Validation of **E**arly Prognostic Data for **R**ecovery Outcomes after Stroke for **F**uture, Higher **Y**ield Trials:
A Biomarker Validation Study

Virtual Investigator Meeting Agenda

1. **Introductions & Goals** (Steve Cramer & Cathy Stinear)
2. **Study Updates & Protocol** (Pooja Khatri)
3. **Behavioral Measures** (Steve Cramer)
4. **TMS** (Cathy Stinear)
5. **Imaging** (Brady Williamson)
6. **Safety Reporting** (Lisa Mundo & Kalli Beasley)
7. **Informed Consent Overview** (April Williams)
8. **Q & A/Discussion** (All)
9. **Closing Remarks** (All)

Meeting Goals

- Provide study updates
- Review the protocol
- Review start up procedures
- Answer your questions

Walk you through how to enroll

Get you set up for release to enroll in June!

We will fine-tune the MOPP based on your feedback and insights

Sites should complete their independent virtual trainings by end of May 2022

VERIFY Leadership Team

Principal Investigators:

Pooja Khatri, MD, MSc
Professor of Neurology
University of Cincinnati

Steven Cramer, MD, MMSc
Professor of Neurology
University of California, Los Angeles

Cathy Stinear, PhD
Professor of Medicine
University of Auckland, New Zealand

Achala Vagal, MD, MS
Professor of Radiology
University of Cincinnati

Primary Study Statisticians at Medical University of South Carolina:

Lydia Foster, MS
Sharon Yeatts PhD

Project Manager:

K. Lisa Mundo, MA
University of Cincinnati

VERIFY Leadership Team, Continued

NIH StrokeNet National Coordinating Center (NCC) at University of Cincinnati

Joseph Broderick, MD
NCC PI for VERIFY
Professor of Neurology
University of Cincinnati

Laura Benken, MBA, CCRP
NCC Administrative Co-Director

Kalli Beasley, MPH
NCC Project Manager

NIH StrokeNet National Data Management Center (NDMC) at Medical University of South Carolina

Catherine Dillon, MS
NDMC PI for VERIFY

NINDS Project Scientist

Robin Conwit, MD

Introduction – Our VERIFY Site Teams Cont'd

Site	PI	Primary Study Coordinator
Baystate Medical Center, Springfield, MA	Gottfried Schlaug, MD, PhD	Sirisha Nouduri
Duke University Hospital, Durham, NC	Wayne Feng, MD	Randy Smith
Emory University	Michael Borich, PT, PhD	Susan Murphy
Harborview Medical Center, Seattle, WA	Nicole Mazwi, MD	Allison Kunze
Houston Methodist Hospital, Houston, TX	David Chiu, MD	David McCane
Lahey Hospital & Medical Center, Burlington, MA	Siddharth Sehgal, MD	Penhleakhena Ou
Massachusetts General Hospital, Boston, MA	David J. Lin, MD	Julie DiCarlo
Medical University of South Carolina (MUSC)	Kirstin Heise, PhD	Valerie Salisbury
MedStar Washington Hospital Center, Washington, DC	Matt Edwardson, MD	Jamal Smith
Montefiore Medical Center, Bronx, NY	Cynthia Hung, MD	Sandeep Yerra
NYU Langone Medical Center - Tisch Hospital, New York, NY	Heidi Schambra, MD	Lina Demis
OSU Wexner Medical Center, Columbus, OH	Yousef Hannawi, MD	Luke Herren
Penn State Hershey Medical Center, Hershey, PA	Raymond Reichwein, MD	TBD
Pennsylvania Hospital, Philadelphia, PA	Lawrence Wechsler, MD	Nichole Gallatti

Introduction – Our VERIFY Site Teams Cont'd

Site	PI	Primary Study Coordinator
Ronald Reagan UCLA Medical Center, Los Angeles, CA	Jason Hinman, MD, PhD	Cristina Teran
San Francisco General Hospital	Cathra Halabi, MD	Dominica Randazzo
UF Health Shands Hospital, Gainesville, FL	Gabriel Bonnell, MD	Franklin Eschevarria
University of Alabama Hospital, Birmingham, AL	Toby Gropen, MD	Tammy Davis
University of Cincinnati Medical Center, Cincinnati, OH	Pierce Boyne, PT, PhD	Erin Wagner
University of Iowa Hospitals & Clinics, Iowa City, IA	Hannah Roeder, MD, MPH	Heena Olalde
University of Maryland Medical Center, Baltimore, MD	Robynne Braun, MD, PhD	Bisola Amodu
University of Michigan University Hospital, Ann Arbor, MI	Chandramouli Krishnan, PT, PhD	Courtney Wolf
University of Utah Healthcare, Salt Lake City, UT	Lorie Richards, OT, PhD & Jennifer Majersik, MD, MS	TBD
University of Wisconsin University Hospital, Madison, WI	Azam S. Ahmed, MD	TBD
UCSF Medical Center, San Francisco, CA	Cathra Halabi, MD	Dominica Randazzo
UPMC Presbyterian Hospital, Pittsburgh, PA	George Wittenberg, MD, PhD	Jason Weimer
UT Houston (Memorial Hermann Texas Medical Center)	Sean Savitz, MD	Emily Stevens
UT Southwestern Medical Center, Dallas, TX	Nneka L. Ifejika MD, MPH	Maddie Euckert
UVA Medical Center, Charlottesville, VA	Chad Aldridge, PT	Sonya Gunter

Study Update and Protocol Overview

VERIFY Video

Available in
both
English
& Spanish

VERIFY Websites

- Patient-Facing: https://theverifystudy.com (includes study videos)

- Study Team-Facing: https://www.nihstrokenet.org/verify/home (includes newsletters & webinars)

VERIFY Websites Cont'd

- Clinical Trial Data Management System (https://webdcu.musc.edu)

Objective

- Primary: To validate the most promising biomarkers of motor recovery after ischemic stroke in this first large-scale, prospective, generalizable dataset.
  - 557 ischemic stroke patients

- Exploratory: To explore these biomarkers in a convenience sample of concurrently collected patients with intracerebral hemorrhagic stroke, for whom preliminary data are very limited.
  - 100 intracerebral hemorrhagic stroke (convenience sample)

Primary Aims

- **Primary Aim 1:** To externally validate the relationships that TMS and MRI biomarkers of CMS integrity acquired ≤ 7 days after stroke have with UE motor impairment outcome at 90 days after ischemic stroke.
  - Motor impairment outcome = UE Fugl-Meyer (FM) scale score

- **Primary Aim 2:** To externally validate the PREP2 prediction tool used ≤ 7 days after stroke to predict 90-day UE functional outcome for individual patients with ischemic stroke.
  - Motor functional outcome = Action Research Arm Test (ARAT) score.

Exploratory Aims

- **Exploratory Aims**: To derive and internally validate multivariable prediction tools, using TMS and MRI biomarkers as well as baseline clinical factors, to predict 90-day patient reported UE use and global functional outcome in individual patients.
  - Upper extremity use = Motor Activity Log (MAL) score
  - Global functional outcome = modified Rankin Scale [mRS] score

- **Exploratory Cohort**: Aims will also be explored in a convenience sample of 100 patients with intracerebral hemorrhage

Deliverables

- Immediately allow reliable prediction of patient outcomes after ischemic stroke to improve stratification and inform entry criteria in clinical trials

- Enable personalized rehabilitation therapy in the long term

Inclusion Criteria

- Age **18 years** or older
- **Unilateral** stroke due to ischemia or intracerebral hemorrhage
- **Motor deficits** in the acutely affected UE (SAFE score ≤ 8) within 48 to 96 hours of stroke onset (or time last known well).
  - SAFE ≤ 8 **excludes full or nearly full motor** strength in both shoulder abduction and finger extension
- Consent signed within **48 to 96 hours** of stroke onset (or LKW)
- Stated **willingness to comply** with all study procedures and available for duration
- Fluent in **English or Spanish**

Exclusion Criteria

- **UE injury or conditions** on paretic side that limited use prior to the stroke
  Significant functional limitation with examples noted in MOPP
- **Legally blind**
- **Dense sensory loss** on paretic side indicated by a score of 2 on NIHSS sensory item
- Unable to abduct the shoulder or extend the fingers of the **non-paretic UE** on verbal command
- Isolated **cerebellar** stroke
- **Bilateral** acute strokes

Exclusion Criteria Cont'd

- Co-enrollment in a trial of an **intervention targeting the incident stroke** (acute treatment or rehabilitation/recovery intervention) after baseline assessments for VERIFY are initiated

TRIAL	Concept	Considerations	Ok to Co-Enroll?	Plan approved by both trials' PIs
ARCADIA	Apixiban for stroke prevention in setting of atrial cardiopathy	Does not target acute stroke treatment or recovery	YES	X
ARCADIA-CSI	Cognitive (annual phone battery [20 min] administered centrally annually) and MRI at baseline and final visit.	Both observational; limited overlap in cognitive timing	YES	X
ASPIRE	Apixiban for stroke prevention after ICH in setting of atrial fibrillation	Does not target acute stroke treatment or recovery; only annual cognitive assessment	Yes	X
CAPTIVA	ASA with clopidogrel vs ticagrelor vs rivaroxaban for stroke prevention in ICAD	CAPTIVA Team prefers not to co-enroll due to overall study burden of CAPTIVA	NO	X
DISCOVERY	Observational study to understand mechanisms of post stroke cognitive disability	DISCOVERY Team prefers not to co-enroll due to overall study burden of DISCOVERY	NO	X
FASTEST	Factor VIIa for treatment of ICH	Does not target acute stroke treatment or recovery; **If Patient is enrolled via EFIC, patient should only be approached after patient is fully informed of FASTEST.**	YES	X
MOST	Argatroban/eptifibatide for treatment of ischemic stroke	Acute stroke treatment completed by 48 hours. **Patient should not be approached by VERIFY until after MOST consent experience survey on Day 3.**	YES	X
SATURN	Statin discontinuation in setting of ICH to prevent ICH recurrence	Study drug targets acute stroke recovery	NO	X
SATURN-MRI	Follow up MRI for SATURN trial	Study drug targets acute stroke recovery	NO	X
SLEEP-SMART	Early CPAP treatment of OSA for stroke prevention and recovery	Study intervention targets acute stroke recovery	NO	X
TRANSPORT-2	Transcranial direct stimulation for motor recovery	Limited overlap at 2-3 months from onset of stroke. **If co-enrollment planned, then Transport2 enrollment must occur at 3-6 months.**	YES	X

Exclusion Criteria Cont'd

- Known **inability to follow up** through 90 days
- **Major medical, neurological, or psychiatric condition** that would substantially affect functional status

  Examples (end stage cancer, untreated bipolar, moderate to severe neurodegenerative disease) noted in MOPP

- Cognitive or communication impairment **precluding informed consent** by the participant.

  Suggested comprehension questions noted in MOPP

- Non-cerebrovascular diagnosis associated with **unlikely survival at 90 days**
- **Pregnancy**

Exclusion Criteria Cont'd

- **Contraindication to noncontrast MRI** (certain metallic implants, metallic foreign bodies or severe claustrophobia)
- **Contraindication to TMS**
  - Cardiac pacemaker or other electronic devices in the body at or above the level of the seventh cervical vertebra (such as cochlear implant, cortical stimulator, deep brain stimulator, vagus nerve stimulator, cervical spine epidural stimulator, or ventriculoperitoneal shunt)
  - Skull defect related to current stroke
  - Seizure after onset of current stroke
  - Seizure within the last 12 months while taking anti-epileptic medications
  - Previous serious adverse reaction to TMS

Exclusion Criteria Cont'd

- Unable to perform **behavioral assessments within 48-120 hours** of symptom onset (or time last known well).

- Unable to receive **TMS or get MRI within 72-168 hours** of symptom onset (or time last known well).

- **Anticipated instability** to perform study procedures within 168 hours of symptom onset.

Study Schema

HOUR 0 = STROKE ONSET (OR TIME LAST KNOWN WELL)

Visit 1:
Hour 48-96

Visit 1
Consent & Screening
Obtain informed consent; SAFE score; demographics; pregnancy test, if applicable

***Visit 2:**
Hour 48-120

***Visit 3:**
Hour 72-168

**Can occur on same day*

Visit 2
Baseline Clinical Assessments
UE-FM Score, NIHSS

Visit 3
Baseline Biomarker and Clinical History Assessments
TMS, MRI brain,
Medical history,
AE and SAE evaluation,
Rehabilitation utilization assessment

Participant is considered "enrolled" only after starting first TMS stimulation or starting study-specific MRI sequence. A clinical MRI conducted no sooner than 24 hours after stroke onset is acceptable to use for the study MRI. If that clinical MRI did not include the study-required 3D-T1 MRI sequence, then only this sequence will be performed after enrollment.

