. The process includes (but is not limited to) the following steps:

- Consent process begins when a potential subject is initially contacted.
- Presenting information about the study, including the risks and potential benefits, in language understandable to parent/caregiver and at a level that allows for clear understanding.
- Allowing the parent/caregiver adequate opportunity to read the ICD document
- Answering any questions.
- Clearly stating that initial and ongoing participation in the study is voluntary, and that a parent/caregiver may discontinue the child's participation at any time.
- Obtaining relevant signatures on the ICD.
- Continuing to provide information and answers to questions throughout study participation.

2.1 Documentation of the Informed Consent Process

Each subject should have documentation of the informed consent process in the local site's storage. In I-AQCUIRE, a copy of the informed consent is not provided for the child's permanent medical record.

3. HIPAA Authorization

Under U.S. federal law, researchers who use information about the health of their research participants are required, except in specific circumstances, to get written permission to use their participant's protected health information (PHI) for the research study. Each CPS is expected to comply with StrokeNet SOP Number: GCP 05.

K. RANDOMIZATION

Assignment of Subject ID number and randomization both take place centrally via WebDCU™. After confirming initial eligibility and obtaining informed consent (parental permission), an authorized study team member logs onto WebDCU™ to data enter and submit the Subject Enrollment Form and F101: Eligibility. Upon submission of the Subject Enrollment form, the system provides a unique subject ID number. The study team member can then proceed with entry of the remaining screening CRFs.

In order to randomize a subject in WebDCU™, the following CRFs will need to be completed:

- Subject Enrollment Form
- F101: Eligibility
- F102: Randomization

Upon successful randomization, sites will print the Randomization CRF for source documentation of treatment assignment.

Complete step-by-step instructions on how to randomize a subject in WebDCU™ can be accessed in WebDCU™ under [Toolbox] → [Project Documents].

A subject is considered to be in the trial upon randomization (i.e., given a treatment assignment). Randomization cannot be undone, and any subject that is randomized must be followed until End of Study.

Emergency Randomization Instructions:
For randomization difficulties occurring during normal business hours, contact your NDMC I-ACQUIRE Data Manager:

- Sara Butler (butlers@musc.edu, 843-792-1559)

If randomization difficulties occur after hours or on a weekend/holiday, please contact the **WebDCU™ Emergency Randomization Hot Line at 1-866-450-2016.** This hotline is only for randomization emergencies and is available 24 hours a day, 7 days a week.

NOTE: Questions regarding eligibility or protocol implementation should be directed to the **I-ACQUIRE Clinical Email at I-Acquire@vtc.vt.edu**

L. STUDY INTERVENTION

The study is comparing two therapeutic interventions; an intensive therapy protocol called Infant-ACQUIRE therapy (I-ACQUIRE) and usual and customary care. The I-ACQUIRE protocol will be delivered at two different dosages.

L1. The Infant ACQUIRE Clinical Protocol. Licensed therapists in Occupational Therapy (OT) or Physical Therapy (PT) will be trained and monitored by the Treatment Implementation Center at Virginia Tech to implement the I-ACQUIRE Clinical Protocol. I-ACQUIRE is an intensive therapy protocol that has 8 primary components shown in table 1. It is a standardized form of Pediatric Constraint-Induced Movement Therapy (CIMT) that has demonstrated treatment efficacy in multiple Phase I and II trials[16, 66, 82,93,95,96,128].

TABLE 1. OVERVIEW OF CORE TREATMENT COMPONENTS FOR I-ACQUIRE (BOTH DOSES)

1. Constraint of the infant's less-impaired upper extremity for first 17 days of treatment; cast is worn continuously. Infants wear a removable, full-arm lightweight cast for the first 17 of 20 therapy sessions. The cast is removed at the end of the session on treatment day 17. On the last 3 treatment days, after cast removal, we focus on integrating new skills of the hemiparetic UE into bimanual activities.

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

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 to elicit new UE skills and then progress to voluntary control. The methods for setting behavioral goals, 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 and include many self-help activities (eating, dressing, hand washing).

4. Provision of therapy in natural settings. We provide therapy in natural environments, because this promotes generalization and maintenance of skills. For infants, this can include the home or a childcare or early intervention setting. Some clinic settings can be set-up to be similar to home or childcare settings. The primary caregiver is often 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, such as sitting, weight bearing, rolling, crawling, standing, walking. Even with the cast, many gross motor bimanual activities can occur, such as carrying, pushing, pulling, or catching a large object.

6. Home Treatment Module developed as an active Parent-Therapist Partnership. We use a parent-home training module (with supportive written materials and photo/videotapes). The therapist and parent(s) meet when treatment begins. The therapist coaches the parent in I-ACQUIRE methods, particularly concerning effective and ineffective use of operant conditioning. Parents help identify goals, introduce new activities, and adjust therapy activities to encourage the infant's practice of new skills as directed and in team with the treating therapist. Parents are asked to spend about 45 min/day helping their infant practice new skills for 5 of 7 days. (This can occur in shorter bursts throughout the day.) The treating therapist provides activity examples and target areas of practice at the conclusion of each treatment day to assist parents in successful completion of the extra practice with their infant. Parents report time spent on this to the treating therapist.

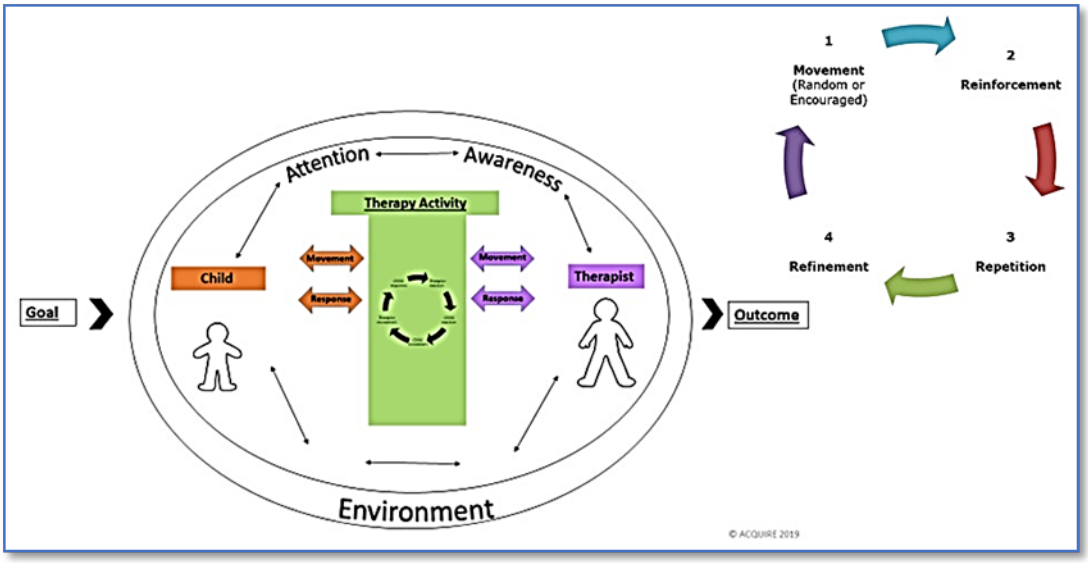
7. Documentation of daily therapy sessions. Each therapist documents treatment with standardized daily logs that record treatment goals worked on, activities completed, and infant behavior (interest level, signs of frustration or fatigue) and any progress or decline.

8. Transfer Package to promote future progress. Therapists develop a written plan with supportive materials to guide the parents in further helping the infant maintain and improve skills post-treatment. This plan will be provided to the parents at the very latest on the final morning prior to starting treatment, providing the caregiver with time to read and discuss questions with therapist. This plan targets motivating daily and special activities, informed by the overall treatment process, how well the infant has progressed across various skill levels, and next steps towards higher-level functional use.

L2. Operant Conditioning. 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 operant conditioning in all therapeutic activities.

