Validation of Early Prognostic Data for Recovery Outcomes after Stroke for Future, Higher Yield Trials: A Biomarker Validation Study

Protocol V1.6 Training

Virtual Training Agenda

1. **Protocol Overview**
   - Study objectives
   - Primary Aims
   - Exploratory Aims
   - Inclusion/exclusion criteria
   - Blinding
   - Consent
   - AE's and reportable events

2. **Virtual Training Overview**
   - Workflow and Study personnel roles and responsibilities
   - TMS
   - Behavioral measures and training

3. **Imaging**
   - VERIFY MRI Protocol
   - What imaging is collected
   - Imaging upload
   - Phantom Scans

VERIFY Leadership Team

Principal Investigators:
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University of Cincinnati

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University of California, Los Angeles

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University of Auckland, New Zealand

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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
PRIME Project Manager for VERIFY
University of Cincinnati

VERIFY Leadership Team

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 for VERIFY

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

Catherine Dillon, MS
NDMC PI for VERIFY

NINDS Program Officer

Scott Janis, PhD

Study and Protocol Overview

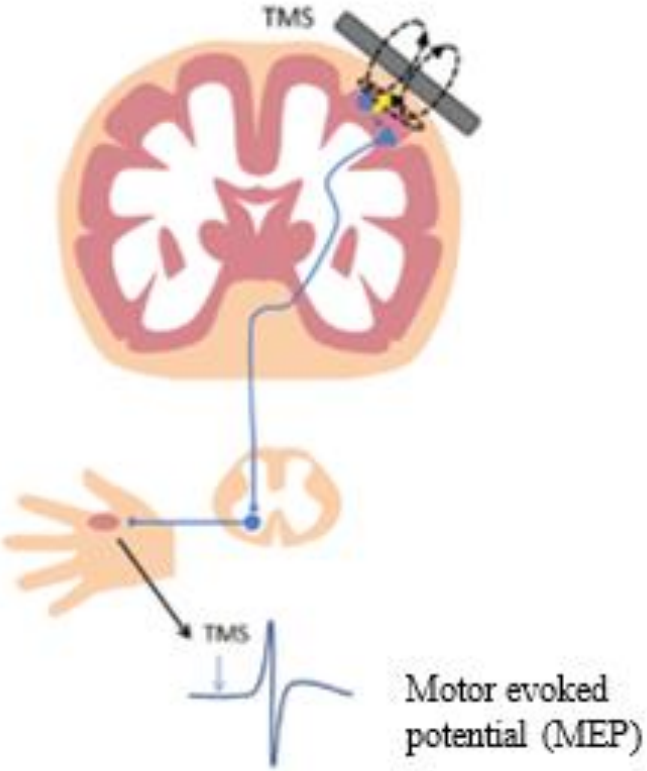
Study Objective

- 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)

Neurophysiology Biomarker

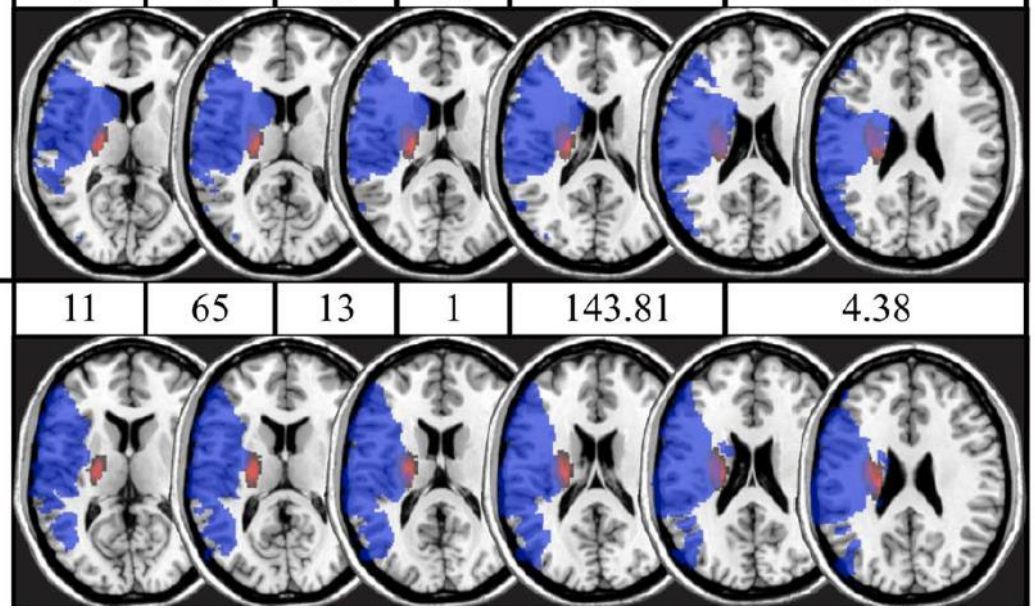
- Transcranial magnetic stimulation (TMS) of ipsilesional motor cortex
- Assess for motor evoked potentials (MEP) in either the extensor carpi radialis and/or first dorsal interosseous
- Presence of MEPs (MEP+) indicates **functionally intact** ipsilesional corticospinal system



Neuroimaging Biomarker

- MRI-DWI
- Assess DWI lesion load along the ipsilesional corticospinal pathways
- Greater lesion load indicates greater **structural damage**

Patients	FM-UE		NIHSS		Lesion Size (cc)	Weighted Lesion Load (cc)
	Acute	3 mo.	Acute	3 mo.		
A	8	8	18	11	149	9.19
B	11	65	13	1	143.81	4.38



Feng, Annals of Neurology, 2015

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

Key Eligibility Criteria—Inclusion

- Age **18 years** or older
- Unilateral **symptomatic** stroke due to ischemia or intracerebral hemorrhage. (Note: **Bilateral acute stroke is permitted if the stroke that is contralateral to the index stroke is asymptomatic).**
- **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
- Provision of signed and dated informed consent form within 48 to 96 hours of stroke onset, (or time last known well).
  - Note: Participant is considered enrolled upon starting TMS (at least one stimulation is delivered) or starting study-specific MRI pulse sequence (at least one MRI beep occurs)
- Stated willingness to comply with all study procedures and availability for the duration of the study, including Day 90 visit which must occur in-person.
- Fluent in **English or Spanish**

See protocol for full inclusionary/exclusionary criteria

Key Exclusion Criteria

- **UE injury or conditions** on paretic side that limited use prior to the stroke
  - *Examples include, amputation, crippling arthritis, substantial hereditary deformity, severe rotator cuff injury and severe brachial plexus injury.*
- **Legally blind**
  - *20/200 or worse visual acuity in better eye, despite corrective lenses and glasses*
- **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
- **Symptomatic stroke** in any location **within 30 days** prior to index stroke.

Key Exclusion Criteria Cont'd

- Contraindications **to noncontrast MRI or TMS**
- Unable to perform assessments/testing in **key time points**
  - Behavioral assessments within 48-120 hours of LKW
  - TMS or MRI within 72-168 hours of LKW
  - Follow up in-person at day 90
- Cognitive or communication impairment **precluding informed consent** by the participant.

  When in doubt, consider using the ICF comprehension questions provided in the "Toolbox" tab in WebDCU. Both English and Spanish versions are provided. If comprehension seems unlikely based on the responses, do not consent.
- **Pregnancy**

See protocol for full inclusion/exclusionary criteria

Eligibility Questions

Consent/enrollment questions?

- Email PMs (Lisa & Kalli) and VERIFY PIs (Pooja, Steve, Cathy, & Achala) <u>altogether</u>
  - One of us will answer back promptly

Mundo, Lisa (mundokl) <mundokl@ucmail.uc.edu>;
Beasley, Kalli (beasleki) <beasleki@ucmail.uc.edu>;
Khatri, Pooja (khatrip) <khatrip@UCMAIL.UC.EDU>;
Steve C. Cramer <sccramer@mednet.ucla.edu>;
Cathy Stinear <c.stinear@auckland.ac.nz>;
Vagal, Achala (vagala) <vagala@ucmail.uc.edu>

Study Schema

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

Visit 1:
Hour 48-96

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

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

**Can occur on same day*

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

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.

The study-required 3D-T1 MRI sequence (with a concurrent DWI) should ideally be performed within 72-168 hours. If the 3D-T1 was already performed clinically within 24-72 hours, then this will be accepted as an exception. For the remainder of the sequences, a clinical MRI is acceptable, even if performed at <24 hours from onset.

