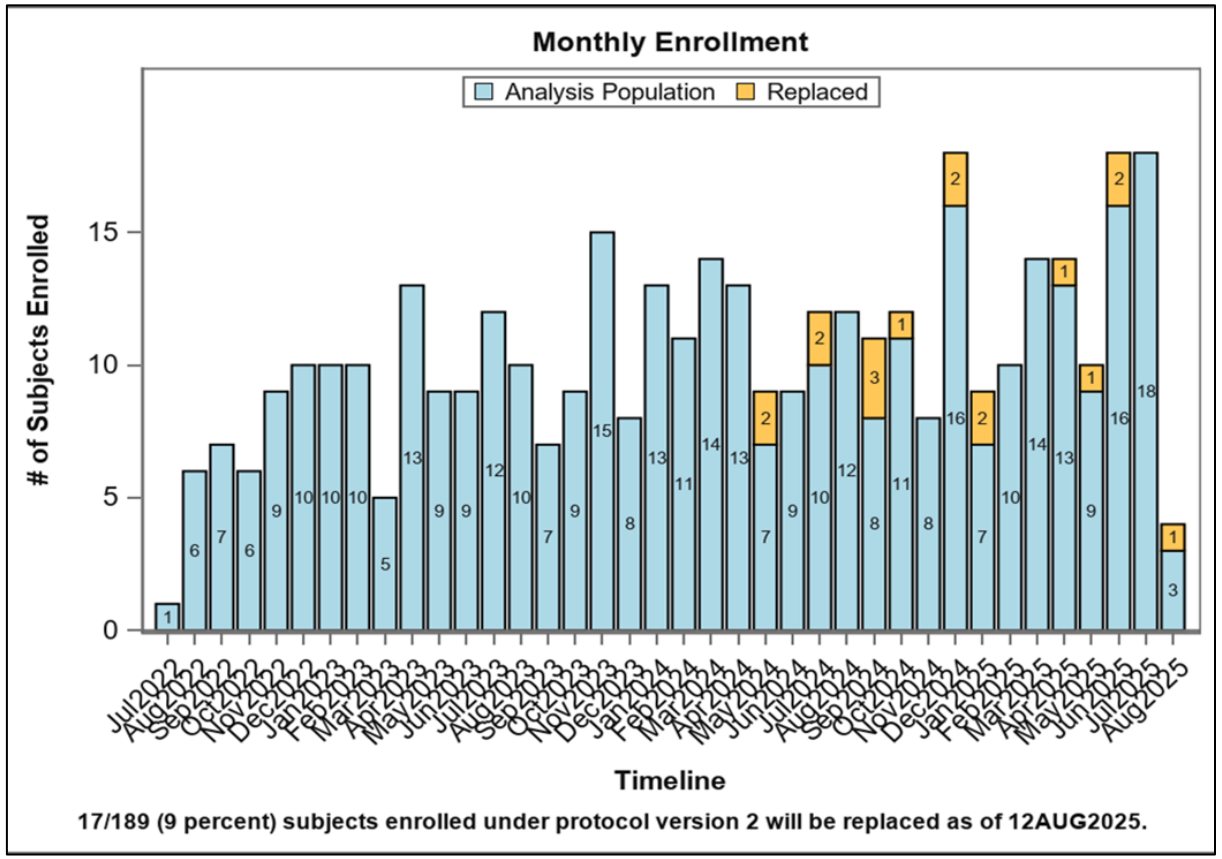
Validation of Early Prognostic Data for Recovery Outcomes after Stroke for Future, Higher Yield Trials: A Biomarker Validation Study

Protocol V2.1 Training

Protocol V2.1 Training: MEETING AGENDA

Enrollment Updates	Pooja Khatri
Main Protocol v2.1 Changes	
Overall Protocol 2.1 – Changes in Context	
Study personnel training Overview	Steve Cramer
FM/ARAT Reminders	Jessica Cassidy
TMS Reminders	Cathy Stinear
MRI Reminders	Achala Vagal/Tyler Behymer
Safety Reporting Reminders and Wrap-Up	Pooja Khatri
Q & A	ALL

Monthly Enrollment



Monthly Goal:

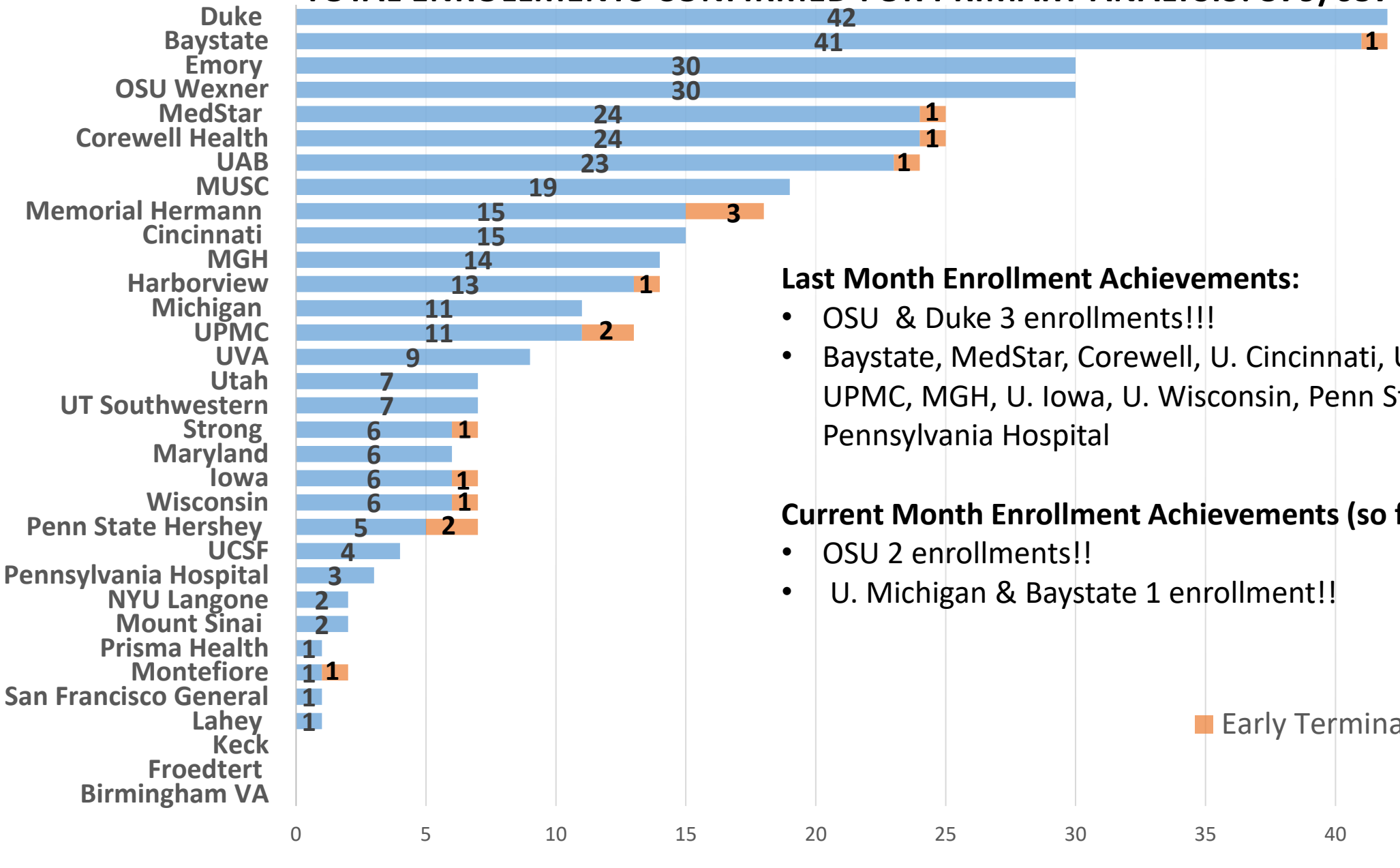
17

- Last patient to be enrolled by 5/31/2026
  - July 2025 Enrollment: 18
  - August 2025 Enrollment (so far): 3 & 1 replaced

RECORD BREAKING !!!

VERIFY TOTAL ENROLLMENTS: 395

TOTAL ENROLLMENTS CONFIRMED FOR PRIMARY ANALYSIS: 379/657



Last Month Enrollment Achievements:

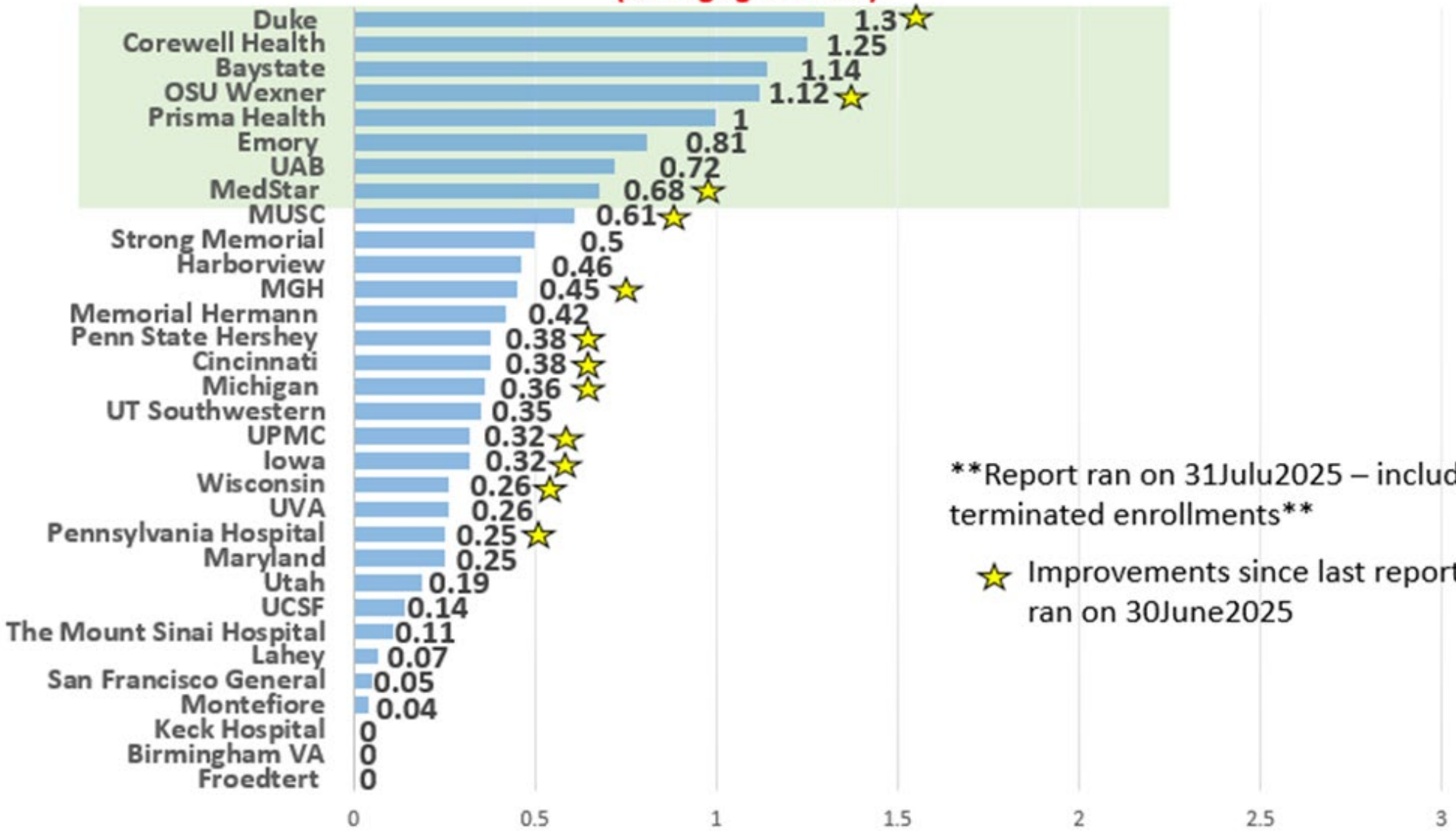
- OSU & Duke 3 enrollments!!!
- Baystate, MedStar, Corewell, U. Cincinnati, U. Michigan, MUSC, UPMC, MGH, U. Iowa, U. Wisconsin, Penn State Hershey & Pennsylvania Hospital