Study Schema

HOUR 0 = STROKE ONSET (OR TIME LAST KNOWN WELL)

Visit 1:
Hour 48-96

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Obtain informed consent; SAFE score; demographics; pregnancy test, if applicable

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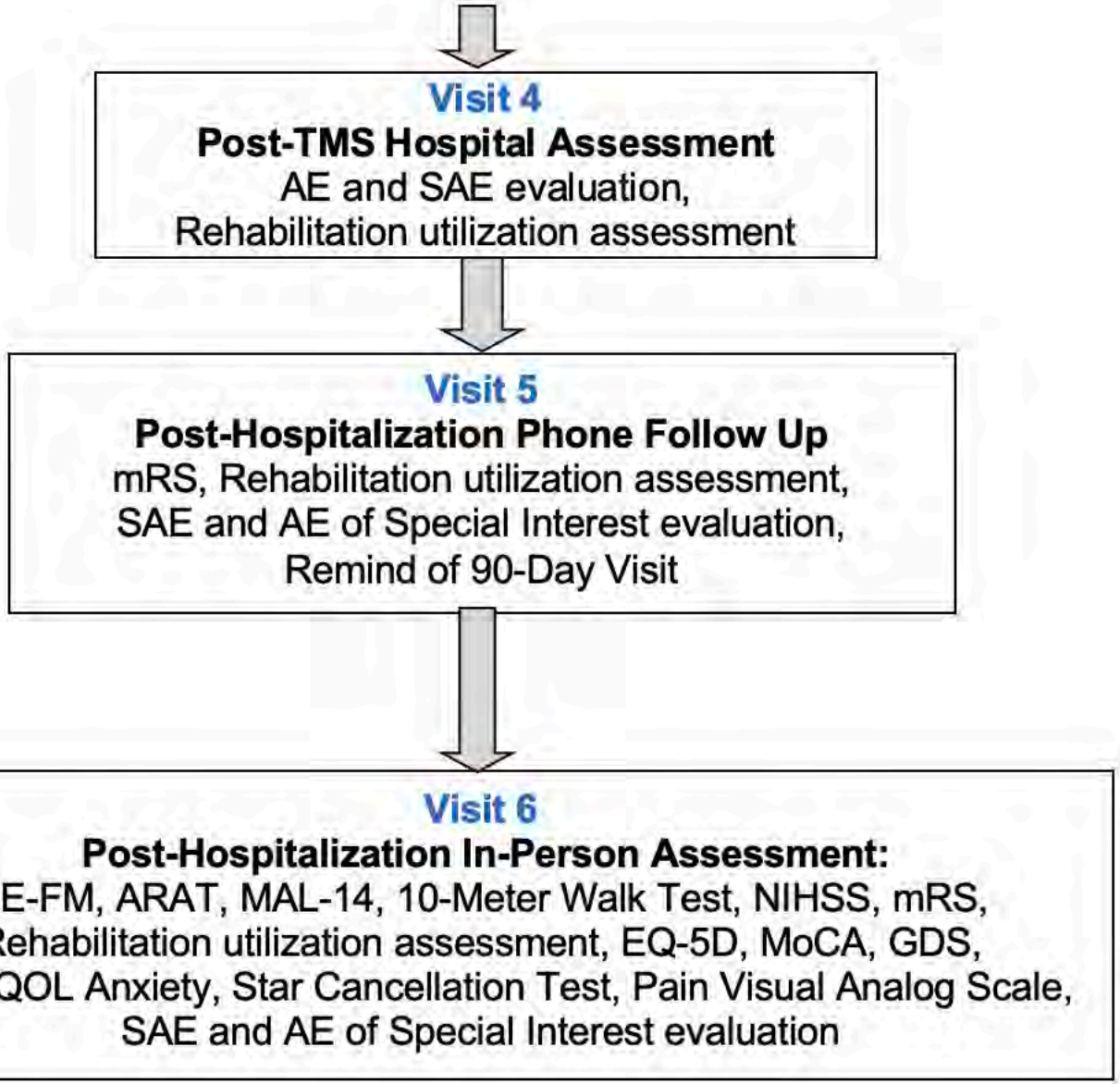
Study Schema Continued

Visit 4:
Discharge Day±1
or Post-TMS Day 5±1,
Whichever is Sooner

Visit 5:
Day 30±7

Visit 6:
Day 90±14



Screening/Consent Workflow

1. **Daily Chart Screening**
   - Identify all stroke patients (ischemic and ICH) in EMR with the following:
     - <36 hours of onset at admission
     - Some upper extremity weakness
     - Alert and able to consent themselves
     - No TMS & MRI contraindications
   - Above subset of pts eligible based on full eligibility criteria?
     - NO→enter in screen failure CRF
     - YES→proceed to next step
2. **Ask clinical team physician for the following:**
   - Confirm that patient has "some" weakness in shoulder abduction and/or finger extension?
     - NO→enter in screen failure CRF
     - YES→proceed to next step
   - Mention study and ask if study team may approach
     - NO→enter in screen failure CRF
     - YES→proceed to next step
3. **Patient consents?**
   - NO→enter in screen failure CRF
   - YES→proceed to next step
4. **SAFE score </=8?**
   - NO→enter in screen failure CRF
   - YES→proceed to next step
5. **Remains eligible until 1st TMS stimulation or start of study-specific MRI?**
   - NO→enter in screen failure CRF
   - YES→participant is now enrolled!

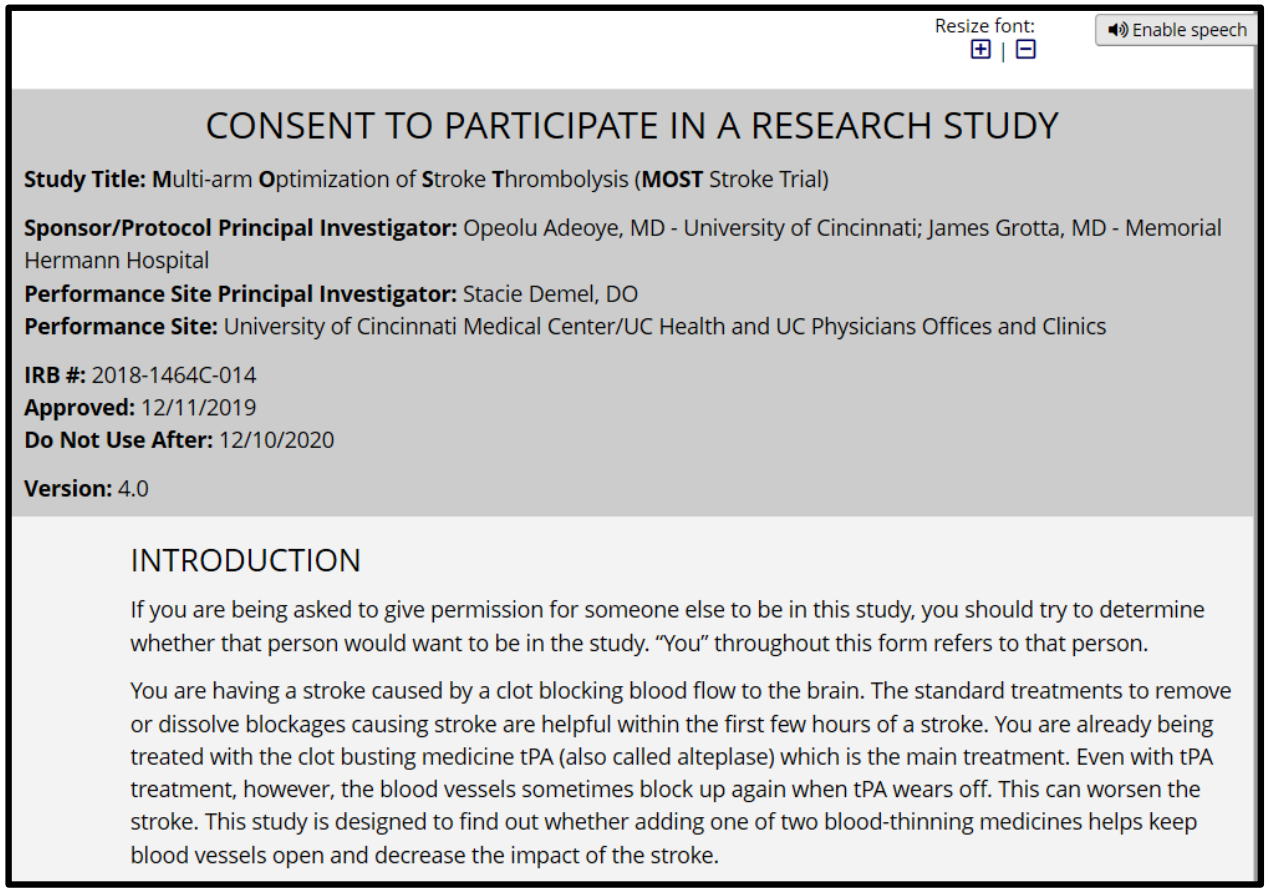
E-Consent Overview

- REDCap is a **mature, secure web application** for building and managing online surveys and databases.
- Facilitates **presentation of an electronic Informed Consent Document** (eICD) and capturing the **patient's signature**.
- To access and complete the eICD, the patient must have access to a **smartphone, tablet or computer** with Wi-Fi or cellular internet connectivity.
- Individuals provide a **handwritten signature** by using a computer mouse, or by using their finger on a cell phone or tablet touchscreen.
- REDCap **automatically saves** the signed eICD on its secure server and maintains an **audit trail** that logs all user actions.