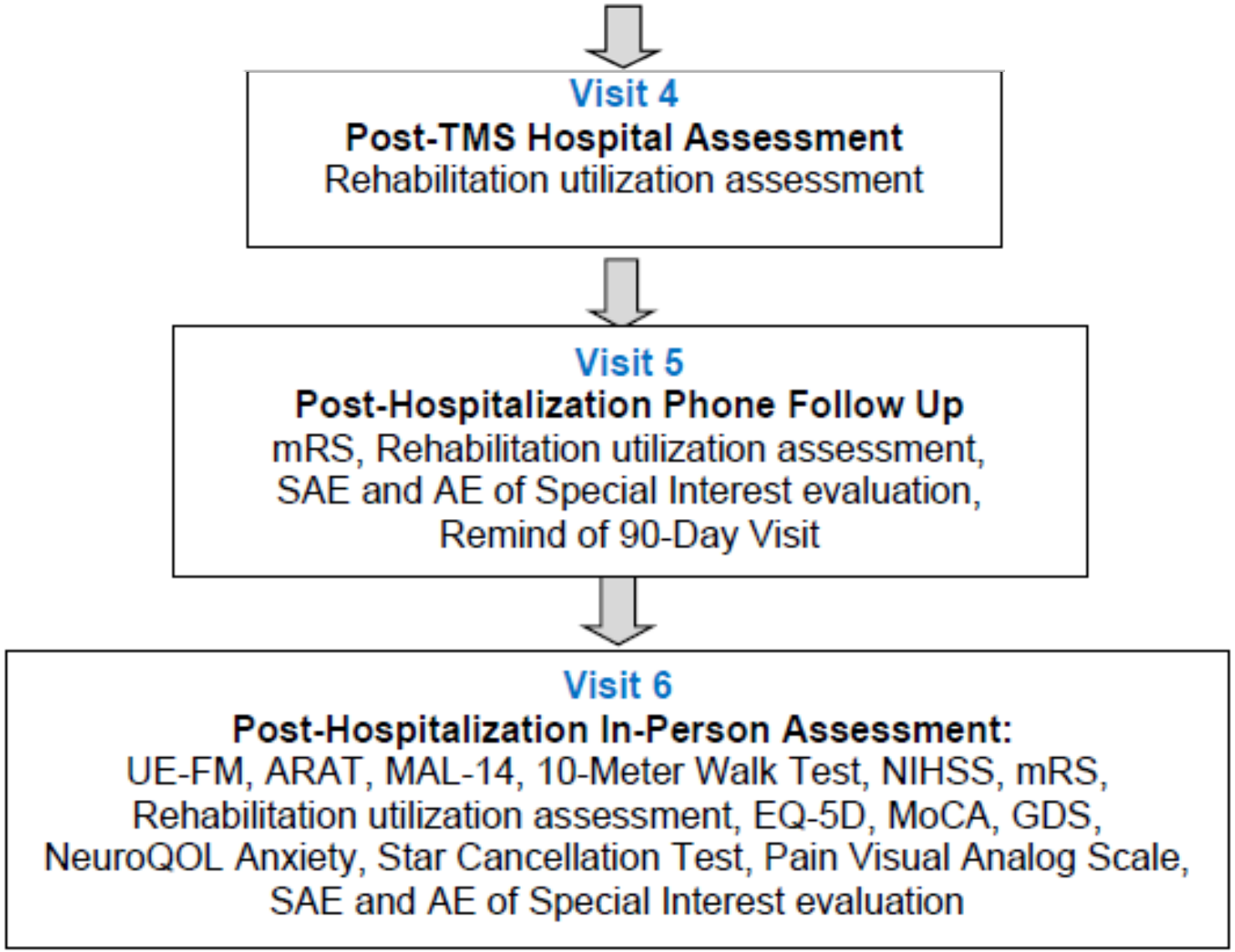
VERIFY

Study Schema

Visit 4:
Discharge Day±1

Visit 5:
Day 30±7

Visit 6:
Day 90±14



MEASURES TO MINIMIZE BIAS: BLINDING

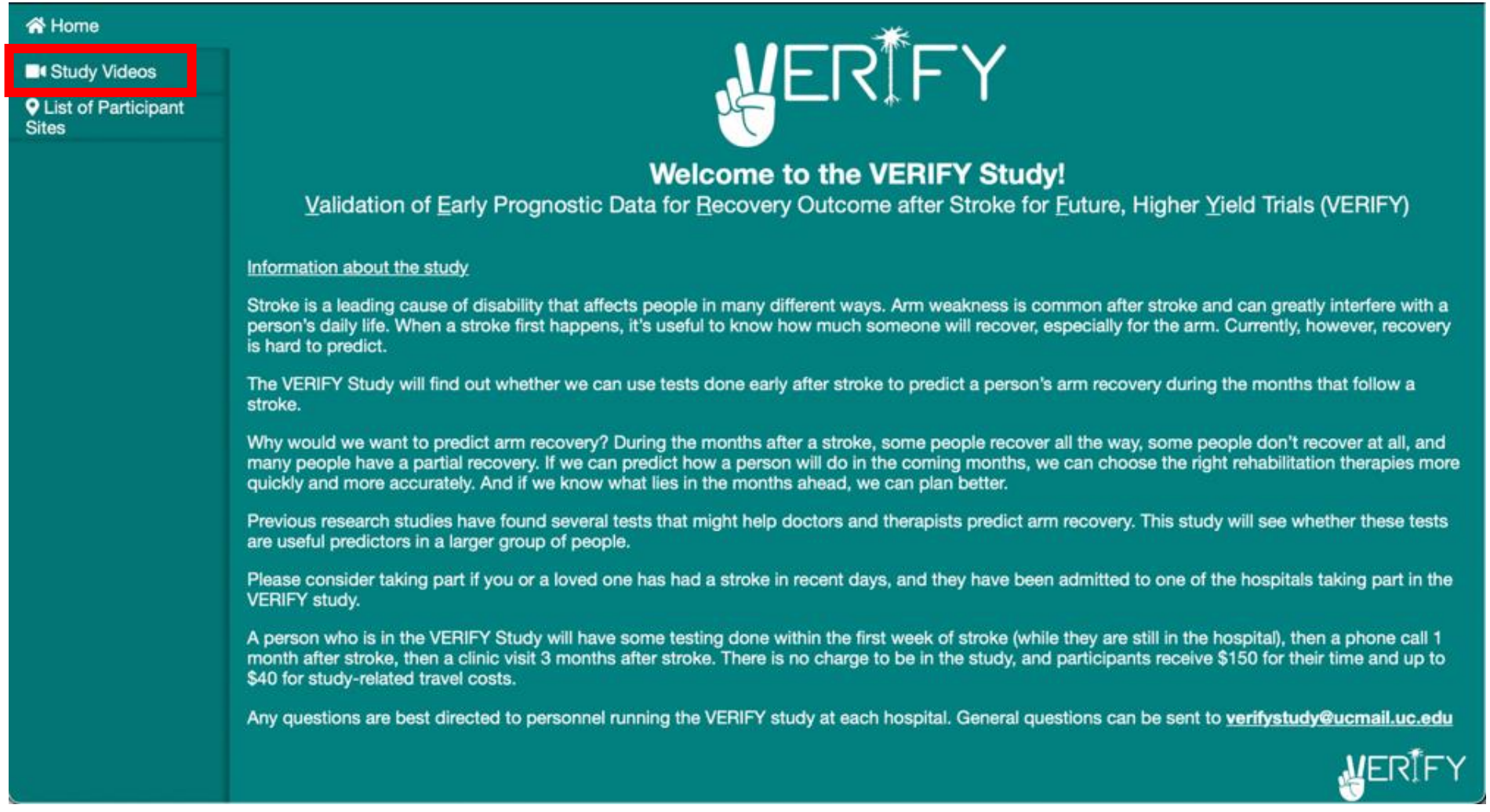
- Central reviewers of TMS and MRI data will be blinded to the results of all clinical assessments.

- Both participants and UE-FM & ARAT assessors will be blinded to TMS and MRI findings.

- Baseline/Day 90 UE-FM & Day 90 ARAT outcomes will be obtained by a trained investigator who was not involved with the acquisition of the TMS data and did not review the MRI data.

Recruitment Tools

- Patient-Facing Website: https://theverifystudy.com (includes study informational videos in both English and Spanish)



Study Windows –Study Tool

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*

VERIFY Schedule of Activity Calculator

Subject ID: _____

Date and Time of Stroke Onset/Last known well:	3/12/2023 11:00 AM
Hospital Discharge Expected date:	3/17/2023 1:00 PM

Visit #	Visit Window opens:	Target Date/Time:	Visit Window closes:
Visit #1 Hour 48-96 (Informed Consent, SAFE score Demographics and Pregnancy Test)	3/14/2023 11:00 AM	within hourly window	3/16/2023 11:00 AM
Visit #2 Hour 48-120 (UE-FM, Pre-stroke mRS and NIHSS)	3/14/2023 11:00 AM	within hourly window	3/17/2023 11:00 AM
Visit #3 Hour 72-168 (MRI, TMS and Medical History)	3/15/2023 11:00 AM	within hourly window	3/19/2023 11:00 AM
Visit #4 Day discharged from hospital ± 1	3/16/2023 1:00 PM	3/17/2023 1:00 PM	3/18/2023 1:00 PM
Visit #5 Day 30 ± 7	4/4/2023 11:00 AM	4/11/2023 11:00 AM	4/18/2023 11:00 AM
Visit #6 Day 90 ± 14	5/27/2023 11:00 AM	6/10/2023 11:00 AM	6/24/2023 11:00 AM

A schedule of activity calculator is available for you to use in the Toolbox tab of WebDCU. This calculator can help determine the timeframe a visit should occur (when a visit window opens and closes).