Current Month Enrollment Achievements (so far):

- OSU 2 enrollments!!
- U. Michigan & Baystate 1 enrollment!!

VERIFY SITE ENROLLMENT AVERAGE PER MONTH:

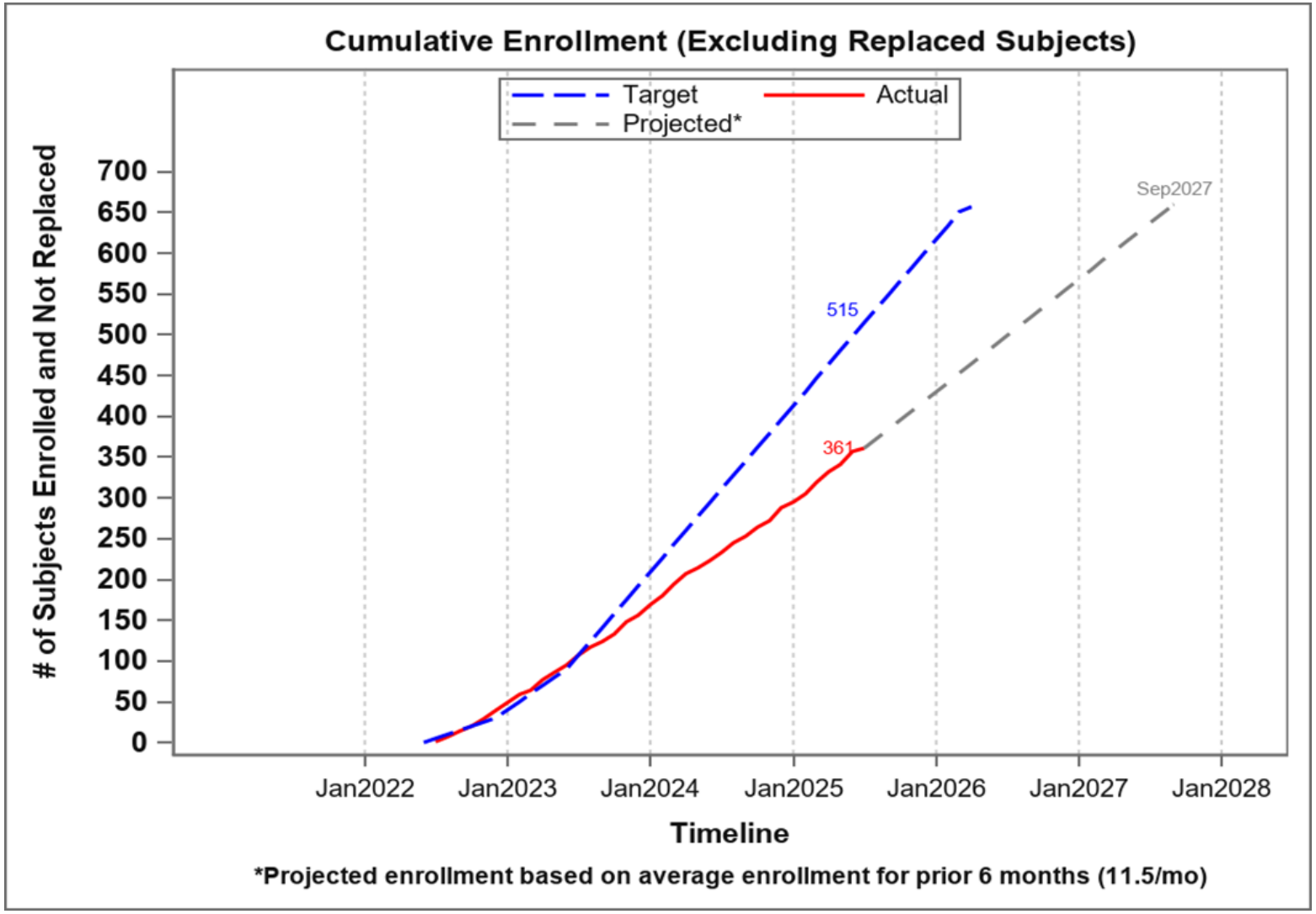
(Average goal is .64)



Report ran on 31Julu2025 – includes early terminated enrollments

★ Improvements since last report ran on 30June2025

Projection Curve: Target vs Actual Enrollment



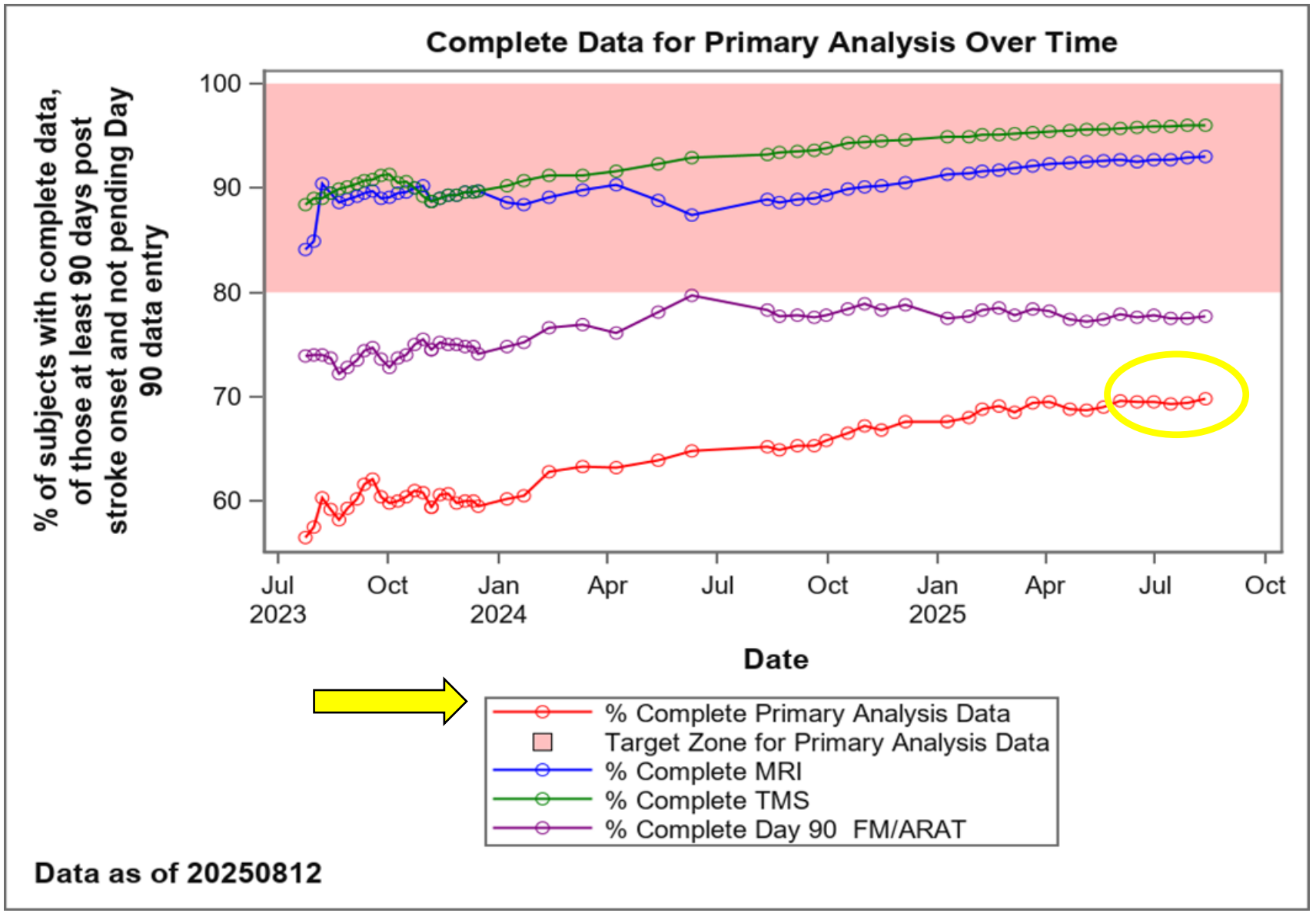
Missing Primary Data - Update

229 (69.8%) enrolled pts have complete data (8/12)

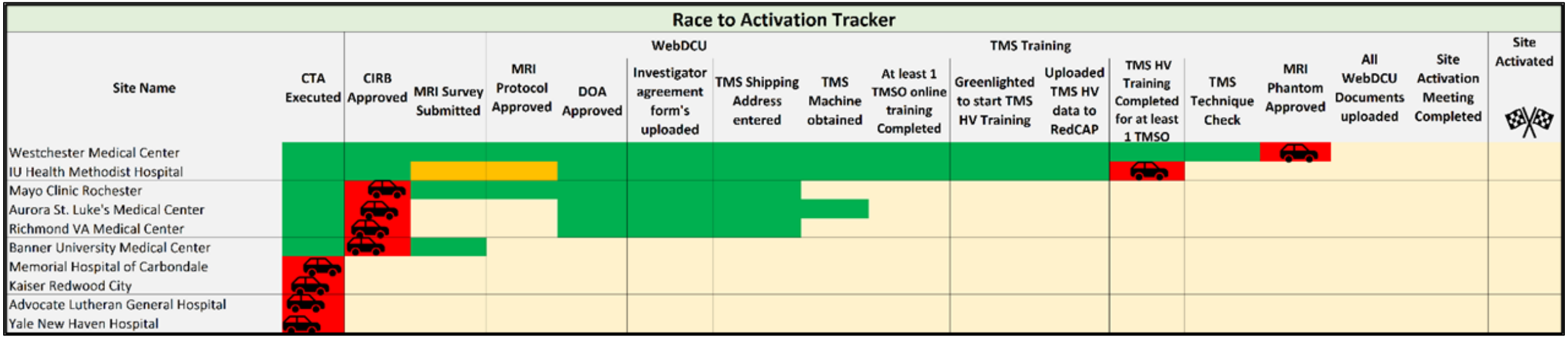
- +.5 % change from July (7/14)

