17 March 2020

**COVID-19 Guidelines for The I-ACQUIRE Study**

**STOP ALL IN-PERSON ACTIVITIES RELATED TO THE I-ACQUIRE STUDY IMMEDIATELY.**

**PLEASE READ FULL DETAILS BELOW.**

**SEND EMAIL QUERIES to Sharon Ramey (****slramey@vt.edu****) or Warren Lo (warren.lo@nationwidechildrens.org).**

**YOU HAVE PERMISSION TO SHARE THIS WITH ALL WHO ARE INTERESTED IN OUR TRIAL.**

Preface. On 10 March 2020, the I-ACQUIRE Study team sent a communication via email to all I-ACQUIRE Clinical Site PIs/CoIs and Study Coordinators about our concern for the health and well-being of all study participants and I-ACQUIRE staff. This is a follow-up with specific details about how to handle disruptions based on when they occur in the cycle for a given child and family.

**First and foremost, safety and health are the most important considerations.** The I-ACQUIRE Study recommendations are informed by the evolving actions taken by local, government, and health experts and entities. This includes CDC, NIH, your local and state governments and agencies, and WHO, among others. Yesterday, NIH issued additional guidelines for clinical trials, and last week StrokeNet issued guidelines. In the past week, many of our universities and local governments imposed restrictions on work-related and personal activities. Because The I-ACQUIRE Study has 12 clinical sites and 6 central infra-structure sites there are many independent factors impacting of our activities. (Officially, the PRIME recipient for our trial is Virginia Tech, where in-person research activities for studies such as I-ACQUIRE have been “paused” until further notice.)

**Ongoing re-evaluation of recommendations**. Our I-ACQUIRE Executive Steering Committee will meet virtually at least weekly to review these guidelines and emerging new information. We will issue updates when changes occur.

**MAJOR RECOMMENDATION:** **AS OF 16 MARCH 2020, ALL IN-PERSON HUMAN SUBJECTS ACTIVITIES AND ALL STUDY-RELATED IN-PERSON MEETINGS WILL BE CANCELLED**. *Our best estimation at this time is that these cancellations will be in effect for at least 8 weeks.*

We anticipate there will be further changes and new information as the COVID-19 situation evolves. Accordingly, the specific recommendations below are informed by our current knowledge. Our primary objective is to protect the health and safety of all connected to The I-ACQUIRE Study. Secondary to that, we seek to adhere to the original I-ACQUIRE Protocol to the greatest extent possible. We try to provide our rationale for decisions that may lead to modifications.

