National Institutes of Health (NIH) Bio**mark**ers for **V**ascular Contributions to **C**ognitive **I**mpairment and **D**ementia Consortium (**MarkVCID**)

MarkVCID2 Manual of Operating Procedures

v1.8.25
MarkVCID Consortium

Sponsors: The MarkVCID Consortium is funded by the National Institutes of Health through the National Institute of Neurological Disorders and Stroke and National Institute on Aging (Cooperative Agreement U24NS100591).

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1. Communication and Organization

MarkVCID consists of several academic medical centers conducting biomarker research for small vessel diseases of the brain and one Coordinating Center (CC). Participating sites, key personnel and investigators are listed below.

The Consortium's primary means of communication include regular conference calls, email, the MarkVCID website, and annual conferences. The MarkVCID website (https://markvcid.partners.org/) is used to communicate with the public, featuring consortium research projects, news, and points of contact and as a secure internal communication tool for guiding documents, announcements, meeting information, and trainings. Consortium staff must have an approved user account to utilize the internal website.

MarkVCID2 Coordinating Center Key Personnel		
Name	Contact	Role in Study
Steven M. Greenberg	617-724-1874 sgreenberg@mgh.harvard.edu	CC PI
Kristin Schwab	617-726-6227 kschwab@mgh.harvard.edu	Administrative Core Director
Karl Helmer	617-726-8636 khelmer@mgh.harvard.edu	Data Core Director
Pia K. Webb	pwebb@mgh.harvard.edu	Co-Investigator, Biospecimens
Deborah Blacker	dblacker@mgh.harvard.edu	Co-Investigator, Clinical data
Alexander Sherman	avsherman@mgh.harvard.org	Co-Investigator, Data Core
Herpreet Singh	hsingh6@mgh.harvard.edu	Project Manager
Carissa Tuozzo	carissa.tuozzo@mgh.harvard.edu	Project Manager

MarkVCID2 Research Sites and PIs/MPIs	
Site	Name
Rush University, Illinois Institute of Technology, University of Illinois Chicago	PI - Konstantinos Arfanakis MPIs - Julie Schneider, David Marquez
University of Kentucky	PI - Donna Wilcock MPI - Gregory A. Jicha
University of Southern California	PI - Danny JJ Wang MPIs – John Ringman, Jason Hinman, Amir Kashani
University of California San Francisco, Davis, Los Angeles, Olive View	PI - Joel Kramer MPIs – Pauline Maillard, Jason Hinman, Keith Vossel
Johns Hopkins University School of Medicine & University of Maryland, Baltimore	PI - Hanzhang Lu MPI - Marylin Albert, Peiying Liu
University of New Mexico Health Sciences Center	PI - Gary Rosenberg MPI - Arvind Caprihan
UT Health - San Antonio & Houston, University of Vermont, University of Washington	PI - Claudia Satizabal MPIs - Sudha Seshadri, Myriam Fornage, Sean Savitz, Russell Tracy, Bruce Psaty
Washington University St. Louis & University of Texas Southwestern	PI Jin-Moo Lee MPIs Andria Ford, Hongyu An, Rong Zhang
Mayo Clinic Rochester & Florida, University of Mississippi	PI Ron Petersen MPIs Prashanthi Vemuri, Neill Graff-Radford, Thomas Mosley

2. Site Activation

Each consortium site must be activated by the Coordinating Center (CC) prior to enrolling patients and sharing data with the Coordinating Center. An activation letter will be issued to individual sites once an approved IRB protocol and consent, signed Research Agreement, and personnel training certificates are on file with the Coordinating Center.

2.1. IRB Protocols and Informed Consents

Each site is responsible for obtaining IRB approval for its recruiting protocol and informed consent form. Site specific protocols and informed consent forms must allow for the collection of MarkVCID2 common data, imaging and biosamples at the required timepoints and sharing of these with investigators and the Coordinating Center (see sections (3) and (4) for collection protocols and required procedures).

2.2. Template Consortium Consent Language

The MarkVCID Protocol, Recruitment, Diversity and Retention Subcommittee developed template consent language for sites to use in developing its site consent form. This language was developed to ensure MarkVCID patients are informed of how their data and biosamples will be used in research and shared with the Consortium and broader research community.