Informed Consent

- Consent should be obtained ONLY by staff who have been delegated this responsibility on the DOA

- Subject must be able to consent themselves
  - No LARs are allowed

- An impartial witness may be used when the subject is cognitively capable of providing consent, BUT is:
  - Is illiterate
  - Is consenting using a short form
  - Is unable to physically sign AND date the consent
  - The participant should make their mark if able
- An impartial witness should be used to attest to the process being followed correctly as good clinical practice. If the site cannot find an impartial witness, then they can create a note-to-file to detail the process followed, and the reason an impartial witness was unable to be used. The site can then add the NTF to the ICF they upload for the subject.

Safety Reporting

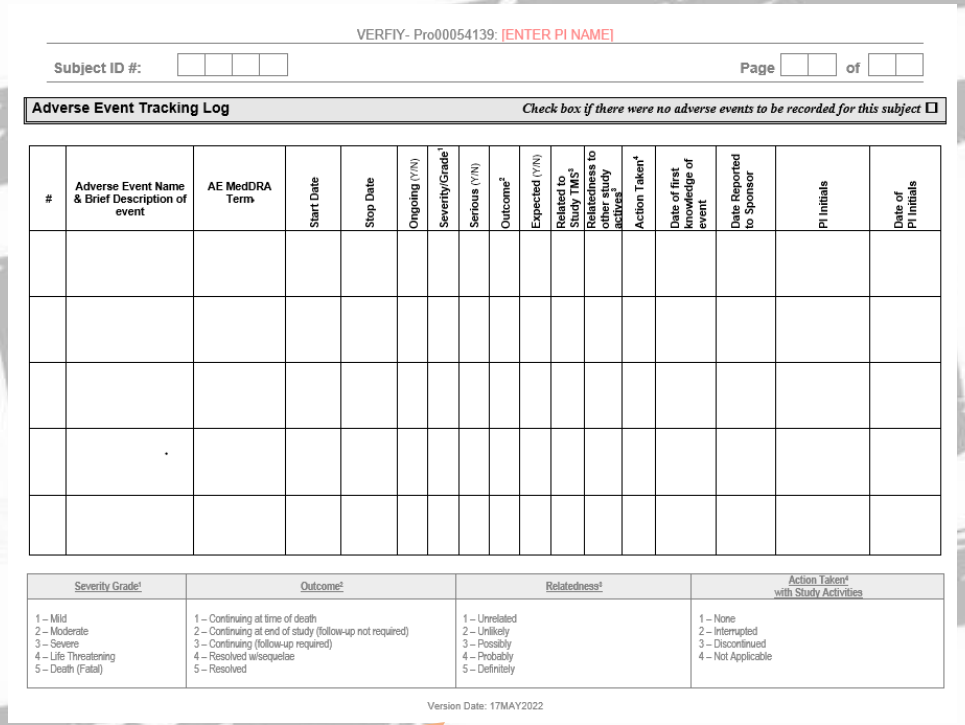
Sites must report SAEs and AEs of interest in WebDCU™ within 24 hours of site awareness of the event

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

AE/SAE log template available in the Toolbox



VERFIY- Pro00054139: [ENTER PI NAME]

Subject ID #: ☐☐☐☐ Page ☐☐ of ☐☐

Adverse Event Tracking Log *Check box if there were no adverse events to be recorded for this subject* ☐

#	Adverse Event Name & Brief Description of event	AE MedDRA Term	Start Date	Stop Date	Ongoing (Y/N)	Severity/Grade[1]	Serious (Y/N)	Outcome[2]	Expected (Y/N)	Related to Study TMS[3]	Relatedness to other study activities[3]	Action Taken[4]	Date of first knowledge of event	Date Reported to Sponsor	PI Initials	Date of PI Initials

Severity Grade[1]	Outcome[2]	Relatedness[3]	Action Taken[4] with Study Activities
1 – Mild 2 – Moderate 3 – Severe 4 – Life Threatening 5 – Death (Fatal)	1 – Continuing at time of death 2 – Continuing at end of study (follow-up not required) 3 – Continuing (follow-up required) 4 – Resolved w/sequelae 5 – Resolved	1 – Unrelated 2 – Unlikely 3 – Possibly 4 – Probably 5 – Definitely	1 – None 2 – Interrupted 3 – Discontinued 4 – Not Applicable

Version Date: 17MAY2022

Safety Reporting

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

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.
- Reported from time of enrollment to completion of study

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

- Reported from time of enrollment to completion of study

Protocol Deviations

Definition:

- Protocol Deviations:
  - 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 **Major Protocol Deviation** (i.e., those that involve potential risk to participants or others) to the **WebDCU Issues Table** within 24 hours of knowledge of the deviation. NCC PM will submit applicable protocol deviations to ADVARRA within 10 days.
- Note that study leadership will track **minor protocol deviations.** Should they accumulate, they may require cIRB/FDA reporting and corrective action.

Examples:

- **Protocol Deviations:**
  - 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.

Unanticipated Problems

Definition:

- Unanticipated Problems: Any incidence, experience, or outcome that is:
  - Unexpected (in terms of nature, severity, or frequency) given the information provided in research-related documents and the characteristics of the subject population being studied
  - Related or possibly related to participation in the research
  - Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized

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.
  - Sites report UAPs to the **WebDCU Issues Table** within 24 hours of knowledge of the event. NCC PMs will report applicable events to ADVARRA within 10 days.

Examples:

- **Unanticipated Problems:**
  - 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.

Serious and Continuing Noncompliance: Definitions

- **Serious Noncompliance Definition:** Any action or omission in the conduct of or oversight of research involving human subjects and that affects the rights and welfare of subjects, increases risk to subjects, increases risk to subjects, or compromises the scientific integrity or validity of the research

- **Continuing Noncompliance Definition:** A pattern of repeatedly failing to comply with applicable regulations, the IRB's Handbook, and/or the determinations and requirements of the IRB that may affect subject's rights and welfare, increases risks to subjects, or may compromise the scientific integrity or validity of the research

Serious and Continuing Noncompliance: Examples and Responsibility

Noncompliance Examples:

- Failure to respond to or resolve previous allegations or findings of noncompliance.
- Inadequate oversight of ongoing research
- Late reporting of an unanticipated problem
- Failure to follow the protocol
- Repeated failures to provide or review progress reports resulting in lapses of IRB approval

Site Responsibility:

- It is the responsibility of the site investigator to use continuous vigilance to identify and report any serious and continuing noncompliance
    - Sites report noncompliance to the **WebDCU Issues Table** within 24 hours of knowledge of the event. NCC PMs will report applicable events to ADVARRA within 10 days.

Training Overview

Staff Roles at Each Clinical Site

PREMISES FOR STUDY STAFFING:

1. FM and ARAT should be performed by PT/OT, MD or site personnel with experience who have obtained approval from study team
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 FM or ARAT assessments
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 SC
3. 1 PT/OT
4. At least one additional staff member(s) and more encouraged
   - 2 SC or 2 PT/OT

Please Train **<u>2 People</u>** 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 SC	X	X		X		X	X		X
1 PT/OT			X					X	
2 SC or 2 PT/OT					X				
Site PI	Supervisory, may serve PT/OT or TMS role in some sites, or be available for backup in other sites								