L3. ACQUIRE Treatment Framework & MR3 Cycle. Therapy activities are aimed at success. Therapy activities are practiced under specified reinforcement contingencies designed to promote movement repetition and skill development. **Figure 1** shows the ACQUIRE therapeutic framework. Therapists are expected to direct activities by a cyclical process that we term the MR3 cycle. The MR3 cycle indicates that movements and or skills are repeated until roughly 70-80% proficiency levels are obtained, at which point the contingency of reinforcement is changed to require a more refined or advanced movement or skill. The treatment framework recognizes that the therapeutic environment needs to be setup and constantly altered based on the interactive exchange between the therapist, the child, and the environmental demands. Combined, these factors lead to increased abilities in the child by progressive completion of activities at successively higher or more complex levels and across differing skills (cause/effect toys, meals, dressing, etc.). The activities are 'shaped' via immediate and varied reinforcement (primarily verbal praise, smiles, and supportive gestures) using successive approximations towards targeted treatment goals. The therapeutic process is different for each child because of individual goals and needs, but the process itself is defined by the cycle supporting progression and the multiple components in the fluid therapeutic interactions. This is based on the principles of operant conditioning. The therapy activities are individualized, but each therapist will promote four activity types as a part of every child's therapy process: 1) Age-appropriate, play-based, participatory activities (e.g., with cause and effect toys, games with back-and-forth activities or simple rules like peek-a-boo or clapping and hand gestures to songs or rhymes), 2) sensory awareness to help guide perceptual developments and improve skills (e.g., attending to differing textures, shapes, sizes of objects), 3) movement-based activities designed to increase range of motion, strength, speed, and endurance (e.g., reaching and grasping, transitioning to different body postures or moving through space using the upper extremities); and 4) self-help activities (e.g., eating, drinking, washing hands, helping with getting dressed).



L4. Dosage Levels. I-ACQUIRE will be delivered at two different dosage levels. One group of children will receive I-ACQUIRE at a moderate dosage of 3 hours a day for 5 days a week for 4 weeks. Another group will receive I-ACQUIRE at a high dosage of 6 hours a day for 5 days a week for 4 weeks. All treatment components other than the dosage are the same.

L5. I-ACQUIRE Daily Schedules. The goal of each day's schedule is to obtain the number of assigned treatment hours via active therapeutic processes that match the daily life schedule of the enrolled child and the child-specific therapy goals. Each child's therapy goals are listed on the daily schedule. Daily therapy activities include age-appropriate daily activities and events relevant for the child and family that can be adapted to allow for active therapy participation of the child. These activities should promote active movement and engagement of the child applying operant conditioning principles.

Almost all young children are most active when therapy begins in the morning. For a child receiving the 6-hr dose of I-ACQUIRE, starting treatment in the morning is particular valuable. Many children in the 8-24 months age range can complete 6-hours of daily therapy activities by starting treatment in the early morning hours and going straight through (e.g., 8:00 a.m. to 2:00 p.m. or 7:00 a.m. to 1:00 p.m.) without needing a nap, particularly when the therapy explicitly involves activities such as feeding and dressing. Sometimes this schedule will include multiple feeding times that serve as both as active therapeutic events and eating/drinking times. If a child must nap, we recommend the nap be no longer than one hour. During the child's nap time period, the therapist can remain onsite and work on daily treatment notes and other study related events. Note: when a child is napping, or for other reasons not able to participate in the therapy (e.g., an unexpected visitor comes and this stops the therapy for more than 5 – 19 minutes), this time does not count toward fulfilling the daily dosage. (Interruptions and start and end times for therapy are noted on the Daily Therapy Log.)

L5A. Missing I-ACQUIRE Therapy Time. In the event that a therapist is ill, we encourage sites to have a second study therapist available to fill in the needed therapy sessions. For child illness or other unexpected events that prevent treatment on a scheduled day, up to 3 treatment days over the 4 weeks can be missed without the treatment being designated as a study protocol deviation. In the event that the child misses more than 3 treatment days, everything possible should be done to schedule make-up sessions within the next 7 days after the originally scheduled end date. Weekend days are allowed at any time throughout treatment. If this can be arranged, then this will not be classified as a study protocol deviation. This would mean that the overall treatment period could extend to 5 weeks to include all 20 treatment sessions. (Note: if the treatment length is extended, the therapist should let the site study coordinator know as soon as possible in order to reschedule study assessments as appropriate. Also, the Treatment Implementation Center at Virginia Tech should be notified, because this impacts the weekly monitoring and the completion of the therapist's daily treatment log.) If treatment disruption occurs due to illness or other events, and re-scheduling is not possible, the treating therapist needs to contact the site PI immediately. The site PI will then need to contact the Treatment Implementation Center, so that the Executive Steering Committee and all other study oversight committees and boards will be informed about the study protocol deviation.

L6. Treatment Documentation. The treating I-ACQUIRE therapist will complete a daily treatment log that will describe each day's treatment activities. The Daily Treatment Log is a pdf form located on the treatment laptop. There are multiple parts to this form. The first part provides descriptive information to identify the child, the therapist, and the treatment day. The next part identifies treatment goals. Treatment goals on this document are representative of the therapist's goals from a therapeutic perspective, but they should be built in part on the goals of the family. There is a section to list parent goals for their child separately, as well. The next section on page 1 is to record the parent's level of participation with their home program (i.e., daily practice or extended treatment activities that are provided by the parent outside of therapy hours). This section documents the number of minutes each night parents report that they spent on these activities with their child. Parents are asked to complete 45 minutes of the home form of treatment with their child for at least 5 of 7 days each week. Each treatment day, the therapists provide sheets labeled "Parents as Partners" (described in section below) to parents to suggest activities that parents can work on with their child. Each morning therapists will take that information and transcribe the amount of time parents completed the previous day doing these suggested treatment activities as official documentation of this time on the daily treatment log. (For the weekend, two forms are given to parents.)

The next section of the daily log has a list of 26 activities that are included in the treatment sessions. They are grouped by activities of daily living, movement-based activities, and other dimensions of therapy.

The therapists document which activity types occurred and for approximately how long (between 0-10 minutes; 10-30 minutes; 30+ minutes). Therapists also provide a brief description of how the child progressed on the activity during the day's session. All treatment activities are guided by principles of operant conditioning (see above); for this reason, therapists document the types of reinforcers used each day. Finally, therapists record the parent engagement for the day and write an overall summary for the day. Note: if an adverse event occurs, an adverse event is reported officially and also is noted in the daily log. Daily Treatment Logs are saved on the therapists' computers and then uploaded to the Virginia Tech (VT) Treatment Implementation site. Certain sections and summary variables from this form that will be data entered later to WebDCU™, the central database.

L6A. Parents as Partners. This is a form for therapists to provide suggested activities to be completed by parents. It also allows parents to record the activities they and their child complete during non-therapy hours. These forms are not entered into the WebDCU™ database, but serve to guide interactions and discussions with parents and therapists about activities outside of therapy hours. The Parents as Partners component of I-ACQUIRE is designed to strengthen the child's newly emerging and improved skills as the parent helps in the generalization from what the child is learning in therapy to application in their natural environment outside the formal therapy sessions with a trained therapist. The therapist spends time with the parent(s) offering instruction, demonstration, and exchanging information related to the parent component of the I-ACQUIRE treatment.

L6B. Transfer Package for Post-Treatment Planning. This plan is developed toward the end of treatment and includes the identification of goals, skills, and movements specific to each child. The plan identifies specific behaviors and movements that are particularly relevant for the child and family (e.g., reaching, grasping and releasing, transferring from floor to sitting and/or standing or the opposite, bilateral activities used in carrying or catching objects) for continued practice and extension, with a strong emphasis on maintaining and extending the newly learned and improved skills with the hemiparetic arm and hand – both in unimanual and bimanual activities. Each focus area should include the top 3-5 activities completed during treatment that would be most helpful for the child to continue with their parents. The Transfer Package includes a list of suggested toys and objects and how these can be used in implementing the Transfer Package. Parents are encouraged to share the Transfer Package with any other therapists, family members, or caregivers who spend a significant amount of time with the child. PDF forms on the I-ACQUIRE therapists' treatment computers will be identified to include 3 different forms, two of which the therapist might be printing. The I-ACQUIRE Example Transfer Package will allow the therapist an example of how to complete the blank form for the transfer package. The blank form is titled I-ACQUIRE_TP_blankform. When naming the form to upload to the VT Treatment Implementation Center, the therapist will need to name it with the similar identification used for the daily treatment notes, using the naming paradigm TP_childid_date for the naming format. (TP stands for transfer package.)

<u>L7. Treatment Video Documentation.</u> Treating I-ACQUIRE therapists will videorecord a minimum of 1 hour of therapy each treatment week for review by the Treatment Implementation Center. Each site has been randomly assigned days of the week for videorecording. On the assigned day, the therapist then selects 1 hour of treatment. The treatment video will then be uploaded after the session is completed so that the VT Treatment Implementation Center can conduct the treatment fidelity scoring. The videotapes along with the daily treatment logs are the basis for the VT Treatment Implementation Center providing individualized feedback to therapists about their implementation of the I-ACQUIRE protocol. Each therapist can provide more than 1 hour of treatment if so desired, and this is encouraged if there are treatment activities that the therapist would like to discuss with the VT Treatment Implementation Center in order to optimize the treatment process. A central goal of measuring treatment fidelity each week is to continually improve the therapists' ability to implement I-ACQUIRE at the highest fidelity levels possible. The VT Treatment Implementation Center leadership team includes highly experienced therapists who can collaborate with local therapists to identify strategies to improve treatment fidelity.