Denominator = 328 patients who have reached 90 days post stroke onset without pending Day 90 data

Main driver is FM/ARAT collection at 90 days



Site Activation Status



- Having problems with TMS online modules or with HV training? Contact Harry Jordan to schedule a 1:1 session! verify.study.tms@gmail.com

- Having issues getting an MRI Phantom? We can help with that! Contact Tyler Behymer to schedule a call or meeting: behymetp@ucmail.uc.edu

- Have any other study related questions or issues? Contact the Project Managers Kalli Beasley and Max Mays!! beasleki@ucmail.uc.edu ; maysmw@ucmail.uc.edu

PROTOCOL V2.1—Main Changes/Updates

- Inclusion Criteria:
  - Officially closed ICH cohort
  - Added flexibility to adjust SAFE score inclusion criteria if needed
  - Allow for additional languages to increase recruitment

- Exclusion Criteria:
  - Expanded exclusion criteria related to device implants, comorbidities, and procedural compliance for improved safety and data quality

PROTOCOL V2.1—Main Changes/Updates (2)

- Strategies for Recruitment and Retention:
  - Enhanced retention strategies: more frequent reminders and touchpoints (Day 30, 60, 90).

- Sample Size Determination:
  - Revised sample size to achieve 80% power
  - Updated sample size language
  - Added plan to monitor MEP- subject proportion for analysis robustness

Study and Protocol Overview

Changes in Context and Some Reminders are Highlighted….

Introduction

- Objective
  - To assess the most promising biomarkers of motor recovery after stroke
    - Validate ischemic stroke patients

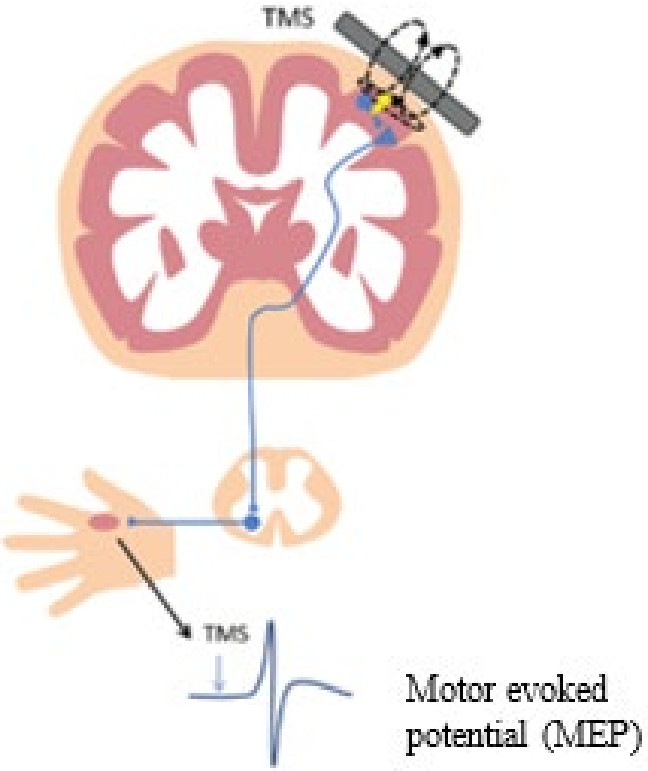
- Outcomes (90-Day)
  - Primary
    - Fugl-Meyer (FM) scale
    - Action Research Arm Test (ARAT)
  - Exploratory
    - Motor Activity Log (MAL)
    - modified Rankin Scale [mRS]

Improve stratification and inform entry criteria in clinical trials

Enable personalized rehabilitation therapy in the long term

Neurophysiology Biomarker

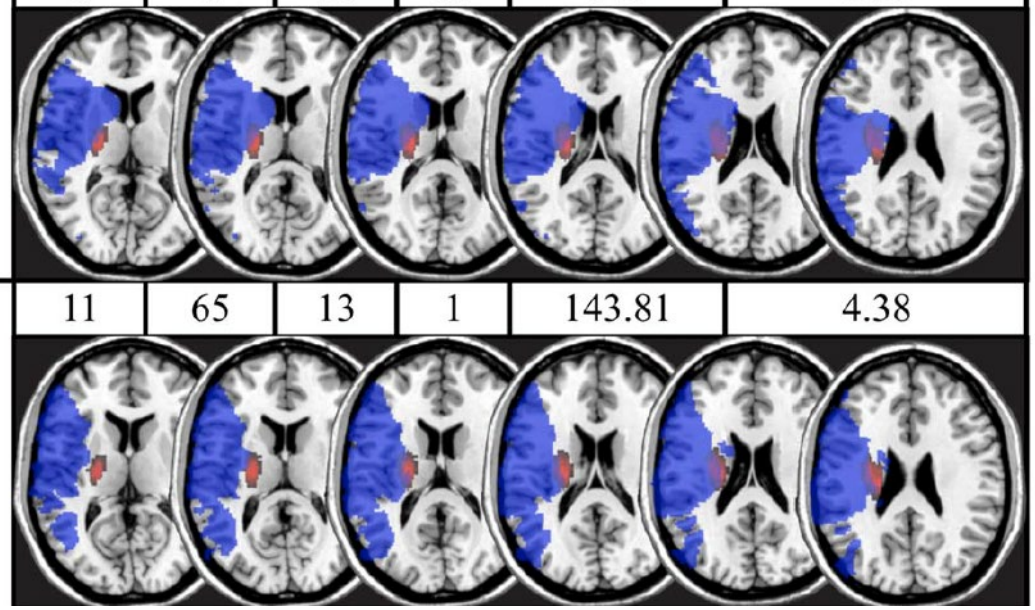
- Transcranial magnetic stimulation of ipsilesional motor cortex
- Assess for motor evoked potentials (MEP) in either the extensor carpi radialis and/or first dorsal interosseous
- Presence of MEPs (MEP+) indicates **functionally intact** ipsilesional corticospinal system



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

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

Eligibility Criteria—Inclusion

1. Age 18 years or older
2. Unilateral symptomatic stroke due to ischemia (Note: Bilateral acute stroke is permitted if the stroke that is contralateral to the index stroke is asymptomatic).
3. Motor deficits in the acutely affected UE, defined as a Shoulder Abduction and Finger Extension (SAFE) score ≤ 8 out of 10 points[20,61] (i.e., excluding full or nearly full motor strength in both shoulder abduction and finger extension) within 48 to 96 hours of stroke onset (or time last known well).
    a) Please note that, if significant imbalance is observed in SAFE score or MEP+ rates, the enrollment threshold for SAFE score may be updated with a formal study memo
4. Provision of signed and dated informed consent form within 24 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)
5. 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.
6. Fluent in study approved languages (i.e., English or Spanish)

Eligibility Criteria - **Exclusion**

1) **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.*
2) **Legally blind**
   - *20/200 or worse visual acuity in better eye, despite corrective lenses and glasses*
3) **Dense sensory loss** on paretic side indicated by a score of 2 on NIHSS sensory item
4) Unable to abduct the shoulder or extend the fingers of the non-paretic UE on **verbal command**
5) Isolated **cerebellar** stroke
6) **Symptomatic stroke** in any location **within 30 days** prior to index stroke.
7) 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
8) Known or expected **inability** to maintain follow-up with study procedures **through 90 days**
9) 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.*
10) Major medical, neurological, or psychiatric condition that would substantially affect functional status
11) Non-cerebrovascular diagnosis associated with unlikely survival at 90 days

Eligibility Criteria – Exclusion Cont'd

12) Pregnancy

13) Contraindication to noncontrast MRI (certain metallic implants, metallic foreign bodies or severe claustrophobia)

14) Contraindication to TMS:

a) Implanted electronic cardiac devices (e.g., Automatic Implantable Cardioverter-Defibrillator [AICD] or pacemaker)
b) Any 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)
c) Ferromagnetic intracranial metallic implant
d) Skull defect related to current stroke
e) Seizure after onset of current stroke
f) Seizure within the last 12 months while taking anti-epileptic medications
g) Previous serious adverse reaction to TMS