Location: MarkVCID2 Protocols & Resources | MarkVCID (partners.org)

Draft informed consent forms must be reviewed by the Coordinating Center prior to IRB submission to ensure the required consortium sharing language has been incorporated.

Consent Form Review Process

1. Each prospectively recruiting site must revise their consent to include the consortium template language. Sites can edit the language to remain compliant with local IRB policies and required language.

2. Submit a draft to the Coordinating Center for review and agree to a final draft that will be submitted to the site's IRB.

3. Submit the final consent form for IRB approval.

4. Once the site receives the IRB's notice of approval, the site emails the final approved copy to the Coordinating Center.

5. Sites must submit annual IRB approval letters and consents to the Coordinating Center.

2.3. Research Agreement

The MarkVCID Research Agreement governs the sharing of data and biosamples across consortium sites and with the Coordinating Center. Each site must have a designated Institutional Official agree to the terms and sign the agreement on behalf of the institution.

The template MarkVCID Research Agreement and signed versions are maintained by the Coordinating Center and are available upon request.

2.4. Trainings

Site staff must take consortium trainings prior to conducting the common clinical data, imaging and biosample collection protocols with participants. These trainings ensure harmonized data collection and entry and inter-rater reliability across the Consortium. Sites must designate trainees for each of the trainings listed below according to their role at the site. If specific credentials are required for certain procedures/trainings, it will be noted below.

Please note that the Neurological Exam portion of the study visits must be completed by a clinician with experience in assessing neurological signs and attributing findings to a particular syndrome. No training is provided for this by the CC.

All trainings are located on SkyPrep. Please fill out the Research Site Staff Form in Smartsheet to add or remove study staff or modify study responsibilities assigned to staff. Contact Carissa Tuozzo (carissa.tuozzo@mgh.harvard.edu) with any questions.

Data Management System Overview

(Applies to all staff; overview of the data management infrastructure)

Clinical Data Collection and Entry

(Applies to staff entering clinical data into the data system)

Virtual Biorepository

(Applies to staff who receive and process samples, print labels, scan and input information into the virtual repository)

Neuropsychological Testing Battery

(Applies to staff administering the battery including MoCA and GDS. NPI-Q, eCOG short form, and CDR must be administered by a clinician or other trained health professional (clinical PhD). Please assign accordingly.)

In addition to completing the MoCA and NP trainings and tests on Skyprep, the trainee must conduct three practice administrations, one of which must be observed by a neuropsychologist or psychometrician. The observer must send an email to the Coordinating Center (CC) confirming they observed the trainee in at least one practice administration and that the trainee is qualified to administer the NP tests.

The CC also conducts a quality control check on NP Battery scoring. Coordinators are required to scan and email at least one of their first three subjects' NP battery forms and worksheets to hsingh6@mgh.harvard.edu. A neuropsychologist at the CC will review scoring and provide feedback. Please deidentify all materials by redacting participant information including IDs replacing them with the MarkVCID ID.

Short Physical Performance Battery

(Applies to staff administering the short physical performance battery)

Fazekas Scale

(Applies to staff responsible for rating scans)

Staff responsible for rating scans must first complete the Fazekas Skyprep training. After the training, the trainee must complete a rater assessment and score 80% or higher to pass. Trainees may take up to four different rater assessments if needed.

In the event the trainee does not pass the rater assessment after their fourth attempt, the trainee will meet with the training instructor from the Coordinating Center to review the training sets and determine whether the staff member requires additional training or can be certified based on their review.

Microbleed/Infarct Rating

(Applies to staff responsible for detection and classification of microbleeds and infarcts on scans)

Raters may be any study staff with basic training from the Coordinating Center, however, staff with knowledge of neuroanatomy may be able to identify microbleeds and lacunar infarcts more quickly and accurately. After reviewing the Microbleed/Infarct Rating SkyPrep training course, the trainee must complete and pass a series of test sets.

Imaging Acquisition

(Applies to staff responsible for acquiring MRIs)

The trainee is required to complete the Imaging Acquisition SkyPrep training course on the MarkVCID2 Imaging Manual and successfully complete an acquisition assessment.