E-Consent Process

1. Each site will be assigned a **static URL** to share with the patient.

https://redcap.research.cchmc.org/surveys/?s=4YKLJC7AYY

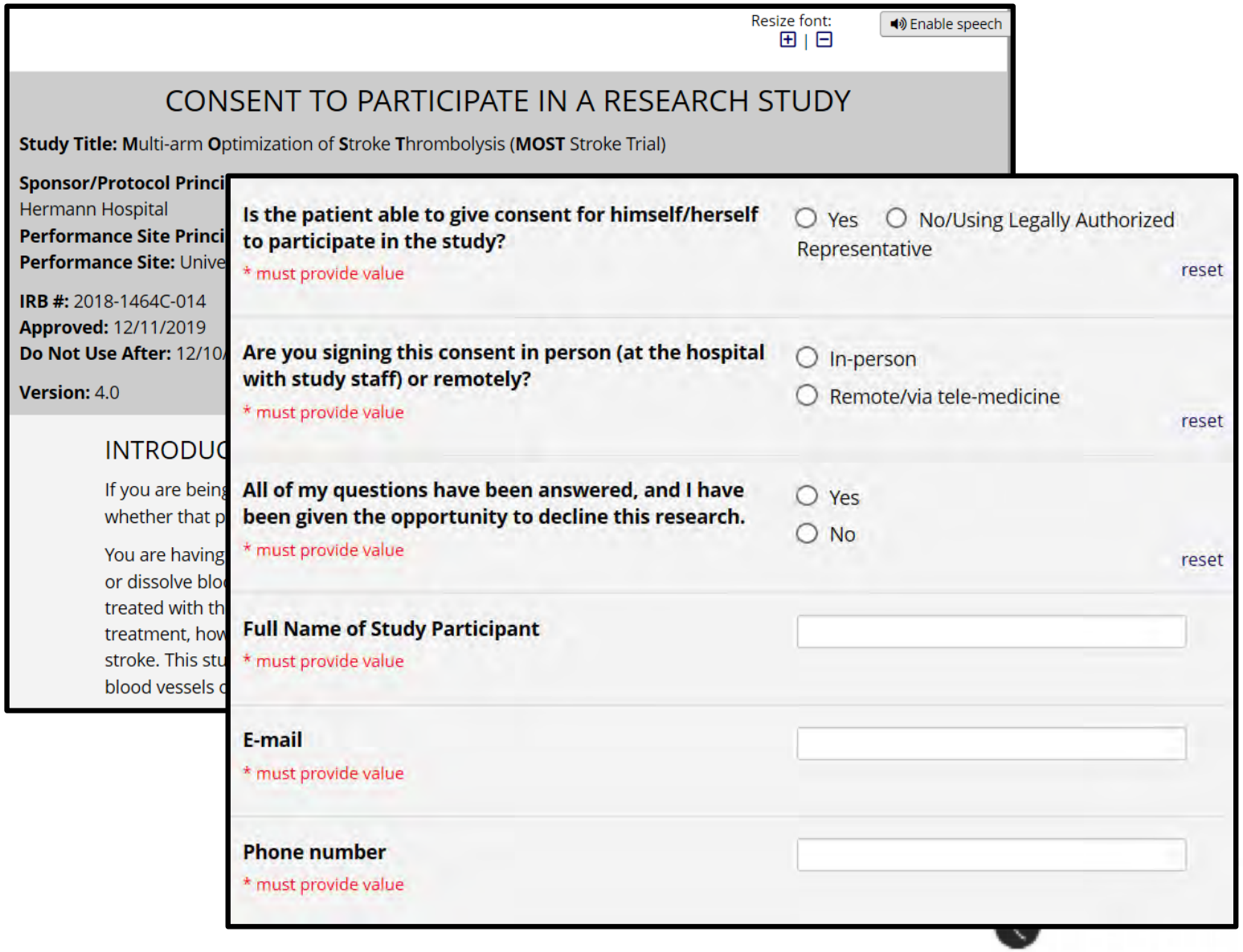


E-Consent Process

1. Each site will be assigned a static URL to share with the patient.

https://redcap.research.cchmc.org/surveys/?s=4YKLJC7AYY

2. The person obtaining consent will review the eICD and **provide instructions** on completing the form.

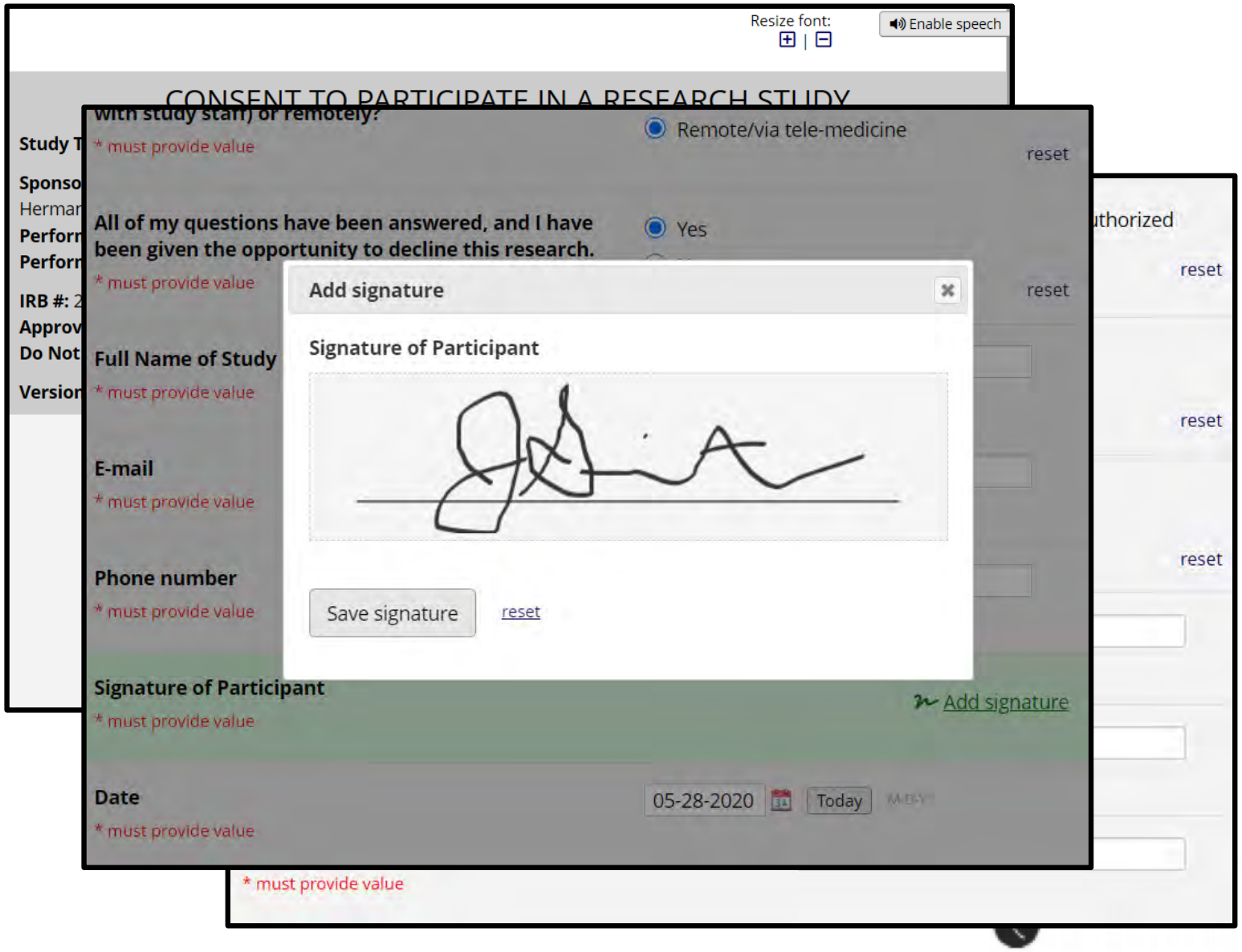


E-Consent Process

1. Each site will be assigned a static URL to share with the patient.

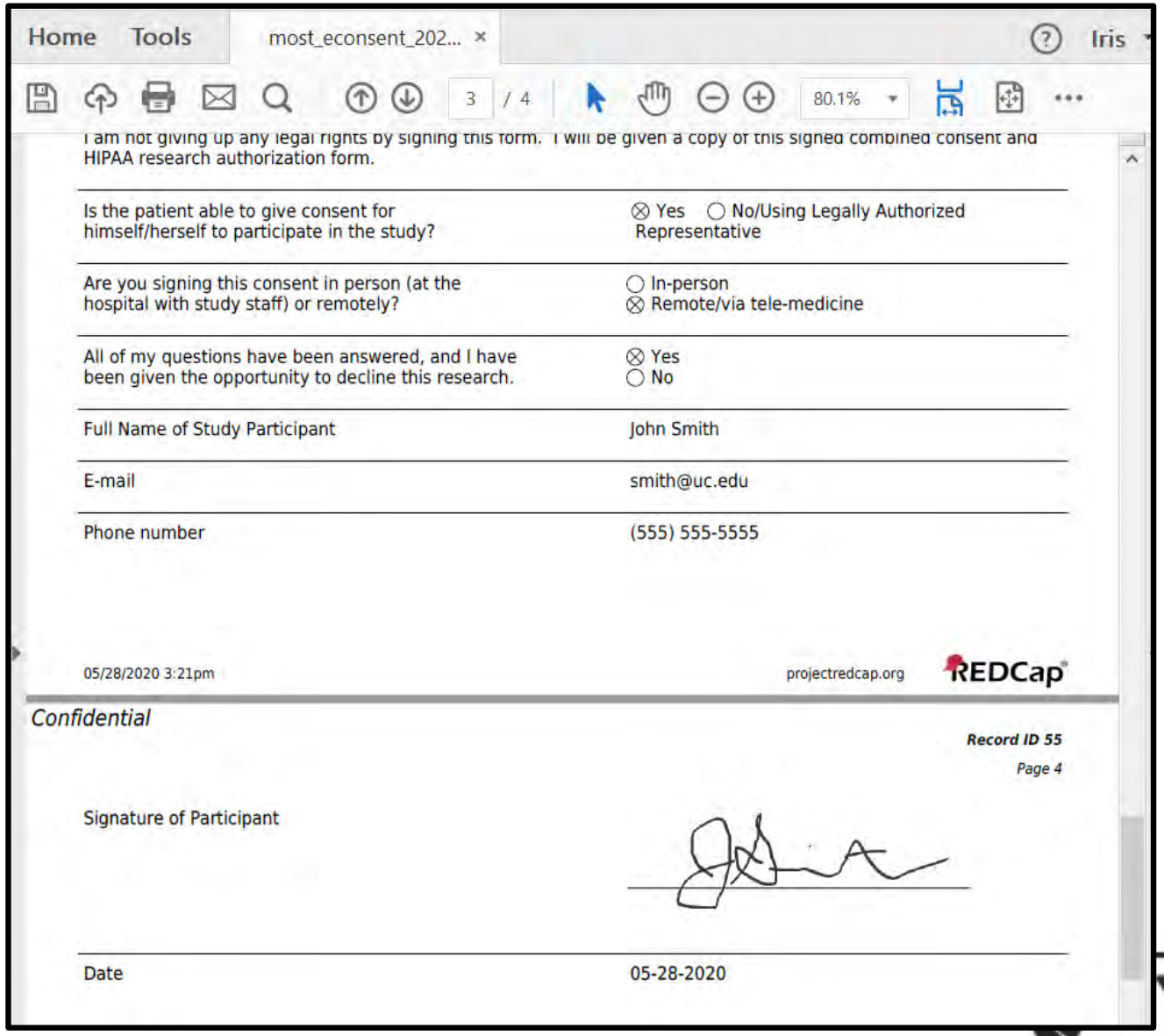
https://redcap.research.cchmc.org/surveys/?s=4YKLJC7AYY

2. The person obtaining consent will review the eICD and provide instructions on completing the form.
3. The patient will **add their handwritten signature** (typically at bedside).



E-Consent Process

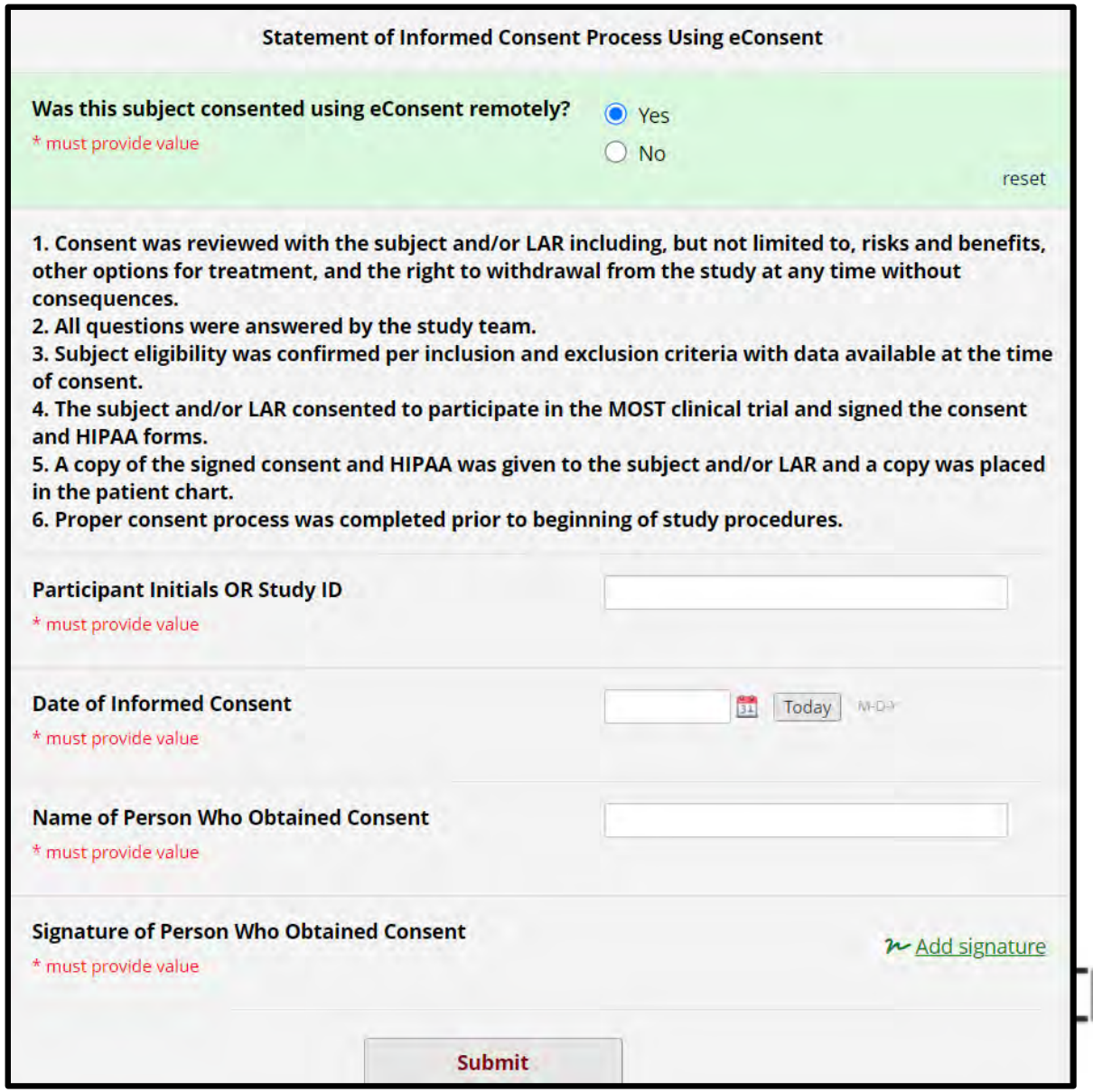
4. Upon completion of eICD, the site's **study team will receive the completed eICD PDF** via automated email.
5. The **participant** may elect to receive the eICD PDF via email.