TMS

TMS Team

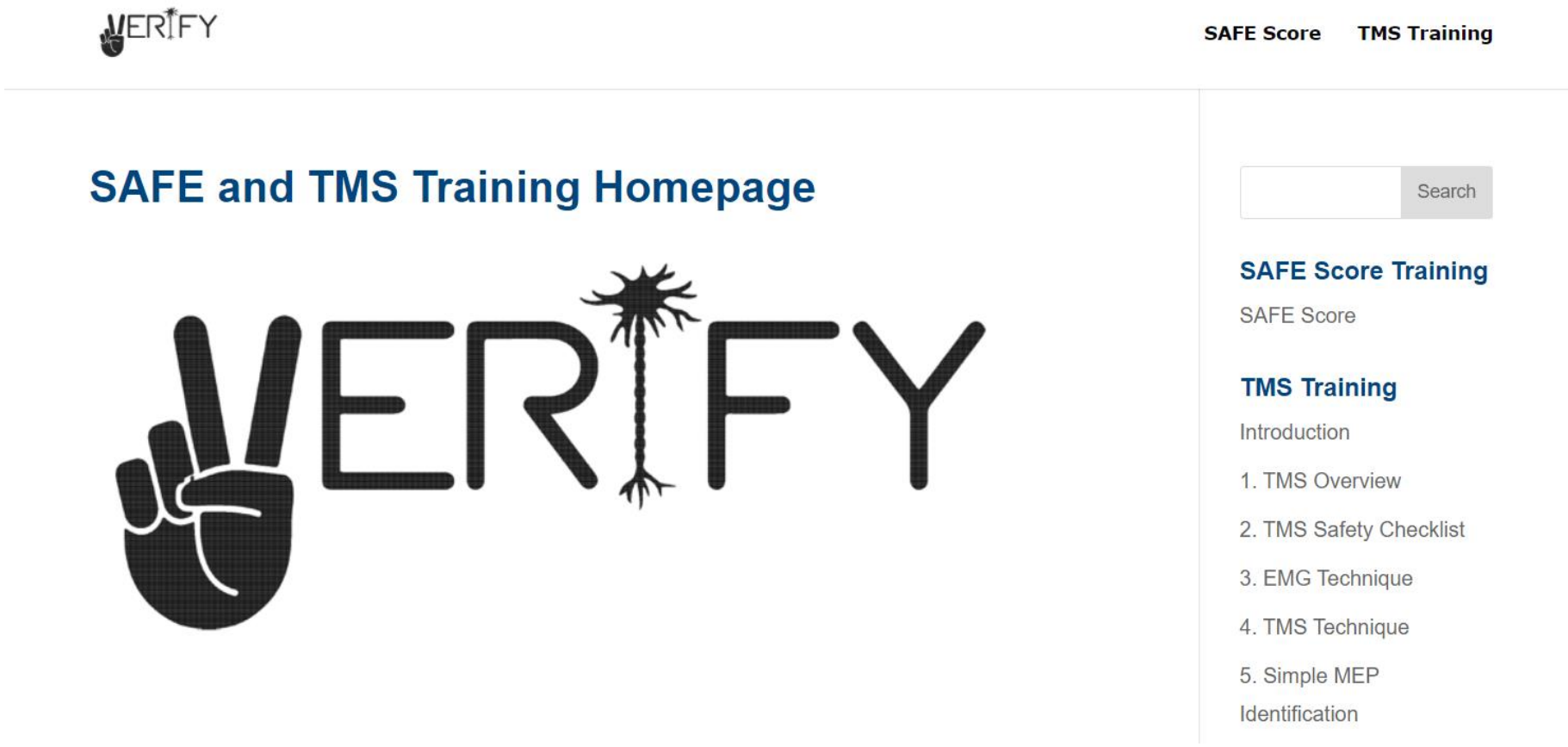
Prof Cathy Stinear

Dr Harry Jordan

SAFE Score and TMS Training

verifytraining.blogs.auckland.ac.nz

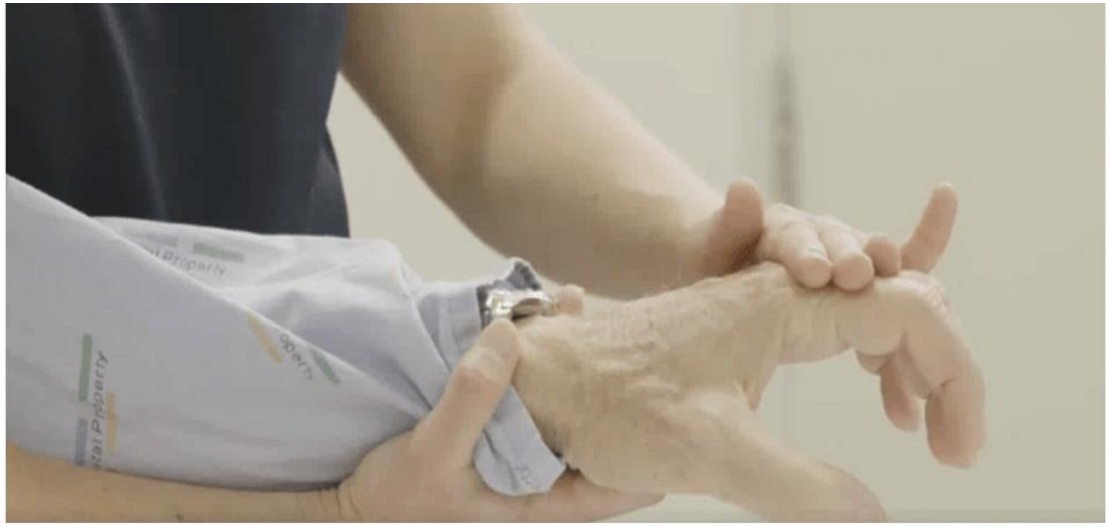
(Click Link to access)



SAFE Score Training

- One page of reading
- A practice quiz – 70%
- A final quiz – 80%
- Certificate sent to you
- Certificate expires after 1 year

Shoulder Abduction out of 5



Finger Extension out of 5

TMS Training

Completed by TMS Operators

THEORY

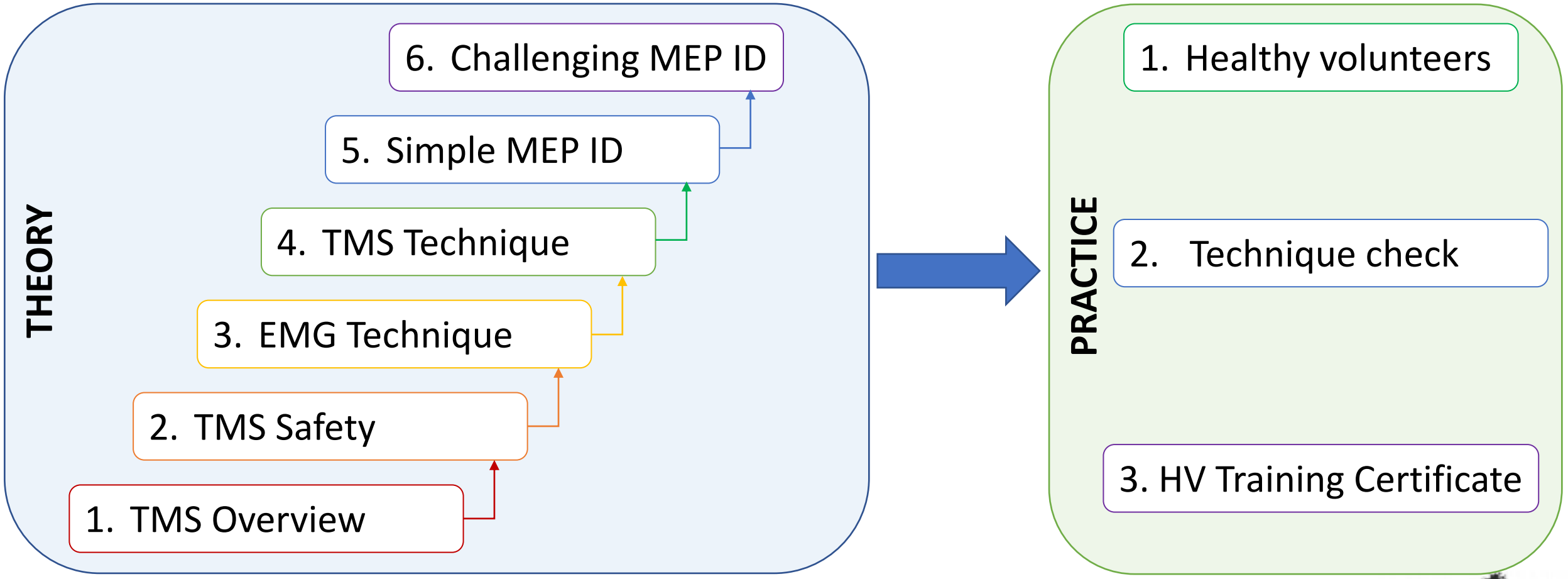
- Online
- Self-directed

PRACTICE

- Healthy volunteers
- Technique check

- Standard Track Training: Sites with no or limited TMS experience. Technique check required.
- Fast Track Training: Sites with TMS expertise in their VERIFY team. No external technique check required.

TMS Training Overview



TMS Online Training

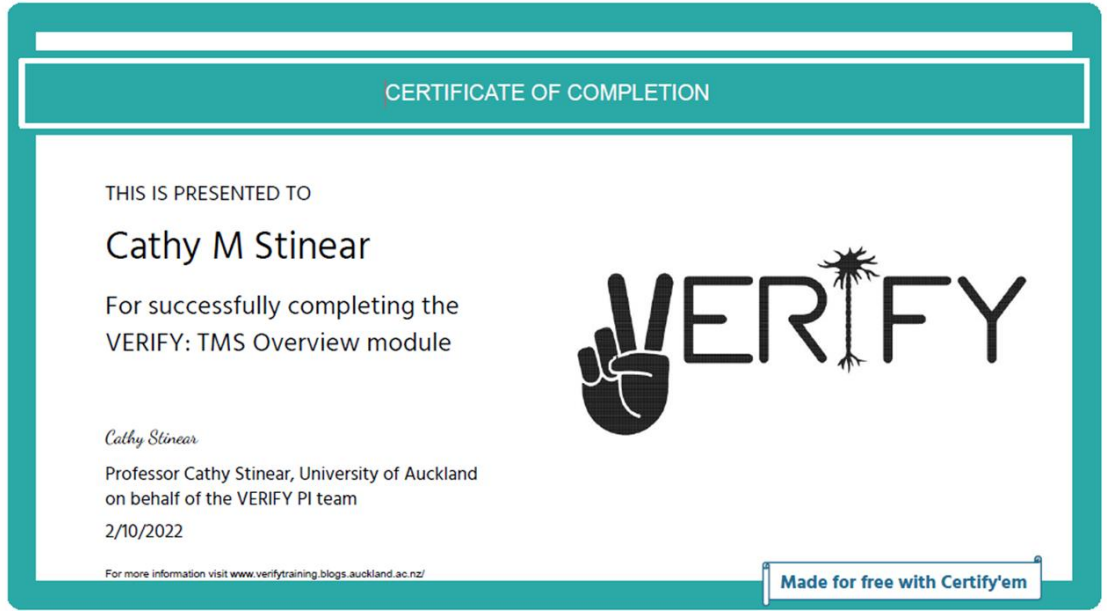
THEORY

Modules 1-6

- Assessed with quizzes – 10 questions
- Practice Quiz 70%
- Final Quiz 80%
- Certificates