L8. Casting, Changing Casts Weekly, and Bathing. The constraint for the two I-ACQUIRE groups is constructed via a light-weight casting material called focused rigidity casting (BSN Delta Conformable). Therapists will be trained in cast construction and the proper angle for the arm and wrist, and the overall length of the cast. The cast should be made after the child has completed the baseline assessment and prior to treatment day 1. The cast should remain with the therapist and placed on the child's arm at the beginning of the first treatment day (and then worn until the end of the 17th day of treatment). [Note: The appointment to make the cast can be combined with a short play session to allow therapists to begin forming a relationship with the child, observe the child's use of the hemiparetic arm and hand, and briefly talk with parents about treatment goals and the process of Parents as Partners.] Casts are constructed with ample padding for wearing the cast 24 hours a day for 7 days each week. The elbow is placed in 90 degrees flexion and the wrist and fingers are all placed in neutral positions. The material is activated to harden (become stiff) when placed in water after opening. Once the cast is rigid, it is univalved for easy removal. The goal is for the child to wear the cast the first 17 of the 20 treatment days. Treatment days 18-20 are bilateral treatment days. The cast should be fully removed by the therapist at the end of the 17th day of treatment. (Photos and videos of this as well as live demonstrations occur during training and in stored training materials.)

Therapists will remove the constraint once a week during the last 30 minutes of that day's session. This allows for observing range of motion, checking skin integrity, and allowing for parents to provide the child with a full bath (if so desired) prior to replacing the cast on the child's arm. Minor skin prickling or a simple rash (mild eczema-like) is sometimes observed when the cast is removed. In addition, many children posture the casted arm (i.e., still hold it as though the cast was on) for the first few minutes' some children may fuss or cry when the cast first comes off. This is all considered within the normal range of responses, and usually settles down when the therapist encourages the child to move the previously casted arm and hand around, and allows parents to give them a bath. Very rarely, after a bath the redness might seem more pronounced. Check to make sure all aspects of the cast are dry and that there are no major ridges that might cause irritation. The cast should remain dry, and parents are encouraged to sponge bathe children during the I-ACQUIRE month of treatment. Some parents do wrap the cast in a plastic bag and allow the child to bathe. If the cast becomes wet, it should be removed to allow the material to dry. If the cast remains on the child's arm and hand while wet there is greater concern for skin irritation. If the cast is wet, the material does allow for placement in a dryer on medium or low heat (we recommend with a towel). If there is any spot on the cast that feels like it might add to any irritation on the child, the therapist will add additional padding in the form of the fleece edger (do not use original cast padding because it is too thick) prior to replacing the cast on the child's arm and hand. If there are any specific concerns, please contact the VT Treatment Implementation Center via the 24-hr contact e-mail address, prior to replacing the cast on the child's arm. Taking photos often can be helpful. Parents should be fully informed at the time the cast is constructed in how to remove the cast in the event of an emergency. If parents do remove the cast at any point during treatment, we recommend that they contact the study therapist at that point to discuss concerns and to decide on cast replacement if the arm and hand appear fine. [Note: In most instances when a parent has removed a cast, the parent thought the child may have appeared distressed; often, however, it turns out that the child's distress was not associated with discomfort due to the cast. If this is the case, the therapist should instruct the parent to replace the cast as soon as possible. If there are concerns regarding the cast, therapists should seek assistance from the VT Treatment Implementation Center and/or the Clinical Site PI or clinical staff. In all circumstances involving I-ACQUIRE, if there is a medical emergency, seek appropriate emergency services first, and parents should be informed to do the same. Formal reporting then will take place as required.]

L9. Training of I-ACQUIRE Therapists. Cross-site training of therapists will occur in Roanoke, Virginia June 18-21st, 2019. The VT Treatment Implementation Center will be responsible for all training activities which will cover all I-ACQUIRE processes. Training activities will be video recorded for future use. The VT Treatment Implementation Center will also be responsible for conducting future trainings and or any corrective action training throughout the course of the study. Training outside these dates for future therapists will be determined as needed, but therapists will be evaluated routinely for Treatment Fidelity

and ongoing training will take place via interaction with the VT Treatment Implementation Center distally and in-person as deemed necessary.

L10. Fidelity of I-ACQUIRE Treatment. We will monitor Fidelity of Treatment by reviewing and scoring weekly videotapes of treatment sessions with a standardized, reliable tool. Senior I-ACQUIRE therapists at the VT Treatment Implementation Center (trained to high kappa inter-rater reliability of 0.86 across items) will score four 15-minute segments/session and review the week's daily therapy logs. Feedback to local therapists will include summary of fidelity scores along with specific corrective actions for any item scored as 1 (inadequate) or 2 (partially adequate) (3=all criteria met; 4=exemplary). We have used this tool to measure treatment fidelity in other multi-site trials. Corrective actions involve discussion followed by coding new therapy videos the therapist submits to show correction. If needed, we will conduct corrective site visits and work in the field with the therapist.

L10A. Monthly Calls with I-ACQUIRE Therapists. We will hold monthly conference calls for all study therapists. Every 3 mos, we will convene a video conference with all therapists to go over specific case-examples. [Note: These will involve children who have completed all study protocols or will be examples from other studies. Cases will only be used if parents have given written permission for their child's treatment videos to be used in training sessions, and cases will be chosen to address common questions identified during monthly conference calls.]

L11. Rationale for selecting the 3 hr and 6 hr dose levels. We originally selected a 6-hr daily session because this comprises a large portion of the waking day, similar to the time infants and young children spend in childcare, early intervention programs, or school. This is the most tested dosage for a "signature form" of pediatric CIMT.[17] We selected the 3-hr dose as similar to a half-day session in childcare, early intervention, or school. Both practically and clinically, the difference between 3 and 6 hrs 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 to inform the vigorous debate about the different dosage levels and reduce the cost of delivering I-ACQUIRE to eligible infants.

L12. Description of the Usual & Customary Treatment (U&CT) (control) group: We expect infants assigned to U&CT will be participating in ongoing treatment (arranged by their parents); they will continue with their U&CT. (Parents will understand they are responsible for U&CT costs, us*ually covered by insurance/Medicaid*.) Ongoing treatment/therapy we expect to consist most often of Physical and Occupational Therapy. Parents will report on types and amounts of therapies that children in the U&CT treatment are receiving. We will also ask parents to explicitly describe types of therapy activities completed during therapeutic processing (e.g. parent-education, mobility practices, upper-extremity training, and direct therapist led activities).

L12A. Documenting U&CT Treatment. Parents will be asked to report on all U&CT their child received over the designated 4 weeks of treatment in the study timeline. Parents will receive a form to record the types and amount of active therapies the child receives. The data provided by parents then will be entered into WedDCU™ by the site coordinator.

M. BLINDING AND UNBLINDING and MONITORING FOR BIAS

Each national study center has a blinded and unblinded director. For the Treatment Implementation Center at Virginia Tech, the blinded director is Craig Ramey and the unblinded director is Stephanie DeLuca. For the Assessment Center at OSU, the blinded director is Jill Heathcock and the unblinded director is Amy Darragh. This division in leadership blinding allows all study procedures to be monitored throughout the course of the study by one director who can be directly informed by participant group assignment, if necessary while eliminating bias to the best extent possible. This will allow for appropriate guidance of therapists and assessors in situations where questions may arise. Simultaneously, designation of the blinded directors allows for any unplanned events to be considered and evaluated for data analysis and/or study implications without the biases that could be associated with revealing participant or site-specific information.

The blinded assessors (BAs) will be blinded to group membership. Following each assessment, BAs will complete a brief questionnaire about whether or not they believe they were unblinded. If so, the Assessment Center at OSU will review the Bayley and GMFM from the videorecordings and consider re-scoring. In addition, BAs will contact the Assessment Center if they believe there is unblinding on the video (e.g., a parent mentions the cast during the assessment). In this case, the unblinded member of the Assessment Center will remove the audio sections before the videos are cleared for coding by the blinded coders.