E-Consent Process

6. When the study team and the participant are **not in the same physical location**, which will be uncommon in VERIFY, both parties are not able to sign the eICD at the same time.

Only the participant will sign in real time and the **person obtaining consent** will subsequently complete a **remote consent attestation form**.



Responsibilities

NCC Responsibilities

- **Create** a REDCap project for each site
- Ensure that the **most recent** CIRB-approved version of the site-specific ICD is available in REDCap for eICD use.
- Provide the site with their **cIRB approval** to use the central E-Consent process and **access** to their study-specific and site-specific REDCap project.
- Maintain the **list of individuals who receive the completed eICD PDF** via automated email according to the site's DOA in WebDCU™.

Site Responsibilities

- **Designate a primary and back-up user** to access to their REDCap E-Consent project.
- **Ensure the Remote Consent Attestation is completed**, when required, by the person who obtained consent remotely.
- Ensure the PDF versions of the eICD and Remote Consent Attestation, as applicable, are **combined into one document and uploaded to WebDCU™ within 5 days** of signature.

Site Readiness Activities

CTA Executed and cIRB Approved

Study Staff & Investigator WebDCU Entered

- Delegation of Authority (DoA)
- Investigator Form
- TMS Shipping Address (if applicable)

TMS Machine Received (if applicable)

Online Training Done and Certifications Uploaded

- TMS
- Behavioral Assessments
- Investigators Mtg Webinar

Practical TMS Training Done

- Healthy Volunteers
- Technique check at standard sites

MRI Set Up Completed

- MRI Form Submitted
- Imaging Core Outreach Occurred & Protocol setup
- Phantom Image Approved

Study Materials Received

- Shipping Address Entered

- Materials for Participants
  - Tote Bag
  - Rehab Diary
- Materials for Behavioral Assessments

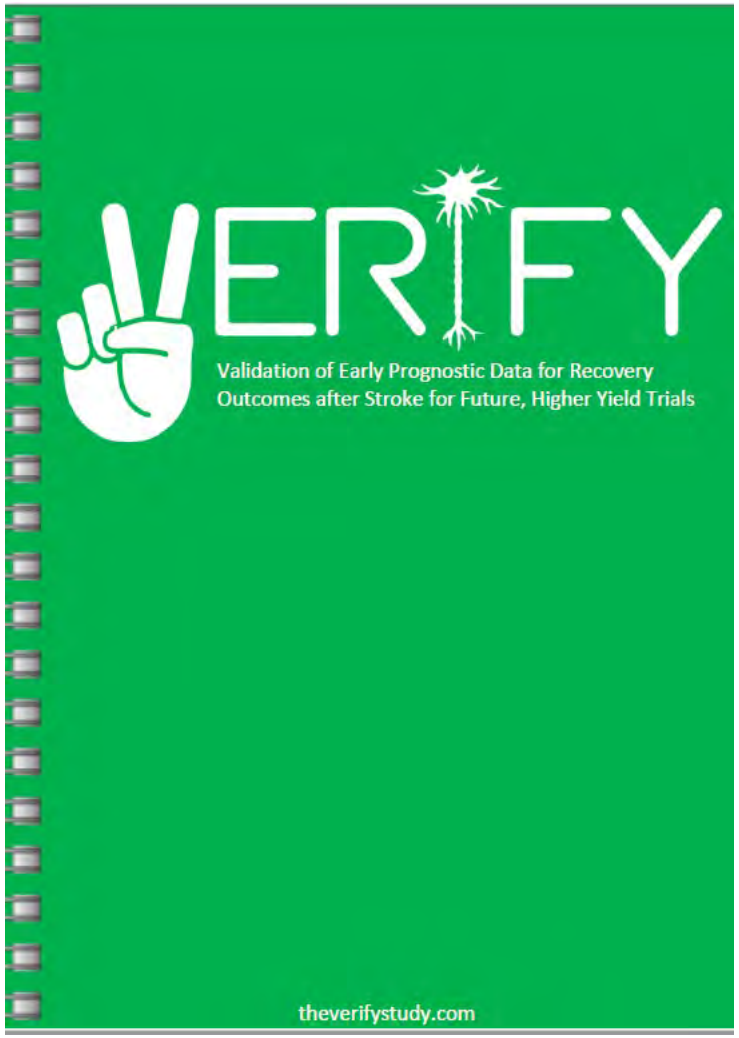
SITE READINESS CALL

&

BEGIN SCREENING!!!

VERIFY

Tote Bag and Rehab Utilization Diary



VERIFY

CTA and cIRB Status

29 Sites:
22 CTAs executed &
14 CIRBs approved (& 10 submitted)

as of Apr 22th 2022

	CTA Submitted	CTA Completed	CIRB Submitted	CIRB Completed
University of Wisconsin University Hospital	■	■	■	■
UVA Medical Center	■	■	■	■
MedStar Washington Hospital Center	■	■	■	■
University of Maryland Medical Center	■	■	■	■
The University of Utah	■	■	■	■
University of Cincinnati Medical Center	■	■	■	■
NYU Langone Medical Center – Tisch Hospital	■	■	■	■
University of Texas Southwestern Medical Center	■	■	■	■
OSU Wexner Medical Center	■	■	■	■
UT Houston (Memorial Hermann Texas Medical Center)	■	■	■	■
University of Alabama Hospital	■	■	■	■
UF Health Shands Hospital	■	■	■	■
Baystate Medical Center	■	■	■	
Medical University of South Carolina (MUSC)	■	■	■	
Montefiore Medical Center	■	■	■	
Emory University	■	■	■	
Duke University Hospital	■	■	■	
University of Michigan University Hospital	■	■	■	
San Francisco General Hospital	■	■	■	
UCSF Medical Center	■	■	■	
Harborview Medical Center	■	■		
Lahey Hospital & Medical Center	■	■		
Pennsylvania Hospital			■	■
UPMC Presbyterian Hospital			■	■
Massachusetts General Hospital			■	
Houston Methodist Hospital			■	
Penn State Hershey Medical Center				
Ronald Reagan UCLA Medical Center				
University of Iowa Hospitals & Clinics				

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as Apr 22th 2022

Who will enroll the first patient???

	CTA Submitted	CTA Completed	CIRB Submitted	CIRB Completed
University of Wisconsin University Hospital	■	■	■	■
UVA Medical Center	■	■	■	■
MedStar Washington Hospital Center	■	■	■	■
University of Maryland Medical Center	■	■	■	■
The University of Utah	■	■	■	■
University of Cincinnati Medical Center	■	■	■	■
NYU Langone Medical Center - Tisch Hospital	■	■	■	■
University of Texas Southwestern Medical Center	■	■	■	■
OSU Wexner Medical Center	■	■	■	■
UT Houston (Memorial Hermann Texas Medical Center)	■	■	■	■
University of Alabama Hospital	■	■	■	■
UF Health Shands Hospital	■	■	■	■
Baystate Medical Center	■	■	■	
Medical University of South Carolina (MUSC)	■	■	■	
Montefiore Medical Center	■	■	■	
Emory University	■	■	■	
Duke University Hospital	■	■	■	
University of Michigan University Hospital	■	■	■	
San Francisco General Hospital	■	■	■	
UCSF Medical Center	■	■	■	
Harborview Medical Center	■	■		
Lahey Hospital & Medical Center	■	■		
Pennsylvania Hospital			■	■
UPMC Presbyterian Hospital			■	■
Massachusetts General Hospital			■	
Houston Methodist Hospital			■	
Penn State Hershey Medical Center				
Ronald Reagan UCLA Medical Center				
University of Iowa Hospitals & Clinics				

Staff Roles at Each Clinical Site

STAFF MEMBERS TO BE TRAINED AND CERTIFIED AT SITES:

1. Site PI
2. 1^0 SC
3. 1^0 PT/OT
4. At least one additional staff member(s) and more encouraged
    - 2^0 SC or 2^0 PT/OT

Please Train **<u>2 People</u>** for Each Sets of Trainings:
(1) TMS (2) ARAT+FM, & (3) Other Behavioral Assessments

Study Timeline

VERIFY Study Timeline	
September, 2021	Grant Notice of Award (NoA) received on Sept 1, 2021 and 29 sites selected
October, 2021	StrokeNet issued Clinical Trial Agreement (CTA) and central IRB packets to sites
Fall/Winter, 2021	Sites completing CTA and CIRB packets
February 28, 2022	Virtual training launch
March/April, 2022	Sites to complete virtual site trainings
April 25, 2022	Investigator meeting (virtual)
May, 2022	Complete remaining training & start up activities
June, 2022	First participant enrolled!

- ✓ **CTA/IRB**
- ✓ **DOAs/Investigator Forms**
- ✓ **Trainings for TMS and Behavorial Assessments**
- ✓ **MRI Set Up**
- ✓ **Study Tool Shipping**
- ✓ **Site Readiness Call**

More Questions after Today?

- Contact Lisa, Kalli, PIs, or others→
- VERIFY Virtual Office Hours (optional)
  - **Weekly on Wednesdays, 2-3pm ET**
- Important Study Coordinator Webinar
  - **Tuesday, May 24th, 12pm-1pm ET**
- Monthly study coordinator/PI webinars
  - **Starting in June 2022**

Contact Information

CIRB/Regulatory

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All Other Questions

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NCC PM Kalli Beasley beasleki@ucmail.uc.edu

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Achala Vagal vagala@ucmail.uc.edu

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Sasha Simms simmssc@ucmail.uc.edu 513.558.3924

All Other Questions
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NCC PM Kalli Beasley beasleki@ucmail.uc.edu

VERIFY PIs:
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Cathy Stinear c.stinear@auckland.ac.nz
Achala Vagal vagala@ucmail.uc.edu

Behavioral Measures

7 Study Specific Behavioral Assessment Trainings

Accurate measurement of behavior is critical to correctly capturing patient outcomes and to measuring key patient characteristics.

Studies show that formal training improves the accuracy of, and reduces variability in, behavioral assessment scoring.

The VERIFY Study has 13 Specific behavioral assessments for which training, and certification are needed.

These certifications can be obtained through 7 different trainings distributed across 3 different web-based platforms.

7 Study Specific Behavioral Assessment Trainings

BlueCloud

1. Upper Extremity Fugl-Meyer Scale
2. Action Research Arm Test
3. Rankin Focused Assessment

MoCA website

4. Montreal Cognitive Assessment

PDF Slide Deck & Survey Link

5. Behavioral Assessments Training Certification which includes the following assessments:
    1. Motor Activity Log-14 (amount of use)
    2. 10-Meter Walk Test
    3. EQ-5D (EuroQol-5D)
    4. Geriatric Depression Scale-15Q
    5. NeuroQOL-Anxiety-8Q
    6. Star Cancellation Test
    7. Pain Visual Analog Scale

DCU Campus

6. Modified Rankin Scale
7. NIH Stroke Scale

7 Study Specific Behavioral Assessment Trainings

BlueCloud

1. Upper Extremity Fugl-Meyer Scale
2. Action Research Arm Test
3. Rankin Focused Assessment

Examiners must use only use the specific versions of case report forms and specific assessment kits provided by the VERIFY Study.