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

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| TIME WHEN ACTIVITIES ARE DISPRUPTED | RE-SCHEDULING PARAMETERS AND IMPACT |
| When a new family contacts us seeking to be consented and enrolled (randomized) | Wait to consent and enroll after trial resumes. IMPACT: This will delay overall recruitment and trial progress, but does not change any aspect of the study protocol. Note: speaking with parents whose child may be eligible and who seek to find out more about the study is acceptable. Let them know that you will get back as soon as the trial becomes active again. *NOTE: We are likely to allow recruiting children who currently (i.e., as of today’s date) are under 24 months old but would “age out” by the time they would be enrolled and/or treated to be in the trial – however, this decision is not yet finalized and approved.*  |
| Pre-treatment (Baseline) through Casting and Day 1 of Treatment | Do not proceed. Re-schedule when trial resumes. IMPACT: Some children may be older than the original designation of 24 months when their treatment begins. If need be, we can consider this age variable in post hoc data analyses.  |
| During the 4 weeks of I-ACQUIRE Treatment (Tx) but prior to Day 17 | Stop Tx immediately. Re-schedule when the trial resumes. IMPACT: #1. For a child who has completed 10 or more days, the child would meet the original study exclusion criterion of having had a prior high-dose CIMT treatment. Despite this protocol deviation, we will offer the fully planned I-ACQUIRE treatment when the trial becomes active again. (In other words, we will have a waiver of this exclusion criterion.) We will be able to look at this post hoc when we conduct data analyses. #2. The child can be re-scheduled when the trial resumes, even if the child is older than 24 months. *The re-scheduling will necessitate collecting a new pre-treatment (baseline) assessment as well as implementing the full I-ACQUIRE treatment. (Offering just the “missed” days would not be considered acceptable since the theory guiding the I-ACQUIRE treatment assumes that the high-intensity and high-density of treatment – involving shaping, massed practice, and extension of new skills - is a “package” that produces permanent changes in the child’s voluntary control of the hemiparetic upper extremity collectively. Having a long break in the 4 weeks of treatment would not be considered equivalent to the treatment package being tested in this trial.* **#3.** We anticipate that parents who already have been providing the home component of the I-ACQUIRE treatment will, understandably and ethically, continue to implement their own best version of being supportive of their child’s continued positive development. We should not instruct parents to “stop” this – encase we do not think it could be harmful, nor do we think the coronavirus risk would be affected by this. **#4.** Almost certainly, the disruption will extend to the Post-Treatment 1 assessment. See below about how this will be handled. (In other words, most children will have both Treatment and Assessment disrupted and guidelines for each will be followed, if feasible.) |
| Between Day 17 and Day 20 of I-ACQUIRE treatment.  | Stop Tx. At this particular time, the child will have qualified for receiving what was a priori defined as a sufficiently “full dose” of the treatment. However, we realize that Days 17 – 20 are distinctive because: i) we remove the cast; ii) we concentrate our focus on promoting bilateral activities – during formal therapy session and during parent-enacted home treatment; and iii) at the end, parents and the therapist finalize a post-treatment plan. For children and families who have their study participation disrupted at this timepoint, we propose working distally with the parents to provide bilateral shaping and activities and to develop the Post-treatment plan. We propose documenting these in the Web-DCU system using the Daily Log format we already have. The child and family will not require a new complete (or partial) treatment. IMPACT: #1. Additional time will be needed for The I-ACQUIRE Study central team at the Virginia Tech Treatment Implementation center to develop individualized and online modules for Days 17 – 20. #2. The post-treatment assessment 1 likely will not be conducted. (See below for how this will be handled.) |
| During Usual and Customary treatment (UCT), from start to end of the 4 week period | For children in the UCT group, the local study coordinator or a team member needs to be in contact with a family to determine if there are disruptions in the child’s receipt of usual therapy. Examples – a clinic has closed, the family is not leaving home, early interventionists who treat the child at home have been suspended from work. Note: we will not be advising parents about whether to continue or to stop the UCT that they arrange and for which they are responsible. Any disruption to the child’s UCT will result in the need to re-schedule when the trail resumes. As above, this will necessitate scheduling a new pre-treatment (baseline) assessment as well as the treatment month. Also, a child may be over 24 months old (as above) and this is okay. Finally, it is likely a disrupted UCT period will be associated with a disruption to the Post-treatment Assessment 1 (see below). |
| At Post-treatment Assessment 1 | STOP. This can be re-scheduled when the trial resumes. IMPACT: At this time, we are recommending allowing a protocol deviation for this to extend to 3.49 months after treatment ends (rather than the current recommendation of 2 weeks). We may need to re-consider this proposed endpoint for this assessment.  |
| At Post-treatment Assessment 2 (6 months later) | STOP. Re-schedule when trial resumes. IMPACT: Current protocol allows up to 2 months delay. We hope that this will be adequate for most disruptions. However, we are not certain. We will re-consider whether we will permit obtaining this assessment even later than 8 months post-treatment and notify sites if we propose extending this time window.  |
| For Phase 2, UCT families only: Pre-treatment up to day 1 I-ACQUIRE  | DO NOT PROCEED. DO NOT RE-CONSENT UNTIL THE STUDY RESUMES. The okay to re-consent and re-schedule when the trial resumes. All of the above guidelines are the same for the crossover children. If treatment is re-scheduled after the family has re-consented but before Treatment has started, then the child will need to have a new pre-treatment assessment 1 (baseline). (Remember that for the UCT children their 6-month assessment serves as their new baseline for the crossover treatment phase.).  |
| During the 4 weeks of TreatmentBetween Day 17 and Day 20 of Treatment | See above |
| At Post-treatment Assessment 1 | See above |
| At Post-treatment 2 Assessment (6 months later) | See above |

**Implications for local sites in terms of keeping staff and covering expenses.** NIH realizes, as do we, that there will be cost implications of the COVID-19 disruptions to clinical trials. Currently, NIH states these will addressed on a per trial basis and require documentation. Covering these additional costs is to be handled as a supplement to the original award.

We plan to start delineating the full projected types of cost implications. We are deeply sorry for the trouble and fiscal and psychological burden this places on everyone – and most especially the frontline research team members and the families themselves. We are seeking permission to use study funds to cover unexpected COVID-19 documented travel-related costs for families or for staff. We will communicate with you about this as soon as we have pertinent information to share.

**Disruption to data coding and entry.** Due to multiple issues about security and protection of privacy and anonymity, we anticipate there will be delays in some aspects of the centralized coding and the local site and centralized entry of data into Web-DCU. Also, we anticipate that responses to queries from the NDMC staff at MUSC could be delayed. Please store all raw data in the same safe, secure places noted in our CIRB APPROVED Study Protocol. We will be allowed to use these data that were collected according to study protocol and accept them at a later time. Some data entry may be acceptable and ongoing.

Effective now, the WebDCU system for our trial will have central restrictions on randomization and will flag any new data collected after this date (which is prohibited if the data involve in-person contact to obtain).

**Staying in contact electronically and by phone with enrolled families.** All local sites are encouraged to stay in contact with families in anticipation that the trial will resume. When in doubt about any situation related to an enrolled family, please contact the I-ACQUIRE Co-PIs, Sharon Ramey and/or Warren Lo – who will pass on queries to others on our team as needed. Remember to protect the anonymity and privacy of participating children and families, as always.

**Big thank you! We are so grateful to have you as our colleagues. We appreciate your cooperation. And as always, we welcome your suggestions and ideas about ways to improve our plans to handle this unanticipated and serious Pandemic**.

Finally, we end this communication with what we stated at the top: Things are rapidly changing; new information and guidelines cannot be fully or accurately specified at this time; we are doing our best; and we will stay in close communication with you.