Modules 7-9

- Help with practical TMS training
- Not assessed


CERTIFICATE OF COMPLETION

THIS IS PRESENTED TO

Cathy M Stinear

For successfully completing the VERIFY: TMS Overview module

VERIFY

Cathy Stinear

Professor Cathy Stinear, University of Auckland on behalf of the VERIFY PI team

2/10/2022

For more information visit www.verifytraining.blogs.auckland.ac.nz/

Made for free with Certify'em

- Certificates are obtained after completing each of modules 1-6
- These certificates do not need to uploaded anywhere- just filed locally
- The TMS team will track the completion of all modules and TMSOs will be sent an email greenlighting them to start the practical TMS training

VERIFY

TMS Training

PRACTICE

1. Healthy volunteers
2. Technique check
3. HV Training Certificate

1. Information Sheet
2. Written Informed Consent/eConsent
3. TMS Safety Checklist

$25 per session
Up to 4 sessions per individual
$1,000 provided per site

Standard: 5 datasets approved per TMS Operator
Fast track: 2 datasets approved per TMS Operator

These datasets need to be uploaded to a REDcap website, and further details regarding the practical training can be found HERE

RedCAP TMS Data Entry Access

- To obtain access to the REDCap VERIFY TMS data entry project each user must request a CCHMC specific REDCap user ID by following the below instructions:
  - Cincinnati Children's CCHMC REDCap Access:
    - For individuals who do not have access to CCHMC REDCap, a self-request survey can be filled out here: https://redcap.research.cchmc.org/surveys/?s=RE8EHCK9YH
    - When asked, 'Would you like to inform another person of your REDCap Account Creating and REDCap Username', please respond 'Yes' and enter verifystudy@ucmail.uc.edu – this will allow us to add you as a user to your VERIFY eConsent project.
  - For individuals who have CCHMC REDCap access, you can login at the following link:
    - https://redcap.research.cchmc.org
      - Ensure Cincinnati Children's Hospital Medical Center is selected under the Select your identity provider section, then click Go to Login page button. REDCap will redirect you to the CCHMC federated login page. Enter your CCHMC credentials (individual's email address) and click Login.
        - As of January 2022, CCHMC REDCap will use Multi Factor Authentication (MFA) and users will be prompted to use Duo for authentication. Sites will need to set up Duo MFA Registration to get their account ready: https://mfa.research.cchmc.org (please refer to step by step instructions here: https://confluence.research.cchmc.org/display/RESITHUB/Duo+MFA+Registration).
      - Once authenticated with CCHMC, users will be redirected back to REDCap.
- Email PMs Lisa Mundo and Kalli Beasley to be manually added to the VERIFY specific projects
  - Note: to be provided access the user must be delegated the consenting task on the DOA in WebDCU to gain access to the HV consenting project

TMS Safety

- TMS Safety Checklist is Required for ALL participants
    1. Healthy volunteers during training and technique checks
    2. Patients consented/enrolled in VERIFY study
        - Checklist should be kept on site as evidence of completion in the subject binder

- TMS Safety Training:
    - The TMS Safety checklist should be completed/signed by a **trained** Site Coordinator or TMS Operator.
        - Training is available in module 2 HERE
    - Module 2 training certificate should be kept on site as evidence of completion in the regulatory binder.

- A TMS Assistant is required for every TMS session

- The subject & study personnel who is performing the baseline FM and 90-Day FM & ARAT should be blinded to the TMS results.

MEP Status Blinding

The patient and family should always be blinded to their MEP status (+/-)

Suggestions:

- Practice with your healthy volunteers.
- Resist the urge to make positive comments when you see MEPs, or negative comments if you don't.
- Use coded language to be discreet and keep the subject blinded to their MEP status.
- For example, the TMSO can just tell the assistant to increase the intensity or that the test is finished, without telling them anything about whether MEPs were observed.

TMS Training- Technique Check

PRACTICE

1. Healthy volunteers
2. Technique check
3. HV Training Certificate

TMSOs at standard track sites will have to complete an in-person technique check with a regional expert

To qualify for scheduling the onsite technique check standard track sites must have completed the following:

1. All TMSOs have completed the 6 online training modules
2. All TMSOs have met with the TMS study team over Zoom before or after submitting their first dataset in RedCAP
3. Each TMSO has had at least one dataset approved

Technique checks are optional for TMSOs at fast track sites but we encourage the local TMS expert to check the TMSOs are safe and capable of performing the protocol

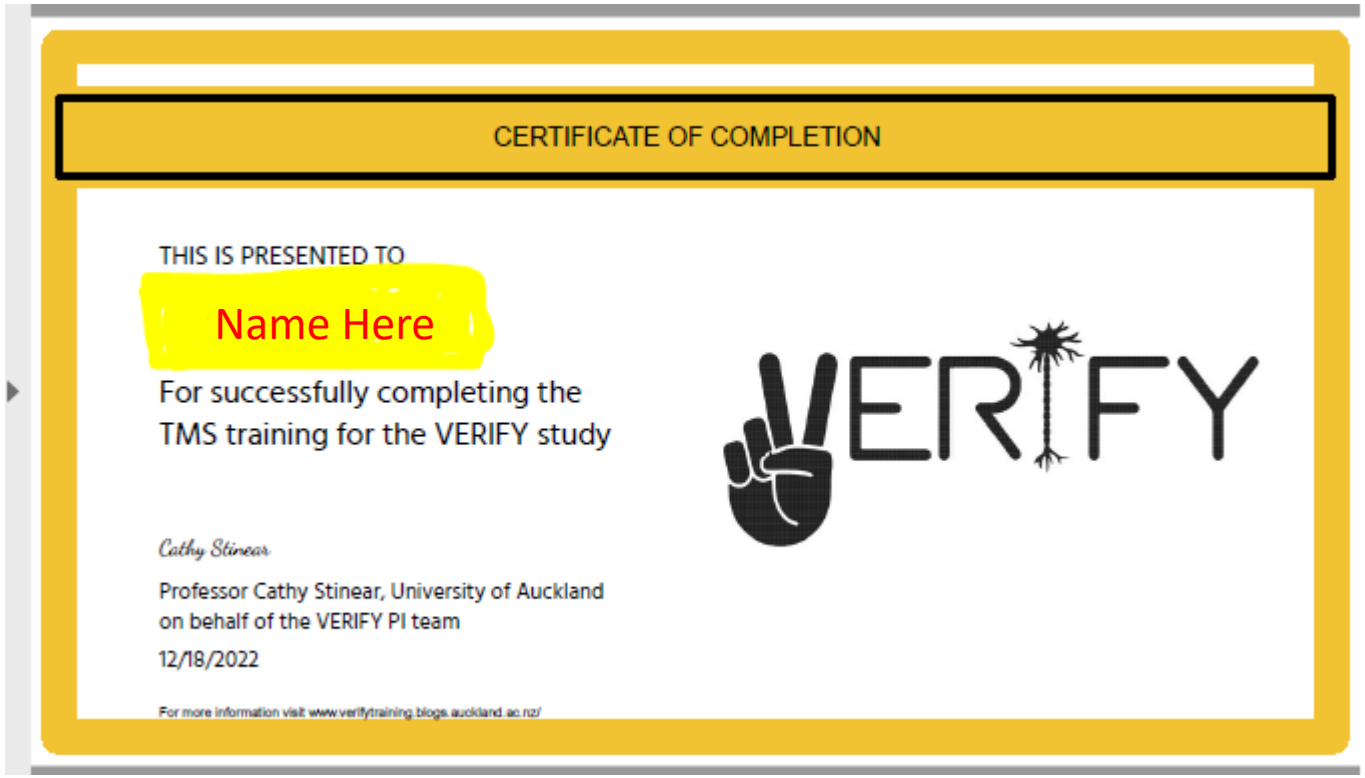
TMS Training

PRACTICE

1. Healthy volunteers
2. Technique check for Standard sites
3. VERIFY patients

Golden TMS HV Certificate:

- An email survey will be sent to TMSOs once they have completed the HV TMS training, and technique check (if required).
- Once the survey is completed the TMSO will be emailed a gold TMS certificate that should be uploaded in WebDCU.