MoCA website

4. Montreal Cognitive Assessment

PDF Slide Deck & Survey Link

5. Behavioral Assessments Training Certification which includes the following assessments:
    1. Motor Activity Log-14 (amount of use)
    2. 10-Meter Walk Test
    3. EQ-5D (EuroQol-5D)
    4. Geriatric Depression Scale-15Q
    5. NeuroQOL-Anxiety-8Q
    6. Star Cancellation Test
    7. Pain Visual Analog Scale

DCU Campus

6. Modified Rankin Scale
7. NIH Stroke Scale

7 Study Specific Behavioral Assessment Trainings

	Frequency of recertification
BlueCloud	
1. Upper Extremity Fugl-Meyer Scale	Every 6 months
2. Action Research Arm Test	Every 6 months
3. Rankin Focused Assessment	Every 2 years
MoCA website	
4. Montreal Cognitive Assessment	Every 2 years
PDF Slide Deck & Survey Link	
5. Behavioral Assessments Training Certification which includes the following assessments:	Every 1 year
1. Motor Activity Log-14 (amount of use)	
2. 10-Meter Walk Test	
3. EQ-5D (EuroQol-5D)	
4. Geriatric Depression Scale-15Q	
5. NeuroQOL-Anxiety-8Q	
6. Star Cancellation Test	
7. Pain Visual Analog Scale	
DCU Campus	
6. Modified Rankin Scale	Every 2 years
7. NIH Stroke Scale	Every 2 years

7 Study Specific Behavioral Assessment Trainings

	Frequency of recertification
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4. Geriatric Depression Scale-15Q	
5. NeuroQOL-Anxiety-8Q	
6. Star Cancellation Test	
7. Pain Visual Analog Scale	
DCU Campus	
6. Modified Rankin Scale	Every 2 years
7. NIH Stroke Scale	Every 2 years

- If you have recently trained and certified on a particular scale, you can upload this to WebDCU.
- Your next recertification will be according to this schedule.

Training and certification- BlueCloud

BlueCloud
1. Upper Extremity Fugl-Meyer Scale
2. Action Research Arm Test
3. Rankin Focused Assessment

1. Go to https://secure.bluecloud.net/verify-study
   - IF ALREADY REGISTERED, CONFIRM YOUR ACCOUNT: If you previously registered at BlueCloud, confirm your personal account is active by logging in using your previously registered e-mail address.
   - IF YOU ARE NOT ALREADY REGISTERED, CREATE AN ACCOUNT: If you do not have a BlueCloud account, register and create your own personal account.

2. Send an email to Dr. Cramer's lab (cramerlab@mednet.ucla.edu) indicating that you have a registered BlueCloud account. Send this from the email account you used to register at BlueCloud.

3. We will assign you the 3 BlueCloud training courses and then send you an email to let you that these have been assigned. Further instructions will be provided in that email.

Training and certification- MoCA website

MoCA website
6. Montreal Cognitive Assessment

1. Go to https://www.mocatest.org/members/register/

2. Fill in the blanks to create an account and register.

3. Go to https://www.mocatest.org/get-certified to begin the certification process.

4. Towards the bottom of the page, enter **VpXa6RwYk** in the Enter Group Code box. This code is for the VERIFY study only—please do not share this code or use it in any other context.

5. Proceed with MoCA training and certification. Note that we will be using paper case report forms for MoCA testing, and not electronic MoCA testing.

6. When you have completed and passed MoCA certification, take a screen snapshot of your Certificate of Completion and then please upload it to WebDCU.

Training and certification- PDF Slide Deck and Survey Link

Behavioral Assessments Training Certification:

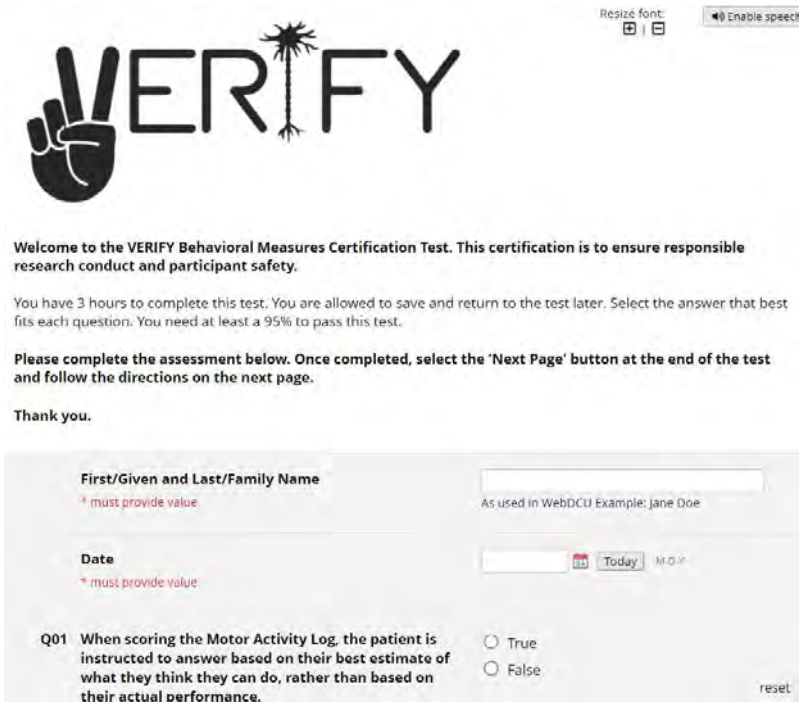
1. Motor Activity Log-14 (amount of use)
2. 10-Meter Walk Test
3. EQ-5D (EuroQol-5D)
4. Geriatric Depression Scale-15Q
5. NeuroQOL-Anxiety-8Q
6. Star Cancellation Test
7. Pain Visual Analog Scale

1. The PDF Slide Deck for the Behavioral Assessments Training Certification that incorporates these 7 scales will be provided:
    1. In the WebDCU VERIFY study toolbox https://webdcu.musc.edu/login.asp
    2. Via e-mail upon request from the Project Manager
2. After you finish viewing the training slides, open the URL provided on the last slide: https://redcap.link/VerifyBehavioralMeasuresCertification

Training and certification- PDF Slide Deck and Survey Link

Behavioral Assessments Training Certification:

1. Motor Activity Log-14 (amount of use)
2. 10-Meter Walk Test
3. EQ-5D (EuroQol-5D)
4. Geriatric Depression Scale-15Q
5. NeuroQOL-Anxiety-8Q
6. Star Cancellation Test
7. Pain Visual Analog Scale



1. The PDF Slide Deck for the Behavioral Assessments Training Certification that incorporates these 7 scales will be provided:
   1. In the WebDCU VERIFY study toolbox https://webdcu.musc.edu/login.asp
   2. Via e-mail upon request from the Project Manager
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Training and certification- PDF Slide Deck and Survey Link

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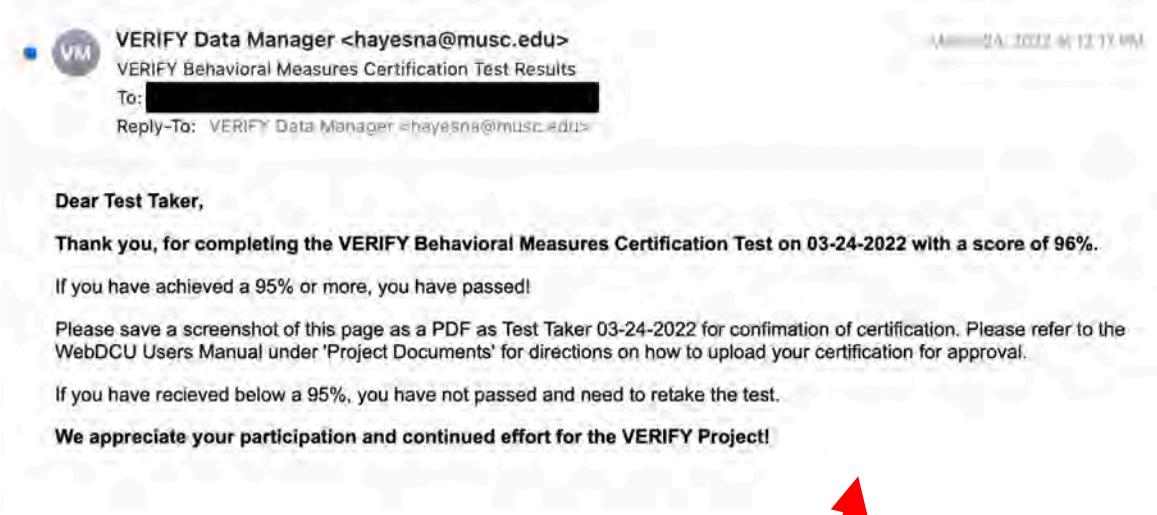

VERIFY Data Manager <hayesna@musc.edu>
VERIFY Behavioral Measures Certification Test Results
To: [redacted]
Reply-To: VERIFY Data Manager <hayesna@musc.edu>

Dear Test Taker,

Thank you, for completing the VERIFY Behavioral Measures Certification Test on 03-24-2022 with a score of 96%.

If you have achieved a 95% or more, you have passed!

Please save a screenshot of this page as a PDF as Test Taker 03-24-2022 for confimation of certification. Please refer to the WebDCU Users Manual under 'Project Documents' for directions on how to upload your certification for approval.

If you have recieved below a 95%, you have not passed and need to retake the test.

We appreciate your participation and continued effort for the VERIFY Project!

1. The PDF Slide Deck for the Behavioral Assessments Training Certification that incorporates these 7 scales will be provided:
   1. In the WebDCU VERIFY study toolbox https://webdcu.musc.edu/login.asp
   2. Via e-mail upon request from the Project Manager
2. After you finish viewing the training slides, open the URL provided on the last slide: https://redcap.link/VerifyBehavioralMeasuresCertification
3. Once you pass this test, you must upload a PDF of the passing notification into WebDCU. Two options:
   1. Take a screenshot of the webpage, save it as a PDF, and upload to WebDCU, OR
   2. Select the option to have the results emailed to you. Then save that email as a PDF and upload it to WebDCU

Training and certification- PDF Slide Deck and Survey Link

Behavioral Assessments Training Certification:

1. Motor Activity Log-14 (amount of use)
2. 10-Meter Walk Test
3. EQ-5D (EuroQol-5D)
4. Geriatric Depression Scale-15Q
5. NeuroQOL-Anxiety-8Q
6. Star Cancellation Test
7. Pain Visual Analog Scale

If you did not pass this test:
--Review the training materials, and then
--Retake the test

NOTE: This training will be available in the future through the DCU Training Center.

1. The PDF Slide Deck for the Behavioral Assessments Training Certification that incorporates these 7 scales will be provided::
   1. In the WebDCU VERIFY study toolbox https://webdcu.musc.edu/login.asp
   2. Via e-mail upon request from the Project Manager
2. After you finish viewing the training slides, open the URL provided on the last slide: https://redcap.link/VerifyBehavioralMeasuresCertification
3. Once you pass this test, you must upload a PDF of the passing notification into WebDCU. Two options:
   1. Take a screenshot of the webpage, save it as a PDF, and upload to WebDCU, OR
   2. Select the option to have the results emailed to you. Then save that email as a PDF and upload it to WebDCU

Training and Certification- DCU Training Center

DCU Campus
4. Modified Rankin Scale
5. NIH Stroke Scale

1. Go to https://dcu.musc.edu/campus/

2. Click on mRS Training Video

3. When you finish watching the video, click on mRS Certification Test. Enter your data in the Test Registration boxes and hit Submit. Take the test.

4. When you pass the mRS test, hit “Print mRS Certificate” and then save your certificate. Then please send it to your site coordinator, who will later upload it to WebDCU^^.