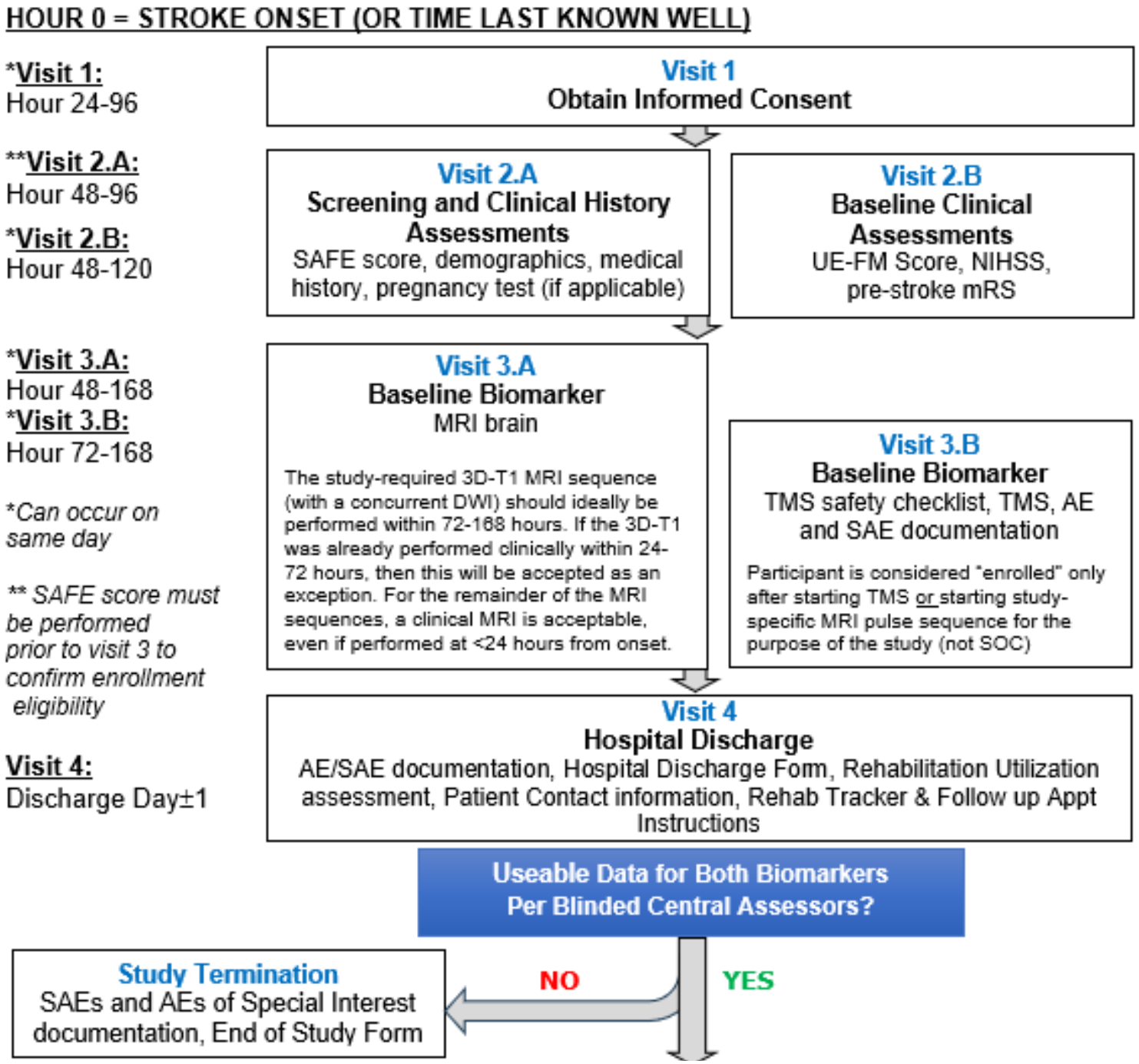
15) Anticipated inability to perform study procedures within 168 hours of symptom onset

a) Unable to perform behavioral assessments within 48-120 hours of symptom onset (or time last known well).
b) Unable to receive TMS within 72-168 hours or get MRI within 48-168 hours of symptom onset (or time last known well).

Eligibility Questions

- **Have an enrollment question?**
  - Email: verifystudy@ucmail.uc.edu
    - **Please include “**VERIFY Enrollment Question”** in the email subject line**
    - This will allow for the email to be automatically forwarded to study leadership and project managers

Study Schema

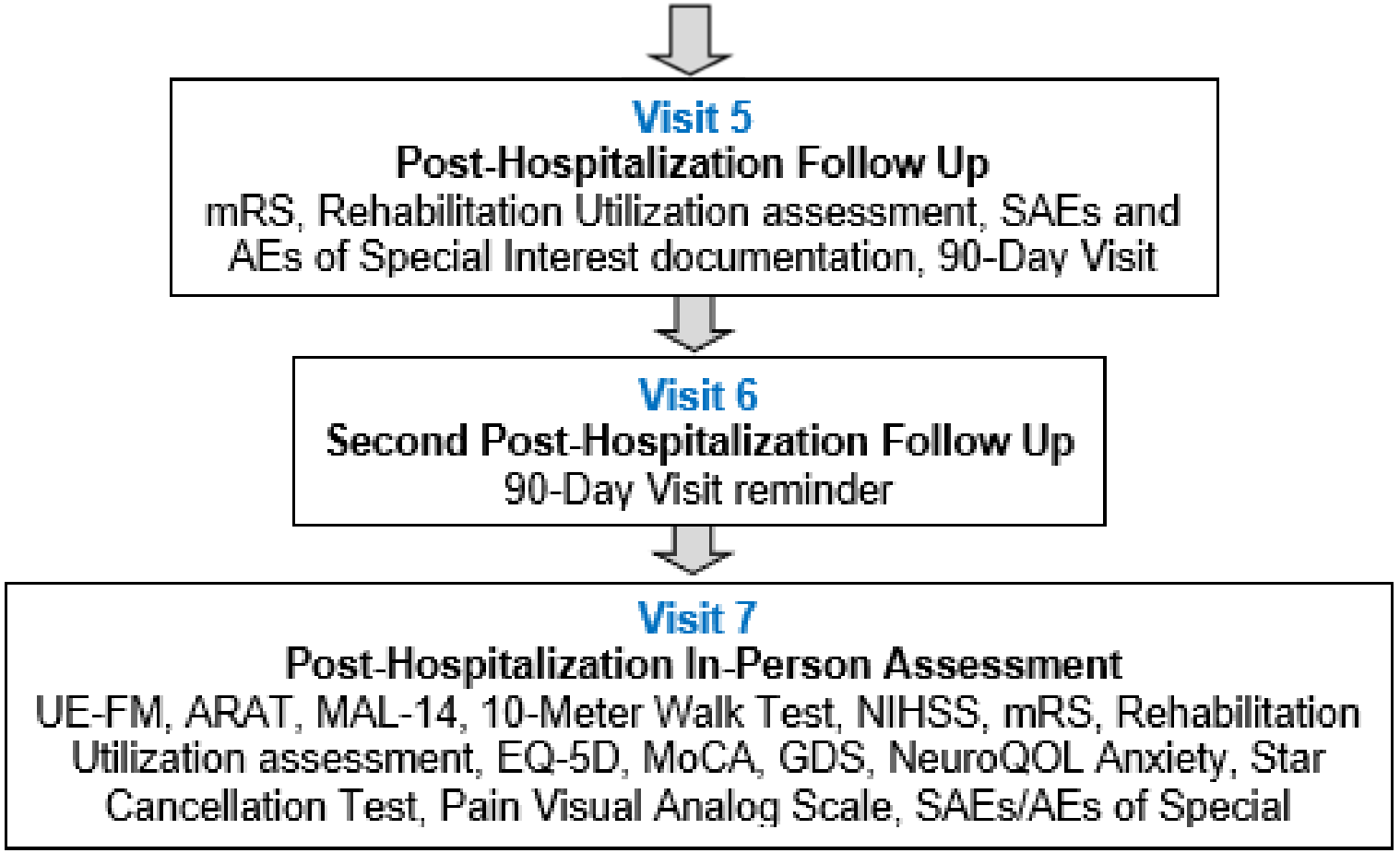


Study Schema

Visit 5:
Day 30±7

Visit 6:
Day 60±14

Visit 7:
Day 90±14



Schedule of Activities

Procedures	Baseline					Hospital Discharge	Day 30	Day 60	Day 90
	STUDY VISIT 1** Informed Consent Hour 24-96*∞	STUDY VISIT 2A** Screening & Clinical History Assessments Hour 48-96*	STUDY VISIT 2B** Clinical Assessments Hour 48-120**	STUDY VISIT 3A** MRI Biomarker Hour 48-168*	STUDY VISIT 3B** TMS Biomarker Hour 72-168*	STUDY VISIT 4 Hospital Discharge Day ±1	STUDY VISIT 5 Post-Hospitalization Day ±7	STUDY VISIT 6 Second Post-Hospitalization Day ±14	STUDY VISIT 7 Post-Hospitalization In-Person Assessment Day ±14
Informed consent ∞	X								
SAFE score		X							
Demographics		X							
Pregnancy Test, if applicable		X							
Medical history		X							
UE-FM			X						X
NIHSS			X						X
Pre-stroke mRS			X						
mRS via RFA							X†		X†
MRI***				X#					
TMS					X#				
Rehab Utilization Assessment						X	X†		X†
Hospital Discharge Form						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 (only the shoulder of the affected side)									X
End of study visit Form						X¥	X¥	X¥	X¥
Adverse Events (AEs)	μX	μX	μX	μX	μX	μX			
Serious AEs and AEs of Special Interest	X	X	X	X	X	X	X†	X†	X†
Complete CRFs	X	X	X	X	X	X	X	X	X

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

∞ *Informed consent is to be performed at least 24 hours from stroke onset, and only after presumed clinical stabilization, and also at least 24 hours after any potential acute reperfusion therapy; the consent must be obtained prior to hospital discharge.*

** *Study Visit 1, 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 48-168 hours. If the 3D- T1 was already performed clinically for standard of care within 24-48 hours, then this will be accepted as an exception. For the remainder of the image sequences, a clinical MRI is acceptable, even if performed at <24 hours from onset.*

\# *Participant is considered "enrolled" only in the data collection system (WebDCU) after starting TMS (at least one stimulation is delivered) or starting study-specific MRI pulse sequence (at least one MRI beep occurs). For sites that have the study-specific MRI sequence (3D-T1) as part of their SOC MRI, adding a "new subject" in the data collection system is based on starting TMS alone.*

¥ *End of Study Visit Form is completed after the last completed visit for the study.*

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

† *Assessments that can be done by phone or videoconference. Note that a portion of EQ-5D, consisting of the visual analog cannot be performed by video or phone.*

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Screening/Consent Workflow

1. **Daily Chart Screening**
   - Identify all stroke patients (ischemic) in EMR with the following:
     1. <96 hours of onset at admission
     2. Alert and able to consent themselves
     3. No TMS & MRI contraindications
     4. **patient has any upper limb symptoms?**

   - NO→ do not move forward with screening
   - YES→proceed to next step

2. **Patient is eligible based on full eligibility criteria?**
   - NO→enter as a Pre-screen failure
   - YES→proceed to next step

3. **Patient consents?**
   - NO→enter as a Pre-screen failure
   - YES→proceed to next step

4. **SAFE score ≤ 8?**
   - NO→enter as a screen failure
   - YES→proceed to next step

5. **Remains eligible and 1st TMS stimulation or study-specific MRI is started?**
   - NO→enter as a screen failure
   - YES→participant is now enrolled!