N. PARTICIPANT EVALUATIONS AND FOLLOW-UP

Table 2: Schedule of Activities (SOA)

Procedures	Screening	Pre-treatment Assessment	One-month of Assigned Treatment	End of Treatment Assessment	6 mos Post-Treatment Assessment
Informed Consent	X				
Demographics	X				
Clinic MRI Requested and Reviewed	X				
Randomization to Treatment Groups	X				
Medical & Treatment History	X				
Neurology Exam (PSOM)		X			
Mini-MACS Rating[1]		X			
GMFCS level		X			
Emerging Behaviors Scale		X		X	X
Structured play session (Mini-AHA)		X		X	X
Bayley-4		X		X	X
GMFM		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 Life and Other Stressors		X		X	X
Parent Report of Therapy		X		X	X
Treatment Delivered and Fidelity Measured Weekly and Overall			X		
Information Exchange-Therapist				X	
Information Exchange-Parent				X	
Adverse Event Review and Evaluation	X>>>X				

[1]If subject is less than 12 months, the Mini-MACS rating will be completed at the first assessment where the child becomes age-eligible for this rating scale.

a. Blinded Assessor Training and Reliability

b. Screening

All items in the SOA table above listed under “Screening” are performed prior to randomization. The inclusion/exclusion must be completed to determine if the patient meets the eligibility requirements for the study. If the patient is eligible and the consent form is signed by the patient or authorized representative, then the randomization procedure should occur immediately.

c. Study Measures

There are three primary time-points for assessment: Pre-Treatment, End of Treatment (post-treatment 1), and 6-Month Post-Treatment Follow-Up (post-treatment 2). Assessments include a physician-administered medical history and neurological exam; behavioral assessments completed by Blinded Assessors (BA) at each site; and parent-reported measures, completed by participant parents/caregivers.

All study assessments and associated time-points are detailed below.

Pediatric Neurologist or Physiatrist-administered measures.

Prior to treatment, the pediatric neurologist/physiatrist will administer the medical/treatment history form and the Pediatric Stroke Outcome Measure (PSOM). These scores are enter into WebDCU™ by the Research Coordinator, pediatric neurologist/physiatrist, or study-site designee. Data are to be entered within five days of assessment. These are administered only once, prior to treatment as part of the pre-treatment assessment.

Behavioral Outcome Measures.

There are four behavioral assessments in the study: the Bayley Scales of Infant and Toddler Development-4 (Bayley-4), the Gross Motor Function Measure-88/66 (GMFM-88/66), the mini-Assisting Hand Assessment (mini-AHA), and the Emerging Behaviors Scale (EBS).

Blinded Assessors will complete three assessments at each of the three time-points: Pre-Treatment, End of Treatment (post-treatment 1), and 6-Month Post-treatment Follow-Up (post-treatment 2). The three BA administered assessments are the Bayley-4, the GMFM-88/66, and a Structured Play Session (from which the Mini-Assisting Hand Assessment (mini-AHA) will be scored and EBS partially scored). A snack break is encouraged. If the child takes a snack break where finger foods and self-eating occur, the snack break should be videotaped. Bottle feeding and nursing do not need to be recorded. These assessments also will be used to derive the Emerging Behaviors Scale. The Assessment Center will score the Emerging Behaviors Scale and mini-AHA from the video, assessment scores, and survey results.

Blinded Assessors will confirm two classification instruments: the Gross Motor Function Classification System (GMFCS), the mini-Manual Abilities Classification Scale (mini-MACS).These are not outcomes, but rather a way to classify gross motor and manual abilities to describe the participant.

Behavioral measures are:

The Bayley Scales of Infant and Toddler Development (Bayley-4)

The Bayley is the most widely used tool to assess infants. For the purposes of I-ACQUIRE, the following subtests will be administered: Cognitive, Receptive Communication, Expressive Communication, Fine Motor, and Gross Motor domains. Assessors will administer the Bayley-4 according to standardized procedures, with one study-specific modification. The fine motor subtest will be administered on each side (the Right and the Left) and all participants, regardless of age, will start the Fine Motor subtest at item 13 Block Grasp Series.

The BA will document the Bayley on the paper form or electronic form, score, and enter into WebDCU™ using the study provided laptop. A PDF of the paper copy score sheet should be uploaded into the I-ACQUIRE box folder. Paper copies of the assessment should be

maintained by the site as per site storage protocols. The Bayley-4 will be administered at Pre-Treatment, End of Treatment (post-treatment 1), and 6-Month Post-Treatment Follow-Up (post-treatment 2).

The Gross Motor Function Measure (GMFM-88/66)

The GMFM-88/66 measures gross motor function in children with cerebral palsy. The -88 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); BA will score all -88 items and enter the score for each item in WebDCU™.

The BA will use the GAEM software (on the I-ACQUIRE computer) to calculate the GMFM-88/66 summary scores and enter those summary scores into WebDCU™. The GMFM-88/66 will be administered at Pre-Treatment, End of Treatment (post-treatment 1), and 6-Month Post-Treatment Follow-Up (post-treatment 2).

Structured Play Session

A structured play session will assess how well a child engages and explores toys with the upper extremities. There is an emphasis on bilateral use and how the child uses the more affected UE as an "assisting hand." The Assessment Center will use this session to score the mini-AHA to determine how the hemiparetic UE is used an "assisting hand" in bimanual activities, recognizing that children with hemiparesis are unlikely to use their hemiparetic UE as their dominant UE. Blinded assessors will administer the assessment according to standard procedures. The Structured Play Session will be completed at Pre-Treatment, End of Treatment (post-treatment 1), and 6-Month Post-Treatment Follow-Up (post-treatment 2).

The mini AHA will be scored centrally by the Assessment Center staff using the video. The structured play session may also be used to confirm mini-MACS level (see below) and score the EBS.

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. 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-III, Bayley-4, Peabody Scales of Motor Development-2, the QUEST, NIH Toolbox). The EBS requires that the child display each skill at least twice. Coding is completed by the Central Assessment Center staff based on the videotaped session that includes the full Bayley-4, the GMFM, the standardized play session including the Mini AHA, an encouraged snack break, the Infant Motor Activity Log (the I-MAL), and other parent-reported outcomes. This is scored centrally by the Assessment Center and entered into WebDCU™ for time points Pre-Treatment, End of Treatment (post-treatment 1), and 6-Month Post-Treatment Follow-Up (post-treatment 2).

The Gross Motor Function Classification System (GMFCS)

The GMFCS classifies the child's gross motor functioning in 5 functional levels. The BA can complete the classification for this system based on observation of the child throughout the pre-test assessment. This will be entered by the BA into WebDCU™ within 5 days of the Pre-Test Assessment. **The GMFCS will be completed only once, at the Pre-Treatment Assessment**.

The mini Manual Ability Classification System (mini-MACS).

The mini-MACS classifies how the child uses his/her hands while handling objects and starts at 12 months in 5 levels. The BA can complete the classification for this systems based on observation of the child throughout the pre-test assessment. For participants who have a pre-treatment assessment before 12 months of age, the mini-MACs will be completed at the first assessment visit where the child is 12 months or older. This will be entered by the BA into WebDCU™ within 5 days of the Pre-Test Assessment. **The mini-MACS will be completed only once, either at the Pre-Treatment Assessment or at the first assessment visit where the child is 12 months or older.**

Parent/Family Reported Outcome Measures

Overview:

The following completed measures are completed by the family and will be collected by the BA from the family: the Infant Motor Activity Log (I-MAL), the Perceived Stress Scale-14 (PSS-14), MacArthur-Bates Communicative Development Inventories (CDI), the Parent Report of Life and Other Stressors (PRLOS), the Parent Report of Therapy (PRT), and the Information Exchange-Parent. All parent reported measures will be entered into WebDCU™ by the Research Coordinator (or designee).

The Infant Motor Activity Log (IMAL)

The IMAL is 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. Both unilateral and bilateral tasks are included. Items from the IMAL will be used to score the EBS. **This is entered in to WebDCU™ by the RC or other site designee**. The IMAL will be collected at Pre-Treatment, End of Treatment (post-treatment 1), and 6-Month Post-Treatment Follow-Up (post-treatment 2).

MacArthur-Bates Communicative Development Inventories (CDI)

The CDI a standardized reliable tool to assess the child's communicative competence. Research Coordinators are responsible for ensuring that families have the correct version for their child, based on the child's age. The MacArthur Bates CDI Words and Gestures is designed for infants and toddlers 8 – 18 months. The MacArthur Bates CDI Word and Sentences is designed for toddlers 18 – 30 months of age. The MacArthur Bates Communicative Inventories –III is designed for toddlers 30 – 37 months. This is entered in to WebDCU™ by the RC or other site designee within 5 days of the assessment visit. The CDI will be collected at Pre-Treatment, End of Treatment (post-treatment 1), and 6-Month Post-Treatment Follow-Up (post-treatment 2).

The Perceived Stress Scale-14 (PSS-14)

The PSS is a standardized assessment of general stress. This is entered in to WebDCU™ by the RC or other site designee within five days of the assessment visit. The PSS will be collected at Pre-Treatment, End of Treatment (post-treatment 1), and 6-Month Post-Treatment Follow-Up (post-treatment 2).