Imaging Data Management

(Applies to staff responsible for anonymizing and uploading MRIs into the data system)

The trainee is required to complete the Imaging Data Skyprep training course and then conduct a mock scan anonymization and data-upload to confirm knowledge of the process and identify any technical issues.

Cerebrovascular Reactivity (CVR) Scanning

(Applies to staff involved in the CVR portion of the MRI scanning protocol)

If the trainee did not attend a comprehensive in-person training session with JHU staff, then they are required to complete the CVR SkyPrep training course that reviews set-up, steps to take during the scanning protocol, and processing.

3. Prospective Site Recruitment and Procedures

Sites will maintain their MarkVCID2 IRB approved protocols throughout the 5-year period, amending them, if necessary, to include the collection of the required clinical data, imaging and biosamples. All shared patient data and biosamples must be collected using an IRB approved informed consent form that contains consortium required data and biosample sharing language (see section 2.2. for informed consent requirements).

Each enrolled participant should have a baseline visit followed by up to **3** annual follow-up visits. At each visit, clinical data, imaging, and biosamples should be collected in accordance with the common protocols and best practices. Patient data that is collected by fully trained site staff using the common consortium protocols/best practices (clinical, imaging and fluid) should be entered into the MarkVCID data system.

3.1. Screening

Sites are responsible for maintaining a prescreening log locally that captures at minimum participants who were contacted but deemed ineligible, or who declined enrollment. Deidentified data will be shared with the CC every six months including method of contact, enrollment status, date of contact, age at time of contact, biological sex, race/ethnicity, cognitive status, and reason not enrolled into MarkVCID2. Please utilize the template provided on the MarkVCID2 website.

After consent is obtained and a participant is screened and deemed eligible for the study, the study team must complete the following forms: Enrollment Criteria, Vascular Risk Criteria, and Enrollment Confirmation Checklist CRFs (pages 3-8 in the Baseline CRF package). Participants should not be registered or added to the data system significantly before their scheduled baseline visit.

Research site personnel are **strongly encouraged** to enroll study participants with a co-participant/informant to gather information about the study participant. If a participant is unable to provide an informant, the site may proceed with the enrollment. Please see section 3.2.3 for

additional guidance regarding informants.

3.1.1. Participant Co-enrollment

Sites are requested to review the source of enrollment of participants who have reasonable likelihood of co-enrollment. If a participant is eligible for the MarkVCID study and is co-enrolled (or may in the future) in interventional research that goes beyond current standards for preventing disease progression, the site must maintain this information in a local enrollment log that will be shared with the Coordinating Center as requested, and confirm there are no 1) conflicts with MarkVCID inclusion/exclusion criteria (section 3.2), and 2) at least a six-month gap between clinical/cognitive assessments to minimize any practice effects between visits. Please refer to the MarkVCID case report form for more details on how to document co-enrollment data.