6. **TMS MEP status AND 3DT1 MRI sequence quality are reviewed by blinded study assessors and are deemed useable?**
   - NO→ Subject is moved to end of study visit in WebDCU and are terminated from the study
   - YES→participant is now enrolled with follow-up and will be followed until the in-person day 90 visit

Recruitment Tools

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

Study Windows –Study Tool

*__Visit 1:__
Hour 24-96

**__Visit 2.A:__
Hour 48-96

*__Visit 2.B:__
Hour 48-120

*__Visit 3.A:__
Hour 48-168

*__Visit 3.B:__
Hour 72-168

Can occur on same day

** SAFE score must be performed prior to visit 3 to confirm enrollment eligibility*

__Visit 4:__
Discharge Day±1

__Visit 5:__
Day 30±7

__Visit 6:__
Day 60±14

__Visit 7:__
Day 90±14

Date and Time of Stroke Onset/Last known well:	11/22/2022 11:00 AM
Date Patient expects to Discharge from Hospital	11/17/2022 1:00 PM

Visit #	Visit Window opens:	Target Date/Time:	Visit Window doses:
Visit #1 Hour 24-96 (Informed Consent)	11/23/2022 11:00 AM	within hourly window	11/26/2022 11:00 AM
Visit #2.A Hour 48-96 (SAFE score, demographics, medical history & pregnancy test)	11/24/2022 11:00 AM	within hourly window	11/26/2022 11:00 AM
Visit #2.B Hour 48-120 (UE-FM, Pre-stroke mRS and NIHSS)	11/24/2022 11:00 AM	within hourly window	11/27/2022 11:00 AM
Visit #3.A **SOC MRI** (w/ 3D T1) Hour 24-168	11/23/2022 11:00 AM	11/24/2022 11:00 AM	11/29/2022 11:00 AM
Visit #3.A **Resesarch MRI** (3D T1 + DWI) Hour 48-168	11/24/2022 11:00 AM	within hourly window	11/29/2022 11:00 AM
Visit #3.B Hour 72-168 (TMS)	11/25/2022 11:00 AM	within hourly window	11/29/2022 11:00 AM
Visit #4 Day of discharge from hospital ± 1	11/16/2022 1:00 PM	11/17/2022 1:00 PM	11/18/2022 1:00 PM
Visit #5 Day 30 ± 7	12/15/2022 11:00 AM	12/22/2022 11:00 AM	12/29/2022 11:00 AM
Visit #6 Day 60 ± 14	1/7/2023 11:00 AM	1/21/2023 11:00 AM	2/4/2023 11:00 AM
Visit #7 Day 90 ± 14	2/6/2023 11:00 AM	2/20/2023 11:00 AM	3/6/2023 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 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.

Informed Consent

- Use the most current cIRB approved version of the ICF when obtaining consent
  - Available in WebDCU
- eConsent is available through the RedCAP platform
  - Your site's eConsent will always be the most recent version of the approved ICF (maintained by StrokeNet NCC)
  - Only English eConsents are available currently *Spanish coming soon*
  - Site Coordinators need to have a Cincinnati-specific RedCAP user ID
    - ID must be requested to obtain access
    - Personnel are manually added to the project by the NCC
  - Investigators and patients can easily access and complete the eConsent through a site-specific link
    - No password required
    - This link can be texted or emailed to each other

Common DCRs/Queries on Informed Consents:

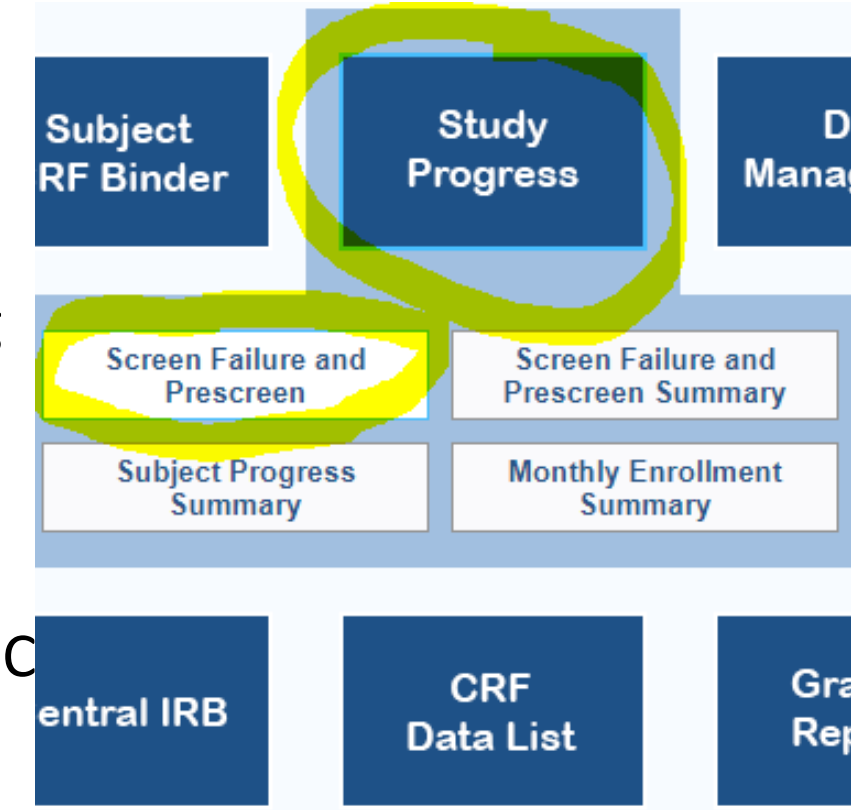
- Do utilize **consent process checklist** to confirm the consent process is being followed
  - Your site may have a local consenting checklist available
  - If one is not available, it is recommended that you create your own

- Consents uploaded to WebDCU **should not be redacted** & all pages should be included in the uploaded PDF packet

- Do generate a **Note-To-File explaining consent errors**, immediate response, and corrective action and upload with the consent form
  - Reasons for a NTF may include:
    - Forgetting to sign or date the consent form at the time of consent
    - Subject or consenter signs/dates in the incorrect location
    - The use or failure to obtain an impartial witness

Screen Failures

- Participants are categorized as “Screen Failures” if consented but not enrolled to participate in the study.
  - This means that the participant does not subsequently receive a single TMS stimulation or undergo any scanning for a study-specific MRI sequence for the purpose of the study.
  - If a subject refuses to get TMS or the study MRI prior to the other biomarker being collected (does not include SOC MRI), the site should then move forward with screen failing the patient
    - Both biomarkers must be able to be collected before moving forward with enrollment
  - Prescreen and screen failures are added to the Screen Failure and Prescreen log located in WebDCU under Study Progress



Discontinuation of Study- Early Termination

- No further study activities will be performed on participants who receive TMS or study-specific MRI (3D-T1 sequence) procedures but do not ultimately have useable data for both (i) MEP status on TMS data and (ii) lesion load on 3D-T1 MRI sequence. These enrollments with unusable biomarker data will be replaced.

1) Useability is determined by central assessors, who are blinded to clinical data, based on quality and adequate compliance with the protocol to make definitive determinations about MEP status and volume of lesion load on the corticospinal tract.

2) Enrolled participants determined to have unusable data for any biomarkers will be moved to "end of study."
   - The site will have to add the end of study visit to each of these subjects by adding a new study visit in the subjects CRF binder and selecting end of study visit.
   - Subjects should be notified of their terminated status by phone or mail (CIRB early terminated letter available in the toolbox in WebDCU

CRF	Baseline	Hospital Discharge	Day 30	Day 90	End of Study

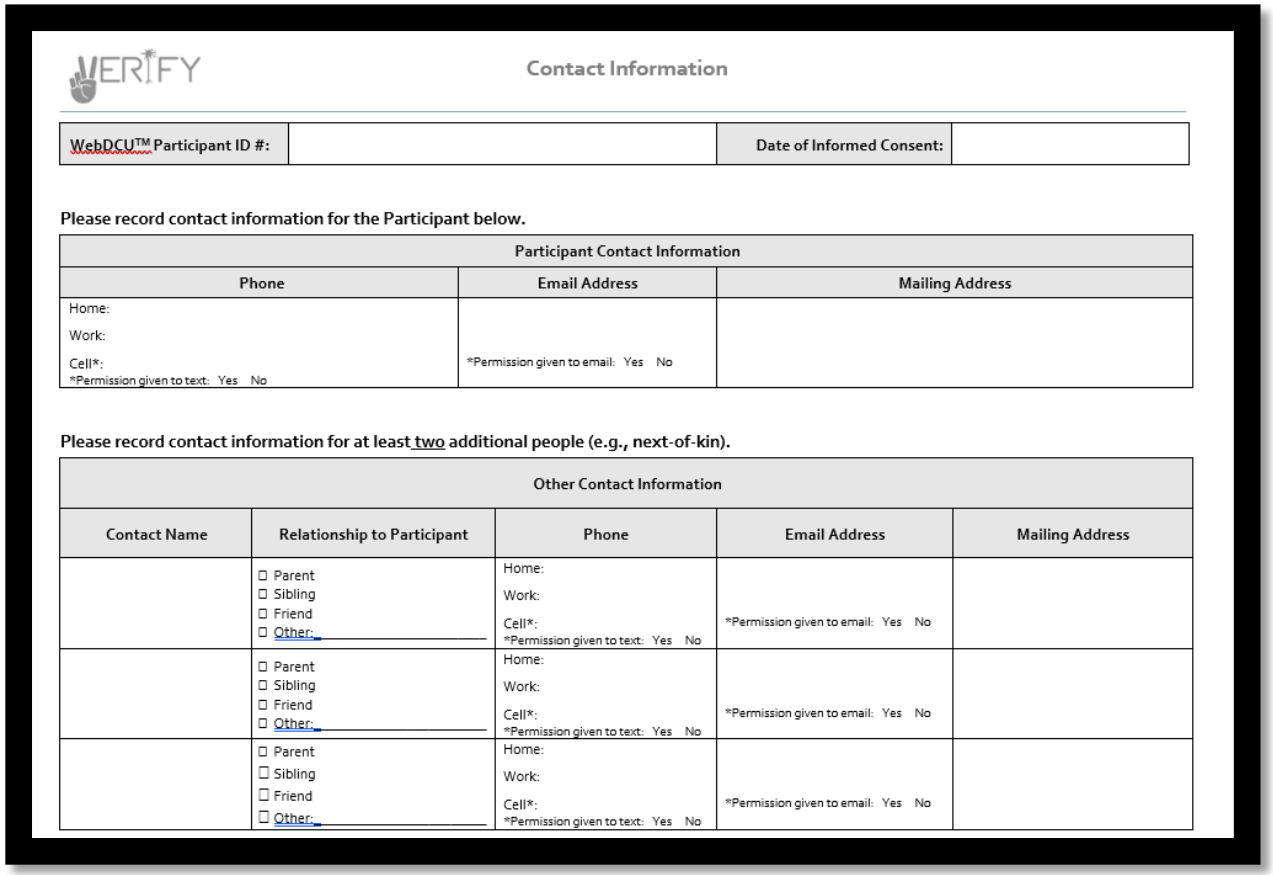
Measures to Minimize Bias: Blinding

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

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

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

Hospital Discharge



VERIFY

Contact Information

WebDCU™ Participant ID #:		Date of Informed Consent:	

Please record contact information for the Participant below.

Participant Contact Information		
Phone	**Email Address**	**Mailing Address**
Home: Work: Cell*: *Permission given to text: Yes No	*Permission given to email: Yes No	

Please record contact information for at least two additional people (e.g., next-of-kin).