The Parent Report of Life and Other Stressor (PRLOS)

The PRLOS is a study-specific measure of the extent to which life (work, finances, health, etc) and treatment affect perceptions of stress. This is entered in to WebDCU™ by the RC or other site designee within five days of the assessment visit. The PRLOS will be collected

at Pre-Treatment, End of Treatment (post-treatment 1), and 6-Month Post-treatment Follow-Up (post-treatment 2).

The Parent Report of Therapy (PRT)
The PRT is a study specific assessment of the therapies a child has participated in during the prior month. This is entered in to WebDCU™ by the RC or other site designee within five days of the assessment visit. The PRT will be collected at Pre-Treatment, End of Treatment (post-treatment 1), and 6-Month Post-Treatment Follow-Up (post-treatment 2).

Information Exchange-Parent (IE-P)
The IE-P is a report of the relationship between parent and therapist. This is entered in WebDCU™ by the RC or designee. The IE-P will be collected only the end of treatment assessment (post-treatment 1).

NOTE:
Information Exchange-Therapist
The treating therapist also will complete an Information Exchange-Therapist. This will be returned by the TT to the RC directly as part of the end of treatment assessment (post assessment 1).

d. Assessment Procedures

Behavioral Measures:

Video recorded Assessment Sessions.
The entire session should be video recorded. The video should be uploaded using the study provided laptop. Blinded assessors will upload videos and enter assessment data for the GMFCS, mini MACS, the GMFM, and the Bayley-4 into WebDCU™. Blinded assessors will upload the video for the Structured Play Session. The Assessment Center will score the mini-AHA using this video and the EBS from all tools and videos. In addition, BAs will answer questions in WebDCU™ about whether they may have become unblinded to the child's group assignment. If assessors observe that the unblinding may be on video, they will either: 1.) Submit the video with sound removed for that section or 2.) Inform the Assessment Center so that the unblinded staff can remove the audio prior to central scoring.

The assessment session with the BA and child includes the Bayley Scales of Infant Development-4 (Bayley-4), a structured play session that will be used to score the Mini-Assisting Hand Assessment (mini-AHA), the Gross Motor Function Measure (GMFM-88/66), and an encouraged snack break. Given the timing of the Bayley-4 release (scheduled for Sept 10, 2019), some children may be initially tested using the Bayley-III the assessment center will make scoring adjustments if this occurs). The **entire** session should be video recorded. **The video should be uploaded to Virginia Tech using the study provided laptop**. The Emerging Behaviors Scale (EBS) is also scored using all assessment videos, item-level responses, and surveys. Details about camera placement and video recordings are detailed in the BA self-study training materials. In brief, if the child is not mobile (no crawling or walking) or seated, the camera should be at an oblique angle in front of the child on the non-hemiparetic side. This means if the child is seated at a table and has a left hemiparesis, the camera should be placed on the right side approximately half way between the head and shoulder. If the child is supine, the camera should also be placed on the right side near the feet, approximately half way between the feet and the hip. When the child is mobile or the GMFM is tested the camera should be placed to view the entire child without obstruction of the view. The most common obstruction is the BA accidently placing themselves between the camera and child.

Confirmation of a good view and that camera is recording must be confirmed before the start of the assessment and checked regularly. Having a second person occasionally check the view is helpful.

Assessment sessions should be scheduled for 2 hours each on 2 consecutive days to allow for full administration of all tools. Snack, snuggle, and nap breaks are allowable. The assessments will be shorter for younger participants. If the entire assessment session is completed on the first day, the second day can be cancelled. Research staff should discuss the importance of completing the whole assessment with families and promote a family-friendly schedule. Assessments can be completed in the home, natural environment, clinic, or laboratory space.

Parent Measures:

Parent measures are to be provided to the family by the Research Coordinator or designee PRIOR to the assessment, with instructions to complete prior to the assessment and to bring the completed packet with them. Research Coordinators should ensure that there are extra copies on hand for each assessment, with subject ID, in case families do not bring the forms with them. RC should inform families that they can direct questions about completing the forms the RC.

Should families have questions about these measures, they can ask the RC or the BA, with one exception: **questions about the Parent Report of Therapy and the Parent Report of Life and Other Stressors should be directed only to the RC given the risk of unblinding**.

These measures should be returned to the BA by the family and the BA will return the packet of Parent/Family Reported Outcome Measures to the RC. Any incomplete information on the forms will require that the RC follow up with the family to gather the missing information and then the BA can deliver them to the RC for data entry into WebDCU™. This is entered in to WebDCU™ by the RC or other site designee**.**

e. Timeline for Data Entry:

BA and RC (or designee) will enter assessment data into WebDCU™ within 5 days of each assessment visit.

f. Training for Assessment tools:

BA will complete self-study modules on the GMFM, Bayley, parent surveys, and structured play session available to I-ACQUIRE blinded assessors on a shared drive. Depending on the previous experience of the BA with the assessment tools the self-study is anticipated to take 6-12 hours. The self-study materials contain videos, power point presentations, written instructions, diagrams, and practice videos.

Intra- and Inter-rater reliability will be measured using a combination of pre-recorded video assessments provided by the Assessment Core and shared with the BA; and an assessment done by the BA and a practice child at their site and shared with the Assessment Core. The assessment done by the BA is a child 8 – 36 mos of age (with hemiparesis preferred). Intra- and Inter-rater reliability are measured with ICCs. BAs with Kappa scores > .85 are considered study certified. The assessment core will monitor test administration accuracy and reliability yearly on 10 – 20% of the data collected. If drift is detected the assessment core will provide additional training, corrective action, and re-score assessments from the video.

O. PARTICIPANT RETENTION

a. Missing Data / Lost to Follow-Up (LTFU)

A participant will be considered LTFU 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 and reschedule the missed visit and counsel the parent on the importance of maintaining the assigned visit schedule and ascertain if the parent wishes to and/or should continue in the study.
- Before a participant is deemed LTFU, the investigator or designee will make every effort to regain contact with the parent of the participant (where possible, 3 telephone calls 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 LTFU.

b. Withdrawal of Consent

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.

A subject or their LAR may decide at any time during the study to no longer participate in the study. Every study subject has the right to withdraw voluntarily from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. Subjects wishing to revoke their authorization for the research use or disclosure of health information must do so in writing to the site PI as outlined in the ICD provided the subject at the time of consent. Written correspondence revoking consent should be retained in the study/subject file in a secure/confidential manner. The subject data collected prior to the time of withdrawal will remain as part of the study records.

P. CONCOMITANT MEDICATIONS

We will collect minimal medication information. Each enrolled child will see a neurologist who will complete the pediatric stroke outcome measure[32] collect the child's medical history, and record any medications that the enrolled child routinely takes. We have one medication exclusion criteria: that is, if a child received botulinum toxin in the 3 months prior to enrollment they are ineligible to enroll in the I-ACQUIRE study. Parents are instructed at time of providing parental permission that children are not to receive botulinum until after the 6-month post-treatment assessment (if their physician should recommend that).

Q. SAFETY REPORTING

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant that has received treatment and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of the treatment, whether or not considered related to that treatment. Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject.

For the purposes of this trial, all AEs will be collected from the time of randomization through end of study treatment. Only SAEs will be collected from the end of study treatment through the end of study.

A **Serious Adverse Event** (SAE) is defined as any untoward/undesirable 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 a 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).

Severity of Event:
The severity of all AEs 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.

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 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

Expectedness:
The **Independent Medical Safety Monitor (IMSM)** will be responsible for determining whether an SAE is **expected** or **unexpected**. An SAE will be 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.

Time Period and Frequency for Event Assessment and Follow-Up:
At each study visit, the investigator or designee will inquire about the occurrence of any adverse events since the last visit. Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, may meet the definition of an AE or SAE and should be reported accordingly.
The site investigator should report all AEs from the time of randomization to the end of study treatment and only SAEs from the end of study treatment to the end of study. All such events will be captured on the AE CRF and entered into WebDCU™. Information to be collected includes event description, date/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), date/time of resolution/stabilization of the event, a description of the event, relevant history, and concomitant medications/procedures. All AEs and SAEs will be followed for outcome information until the subject's participation in the study ends. The information in WebDCU™ should be updated as more information becomes available.

Serious Adverse Event Reporting:
Sites are required to submit the AE CRF in WebDCU™ within 24 hours of their awareness of an SAE. All SAEs will be followed until the end of the subject's study participation. All submitted SAEs will be reviewed by the medical safety monitor for his/her determination of relationship and expectedness. This information will be reported in the DSMB reports.