CERTIFICATE OF COMPLETION

THIS IS PRESENTED TO

Name Here

For successfully completing the TMS training for the VERIFY study

VERIFY

Cathy Stinear

Professor Cathy Stinear, University of Auckland
on behalf of the VERIFY PI team

12/18/2022

For more information visit www.verifytraining.blogs.auckland.ac.nz/

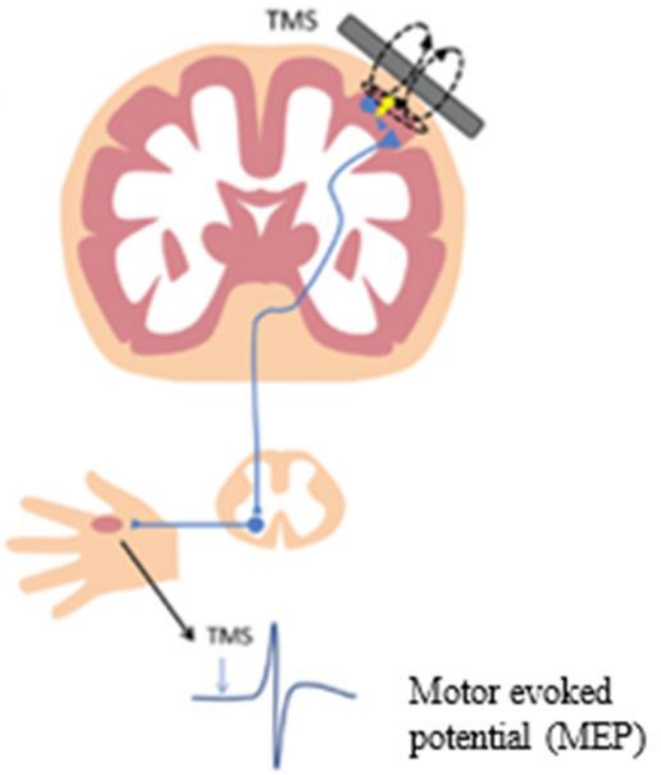
TMS- Enrolled Subjects

Once your site is activated the NZ TMS team will review the TMS data for each patient and perform an independent blinded MEP status determination

TMS team will contact sites if there is:

- A need for TMS to be repeated with the subject
- MEP status disagreement
- Consistent EMG issues

Please upload TMS data and respond to patient TMS ASAP because TMS may need to be repeated within 168 hour window



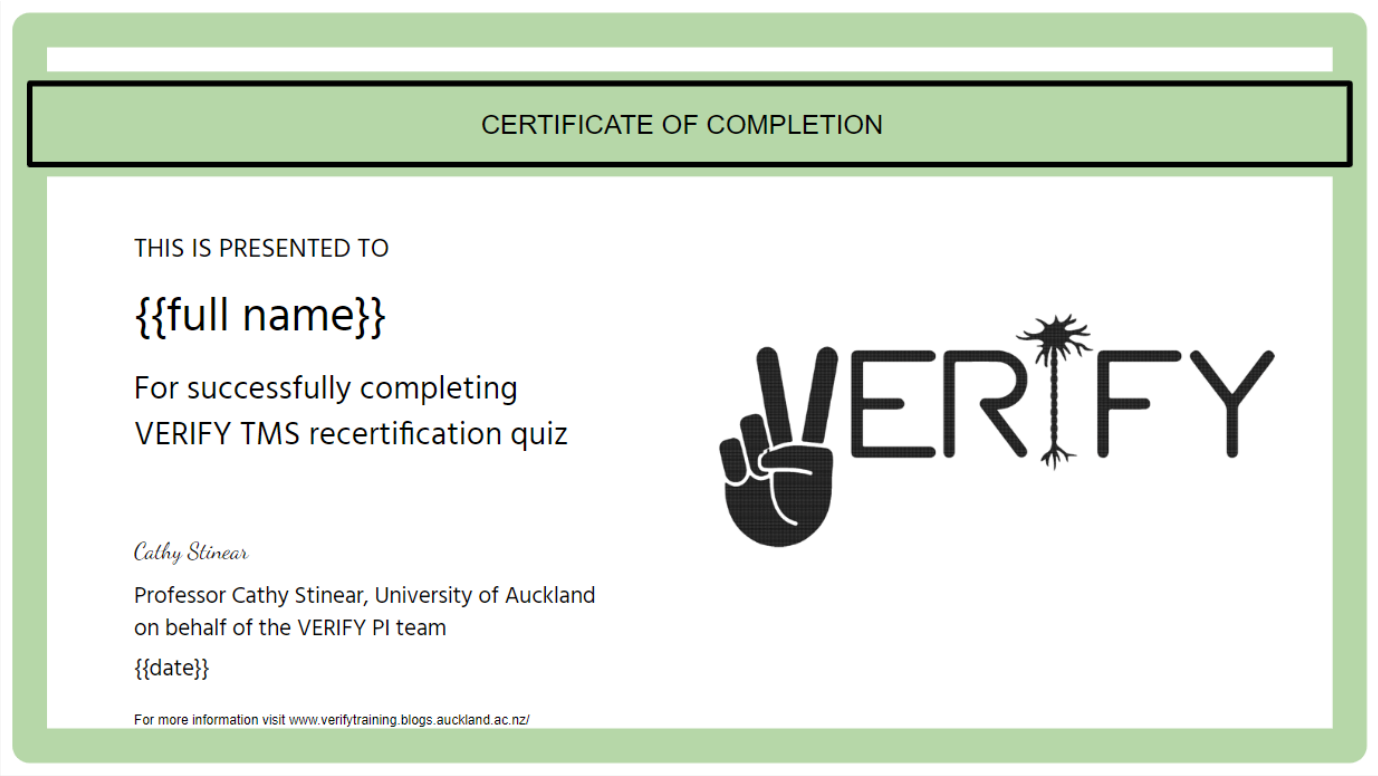
TMS- Enrolled Subjects Reminders

- TMSOs should use the comments section on the TMS source documentation if the TMS procedure did not go as planned.
- Redo TMS sessions with stroke patients if you don't get MEP status or data didn't save in initial session
- Save MEGA-TMS dataset as soon as you finish the session and check it

TMS Operator Recertification Training

Retraining will be:

- Annually
- Consents of a single short quiz
- Is to be uploaded into the TMS training placeholder in WebDCU
- Accessible through the TMS Website
  - ➢ https://verifytraining.blogs.auckland.ac.nz/


CERTIFICATE OF COMPLETION

THIS IS PRESENTED TO

{{full name}}

For successfully completing
VERIFY TMS recertification quiz

VERIFY

Cathy Stinear

Professor Cathy Stinear, University of Auckland
on behalf of the VERIFY PI team

{{date}}

For more information visit www.verifytraining.blogs.auckland.ac.nz/

TMS and Other Questions

- Urgent TMS questions (during session)
  - Call or text hotline at : (833)337-2227
  - Monday – Friday 0800 – 2100h ET

- Non-urgent TMS questions
  - Email us at verify.study.tms@gmail.com

Behavioral Measures and Training

Schedule of Assessments

Procedures	Baseline			Hospital Discharge	Day 30	Day 90
	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	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)			µX	µX		
Serious AE and AE of Special Interest			X	X	X	X†
Complete CRFs	X	X	X	X	X	X†

* *Stroke onset (or time last known well) is Hour 0*

** *(i) At least 24 hours from stroke onset, and only after presumed clinical stabilization, at least 24 hours after any potential acute reperfusion therapy, and prior to discharge; (ii) Study Visit 2 and 3 may be performed on same day.*

*** *The study-required 3D-T1 MRI sequence (with a concurrent DWI) should ideally be performed within 72-168 hours. If the 3D-T1 was already performed clinically within 24-72 hours, then this will be accepted as an exception. For the remainder of the sequences, a clinical MRI is acceptable, even if performed at <24 hours from onset.*

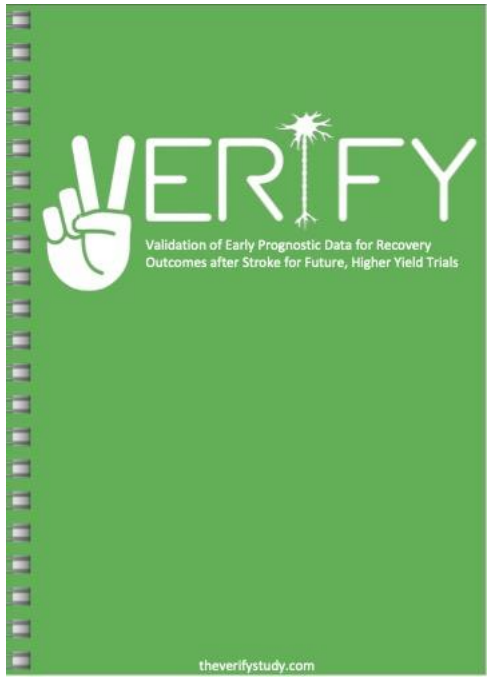
µ AEs reported from time of enrollment until 5 days post-TMS administration or hospital discharge, whichever is sooner.