Other Contact Information				
Contact Name	**Relationship to Participant**	**Phone**	**Email Address**	**Mailing Address**
	☐ Parent ☐ Sibling ☐ Friend ☐ Other:_____	Home: Work: Cell*: *Permission given to text: Yes No	*Permission given to email: Yes No	
	☐ Parent ☐ Sibling ☐ Friend ☐ Other:_____	Home: Work: Cell*: *Permission given to text: Yes No	*Permission given to email: Yes No	
	☐ Parent ☐ Sibling ☐ Friend ☐ Other:_____	Home: Work: Cell*: *Permission given to text: Yes No	*Permission given to email: Yes No	

- **Ensure the contact information form is fully completed before the participant is discharged from the hospital.**
  - Record at least 2 additional people who can help reach the participant.
  - Confirm with the participant how they like to be contacted:
    - Phone, Text, Email
  - Confirm what time of day they prefer to be contacted
    - Morning, Afternoon, Evening
- **Schedule Day 90 visit with participant before they are discharged.**
  - In-home visits is an option if your institution allows (gas mileage is reimbursed).
  - Transportation to a clinic visit from rehab/nursing facility is also an option (study will pay invoice for transportation cost).
  - Write the time/date in their rehab diary or help the put the time/date in the participant's calendar.
- You might see whether a standard of care (SOC) clinic visit can be scheduled in the same timeframe as Day 90
  - Can plan to complete Day 90 before or after SOC visit to help reduce burden on participant, if preferred.

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Day 60 Visit (Study Visit 6)

- Study visit 6 consists of contacting the patient by in-person, phone, email or mail (certified letter) AND receiving their confirmation of in-person day 90 appointment
- If the patient is unreachable a certified letter should be sent

Day 90 Visit (Study Visit 7)

- Study Visit 7 should occur **in-person**
  - If not possible, then certain assessments can still be done by videoconference or telephone as noted in the protocol.

- Study staff should train participants **not to unblind their visit 7 assessors;** this includes whether their hand moved during the TMS procedure and not to disclose this information to the FM/ARAT assessor.

- The study coordinator may perform **gait testing** only if the participant has already been specifically cleared to walk (e.g., could be physicians, NP or PT/OT decision).
  - Otherwise, a licensed OT or PT should assist the study coordinator with performing the gait testing to ensure participant safety.

- The FM at Visit 2 & 7 should be performed by **same person**.

Subject Lost to Follow-Up

- Sites should attempt to contact the subject 3 different times by phone, email, or mail when scheduling/completing any of the study visits.
  - These attempts should be documented in the EMR or subject binder.

- If the subject is unable to be contacted to schedule/complete the day 30, 60 or 90 visit, then the site should send a certified letter to the subject.
  - Follow up letter template has been cIRB approved and it is available in the Toolbox tab of WebDCU.
  - This letter may also be sent as the day 60 visit (visit 6)

VERIFY

Follow Up Letter

(Date)

(Subject Name)

(Subject Address)

Dear (Subject Name),

This letter is being sent to you as a participant in the VERIFY study. According to our records, you were scheduled for a study visit on (enter date). Our attempts to reach you by telephone at [Insert telephone number(s)] on three separate occasions have been unsuccessful. Please contact us at [Insert telephone number(s) (and site contact name and title)] so that your study visit can be rescheduled either in-person or remotely.

If you have decided to discontinue your study participation, please notify us of your decision so that we can update our records [and conduct any final study procedures]. Your prompt attention is appreciated.

Sincerely,

[Insert PI name]

(PI Signature)

Entering Data in WebDCU:

- **TMS data should be entered and uploaded within 24 hours of TMS occurring:**
  - If the MEP status determination is not deemed usable by the central assessors then your site will need time to re-perform the TMS to obtain a usable determination.

- MRI time and date information should be entered within 24 hours of MRI occurring:
  - This is so our data team can ensure the research sequence was performed within the time window.

- All other study data should be entered within 5 business days of the visit.

- Please utilize the visit study window calculator to ensure visits are completed within the study window.

Training Overview

Staff Roles at Each Clinical Site

PREMISES FOR STUDY STAFFING:

- FM and ARAT should be performed by PT/OT, MD or site personnel with experience who have obtained approval from study team
- The study requires that FM at Study Visit 2 & 6 is performed by same person
- Neither TMS operator nor TMS assistant should do FM or ARAT assessments
- Site PIs may not have daily availability at many sites
- Individual variations to recommended model may be needed

STAFF MEMBERS TO BE TRAINED AND CERTIFIED AT SITES:

- Site PI
- 1 SC
- 1 PT/OT
- At least one additional staff member(s) and more encouraged
  - SC, PT/OT, or other study personal

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

RECOMMENDED VERIFY SITE TEAM MODEL

	Visit 1: Screening/Consent	Visit 2 & 3 (Inpatient)				Visit 4: Post-TMS Hospital Assessment (DC Day)	Visit 5: Post-hospitalization Follow Up (30d)	Visit 6: Second Post-hospitalization Follow Up (60d)	Visit 7 (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
SC	X	X		X	X	X	X	X		X
PT/OT			X						X	
Other	X	X		X	X	X	X	X		X
Site PI	Supervisory, may serve PT/OT or TMS role in some sites, or be available for backup in other sites									

Study Specific Trainings

Recertifications

Table shows when you need to be recertified on each behavioral assessment.

FM & ARAT require recertification every 6 months.

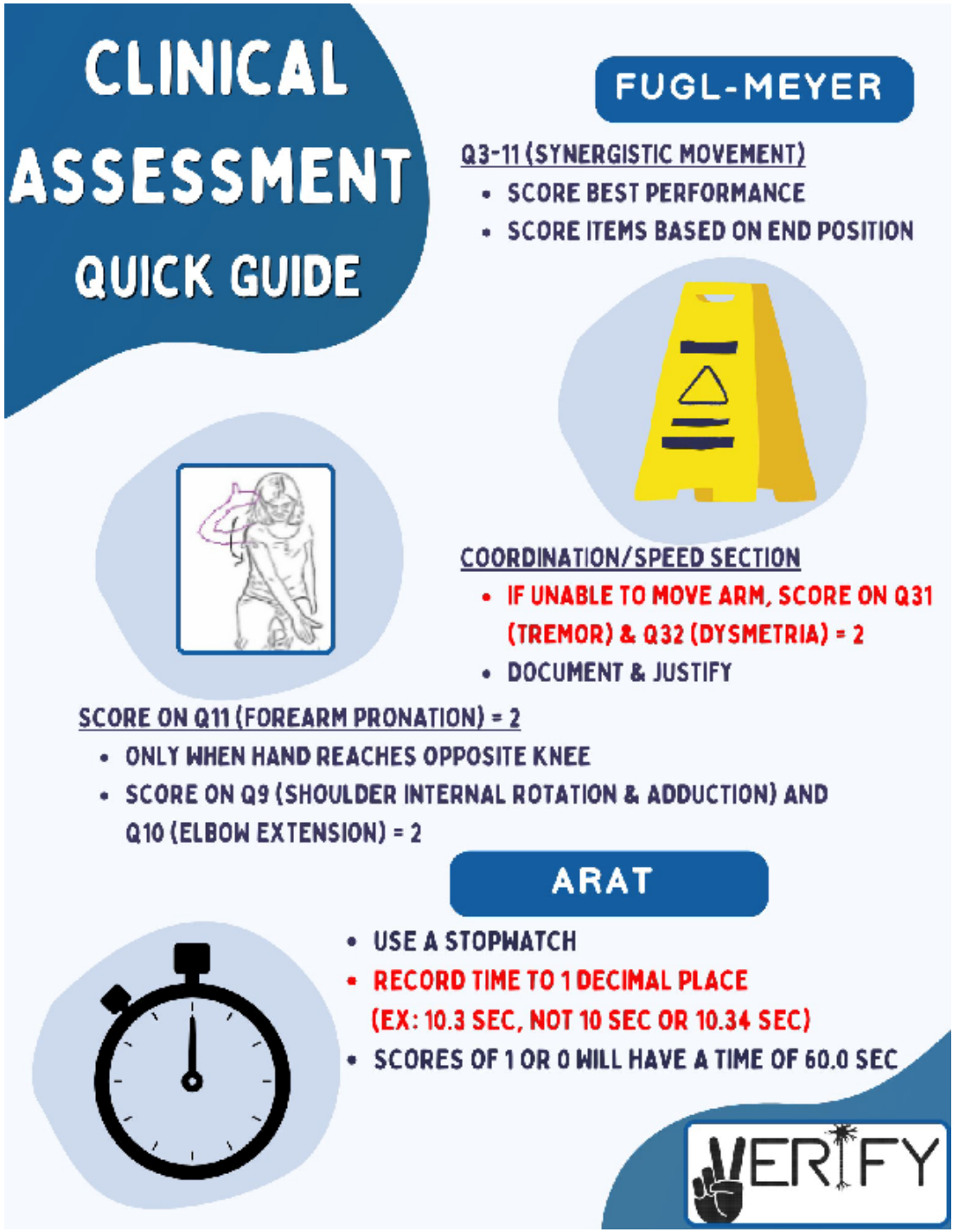
- The Cramer Lab will send reminder emails at 1 month AND 1 week prior to your training expiring. This will serve as a reminder to complete your recertification.

- TMS NOW requires refreshment trainings at 4 months from the last performed VERIFY TMS session for each individual TMS operator.
  - The last VERIFY TMS session could have been performed/conducted with either a stroke patient or healthy volunteer.
  - Contact the VERIFY TMS Core with any questions verify.study.tms@gmail.com

Please review the **VERIFY Study Assessments and Training information** slides available in the toolbox for links and additional details regarding trainings!