R. DATA AND SAFETY MONITORING RESPONSIBILITIES

Safety oversight is under the direction of the NINDS-appointed Data and Safety Monitoring Board (DSMB), composed of individuals with the appropriate expertise. Members of the DSMB are independent from the study conduct and free of conflict of interest, or measures will be in place to minimize perceived conflict of interest. The DSMB will meet regularly in person or by teleconference to assess safety and efficacy data. The DSMB provides its input to NINDS, NCC, NDMC and the protocol PIs for I-ACQUIRE.

S. PROTOCOL VIOLATIONS AND CORRECTIVE ACTION PLANS

Protocol violations must be assessed throughout each subject's participation in the study. Protocol violations that meet the definition of unanticipated events must be reported in the Unanticipated Event Report form in WebDCU™ for reporting to the CIRB. CRF data in WebDCU™ should be updated to reflect protocol violations, when applicable. Serious or repeated protocol violations will require the development of a Corrective Action/Preventative Action (CAPA) plan. Protocol violations that pertain to randomization, enrollment/eligibility and treatment/adherence will be reported to the CIRB as well as the DSMB.

Development of a CAPA plan may be initiated by the site study team/sponsor, CIRB, the NDMC, or the NCC. Potential triggers include protocol violations, data quality problems, or systematic problems identified by study teams or monitors. A CAPA plan includes a corrective and preventative component. The corrective action describes what action will be taken to correct the deficiency (e.g., re-consenting a subject who was consented with an incorrect form, reporting recurrent protocol deviations to the IRB). The preventative action describes what will be done to prevent the problem from recurring, or, in the case of identified potential problems, how to prevent the problem from occurring. CAPA plans should address the root cause of the problem with the goal of eliminating the root cause to prevent the problem from occurring again. Short-term solutions are not preventative actions. Initiation of a CAPA plan will require that appropriate data is captured to ensure progress and elimination of the underlying problem. The type of data to be collected will vary depending on the identified deficiency. CAPA plans must be reviewed and approved by the appropriate site study team members, CIRB, NCC, NDMC or protocol PIs based on the nature of the corrective action needed. Once a CAPA plan has been approved and enacted, data must be collected as agreed upon in the plan until the study team demonstrates that the issue has been resolved. The criteria for determining this point will vary depending upon the frequency and severity of the issue.

T. DATA COLLECTION AND STUDY FORMS

The most recent versions of the I-ACQUIRE CRFs (Study Book) and Data Collection Guidelines can be accessed from the WebDCU™ (https://webdcu.musc.edu/login.asp) via the I-ACQUIRE project icon under [Toolbox] → [Project Documents].

U. DATA MANAGEMENT

The data management team at the NDMC is involved in a wide scope of tasks to ensure timely and accurate collection and processing of data. Prior to the study initiation, the data management team digitizes the study protocol, develops the case report forms, conducts database end user validation, and provides user training. During the trial operation period, data managers and monitors oversee the quality and efficiency of trial conduct and clinical data collection across all clinical sites, and provide instructions and technical support for WebDCU™ users.

The NDMC complies with regulatory requirements and guidelines, including Code of Federal Regulations Title 21, HIPAA, ICH guidelines, and a complete set of internal SOPs for trial management. A personal user account and password will be required to logon to the study website and users will be granted data access based on their roles in the study as documented on the electronic delegation of authority log. Passwords will be encrypted in the database. All user logon attempts will be tracked. Additionally, after successfully logging on to the study website, all user navigation activities will be tracked by the system. If the user remains idle for a pre-specified amount of time, they will automatically be logged off of the system. Refer to StrokeNet WebDCU™ User Manual located in WebDCU™ under [ToolBox]→[Project Documents] for further details.

V. QUALITY ASSURANCE AND QUALITY CONTROL PROCEDURES

Data quality assurance processes at the NDMC include:

- Logic and rule checks built into the study database;
- Real-time, central monitoring by the data managers and statistical programmers at the NDMC; and
- Remote and on-site risk-based source verification monitoring by clinical research associates and data managers at the NDMC.

W. SITE MONITORING

The purpose of site data monitoring is to ensure that:

- The rights and well-being of human subjects are protected
- Trial data are accurate, complete, and verifiable from source documents
- The trial is conducted in compliance with the current approved protocol, with GCP, and applicable regulatory requirements

Scope of Monitoring

On-site monitoring: The monitor will verify specified data entered into the WebDCU™ study specific database against source documents. Source documents are original documents, data, and records. Monitors will query any detected inaccuracies between the source documents and the WebDCU™ database, including the omission of data.

Remote monitoring: Source document verification may be performed remotely by reviewing source documents that have been uploaded into WebDCU™, sent securely to the monitor, or via remote access to electronic medical records (EMR). For I-ACQUIRE, signed informed consent forms will be uploaded into WebDCU™ and remotely verified by authorized NDMC study team members.

Central monitoring: National Data Management Center (NDMC) staff members will conduct central monitoring using web-based data validation rules, DM review of entered data, statistical analysis, and on-going review of site metrics.

Nature and Extent of On-site Data Monitoring

NDMC, in conjunction with the study team, is responsible for determining the number of anticipated on-site monitoring visits, based on the complexity of the study design, its phase of development, previous site experience and compliance with study requirements, rate of subject enrollment, and any other unique attributes of the study and the site. The intensity of site monitoring will be variable across sites. The NDMC is responsible for determining the scheduling of site monitoring visits, routine, for-cause, and closeout visits based upon risks, as well as determining if the site visit may be conducted remotely. Remote site monitoring visits are conducted in the same fashion as on-site visits, except that certain activities may be omitted, such as investigational product accountability. The NDMC relies heavily on central monitoring activities to determine when a site monitoring visit is required and to target the work to be performed on-site, in order of priority. The NDMC typically skews site monitoring visits towards the earlier stages of a study so that mistakes are quickly identified, corrected, and alleviated for future enrollments. Upon request from NDMC staff, the site monitor will work with the site to schedule the visit. The objectives of a site monitoring visit will be defined and prioritized by the NDMC prior to the monitoring visit. All work performed, issues identified, and action items by the monitor will be captured via the WebDCU™ monitoring module. It is expected that each study site will be visited after a small number of subjects are enrolled. At the completion of a site visit, the Monitoring Report will be available for review and sign-off by the site PI via WebDCU™.

X. STUDY COMPLETION AND CLOSEOUT PROCECURES

At the completion of the trial the site staff will need to review the StrokeNet GCP "Onsite Subject Study File SOP" and "Onsite Regulatory Document Checklist SOP". These documents will guide the site regarding the expectations for necessary documentation and retention requirements of trial related information. Access to cited NIH StrokeNet Administrative SOPs can be obtained via the following link: http://www.nihstrokenet.org/documents. These documents are in harmony with the Protocol Trial expectations and the StrokeNet Administrative (ADM) and Good Clinical Practice (GCP) Policies. In addition to these noted SOPs, the CPS may also be required to follow specific local requirements. When payment for the final subject follow-up is completed, the financial components of the CTA will have been met.

A Site Closeout Visit concludes the study at an individual site. A site may be closed for many reasons which include study completion, early discontinuation of the study by the sponsor, or investigator request to discontinue the study at their site. The monitor may conduct the visit on- site or remotely, as determined by the NDMC, study team/sponsor and PM, based on the number of subject enrollments, amount and nature of outstanding items to be monitored, and whether the monitor's direct access to the subjects' electronic medical record (EMR) has been permitted by the institution.

During a Site Closeout Visit, the monitor should complete the items required for a routine monitoring visit. In addition, the monitor should ensure that the items listed in the "Site Requirements" and "Site Monitor Requirements" sections of the site Close-out Checklist are complete. Once the required sections are complete, the Close-Out Checklist will be uploaded into WebDCU™.

Y. POLICIES

1. Publications Policy

Publication guidelines will be established by the StrokeNet Steering Committee (SC) and the I-ACQUIRE Trial Publications Committee. Investigators are encouraged to publish and to publicly release and disseminate results, data and other products of the StrokeNet clinical trials as determined in collaboration with the Steering Committee. All publications must acknowledge the contributions of NINDS and the NIH StrokeNet. All affiliated study personnel are required to align with these procedures as outlined in the StrokeNet Publications Committee and Policy SOP Number: ADM 03

1.2 Data Sharing

Because of the extensive effort that went into collecting data by investigators and study participants, it is important that datasets from completed studies be available for further research so that the full potential of the datasets is maximized. NDMC will submit to NINDS Office of Clinical Research a complete, cleaned, and de-identified dataset and any supporting documentation (including but not limited to the study protocol, statistical analysis plan (SAP), and data dictionary) required for the analysis of the data within one year of the primary publication or within 18 months of the last study visit of the last subject, whichever occurs first. For more information, see the NIH guidelines on sharing research data (http://grants.nih.gov/grants/policy/data_sharing/).