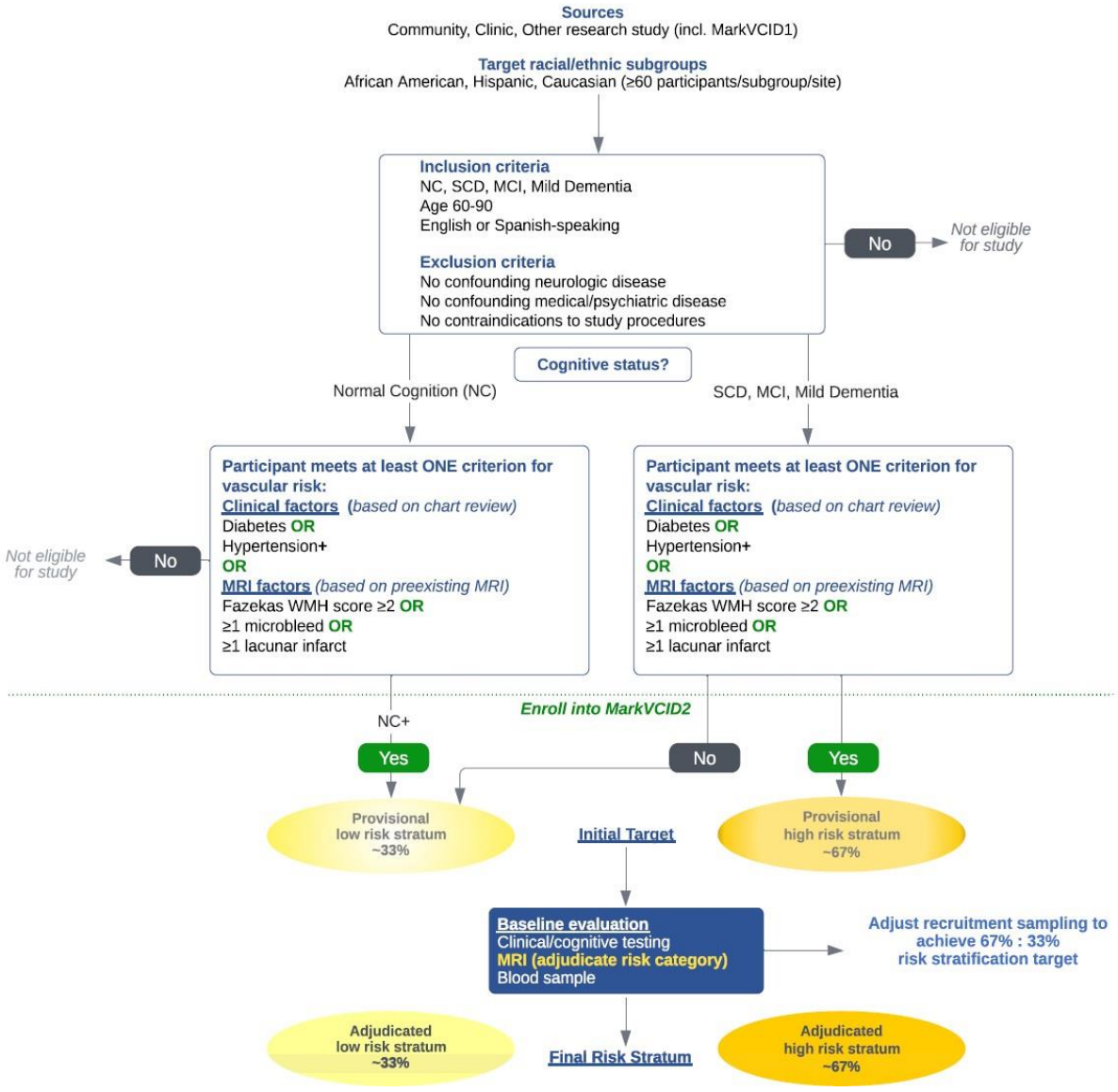
Research site staff are requested to contact the Coordinating Center for guidance if they are unsure of a participant's eligibility in the MarkVCID study due to co-enrollment in another study.

3.2. Eligibility Requirements

To be eligible for MarkVCID2 enrollment, participants must meet the following criteria:

- Age ≥ 60 and ≤ 90 years
- Diagnosis of normal cognition[1] with at least one criterion for vascular risk (see section 3.1.2), subjective cognitive decline[2] (preliminary diagnosis based on self-report question or eCog-12; see footnote for confirmed diagnosis), mild cognitive impairment[3], or mild dementia[4] based on standard research criteria
- Fluent in English or Spanish
- No contraindications to MRI including CVR
- No confounding neurologic, psychiatric, or medical disease (see section 3.1.1.)

Please refer to the MarkVCID2 adaptive enrollment strategy flowchart below.



[1] Normal cognition includes participants with normal subjective and objective cognition, and who meet high risk criteria based on pre-existing MRI or clinical criteria.

[2] Molinuevo JL, Rabin LA, et al. Implementation of subjective cognitive decline criteria in research studies. Alzheimers Dement. 2017;13(3):296-311. doi:10.1016/j.jalz.2016.09.012

[3] Albert MS, DeKosky ST, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):270-279. doi:10.1016/j.jalz.2011.03.008

[4] McKhann GM, Knopman DS, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005

3.2.1. Confounding Neurologic, Psychiatric, or Medical Disease

Neurologic Disease:
Based on the available data and investigator's impression, exclude those with confounding neurologic disease that would interfere with test performance or with biomarker analysis:

Exclude

- Frontotemporal lobar degeneration (FTLD)
- Lewy body dementia (LBD)
- Parkinson's disease
- Multi system atrophy
- Traumatic brain injury (TBI)-related cognitive impairment
- TBI that interferes with MRI biomarker analyses (e.g., large volume traumatic lesion)
- Non-small vessel strokes that interfere with test performance (e.g., post-stroke cognitive impairment or aphasia)
- Non-small vessel strokes that interfere with MRI biomarker analysis (e.g., large volume strokes)
- CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy)
- Individuals known to be receiving, or planning to receive, anti-amyloid immunotherapy*
- Other neurologic conditions that interfere with test performance or biomarker analysis

*Individuals prescribed anti-amyloid immunotherapy *after* MarkVCID enrollment should be kept in the study.

Do NOT exclude

- Alzheimer's (mild dementia CDR score ≤1)
- Small vessel disease strokes (e.g., lacunar infarcts)
- Non-small vessel strokes or TBI that does not interfere with test performance or MRI biomarker analysis

Medical and Psychiatric Conditions:
Exclude those with medical and psychiatric conditions that would confound the course or interfere with test performance:

Exclude

- Schizophrenia or other active/severe psychotic disorders
- Medical or psychiatric conditions likely to interfere with participation or retention (e.g., metastatic or malignant CNS cancer, active /severe depression or anxiety, HIV-Associated Neurocognitive Disorder)
- Contraindications to MRI procedures, such as:
    - Claustrophobia
    - Cardiac pacemaker
    - Intracranial clips/metal implants
- Contraindications to CVR:
    - COPD or other respiratory condition requiring oxygen therapy
    - Asthma or other respiratory condition requiring current use of medications such as inhalers

    *****All efforts should be made to enroll participants that can complete every study procedure. In exceptional cases, participants with any of the above contraindications to CVR may be enrolled so long as they are able to complete all other study procedures (MRI, cognitive testing, and biosample collection).

Do NOT exclude

- Well-controlled depression or anxiety
- Substance abuse in remission for ≥ 2 years

3.2.2. Vascular Risk Criteria

Participants with normal cognition must meet at least one criterion (diabetes, OR hypertension plus, OR MRI factors) for vascular risk prior to enrollment based on chart review or a pre-existing MRI (referred to as normal cognition plus or NC+). Participants diagnosed with SCD, MCI, or Mild Dementia at screening that do not meet at least one of the vascular risk criteria are considered eligible for the study and categorized in the low risk stratum.

After enrollment, participants will have a full clinical evaluation at their baseline visit, including the standard neuropsychological test battery. The rare individuals in whom these diagnoses and other enrollment criteria are not confirmed will be withdrawn and designated "found ineligible after consent" in the Eligibility/Subject Final Disposition forms. Ineligible participants' baseline visit data (clinical, cognitive, imaging, biosamples) will not be retained in the MarkVCID2 Electronic Data Capturing System.

All eligible participants will be designated in either low or high-risk stratum based on the findings in the baseline MRI.

Diabetes (at least one of the following):

- Fasting (8 hour fast, usually overnight) blood sugar ≥126 mg/dL (≥7 mmol/L, or ≥1260 mg/L)
- Random or Post-prandial blood sugar ≥200 mg/dL (≥11.11 mmol/L, or ≥2000 mg/L)
- HbA1C ≥6.5% (or ≥47.5412 mmol/mol)
- Treatment with an anti-diabetic medicine

Hypertension plus (at least two of the following):

- Use of anti-hypertensive medications for lowering blood pressure for ≥ 10 years
- Current use of two or more anti-hypertensive medications for lowering blood pressure
- One measured blood pressure in a research or clinical setting in the last 2 years with SBP ≥140 or DBP ≥90
- A second measured blood pressure in a research or clinical setting on a different date in the last 2 years with SBP ≥140 or DBP ≥90
- Evidence of likely HTN end organ damage (e.g., LVH, albuminuria, eGFR<60, CHF)

MRI factors (at least one of the following):

- Peri-Ventricular Fazekas Extent Grade or Deep Fazekas Extent Grade ≥ 2
- 1 or more microbleeds
- 1 or more lacunar infarcts

3.2.3. Co-participants/Informants

Research site personnel are **strongly encouraged** to enroll study participants with a co-participant/informant to gather information about the study participant. If a participant is unable to provide an informant, the site may proceed with the enrollment.