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
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	SAFE Score Training	Every 1 year	https://verifytraining.blogs.auckland.ac.nz/
	TMS Safety Checklist Training (Module 2)	Only 1 time	
	Six Online TMS theory training modules (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 with healthy volunteers).	Only 1 time (Repeat training may be requested by the VERIFY TMS Core)	
	Initial Practical TMS training with healthy volunteers (Note: each TMS operator obtains a gold certificate after completing this training is uploaded to the WebDCU TMS training placeholder)	Only 1 time	
	Practical TMS Re-training (Note: each TMS operator must perform TMS on a healthy volunteer or a stroke patient at least every 4 months to maintain training compliance)	Every 4 months (from last VERIFY TMS session)	
	Online TMS Protocol Recertification Quiz (Note: each TMS operator obtains a green certificate after completing this training is uploaded to the WebDCU TMS training placeholder)	Every 1 year	

FM & ARAT Reminders



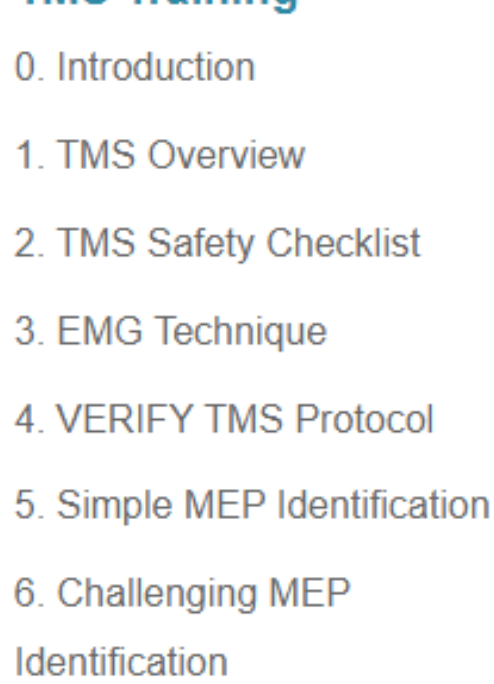
TMS

Training and Certification- TMS website

Every TMS Operator must complete the TMS theory online training **PRIOR** to starting practical TMS training with healthy volunteers.

Completing the full TMS training (mod 1-6) is **ONLY** required for study personnel assigned the role of **TMS Operator** on the DOA

1. Go to: https://verifytraining.blogs.auckland.ac.nz/tms-training-introduction/
2. Read over the provided material and resources for each module
3. Complete Practice Quiz with at least 70% correct for modules 1-6
4. Complete Final Quiz with at least 80% correct for modules 1-6
5. Teal TMS training certificates for each module should be kept on site as evidence of completion in the regulatory binder or regulatory digital file for each module

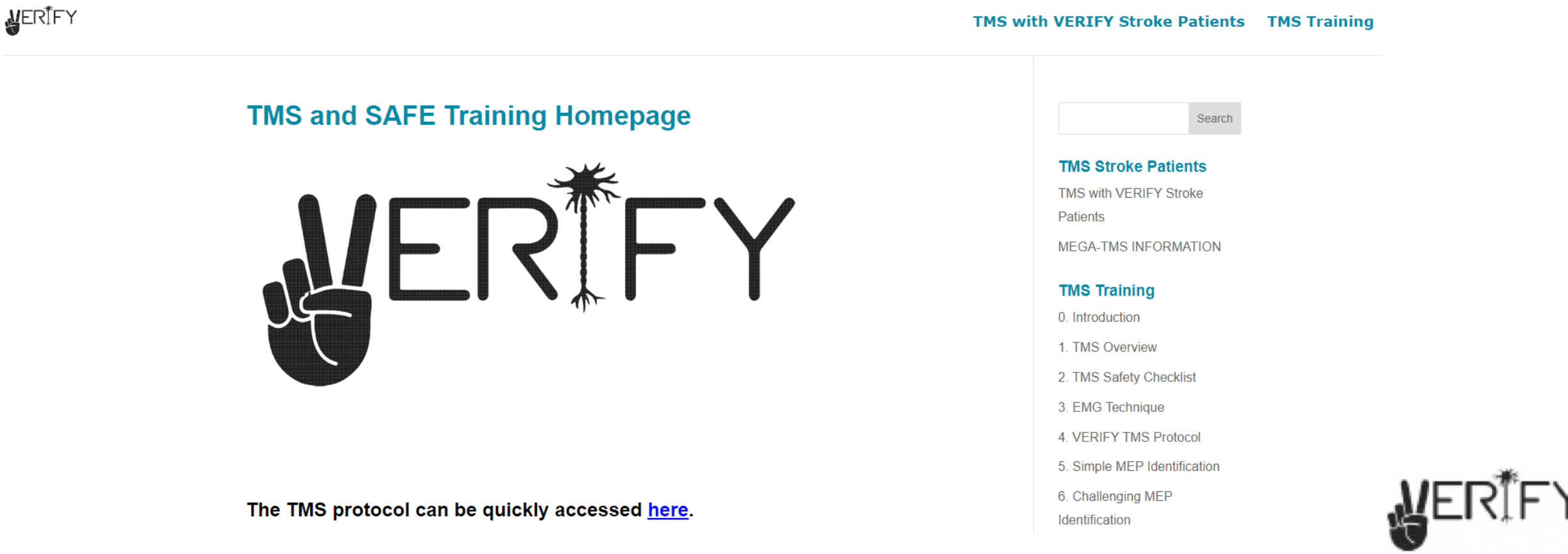


***Please review the TMS training website or the TMS Training process slides available in the Toolbox in WebDCU for additional information regarding TMS training ***

TMS Training website

verifytraining.blogs.auckland.ac.nz

(Click link to access)



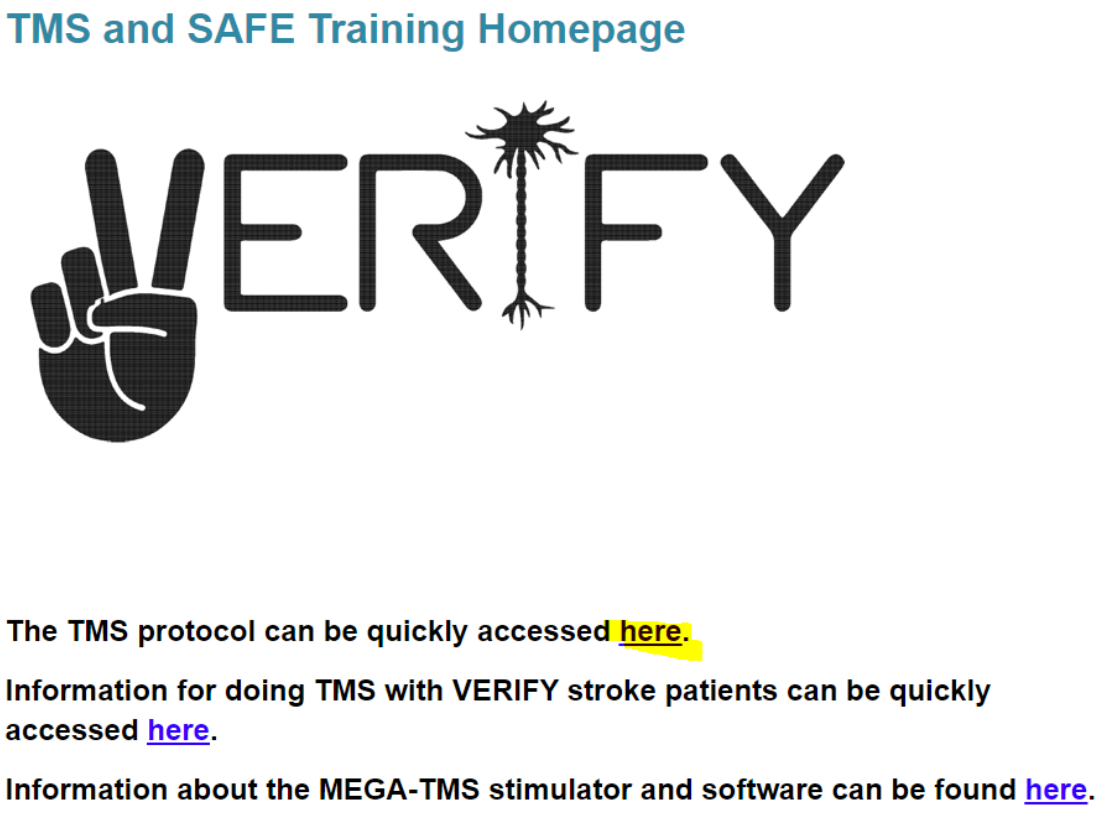
TMS Protocol

TMS Protocol is readily available on the TMS website

- https://www.verifytraining.auckland.ac.nz/tms-protocol

- The site should ensure a paper copy of the TMS protocol is kept with the TMS trolley so it is always available during the TMS training process and with stroke patients.

- Additional resources are also available on the website such as:
  - Videos of EMG preparation and the TMS protocol
  - MEP Traces cheat sheets
  - EMG troubleshooting cheat sheet
  - Tips for TMS with stroke patients
  - Information about the MEGA-TMS stimulator
  - Suggestions for buying new EMG supplies



TMS Facts:

- Repeating TMS:
  - The TMS procedure may need to be repeated if a MEP status determination is deemed unusable by the site or the blinded VERIFY central assessor, assuming no concern for additional risk to the participant.
  - The procedure may be repeated outside the TMS study time window with approval from the central VERIFY team.

- MEP+ status:
  - The participant at rest will be classified as MEP+ if at least 3 MEPs of any amplitude are observed.
  - If no MEPs are observed at 100% MSO with the participant at rest then they will be instructed to perform bilateral facilitation which involves maximum voluntary activation of both UEs to facilitate a response.
    - Only one MEP is needed to classify a participant as MEP+ at 100% MSO during bilateral facilitation

TMS Facts:

- Participants can only be called MEP- if the following have been tried together
  - Stimulator intensity at 100% MSO, and
  - Participant performing bilateral facilitation, and
  - Stimulated at least 5 different scalp locations

- Clarification on Bilateral Facilitation during TMS:
  - **Minimum Requirement**:
    - Deliver **at least 1 stimulus** at **5 different coil positions** over the target motor cortex at **100% stimulator output**.
  - **Recommended Best Practice**:
    - **Continue delivering stimuli beyond the minimum** (as tolerated by the participant)
    - Goal: **Increase confidence** that no MEPs are present.
    - Balance thoroughness with participant comfort—**minimum is 5 positions/1 stimulus each**, but **more is better** when tolerated.