Specific data sharing policies will be developed in accordance with NINDS policy and NIH Guidelines. At the conclusion of each trial, the data will be put in a form suitably formatted for deposit in a national archive. The data will be made publicly available as determined by the SC with NINDS approval.

Z. MOP MAINTENANCE

The responsibility for maintenance of the MOP belongs to the PPI or designee with assistance from the NCC and NDMC, along with any necessary protocol specific training modules and study document templates. Each version of the MOP will display the version number and date on the title page, as well as to what version and date of the protocol the MOP corresponds. Any updates to the MOP will be announced and made available via WebDCU™ and the I-ACQUIRE Trial Website located via the following link: https://nihstrokenet.org/i-acquire/resources.

Appendix 1

I-ACQUIRE Payment Schedule

1) Trial specific per-subject budgets are defined as research related costs with payment amounts that will be non-negotiable.
2) Payments will be made at least quarterly, but not more frequently than once monthly.
3) All payments are contingent on receipt of eCRFs at the relevant study visits.
4) All data for study visits are entered into WebDCU™.
5) All queries are resolved for the subject.
6) Subject payment reads "Ready" in WebDCU™.
7) NCC, NDMC and the I-ACQUIRE trial PIs retain the right to review and question data identified below for completeness.
8) Prior to closeout NCC will verify final payment.

SITE PAYMENTS

Non-refundable start-up payments will be made as follows to each participating RCC or Satellite:

- **Payment in the amount of $1,500.00** (inclusive of IRB fees, as applicable) upon full execution of the FDP Fixed Price Research Clinical Trial Agreement; and CIRB approval for Study Start-Up

- **Payment in the amount of $1,800.00 per person x 2 people per site (Year 1) for a total of $3,600.00** following travel to and attendance at the Investigator Meeting in Year 1

- **Payment in the amount of $11,280.00** upon satisfactory completion of all activities for Training/Travel for Treating Therapist, Training for Blinded Assessors, and released to enroll. Payment inclusive of:
    - Training for Treating Therapists: $1,760.00 per treating therapist x 2 therapist per site = $3,520.00
    - Travel: $2,230.00 per therapist x 2 therapist per site = $4,460.00
    - Training for Blinded Assessors: $1,650.00 per Blinded Assessor x 2 assessors per site = $3,300.00

- **Payment in the amount of $1,800.00 per person x 2 people per site (Year 4) for a total of $3,600.00** following travel to and attendance at the Investigator Meeting in Year 4

Phase 1: Payments will be divided into six (6) incremental payments per subject enrolled for Phase I

Payment 1: Issued after Local Site Screen, Enroll, Consent, and Randomization - $1,227.50 + ($515.55) = $1,743.00

Payment inclusive of: Initial Central Phone Screen, Local Site Screening & Recruitment & bi-monthly subject telephone contacts,
Inclusion/Exclusion, Consent, Enrollment, Randomization & Assessment scheduling, Local Medical Record Collection & Review,
Pediatric MD Neurologic Exam, Clinical Imaging Processing Fee, and Family Travel & Expenses & Remuneration

Payment 2: Issued after Baseline Assessment - $640.00 + ($268.80) = $909.00

Payment inclusive of: Consent, Enrollment, Randomization & Assessment scheduling, Blinded Functional Assessments and data
entry, Parent rating and data entry, and Family Travel & Expenses & Remuneration

Payment 3: **Issued after Treatment Weeks 1 & 2 (Treatment Days 1-10):**

- **6-hour I-ACQUIRE Treatment = $4,997.50 + ($2,098.95) = $7,096.00**
- **3- hour I-ACQUIRE Treatment = $3,265.00 + ($1,371.30) = $4,636.00**
- **Usual & Customary Treatment (U&CT) = No payment**

Payment inclusive of: Consent, Enrollment, Randomization & Assessment scheduling, 6-hour or 3- hour I-ACQUIRE Treatment Implementation Plan

Payment 4: **Issued after Treatment Weeks 3 & 4 (Treatment Days 11-20):**

- **6-hour I-ACQUIRE Treatment = $4,895.00 + ($2,055.90) = $6,951.00**
- **3-hour I-ACQUIRE Treatment = $3,162.50 + ($1,328.25) = $4,491.00**
- **Usual & Customary Treatment (U&CT) = No payment**

Payment inclusive of: 6-hour or 3- hour I-ACQUIRE Treatment Implementation Plan

Payment 5: **Issued after Post-Treatment Assessment #1 - $640.00 + ($268.80) = $909.00**

Payment inclusive of: Consent, Enrollment, Randomization & Assessment scheduling, Blinded Functional Assessments and data entry, Parent rating and data entry, and Family Travel & Expenses & Remuneration

Payment 6: **Issued after Post-Treatment Assessment #2 at 6 months - - $640.00 + ($268.80) = $909.00**

Payment inclusive of: Consent, Enrollment, Randomization & Assessment scheduling, Blinded Functional Assessments and data entry, Parent rating and data entry, and Family Travel & Expenses & Remuneration

Phase 2: Payments will be divided into four (4) incremental payments per subject enrolled in Phase 2

Indirect costs (42% StrokeNet F&A) shown in parentheses. Each payment will be inclusive of the 42% StrokeNet F&A where allowed.

Payment 1: **Issued after Consent & Randomization and Treatment Weeks 1 & 2:**

- **6-hour I-ACQUIRE Treatment = $5,035.00 + ($2,114.70) = $7,150.00**
- **3-hour I-ACQUIRE Treatment = $3,302.50 + ($1,387.05) = $4,690.00**

Payment inclusive of: Consent, Enrollment, Randomization & Assessment scheduling and 6-hour or 3- hour I-ACQUIRE Treatment Implementation Plan

Payment 2: **Issued after Treatment Weeks 3 & 4:**

- **6-hour I-ACQUIRE Treatment = $4,895.00 + ($2,055.90) = $6,951.00**
- **3-hour I-ACQUIRE Treatment = $3,162.50 + ($1,328.25) = $4,491.00**

Payment inclusive of: 6-hour or 3- hour I-ACQUIRE Treatment Implementation Plan

Payment 3: **Issued after Post-Treatment Assessment #1 - $604.00 + ($253.68) = $858.00**

Payment inclusive of: Blinded Functional Assessments and data entry, Parent rating and data entry, Family Travel & Expenses & Remuneration

Payment 4: **Issued after Post-Treatment Assessment #2 at 6 months - $641.50 + ($269.43) = $911.00**

Payment inclusive of: Consent, Enrollment, Randomization & Assessment scheduling, Blinded Functional Assessments and data entry, Parent rating and data entry, and Family Travel & Expenses & Remuneration

Schedule of Events – Phase 1

SOE Recruitment, Assessment & Treatment Phase 1 (N=240)	Local Site Screen, Enroll, Consent & Randomization (Payment #1, N=240)	Baseline Assessment (Payment #2, N=240)	Treatment Weeks 1 & 2 (Payment #3, N=160 only)	Treatment Weeks 3 & 4 (Payment #4, N=160 only)	Post-Treatment Assessment #1 (Payment #5, N=240)	Post-Treatment Assessment #2 at 6 months (Payment #6, N=240)	Total 6-hour I-ACQUIRE Treatment (Direct + Indirect)	Total 3-hour I-ACQUIRE Treatment (Direct + Indirect)	Total U&CT (Direct + Indirect)
Initial Central Phone Screen	X								
Local Site Screening and Recruitment and bi-monthly subject telephone contacts	X								
Inclusion/Exclusion	X								
Consent, Enrollment and Randomization and Assessment Scheduling	X	X	X		X	X			
Local Medical Record Collection and Review	X								
Pediatric MD Neurologic Exam	X								
Blinded Functional Assessments and data entry		X			X	X			
Parent Rating and data entry		X			X	X			
Clinical Imaging Processing Fee	X								
Family Travel & Expenses & Remuneration	X	X			X	X			
U & CT treatment for 4 weeks									
6-hour I-ACQUIRE Treatment Implementation including plan, casting and supplies, daily treatment log, adverse event assessment, parent home activities, and post-treatment plan.			X	X					
3-hour I-ACQUIRE Treatment Implementation including plan, casting and supplies, daily treatment log, adverse event assessment, parent home activities, and post-treatment plan.			X	X					
	Payment 1	Payment 2	Payment 3	Payment 4	Payment 5	Payment 6			
Direct Costs	$1,227.50	$640.00	n/a	n/s	$640.00	$640.00			
Direct Costs for 6-hour CIMT Treatment	n/a	n/a	$4,997.50	$4,895.00	n/a	n/a			
Indirect Costs	n/a	n/a	$2,098.95	$2,055.90	n/a	n/a			
Subtotals	n/a	n/a	$7,096.00	$6,951.00	n/a	n/a	$18,517.00	$13,597.00	$4,470.00
Direct Costs for 3-Hour CIMT Treatment	n/a	n/a	$3,265.00	$3,162.50	n/a	n/a			
Indirect Costs	$515.55	$268.80	$1,371.30	$1,328.25	$268.80	$268.80			
Subtotals	$1,743.00	$909.00	$4,636.00	$4,491.00	$909.00	$909.00			