If the informant is not able to accompany the study participant to the research visit, sites may reach out to the informant within the study visit window by phone or electronic survey to collect the necessary information.

In the event that an informant is not successfully contacted within 14 days of the participant's study visit, sites are advised to conduct a weekly call for 6 weeks following the participant's visit (e.g. including phone, email, and follow-up with the participant for an alternative informant). The site is encouraged to re-attempt contact at the follow-up visit even if the informant was unavailable at baseline. When possible, informants should be the same throughout the study.

In the absence of an informant for the CDR, the clinician or other trained health professional should complete the CDR form using all other available information and their best clinical judgment. Personnel unable to secure an informant should mark 'not collected' and 'reason for not collecting' on the case report form and in the database for the following: Brief co-participant/informant Questionnaire, eCog-12 informant version, and NPI-Q.

3.3. Common Consortium Data, Imaging and Biosamples

The Consortium has agreed to collect common clinical and cognitive data elements, biosamples, and imaging on all MarkVCID patients at the baseline and annual follow up visits. ***Note:*** See section (2) for trainings and section (5) for specific biomarker kit protocols and associated procedural materials.

3.4. Schedule of Events

The chart below is an overview of required events/procedures and timepoints.

- For each timepoint, all imaging, clinical/cognitive data, and blood samples should be collected within **14 days.**
    - In extenuating circumstances, all study procedures can be performed within a 90-day period. Such cases need to be reviewed by the Coordinating Center on a case-by-case basis.

- Annual follow-up window for imaging, clinical/cognitive data, and blood samples is **1 year ± 30 days, 2 years ± 30 days,** and **3 years ± 30 days** from the subject's baseline visit.
    - In extenuating circumstances, an out-of-window follow-up visit may be attempted. All study procedures must be completed **within 90 days** of follow-up window closure.

Deviations from these time windows **must be approved** by the Coordinating Center as soon as possible. Please email deviation requests to CC Project Manager Herpreet Singh.

Events	Screening	Baseline (0-14 days)	Follow-up (12-month ± 30 days)	Follow-up (24-month ± 30 days)	Follow-up (36-month ± 30 days)
Confirm eligibility & vascular risk criteria	X				
Clinical data collection		X	X	X	X
CDR		X	X	X	X
Neuropsychiatric Battery		X	X	X	X
Short Physical Performance Battery		X	X	X	X
Clinical Labs		X	X	X	X
Plasma and serum		X	X	X	X
Packed cells		X			
MRI scan protocol		X	X	X	X
Fazekas (scored after MRI obtained)		X	X	X	X
Microbleed/Lacunar Infarct Rating		X	X	X	X
Brain Autopsy					

3.4.1 Study Visits

Study participants will complete a baseline visit as soon as possible after enrollment. Follow-up visits will then occur at 12-, 24-, and 36-months post-enrollment. During each visit, study participants will undergo a base set of study procedures, noted above. Additional study procedures may be conducted at sites with IRB approval to complete them. Study procedures will be completed by trained, qualified members of the study team whose qualifications are tracked per the site's institutional requirements. Refer to section 3.2.3 for information on engaging with informants.

Every effort should be made for participants to complete all visit procedures in person within the visit window. In extenuating circumstances, participants may complete baseline neuropsychological testing remotely. Please see the Clinical Assessments Remote Administration Evaluator's Manual on the MarkVCID2 website for guidance on completing the neuropsychological battery remotely (https://markvcid.partners.org/markvcid2-protocols-resources).

3.4.2 Participants with Missing Baseline Visit Procedures

Participants missing both MRI **and** biosamples, **OR** missing cognitive testing at baseline should be withdrawn and not counted toward the site's enrollment metrics. To document a participant was withdrawn due to the above criteria, mark "Subject early terminated" and "Patient unable to complete minimum required baseline study procedures" on the Subject Final Disposition form.

If the participant is missing only the MRI scan or only biosamples at baseline and the procedure cannot be completed within the timeline specified in section 3.4, the participant should be kept in the study for relevant biomarker analyses. All visit procedures should be attempted at follow-up visits.