- After TMS:
  - Participants will be clinically monitored with neurological assessments at 15 and 30 minutes after the final TMS pulse is delivered for adverse events such as seizure

TMS Safety

- A signed TMS Safety Checklist is required for ALL participants
  - Checklist should be kept on site as evidence of completion in the subject binder

- TMS Safety Checklist training:
  - The TMS Safety checklist should be completed/signed by **trained** study personnel, which means completing the TMS safety checklist training in module 2 on the VERIFY TMS website
  - 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 with healthy volunteers or stroke patients

- The subject and study personnel who perform the baseline FM and 90-Day FM & ARAT
  must be blinded to the TMS results, and
  cannot enter TMS data into WebDCU

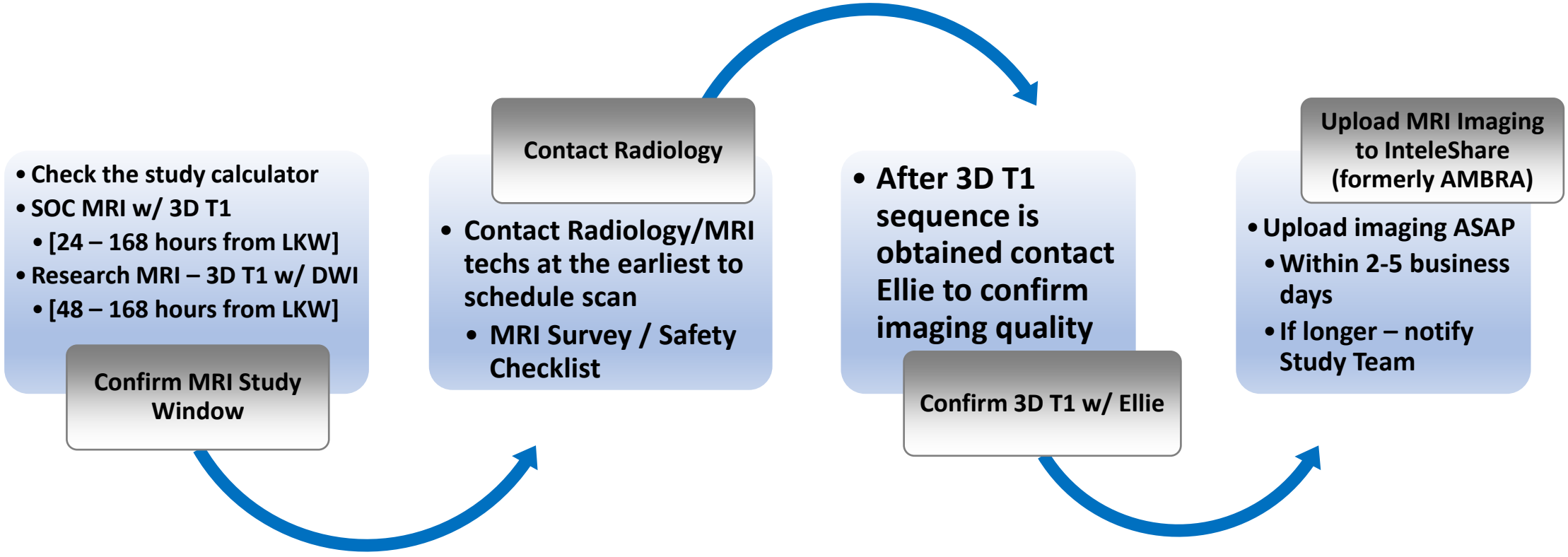
TMS and Other Questions

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

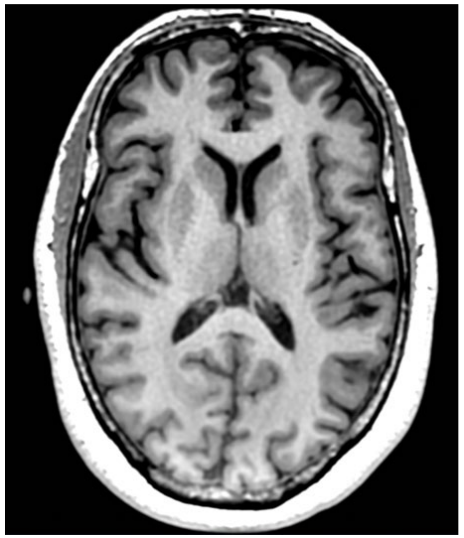
- Non-urgent TMS questions
  - Email us at verify.study.tms@gmail.com

Imaging

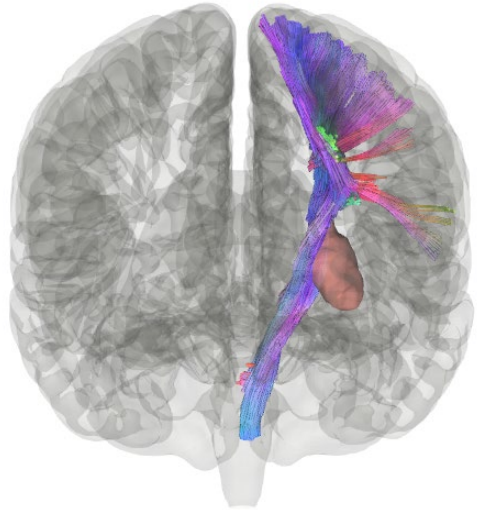
MRI – Imaging Workflow



VERIFY MRI Protocol



- Required sequences of MRI brain scan 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 48-168h
  - #3: **All MRI sequences except 3D-T1** are completed as SOC at 0-168h of onset→ perform 3D-T1 (with DWI) within 48-168h from onset
  - #4: **Clinical MRI not planned** → perform full MRI, including 3DT1, for VERIFY within 48-168h from onset

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

VERIFY MRI Protocol

- Repeating MRI:
  - If the 3D-T1 sequence is deemed unusable by the VERIFY blinded central assessor, an additional scan of the research 3D-T1 sequence and DWI may be performed.
  - This repeat scan will only be performed if the participant is willing, the repeat scan does not interfere with clinical care activities or add any additional risk to the participant.
  - The research 3D-T1 and DWI sequences may be repeated outside the MRI study time window with approval of the VERIFY imaging core.

- *Please review the MRI approval and upload process slides available in the Toolbox in WebDCU*
  - MRI Manual is also available in the toolbox in WebDCU

What Imaging Needs to be uploaded to AMBRA?

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 48-168h
   - If already performed clinically within 24-48h, 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

VERIFY

Questions on Imaging:

- *Questions regarding any imaging questions including **image upload or image check**, please contact :*

  Ellie Johnson: johns8er@ucmail.uc.edu

- *Questions regarding specific questions on image **protocol and acquisition or phantom**, please contact:*

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

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

Reporting

Safety events, unanticipated problems, protocol deviations & serious and noncompliance

Safety Reporting:

What is an Adverse Events (AEs)?

- Definition: 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.
  - **Examples:** worsening of a preexisting medical condition (captured in medical history), petechial hemorrhages (observed in imaging), seizure, syncope and/or headaches (after TMS)

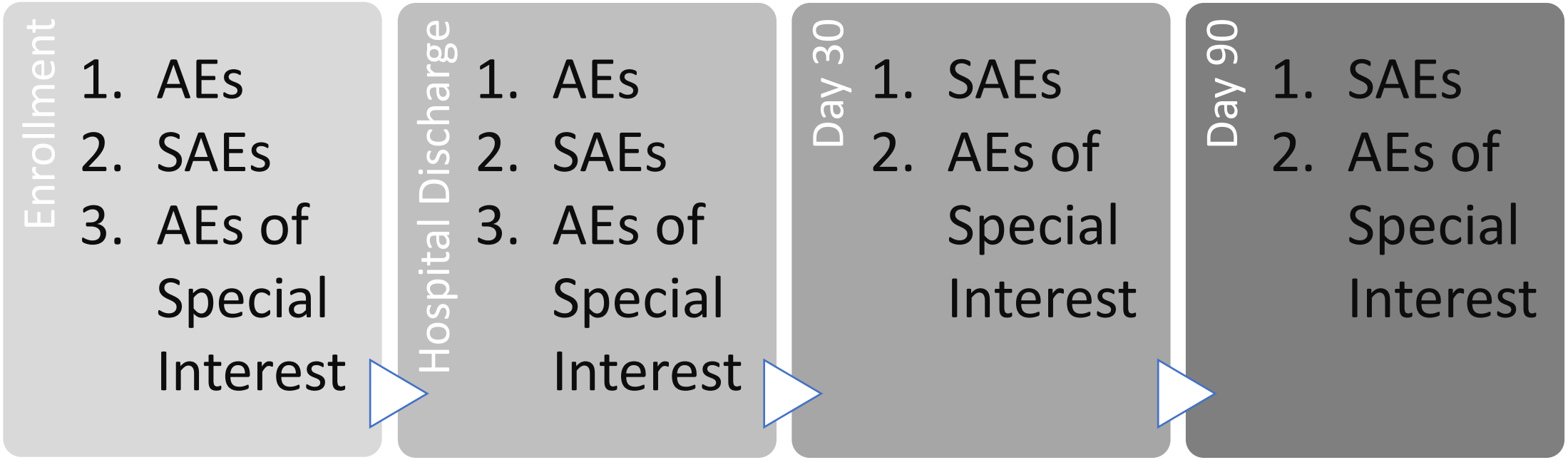
What are Serious Adverse Events (SAEs)?

- **Examples:**
  - 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.

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

SAE/AE Reporting Timeline



*Study enrollment is defined as having started TMS or study-specific MRI sequence
*Hospital Discharge reporting is defined as discharge from initial hospitalization/or up to day 5 post-TMS administration

Safety Reporting in WebDCU continued…

Q01		Adverse Event Name	100 char.

Grade refers to the severity of the AE. The Common Terminology Criteria for Adverse Events (CTCAE) displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 - Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living.
- Grade 3 - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care Activities of Daily Living.
- Grade 4 - Life-threatening consequences; urgent intervention indicated.
- Grade 5 - Death related to AE.

Q02		Grade	○ Grade 1 ○ Grade 2 ○ Grade 3 ○ Grade 4 ○ Grade 5
Q03		Serious	○ No ○ Yes
Q04		Relatedness to study TMS	○ Unrelated ○ Unlikely ○ Possibly ○ Probably ○ Definitely
P01		Relatedness to other study activities	○ Unrelated ○ Unlikely ○ Possibly ○ Probably ○ Definitely
Q05		Date of onset	__ __ - __ __ __ - __ __ __ __ dd-mmm-yyyy
Q07		Outcome	○ Resolved ○ Resolved with sequelae ○ Continuing (Follow up is required) ○ Continuing at end of study (No follow up is required) ○ Continuing at time of death ○ Unknown
Q08	*If Q07 is 'Resolved' or 'Resolved with sequelae'*	Date of resolution	__ __ - __ __ __ - __ __ __ __ dd-mmm-yyyy
Q13		Date of first knowledge of event	__ __ - __ __ __ - __ __ __ __ dd-mmm-yyyy
P02		Seizure during or within one hour of TMS completion	○ No ○ Yes
P03		Recurrent stroke	○ No ○ Yes
P04	*If P03 is 'Yes'*	Brain imaging performed	○ CT/CTA ○ MRI/MRA
P05		Date of image	__ __ - __ __ __ - __ __ __ __ dd-mmm-yyyy
P06		Time of image	
P07		Imaging uploaded to AMBRA	○ No ○ Yes

Data entry guidelines and AE/SAE's reporting are detailed on page 10-14 of the VERIFY Data Collections Guidelines PDF located in WebDCU toolbox

VERIFY Questions (Recap of Contact Info)

Consent/enrollment questions?

- VERIFY Study Email: verifystudy@ucmail.uc.edu

Include: "VERIFY Enrollment Question" on the subject line

TMS questions?

- Urgent (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

Imaging questions?

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

Ellie Johnson: johns8er@ucmail.uc.edu

- *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


Q
A


thank
you