5. Repeat steps 2-4 for the NIH Stroke Scale.

^^*Once the site's electronic DOA log is approved by NCC, the regulatory and training document requirements will be automatically posted based on study team members' roles. The site coordinator will then upload PDFs of the training certifications in WebDCU under [People Reg Doc Submission].*

Things we will mail to you for behavioral assessments

ARAT Kits

Rehab Diaries

2 red sharpie markers

Arm motor Fugl-Meyer test kit

i. stopwatch (with resolution to hundredths of a second)
ii. tennis ball
iii. small cylinder
iv. pencil
v. reflex hammer

Star Cancellation Test, testing sheets (clean copies)

i. 40 copies in English
ii. 30 copies in Spanish
iii. protective folder holding these copies

50-foot tape measure

1 roll of bright orange masking tape

Things we will mail to you for behavioral assessments

ARAT Kits → Will be shipped directly to you from the manufacturer
NeuroQuip
London, UK

Rehab Diaries

2 red sharpie markers

Arm motor Fugl-Meyer test kit

i. stopwatch (with resolution to hundredths of a second)
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Star Cancellation Test, testing sheets (clean copies)

i. 40 copies in English
ii. 30 copies in Spanish
iii. protective folder holding these copies

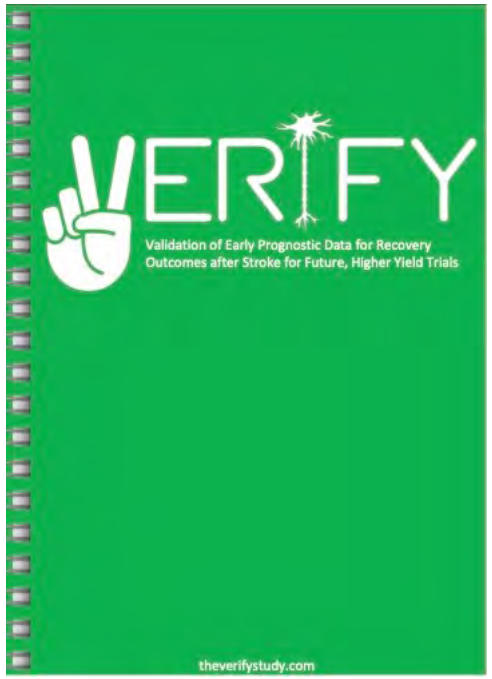
50-foot tape measure

1 roll of bright orange masking tape

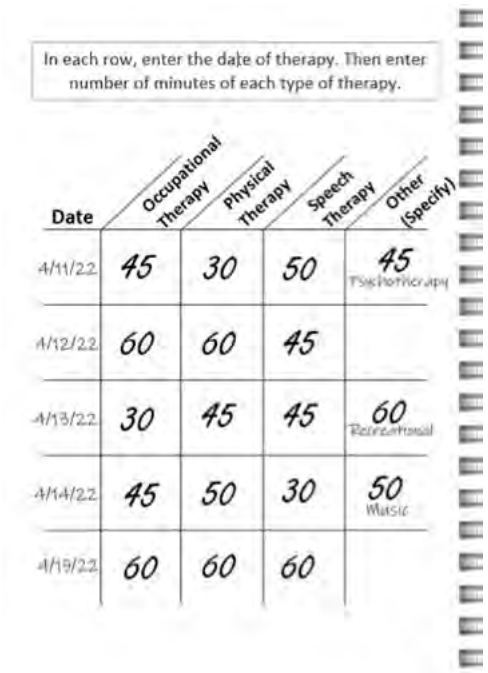
→ Will be shipped directly to you in a single box from
The Cramer lab
Los Angeles, CA

VERIFY

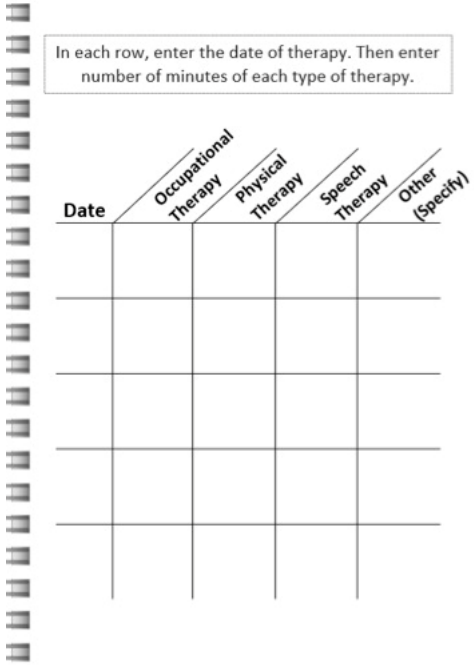
We will also mail Rehab Diaries to you



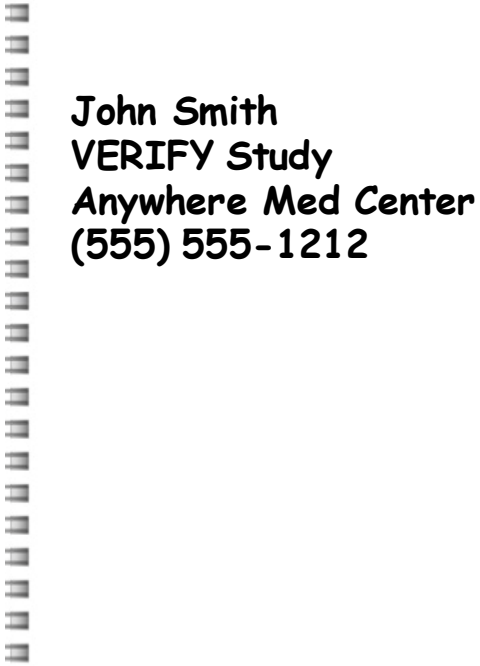
Front cover



Inside front flap



1 of 30 data pages



Back cover
(you can write your name & contact info)

Visit 6: In-person vs. Videoconference vs. Telephone

Procedures	STUDY VISIT 1 Screening & Consent Hour 48-96*	STUDY VISIT 2 Baseline Clinical Assessment Hour 48-120#	STUDY VISIT 3 Baseline Biomarker and Clinical History Assessment (ENROLLMENT) Hour 72-168**	STUDY VISIT 4 Post-TMS Hospital Discharge Day± 1 or Post-TMS Day 5± 1, Whichever is Sooner	STUDY VISIT 5 Post-Hospitalization Phone Follow Up Day Day30 ± 7* By Phone	STUDY VISIT 6 Post-Hospitalization In-Person Assessment Day 90± 14*
Informed consent	X					
SAFE score	X					
Demographics	X					
Pregnancy Test, if applicable	X					
UE-FM		X				X
NIHSS		X				X
MRI***			X			
TMS			X			
Medical history			X			
Rehab Utilization Assessment				X	X	X†
Pre-stroke mRS without RFA		X				
mRS via RFA					X	X†
ARAT						X
MAL-14						X
10-Meter Walk Test						X
EQ5D						X†
MoCA						X†
Geriatric Depression Scale						X†
NeuroQOL Anxiety (8Q)						X†
Star Cancellation Test						X
Pain Visual Analog Scale (for only shoulder of affected side)						X†
Adverse Events (AEs)			X	X		
Serious AE and AE of Special Interest			X	X	X	X†
Complete CRFs	X	X	X	X	X	X†

† *If Study Visit 6 cannot occur by person, then the indicated assessments can be done by videoconference, but note that on a videoconference, EQ5D will be performed without the visual analog portion. If only phone assessment is possible, then the same tests can be performed except for the MOCA, which is skipped for a phone-based visit.*

Additional Tips for Visit 6

- Study staff should train participants not to unblind their visit 6 assessors on whether their hand moved during the TMS procedure.
- The study coordinator may perform gait testing only if the participant has already been specifically cleared to walk independently by an OT or PT.
    - Otherwise, a licensed OT or PT should assist the study coordinator with performing the gait testing to ensure participant safety.

TMS

TMS team

Prof Cathy Stinear

Harry Jordan

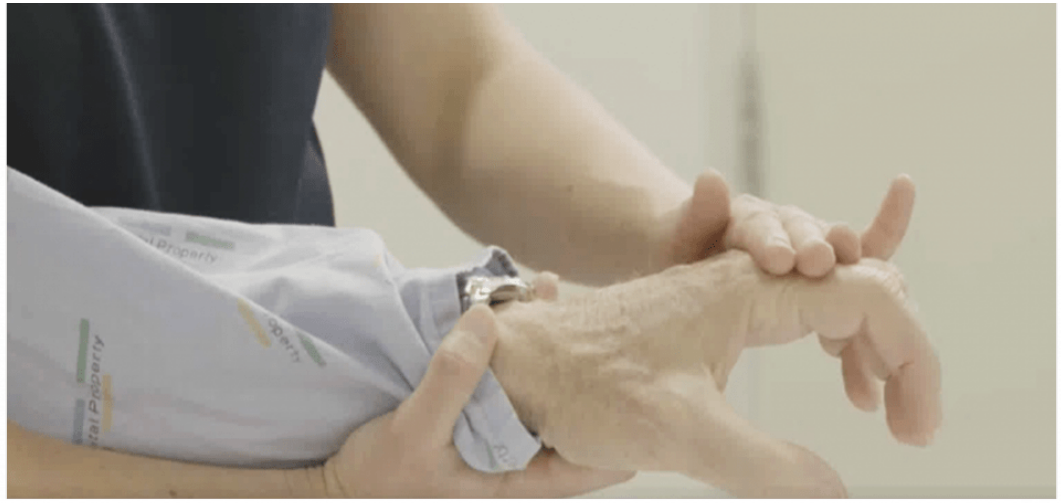
SAFE Score and TMS Training

verifytraining.blogs.auckland.ac.nz

SAFE Score Training

Training Status: 31 people certified
Need full spread of SAFE scores 0 - 8

Shoulder Abduction out of 5



Finger Extension out of 5

TMS Training

Completed by TMS Operators

THEORY

- Online
- Self-directed

PRACTICE

- Healthy volunteers
- Technique check

Online theory training completed by 14 TMS Operators

TMS Assistants- No training but need to be on DOA

TMS Training

	Standard Track
Theory complete	Yes
Practice sessions	Yes
Healthy volunteer data submitted	N = 5
Technique check	Yes

TMS Training

	Standard Track	**Fast Track**
Theory complete	Yes	Yes
Practice sessions	Yes	Yes
Healthy volunteer data submitted	N = 5	N = 2
Technique check	Yes	No

TMS Safety Checklist

Required for ALL participants

- Healthy volunteers during training and technique checks
- VERIFY patients

Requires physician sign-off

- Only once for healthy volunteers – review before each session

Should be kept on site as evidence of completion

Healthy volunteers

Practice the entire protocol
Consent healthy volunteers for practice sessions
$25 per session, maximum of $100
Submit healthy volunteer form with number of sessions completed to generate payment

After you have practiced:
Standard sites
- Submit 5 datasets per operator for checking
- We will arrange a technique check with you

Fast track sites
- Submit 2 datasets per operator for checking

Adverse events of special interest

TMS is considered safe and very low risk for those who pass the Safety Screening Checklist

Adverse events are very unlikely: 0.08% chance, or 8 in 10,000

Seizure – during or immediately after the TMS test
Syncope – due to procedure-related anxiety
Mild headache – usually transient and resolves without analgesia

TMS monitoring

Required for VERIFY patients

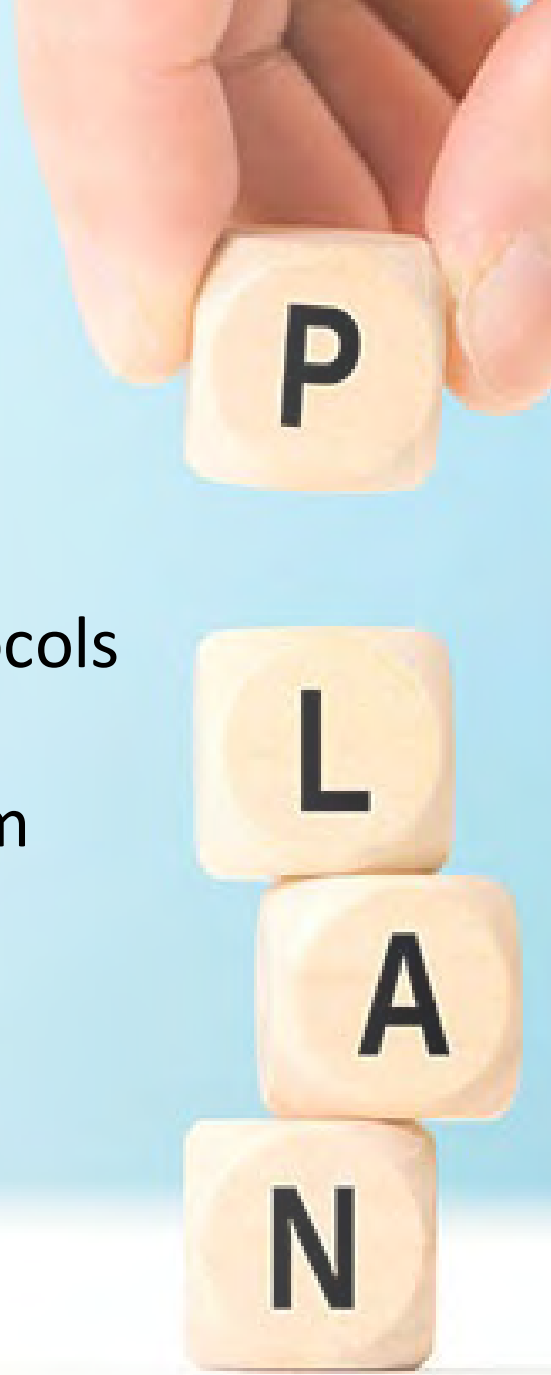
- Throughout the TMS test by visual observation
- Note time of last stimulus and continue observing while packing up
- Observe at 15 and 30 minutes after time of last stimulus
- You are looking for involuntary or unexpected limb movements
- Medical team assumes usual care after 30 minutes