† *Study Visit 6 is required in-person to capture the primary endpoints. But, if not feasible despite full attempts, then some assessments can be done by videoconference as indicated. If only phone assessment is possible, then the same tests can be performed. Note that a portion of EQ-5D, consisting of the visual analog cannot be performed by video or phone.*

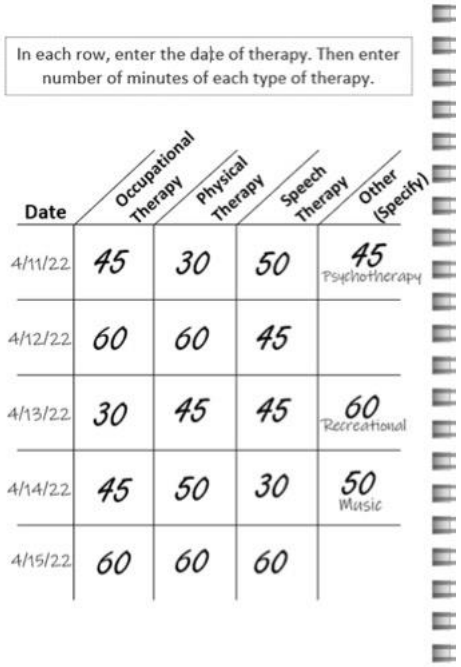
Things we will mail to you for study assessments

- 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

We will also mail Rehab Diary Trackers to you

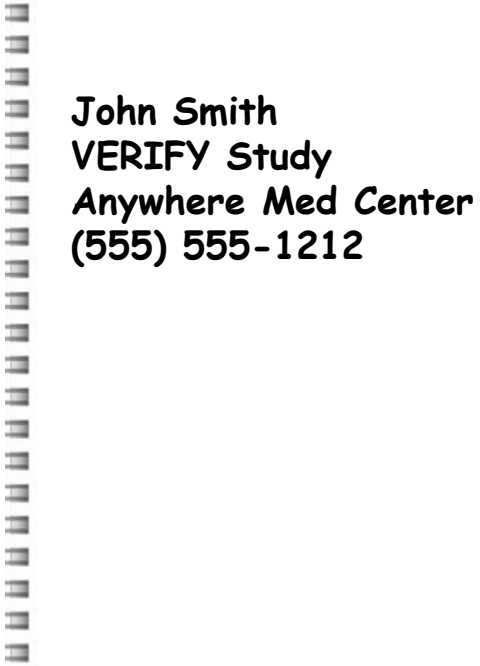


Front cover



Inside front flap

1 of 30 data pages



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

Training and Certification- BlueCloud (1)

BlueCloud
1. Upper Extremity Fugl-Meyer Scale (FM)
2. Action Research Arm Test (ARAT)
3. Rankin Focused Assessment (RFA)

To be assigned the FM/ARAT training study personnel must be delegated this task on the DOA

- Any none PT/OT/MD study personnel must first obtain permission from the Cramer lab before being allowed to be on the DOA/assigned the training for these assessments
  - https://redcap.link/VERIFY_ARAT_and_FM_Survey
- Currently the study allows PT/OT or MDs to perform these assessments without needing permission from the study team

All study personnel are allowed to complete the RFA training

Training and Certification- BlueCloud (2)

BlueCloud
1. Upper Extremity Fugl-Meyer Scale (FM)
2. Action Research Arm Test (ARAT)
3. Rankin Focused Assessment (RFA)

** Note this is a separate/different BlueCloud profile that what is being used for the NIHSS training***

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 and what trainings that you are requesting access to.
   - Send this from the email account you used to register at BlueCloud.

3. We will assign you the **REQUESTED** 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- DCU Campus (1)

DCU Campus
4. Modified Rankin Scale (mRS)
5. NIH Stroke Scale (NIHSS)

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

mRS

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.
   - sign the certificate
   - send it to your site coordinator

NIHSS

2. Click on NIH Stroke Scale Resource
   - and then click on "Click Here To Get Started"

3. Create a BlueCloud account OR Login
   - Go to my activities
   - Search and assign NIHSS to account

4. Complete all modules and print/save certificate.
   - Send certificate to site coordinator

** Note this is a separate/different BlueCloud profile that what is being used for FM/ARAT/RFA training***

Training and certification- DCU Campus (2)

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

-- Must pass with a 95% or above

1. Training PDF Slide Deck for the Behavioral Assessments Training Certification that incorporates these 7 scales will be provided:
   1. In the WebDCU Training Center- under VERIFY (Click HERE)
   2. After you finish viewing the training slides, open the URL provided on the last slide: https://redcap.link/VerifyBehavioralMeasuresCertification
2. 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- 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.

5. Proceed with MoCA training and certification. Note that we will be using paper case report forms (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.

Study Specific Training/Recertifications

Platform	Assessment Name	Recertification	Link to training
Bluecloud	Upper Extremity Fugl-Meyer Scale	Every 6 months	https://secure.bluecloud.net/verify-study
	Action Research Arm Test	Every 6 months	
	Rankin Focused Assessment	Every 2 years	
MoCA Website	Montreal Cognitive Assessment	Every 2 years	https://www.mocatest.org/get-certified
TMS Website	SAFE Score Training	Every 1 year	https://verifytraining.blogs.auckland.ac.nz/
	TMS Safety Checklist Training	Only 1 time	
DCU Campus	Modified Rankin Scale	Every 2 years	https://dcu.musc.edu/campus/
	NIH Stroke Scale	Every 2 years	
	Behavioral Assessments Training Certification: • Motor Activity Log-14 (amount of use) • 10- Meter Walk Test • EQ-5D (EuroQol-5D) • Geriatric Depression Scale-15Q • NeuroQOL-Anxiety-8Q • Star Cancellation Test • Pain Visual Analog Scale	Every 1 year	
TMS Website (TMS Training- Only for TMS Operators)	Online TMS training modules & practical TMS training with healthy volunteers. (Note: After successful completion of online TMS training, TMS operators will receive a "green light" email confirming they can proceed with the practical TMS training).	Only 1 time	https://verifytraining.blogs.auckland.ac.nz/
	Recertification Quiz for TMSOs	Every 1 year	

Recertifications

- Table shows when you need to be recertified on each behavioral assessment.
- Table also located in MOP
  - MOP accessible in Toolbox tab of WebDCU.
- FM & ARAT require recertification every 6 months.
  - The Cramer Lab will send reminder emails at 1 month AND 1 week prior to your training expiring. This will serve as a reminder to complete your recertification.

***** Any study personnel that are not PT/OT/MD must individually obtain permission from the study team to perform the ARAT/FM**

Link to obtain permission:

https://redcap.link/VERIFY_ARAT_and_FM_Survey

The Cramer lab will initially only assign trainings to site staff based on their responsibilities on the DOA.

Once site personnel complete their initial training(s), then their recertification training for those specific assessments will be made available to them vs having all 3 (ARAT, FM, RFA) trainings available for them.***

REDCap Training and Resources

- All sites that are using the VERIFY RedCAP eConsent should ensure that all consenters have completed the network training:
  - https://redcap.link/StrokeNet_eConsent_Training
  - This training certificate should be filed appropriately and easily assessable upon request

- The VERIFY specific eConsent guide is provided in the toolbox
  - Please review prior to your first eConsent

VERIFY REDCap E-Consent Guide

Imaging

Imaging Team

Dr. Achala Vagal; MD,MS

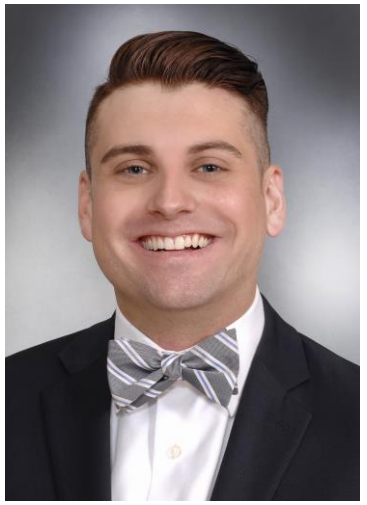
PI, Imaging management Center

Vivek Khandwala, PhD

Database Manager

Brady J. Williamson, PhD

Research Assistant Professor



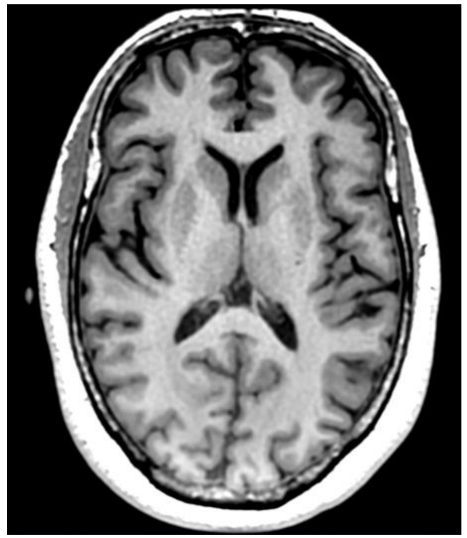
Tyler P. Behymer, BS

Imaging Project Manager

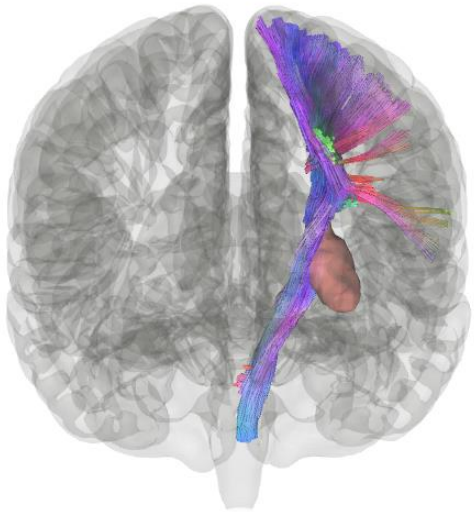
University of CINCINNATI

VERIFY

VERIFY MRI Protocol



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



- Four possible scenarios for your site:
  - #1: **All MRI sequences** above (incl 3D-T1) are completed as standard of care (SOC) at 24-168h of onset → no further VERIFY imaging needed
  - #2: **All MRI sequences** above (incl 3D-T1) are completed as SOC at 0-24h of onset → repeat only 3D-T1 (along with DWI) within 72-168h
  - #3: **All MRI sequences except 3D-T1** are completed as SOC at 0-168h of onset→ perform 3D-T1 (with DWI) within 72-168h from onset
  - #4: **Clinical MRI not planned** → perform full MRI, including 3DT1, for VERIFY within 72-168h from onset