	6 hr	3 hr	U &CT
Total Direct	$13,040.00	$9,575.00	$3,147.50
Subject to F&A	$13,040.00	$9,575.00	$3,147.50
StrokeNet 42%	$5,476.80	$4,021.50	$1,321.95
Total per subject reimbursed to sites	$18,517.00	$13,597.00	$4,470.00

Schedule of Events – Phase 2

SOE Recruitment, Assessment & Treatment Phase 2 (N=80)	*Consent & Randomization (Payment #1, N=80)*	Treatment Weeks 1 & 2 (Payment #1, N=80)	Treatment Weeks 3 & 4 (Payment #2, N=80)	Post-Treatment Assessment #1 (Payment #3, N=80)	Post-Treatment Assessment #2 at 6 months (Payment #4, N=80)	Total 6-hour I-ACQUIRE Treatment (Direct + Indirect)	Total 3-hour I-ACQUIRE Treatment (Direct + Indirect)
Consent, Enrollment and Randomization and Assessment Scheduling	X				X		
Blinded Functional Assessments and data entry				X	X		
Parent Rating and data entry				X	X		
Family Travel & Expenses & Remuneration				X	X		
6-hour I-ACQUIRE Treatment Implementation including plan, casting and supplies, daily treatment log, adverse event assessment, parent home activities, and post-treatment plan.		X	X				
3-hour I-ACQUIRE Treatment Implementation including plan, casting and supplies, daily treatment log, adverse event assessment, parent home activities, and post-treatment plan.		X	X				
	Payment 1		Payment 2	Payment 3	Payment 4		
Direct Costs	n/a		n/a	$604.00	$641.50		
Direct Costs for 6-hour CIMT Treatment	$5,035.00		$4,895.00	n/a	n/a		
Indirect Costs	$2,114.70		$2,055.90	n/a	n/a		
Subtotals	$7,150.00		$6,951.00	n/a	n/a	$15,870.00	$10,950.00
Direct Costs for 3-Hour CIMT Treatment	$3,302.50		$3,162.50	n/a	n/a		
Indirect Costs	$1,387.05		$1,328.25	$253.68	$269.43		
Subtotals	$4,690.00		$4,491.00	$858.00	$911.00		

	6 hour	3 hour
Total Direct	$11,175.50	$7,710.50
Subject to F&A	$11,175.50	$7,710.50
StrokeNet 42%	$4,693.71	$3,238.41
Total per subject reimbursed to sites	$15,870.00	$10,950.00

SUMMARY OF THE TOTAL AMOUNT PAID PER SUBJECT IN EACH OF THE 3 TREATMENT GROUPS IN PHASE 1 AND THE DELAYED TREATMENT GROUP IN PHASE 2 (THE U&CT GROUP in phase 1)

For planning purposes, the local sites may want to know how much is paid for subjects assigned to the 3 treatment groups in Phase 1, and then the additional payments for the subjects whose parents choose for them to receive the delayed treatment in Phase 2. The computations shown below are a simple sum of the payments according to the Schedule of Events (SOE) for each phase, if the subject particiaptes in all activities as planned (see the tables above). It is highly likely there will be some subjects who may miss one or more of the "events," such as missing one of the assessments, so the total amount reimbursed for that particular subject would be reduced accordingly. The amounts below are inclusive of the standard 42% StrokeNet F&A that sites receive. (Note: the F&A as allowed will be included in the reimbursements issued along the way, and do not need to wait until the subejct has completed all trial actviities.)

For planning purposes, each site can make a reasonable assumption that about one-third of the subjects they enroll will be assigend to each of the 3 treatment groups, although a slight variation could be possible. In a given year, for example, the groups may not be perfectly balanced since the randomziation is done centrally (at MUSC) and thus in some years of enrollment and treatment, a site may have a few more (or less) subjects in one (or more) of the 3 treatment groups.

Each total on a per subject basis will be inclusive of the 42% StrokeNet F&A where allowed. The total F&A is shown in parentheses below.

- **Phase I**
    - **6-hour I-ACQUIRE Treatment = $13,040.00 + ($5,476.80) = $18,517.00**
    - **3-hour I-ACQUIRE Treatment = $9,575.00 + ($4,021.50) = $13,597.00**
    - **U&CT = $3,147.50 + ($1,321.95) = $4,470.00**
- **Phase II (for U&CT subjects whose parents re-enroll to have their child receive delayed I-ACQUIRE treatment and assessments.)**
    - **6-hour I-ACQUIRE Treatment = $11,175.50 + ($4,693.71) = $15,870.00**
    - **3-hour I-ACQUIRE Treatment = $7,710.50 + ($3,238.41) = $10,950.00**

Appendix 2

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Appendix 3

I-ACQUIRE Abbreviations/Acronyms

A	
ADM	Administrative
AE	Adverse Events
B	
BA	Blinded Assessor
C	
CAPA	Corrective Action/Preventative Action
CDI	Communicative Development Inventories
CI	Confidence Intervals
CIMT	Constraint-Induced Movement Therapy
CIRB	Central Institutional Review Board
CONSORT	Consolidated Standards of Reporting Trials
CPS	Clinical Performing Site
CITI	Collaborative Institutional Training Initiative
CR	Continuing Review
CRF	Case Report Form
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trials Management System
D	
DOA	Delegation of Authority
DSMB	Data and Safety Monitoring Board
E	
EBS	Emerging Behaviors Scale
EC	Executive Committee
eCRF	Electronic Case Report Forms
EMR	Electronic Medical Record
F	
F&A	Financial & Administrative
FAQ	Frequently Asked Questions
fCOI	Financial Conflict of Interest
FDA	Federal Drug Administration
FWA	Federalwide Assurance
G	
GCP	Good Clinical Practice
GMFM-88/66	Gross Motor Function Measure
GMFCS	Gross Motor Function Classification System

H	
HIPPA	Health Insurance Portability and Accountability Act
HRPP	Human Research Protection Program
HSP	Human Subjects Protection
I	
IC	Informed Consent
ICD	Informed Consent Document
ICH	International Council for Harmonisation
IE-P	Information Exchange-Parent
I-MAL	Infant Motor Activity Log
IMSM	Independent Medical Safety Monitor
IRB	Institutional Review Board
ISC	International Stroke Conference
J	
K	
L	
LAR	Legally Authorized Representative
LTFU	Lost to Follow-up
LPI	Lead Principal Investigator
M	
mini-AHA	Mini-Assisting Hand Assessment
mini-MACS	mini-Manual Abilities Classification Scale
MOP	Manual of Procedures
MPI	Multiple Principal Investigators
MR3	Movement, Reinforcement, Repetition, and Refinement
MRI	Magnetic Resonance Imaging
MUSC	Medical University of South Carolina
N	
NCC	National Coordinating Center
NCI	National Cancer Institute
NDMC	National Data Management Center
NIH	National Institute of Health
NINDS	National Institute of Neurological Disorders and Stroke
O	
OP	Occupational Therapist
OSU	Ohio State University
P	
PAS	Perinatal Arterial Stroke

PHI	Protected Health Information
PI	Principal Investigator
PM	Project Manager
PPI	Protocol Principal Investigator
PRLOS	Parent Report of Life and Other Stressors
PRT	Parent Report of Therapy
PSC	Primary Study Coordinator
PSOM	Pediatric Stroke Outcome Measure
PSS-14	Perceived Stress Scale
PT	Physical Therapist
Q	
R	
RA	Reliance Agreement
RC	Research Coordinator
RCC	Regional Coordinating Centers
RCT	Randomized Controlled Trial
S	
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SC	Steering Committee
SC	Study Coordinator
SMV	Site Monitoring Visit
SOA	Schedule of Activity
SOC	Standard of Care
SOP	Standard Operating Procedure
SubI	Sub Investigator
T	
TT	Treating Therapist
U	
UC	University of Cincinnati
U&CT	Usual & Customary Treatment
UE	Upper Extremity
V	
VT	Virginia Tech
W	
X	
Y	
Z	