Have a plan

Before you begin recruiting

Seizure management – medical staff who will use local protocols

Syncope and mild headache – transient and low risks of harm
Communicate these events to the patient's medical team



TMS Hotline

TMS Hotline available in June 2022
The number will be posted in “Emergency Help” in WebDCU
You can call or text

Monday – Friday 0800 – 2100h ET

For non-urgent questions you can email us at verify.study.tms@gmail.com

SAFE Score and TMS Training

verifytraining.blogs.auckland.ac.nz

SAFE and TMS Training Homepage

TMS Training

0. Introduction
1. TMS Overview
2. TMS Safety Checklist
3. EMG Technique
4. TMS Technique
5. Simple MEP Identification
6. Challenging MEP Identification
7. TMS Case Report Form
8. Practical TMS Training

Resources

MEGA-TMS Software Support

About Us

VERIFY

Imaging

Imaging Team

Dr. Achala Vagal; MD,MS

PI, Imaging management Center

Sholeh Bazrafshan, MD, MS

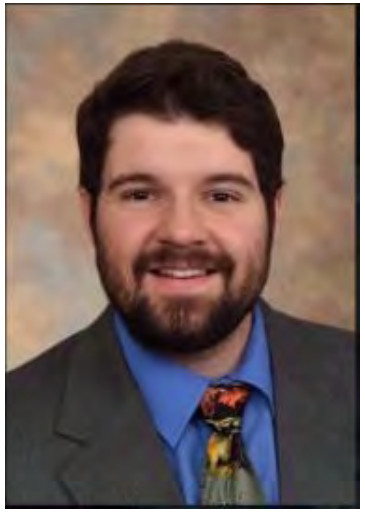
Imaging Project Manager

Vivek Khandwala, PhD

Database Manager

Tyler Behymer, BS

Imaging Project Manager



Brady J. Williamson, PhD

Research Assistant Professor

University of CINCINNATI

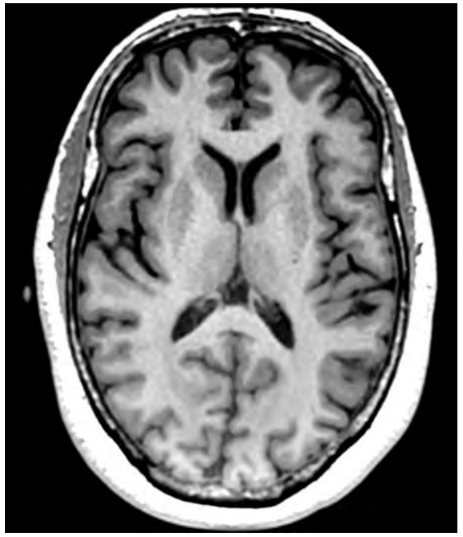
VERIFY

Updates

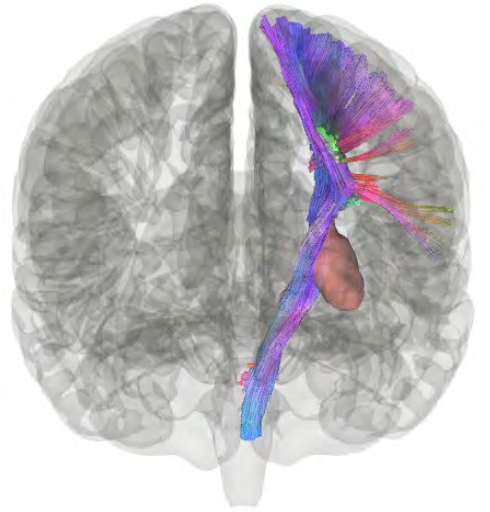
- 21 of 29 sites completed MRI survey
- 8 sites completed their protocol setup
  - 3 more very close
- 6 sites have completed/confirmed image upload training
  - Please work with us to complete this part of the workflow ASAP! We cannot collect phantoms until someone at your site it able to successfully upload images to Ambra

	MRI Survey Received
Baystate Medical Center	
University of Michigan University Hospital	
Duke University Hospital	
University of Maryland Medical Center	
UPMC Presbyterian Hospital	
University of Cincinnati Medical Center	
University of Utah Healthcare	
Emory University	
UVA Medical Center	
University of Wisconsin University Hospital	
UF Health Shands Hospital	
Houston Methodist Hospital	
Ronald Reagan UCLA Medical Center	
NYU Langone Medical Center	
UT Houston (Memorial Hermann Texas Medical	
MedStar Washington Hospital Center	
Massachusetts General Hospital	
Medical University of South Carolina	
Lahey Hospital & Medical Center	
UT Southwestern Medical Center	
Montefiore Medical Center	
University of Iowa Hospitals & Clinics	
Pennsylvania Hospital	
UCSF Medical Center	
San Francisco General Hospital	
OSU Wexner Medical Center	
University of Alabama Hospital	
Harborview Medical Center	
Penn State Hershey Medical Center	

Neuroimaging Protocol



- Required sequences of MRI brain for VERIFY
  - **DWI/ADC, FLAIR, T2, and GRE/SWI:** Routine clinical sequences
  - **3D-T1 MRI:** Not always routine clinical sequence
    - *High-resolution (1mm^3), high-tissue contrast (BRAVO, MPRAGE) T1-weighted image*



- Three scenarios
  - #1: **All MRI sequences** above (incl 3D-T1) are completed as standard of care (SOC) >/= of onset→no further VERIFY imaging needed
  - #2: **All MRI sequences except 3D-T1** are completed as SOC >/=24h of onset→perform 3D-T1 with DWI for VERIFY within 24-168h from onset
  - #3: **MRI not available** as SOC (ie, not performed or performed at <24h) from onset→perform full MRI for VERIFY within 24-168h from onset
  - ***NOTE: "Per patient" budget includes reimbursement for full MRI***
- If 3D-T1 not SOC, work with **Dr. Brady Williamson @** willi3by@ucmail.uc.edu to set it up
- Detailed imaging manual

What Imaging Needs to be Submitted?

- **MRI done at 24-168h** (whether acquired as SOC or study-specific)
  - DWI/ADC, FLAIR, T2, and GRE/SWI
  - 3D-T1 MRI

- **Acute neuroimaging at 0-24h** (only scans performed as SOC)
  - CT/CTA +/- CTP or MRI/MRA +/- MRP

- **Recurrent stroke imaging**
  - First choice: MRI if performed as SOC
  - Second choice: CT scan

How to Submit Imaging?

- All imaging needs to be submitted to core lab –imaging upload is part of payment schedule requirements

- ***Imaging Uploading Manual*** is provided with detailed instruction
    1) How to Submit Imaging
    2) Accessing Ambra Health®
    3) Uploading Images into Ambra Health®

Please contact **Tyler Behymer** @ behymetp@ucmail.uc.edu with any questions.

Best Practices Protocol Set-Up at Your Site

- Contact our team as **early** in the process as possible
- **All questions** are worth asking!
  - We do not mind the extra emails and taking time to answer any concerns you may have, so please reach out as often as needed
- Best if we can work directly with **someone in your radiology/MR dept**
  - Very important to receive your MRI questionnaire for correct contact information
- Most efficient way to achieve setup is to send us your **MRI imaging protocol export** as soon as possible from your scanner(s)
  - We can check the protocol(s) to see if study requirements are met

Phantom Testing

- Phantom testing is **crucial** to the success of the study
  - Ensures consistency across all sites so we know data is comparable
- We only require **standard ACR phantom** that should be available at all sites
  - Typically used for regularly scheduled (daily) scanner QC
- Phantom scan needed **only for study-specific T1**, not whole protocol
  - Only takes as long as the T1 sequence (~4.5-5 minutes)
  - **Maximum 10 min of your MRI tech's time**
- **Twice per year**, starting with study startup
- Needs to be collected **with any scanner hardware/software updates** so we can quantify any deviations

Once phantom MRI scan is approved by imaging core,

you have completed MRI set-up!

FAQs for Imaging

- Q: Which specific scan parameters need to match for the sequence to meet study requirements?
  - A: Sequence type (MPRAGE or BRAVO) and resolution (1mm isotropic)

- Q: How can I ensure that the study protocol is set up?
  - A: We are asking sites to send us the protocol export from their scanner(s) to ensure that the protocol is set up properly and for our records

- Q: Do we need a human volunteer scan after protocol setup?
  - A: No, we are only collecting phantoms before the site is ready to start scanning study participants

Questions on Imaging

- *Questions regarding image **protocol and acquisition**, please contact:*

Brady Williamson, PhD
Research Assistant Professor
University of Cincinnati
Department of Radiology
Email: willi3by@ucmail.uc.edu

- *Questions regarding **image upload**, please contact our imaging coordinator:*

Tyler P. Behymer, BS
Sr. Clinical Research Coordinator
University of Cincinnati College of Medicine
Department of Radiology
Email: behymetp@ucmail.uc.edu

Note: You can also contact AMBRA customer service via the Ambra database for individual upload issues, should they arise.

We will work with your Radiology contact for imaging set-up including phantom scans and imaging uploads

Safety Reporting

Adverse Events (AEs)

Procedures	STUDY VISIT 1 Screening & Consent Hour 48-96*	STUDY VISIT 2 Baseline Clinical Assessment Hour 48-120#	STUDY VISIT 3 Baseline Biomarker and Clinical History Assessment (ENROLLMENT) Hour 72-168**	STUDY VISIT 4 Post-TMS Hospital Discharge Day ± 1 or Post-TMS Day 5± 1, Whichever is Sooner	STUDY VISIT 5 Post-Hospitalization Phone Follow Up Day Day30 ± 7* By Phone	STUDY VISIT 6 Post-Hospitalization In-Person Assessment Day 90± 14*
Informed consent	X					
SAFE score	X					
Demographics	X					
Pregnancy Test, if applicable	X					
UE-FM		X				X
NIHSS		X				X
MRI***			X			
TMS			X			
Medical history			X			
Rehab Utilization Assessment				X	X	X†
Pre-stroke mRS without RFA		X				
mRS via RFA					X	X†
ARAT						X
MAL-14						X
10-Meter Walk Test						X
EQ5D						X†
MoCA						X†
Geriatric Depression Scale						X†
NeuroQOL Anxiety (8Q)						X†
Star Cancellation Test						X
Pain Visual Analog Scale (for only shoulder of affected side)						X†
Adverse Events (AEs)			X	X		
Serious AE and AE of Special Interest			X	X	X	X†
Complete CRFs	X	X	X	X	X	X†

What is an Adverse Events (AEs)?

- Any untoward medical occurrence or worsening of a preexisting medical condition in a research participant that does not necessarily have a causal relationship with the study procedures.

- AEs reported from time of enrollment (defined as having started TMS or study-specific MRI sequence) throughout initial hospitalization or up to 5 days post-TMS administration, whichever is sooner.

VERIFY

Adverse Events (AEs)

Procedures	STUDY VISIT 1 Screening & Consent Hour 48-96*	STUDY VISIT 2 Baseline Clinical Assessment Hour 48-120#	STUDY VISIT 3 Baseline Biomarker and Clinical History Assessment (ENROLLMENT) Hour 72-168**	STUDY VISIT 4 Post-TMS Hospital Discharge Day ± 1 or Post-TMS Day 5± 1, Whichever is Sooner	STUDY VISIT 5 Post-Hospitalization Phone Follow Up Day Day30 ± 7* By Phone	STUDY VISIT 6 Post-Hospitalization In-Person Assessment Day 90± 14*
Informed consent	X					
SAFE score	X					
Demographics	X					
Pregnancy Test, if applicable	X					
UE-FM		X				X
NIHSS		X				X
MRI***			X			
TMS			X			
Medical history			X			
Rehab Utilization Assessment				X	X	X†
Pre-stroke mRS without RFA		X				
mRS via RFA					X	X†
ARAT						X
MAL-14						X
10-Meter Walk Test						X
EQ5D						X†
MoCA						X†
Geriatric Depression Scale						X†
NeuroQOL Anxiety (8Q)						X†
Star Cancellation Test						X
Pain Visual Analog Scale (for only shoulder of affected side)						X†
Adverse Events (AEs)			X	X		
Serious AE and AE of Special Interest			X	X	X	X†
Complete CRFs	X	X	X	X	X	X†

- Thereafter, only AEs that meet the definition of an SAE or AEs of special interest will be reported.