NOTE: "Per patient" budget includes reimbursement for full MRI

What Imaging Needs to be Submitted?

1. **Initial acute clinical neuroimaging** (SOC at hospital admission):
   - CT/CTA +/- CTP Or MRI/MRA +/- MRP

2. **Routine clinical MRI done at 0-168h** (whether acquired as SOC or study-specific)
   - DWI/ADC, FLAIR, T2, and GRE/SWI

3. **3D-T1 MRI sequence (always accompanied by DWI)** done at 24-168h (whether acquired as SOC or study-specific)
   - Should ideally be performed within 72-168h
   - If already performed clinically within 24-72h, then this will be accepted as an exception

4. **Any neuroimaging associated with a recurrent stroke**

- AMBRA has an automated deidentification process
- If your institution requires you to remove the PHI before uploading to AMBRA, make sure:
  - Date and Time of image acquisition stays intact
  - DICOM tags for the imaging study (e.g., slice thickness, MR sequence names, etc.) are retained

How to Submit Imaging?

- **Submitting imaging is part of the payment schedule, therefore, it's important for the sites to upload imaging to the imaging management center in timely manner.** Direct image transfer from the participating sites to the imaging center will occur utilizing Ambra Health® web-based imaging management platform which is accessible directly from your internet browser.
- Ambra Health®
- Requires no separate software download
- Is HIPAA compliant
- EU GDPR compliant for lawful processing of subject health data
- GCP and 21 CFR Part 11 compliant
- Image data shared via secure web link only accessible by authorized personnel
- Ambra Health® privacy policy is available at https://access.ambrahealth.com/privacy

NOTE: VERIFY MRI MANUAL (Upload Manual pg. 12 – 21) can be found on WebDCU > Toolbox > Project Documents > File F1143.pdf

Imaging Upload

- Ambra access given to the site personnel responsible for imaging upload

- One on one and online re-training/support whenever needed

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

FAQs for Imaging

Q: Will the T1 in our SOC stroke protocol meet the needs of the study?

A: In most cases, clinical T1 will be different than what we need for VERIFY. Compare your imaging parameters to those detailed in the imaging manual

Q: When can imaging be collected?

A: Ideally, study-specific T1 is implemented in the SOC MRI. If not, a follow up MRI is required within 72-168 hours of symptom onset

Q: Can I use 1.5 T magnet?

A: Yes – both 1.5 and 3T is allowed, although 3T is preferable

Q: What are required sequences in SOC brain MRI?

A: DWI/ADC, FLAIR, T2, GRE/SWAN

Q: Is Post-contrast T1 allowed?

A: No – PRE-contrast study-specific 3D T1 with DWI needed for imaging analysis

Q: Will phantom scans be needed?

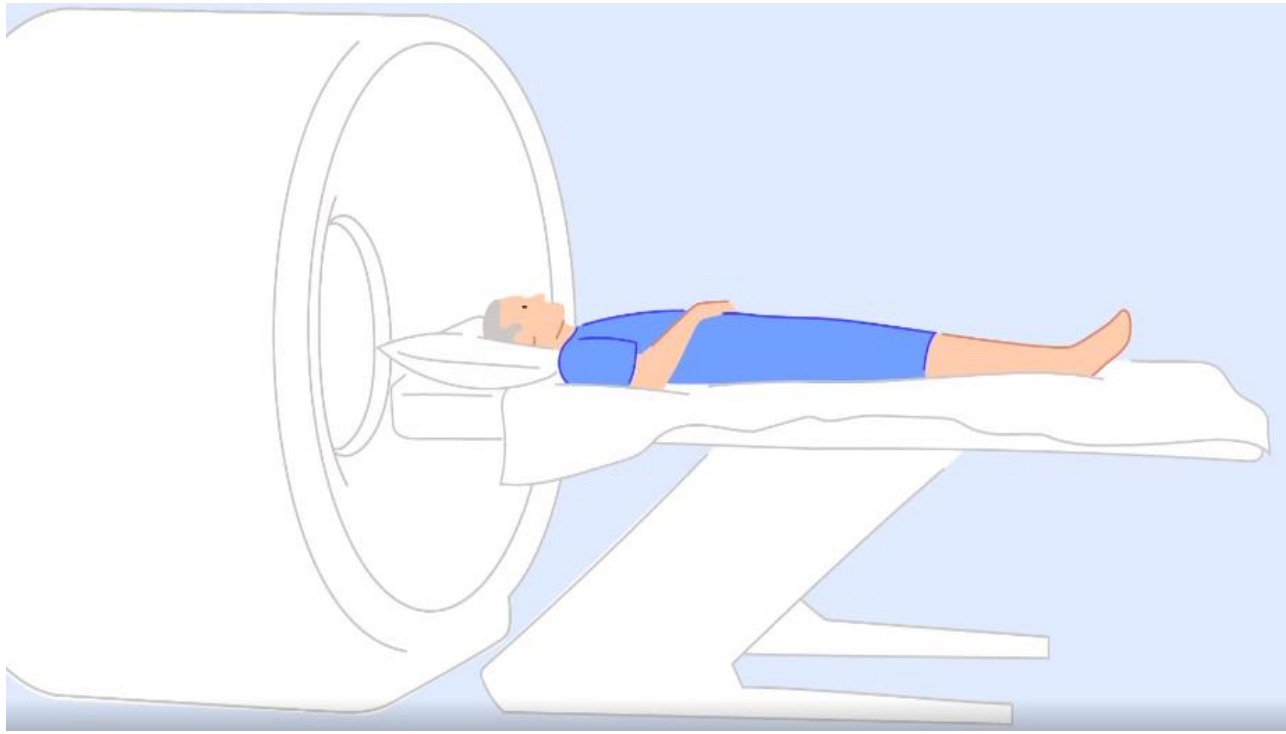
A: Yes - phantom scan of study-specific T1 needed at study start up & biannually

MRI – Phantom Scans

Brief review of process:

- Phantom scan of study-specific 3D-T1 collected at study start up for site activation
- Phantom scan(s) are collected **every 6 months** (2 times per year) to ensure quality certification of MRI protocol over time.
  - This will help to prevent unusable MRI data
- Phantom scan(s) are needed after any **scanner hardware upgrades and/ or software changes** before scanning any new patient
  - Please notify the imaging team of any upcoming MRI upgrade if known in advance
- Email reminders sent out at every 5, 6, and 7-month window interval for upcoming phantom scans set to expire

→ Contact Tyler Behymer with any imaging questions at 513-310-7472 or by email behymetp@ucmail.uc.edu



As a reminder, **we are collecting phantoms of only the study-specific, 3D-T1 sequence (your site's ACR phantom is fine)**

- *Most institutions run their standard ACR phantoms at a scheduled time on a weekly basis*
- *Talk with your Radiology point of contact to determine your site's ACR phantom schedule*

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
Office: 513-558-3955

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

VERIFY Questions (Recap of Contact Info)

Consent/enrollment questions?

- Email VERIFY PMs (Lisa & Kalli) and PIs (Pooja, Steve, Cathy, & Achala) altogether
  - ➢ One of us will answer back promptly

Mundo, Lisa (mundokl) <mundokl@ucmail.uc.edu>;
Beasley, Kalli (beasleki) <beasleki@ucmail.uc.edu>;
Khatri, Pooja (khatrip) <khatrip@UCMAIL.UC.EDU>;
Steve C. Cramer <sccramer@mednet.ucla.edu>;
Cathy Stinear <c.stinear@auckland.ac.nz>;
Vagal, Achala (vagala) <vagala@ucmail.uc.edu>

TMS questions?

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  - Call or text hotline at : (833)337-2227
  - Monday – Friday 0800 – 2100h ET

- Non-urgent TMS questions
  - Email us at verify.study.tms@gmail.com

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Research Assistant Professor
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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
Office: 513-558-3955

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