AEs of Special Interest

Procedures	STUDY VISIT 1 Screening & Consent Hour 48-96*	STUDY VISIT 2 Baseline Clinical Assessment Hour 48-120#	STUDY VISIT 3 Baseline Biomarker and Clinical History Assessment (ENROLLMENT) Hour 72-168**	STUDY VISIT 4 Post-TMS Hospital Discharge Day ± 1 or Post-TMS Day 5± 1, Whichever is Sooner	STUDY VISIT 5 Post-Hospitalization Phone Follow Up Day Day30 ± 7* By Phone	STUDY VISIT 6 Post-Hospitalization In-Person Assessment Day 90± 14*
Informed consent	X					
SAFE score	X					
Demographics	X					
Pregnancy Test, if applicable	X					
UE-FM		X				X
NIHSS		X				X
MRI***			X			
TMS			X			
Medical history			X			
Rehab Utilization Assessment				X	X	X†
Pre-stroke mRS without RFA		X				
mRS via RFA					X	X†
ARAT						X
MAL-14						X
10-Meter Walk Test						X
EQ5D						X†
MoCA						X†
Geriatric Depression Scale						X†
NeuroQOL Anxiety (8Q)						X†
Star Cancellation Test						X
Pain Visual Analog Scale (for only shoulder of affected side)						X†
Adverse Events (AEs)			X	X		
Serious AE and AE of Special Interest			X	X	X	X†
Complete CRFs	X	X	X	X	X	X†

What are the AEs of Special Interest?

1. Seizure, during or within 1 hour of TMS completion

2. AEs deemed by the site investigator as potentially related to study participation

VERIFY

Serious Adverse Events

Procedures	STUDY VISIT 1 Screening & Consent Hour 48-96*	STUDY VISIT 2 Baseline Clinical Assessment Hour 48-120#	STUDY VISIT 3 Baseline Biomarker and Clinical History Assessment (ENROLLMENT) Hour 72-168**	STUDY VISIT 4 Post-TMS Hospital Discharge Day ± 1 or Post-TMS Day 5± 1, Whichever is Sooner	STUDY VISIT 5 Post-Hospitalization Phone Follow Up Day Day30 ± 7* By Phone	STUDY VISIT 6 Post-Hospitalization In-Person Assessment Day 90± 14*
Informed consent	X					
SAFE score	X					
Demographics	X					
Pregnancy Test, if applicable	X					
UE-FM		X				X
NIHSS		X				X
MRI***			X			
TMS			X			
Medical history			X			
Rehab Utilization Assessment				X	X	X†
Pre-stroke mRS without RFA		X				
mRS via RFA					X	X†
ARAT						X
MAL-14						X
10-Meter Walk Test						X
EQ5D						X†
MoCA						X†
Geriatric Depression Scale						X†
NeuroQOL Anxiety (8Q)						X†
Star Cancellation Test						X
Pain Visual Analog Scale (for only shoulder of affected side)						X†
Adverse Events (AEs)			X	X		
Serious AE and AE of Special Interest			X	X	X	X†
Complete CRFs	X	X	X	X	X	X†

What are Serious Adverse Events (SAEs)?

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is an important medical event that may jeopardize the pt or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in above.

VERIFY

SAEs and AEs of Interest

Sites must report SAEs and AEs of interest in WebDCU™ within **24 hours** of site awareness of the event

Relevant information must be provided: description of event, date/time of onset, date of resolution, severity, suspected relationship to the study procedures, and action taken

Additional supporting documentation may be requested by NCC

All SAEs, whether related or not related to study procedures, and AEs of special interest, must be collected from the time of enrollment through the end of study for that participant

Unanticipated Problems

Unanticipated Problems (UPs) vs. AEs:

- An unanticipated problem is unexpected, whereas an adverse event may be either expected or unexpected. Unanticipated problems may or may not be adverse events. Adverse events relate to harm to participants; unanticipated problems may involve an increased risk of harm even if no actual harm occurred.

Reporting of UPs:

- The investigator will report any unanticipated problems and unanticipated adverse device effect to the reviewing IRB (Advarra), sponsor (Project Managers) and the contact PI (Dr. Khatri).
- Report within 10 working days from site awareness.

Examples of UPs:

- A breach in confidentiality resulting from disclosure of confidential information that may involve risk to the subjects or others.
- Complaint of a participant or family member that indicates an unanticipated risk.
- Harm or risk of harm to research staff.
- Laboratory or medication errors that may involve potential risk to the individual or others.
- Any deviation from the IRB-approved protocol that increases risk or affects the participants' rights, safety, or welfare.

Protocol Deviations

Definition:

- Any noncompliance with the clinical study protocol, International Conference on ICH GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

Responsibilities:

- It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations that involve risk to participants or others.
    - Report within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity.

Examples:

- Enrolling a participant who did not meet all the inclusion/exclusion criteria.
- Failing to obtain or document informed consent prior to initiation of study procedures.
- Conducting a study visit outside of the required timeframe.
- Failing to report unanticipated problems involving risks to participants or others to the IRB and sponsor.

Protocol Deviation- Poll Question

Question:

Study visit 6 was completed via telephone. Which of the following assessments would be considered a protocol deviation if completed in this format?

A) Rehab Utilization Assessment
B) Geriatric Depression Scale
C) MoCA
D) NeuroQOL Anxiety (8Q)

Informed Consent Overview

WebDCU™ CTMS Training

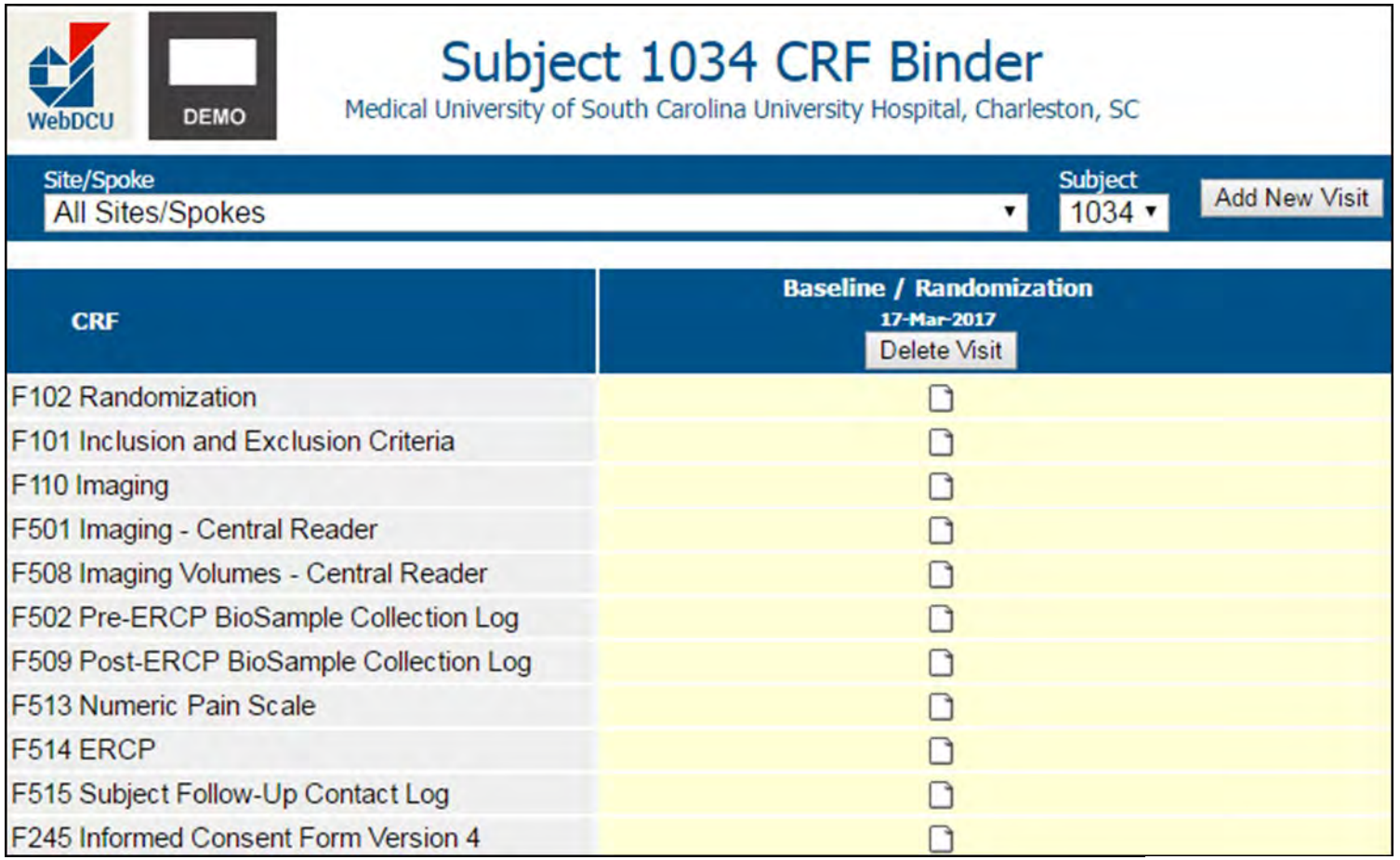
- WebDCU Training: https://dcu.musc.edu/campus/
  - General Overview
  - Data Training
  - Regulatory Management
  - Delegation of Authority Log

Obtaining Informed Consent

- Use the most current cIRB approved version of the ICF when obtaining consent
  - Your eConsent will always be the most recent version of the approved ICF.
  - All approved versions must be uploaded into WebDCU™ immediately upon receipt from the NCC.
  - eConsent will be updated by NCC accordingly.
- Consent should be obtained ONLY by staff who have been delegated this responsibility on the DOA
- eConsent will ensure that all sections have been correctly signed/dated by subject/person obtaining consent.
- Subject must personally sign the econsent. No LAR allowed

Remote Monitoring of Informed Consents

- eConsents will be uploaded by sites as PDFs into WebDCU™ and remotely monitored by the NDMC team.



Common DCRs/queries on Informed Consents

- Do utilize consent process checklist to confirm the consent process is being followed
- eConsents uploaded to WebDCU should not be redacted & all pages should be included in the uploaded PDF packet
- Person obtaining consent was not designated to do so on the site DOA
- Do generate a Note-To-File explaining consent errors, immediate response, and corrective action and upload with the consent form

THANK YOU!

Questions?

Closing Remarks

Extra Slides

Staff Roles at Each Clinical Site

PREMISES FOR STUDY STAFFING:

1. Strongly preferred that FM and ARAT are performed by PT/OT
2. The study requires that FM at Study Visit 2 & 6 is performed by same person
3. Neither TMS operator nor TMS assistant should do 90-day FM or ARAT
4. Site PIs may not have daily availability at many sites
5. Individual variations to recommended model may be needed

STAFF MEMBERS TO BE TRAINED AND CERTIFIED AT SITES:

1. Site PI
2. 1^0 SC
3. 1^0 PT/OT
4. At least one additional staff member(s) and more encouraged
   - 2^0 SC or 2^0 PT/OT

Please Train **2 People** for Each Sets of Trainings:
(1) TMS (2) ARAT+FM, & (3) Other Behavioral Assessments

RECOMMENDED VERIFY SITE TEAM MODEL

	Visit 1: Screening/Consent	Visit 2 & 3 (Inpatient)				Visit 4: Post-TMS Hospital Assessment (DC Day or D5 Post-TMS, whichever is Sooner)	Visit 5: Post-hospitalization Phone Follow Up (30d)	Visit 6 (90d) (Outpatient)	
		Baseline Clinical Assessments and MRI Facilitation (except FM)	FM	TMS Operator (TMS-trained)	TMS Assistant (no training)			FM and ARAT	Rest of Behavioral Assessments
1^0 SC	X	X		X		X	X		X
1^0 PT/OT			X					X	
2^0 SC or 2^0 PT/OT					X				
Site PI	Supervisory, may serve PT/OT or TMS role in some sites, or be available for backup in other sites								

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		Baseline Clinical Assessments and MRI Facilitation (except FM)	FM	TMS Operator (TMS-trained)	TMS Assistant (no training)			FM and ARAT	Rest of Behavioral Assessments
1^0 SC	X	X		X		X	X		X
1^0 PT/OT			X					X	
2^0 SC or 2^0 PT/OT					X				
Site PI	Supervisory, may serve PT/OT or TMS role in some sites, or be available for backup in other sites								