3.4.3 Participant Retention & Participants with Missing Follow-up Visit Procedures

If a participant refuses or cannot complete a follow-up visit in person, they should be offered to complete the visit remotely. Data that can be collected remotely include new medical history, the neuropsychological battery, GDS, eCog-12, and informant measures (informant questionnaire, eCog-12, NPI-Q, and CDR). Subsequent visits should be completed in person when possible.

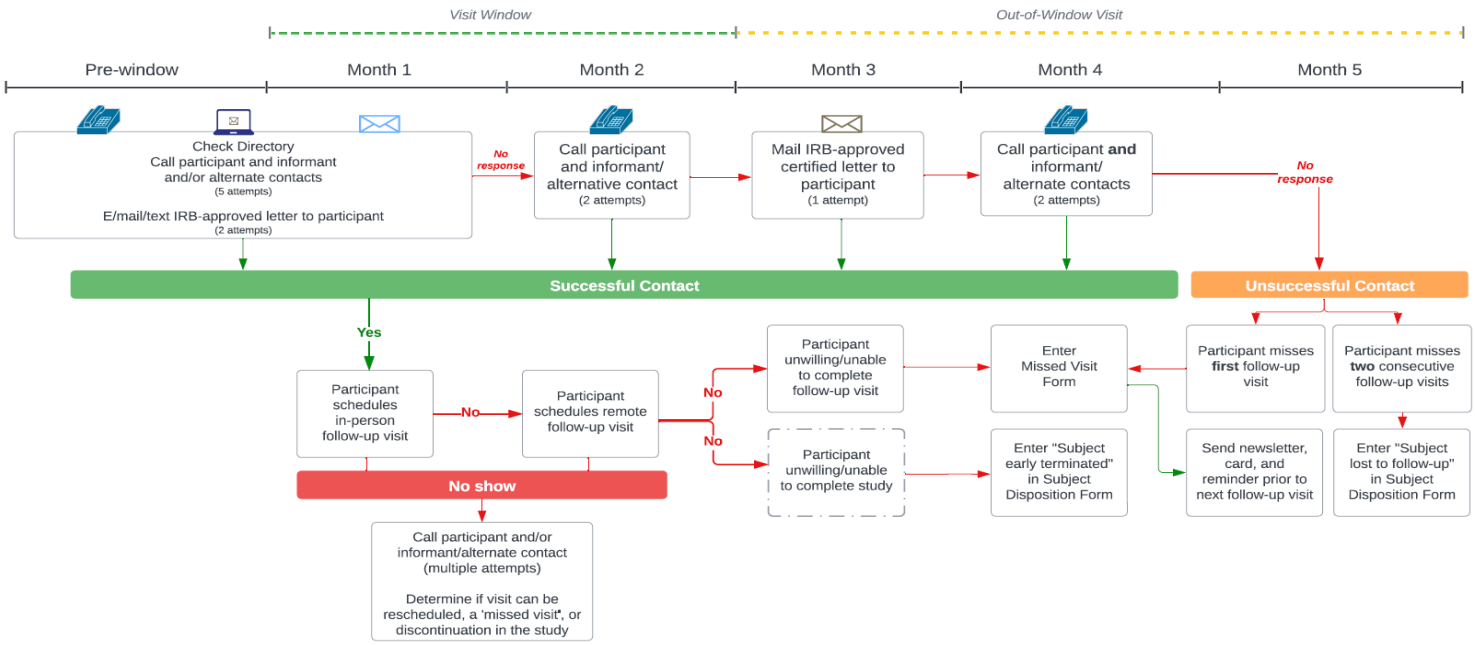
If the participant cannot complete all follow-up visit procedures within the timeline outlined in section 3.4, they should remain in the study. All visit procedures should be attempted again within the next follow-up visit window.

Site personnel should begin contacting a participant before their visit window opens to schedule a follow-up visit. If contact is not successful before the visit window opens, personnel are advised to attempt contact throughout the visit window at varying times in the week and use various IRB-approved methods (phone, email, text, certified letter, etc.). Please attempt to contact the participant and informant/alternative contact a minimum of 10 times based on the site personnel's best judgment of each case and document this information in the site's local contact log. **Please refer to the MarkVCID2 Participant Follow-up Contact Schedule below.**

If a participant misses a visit and they are unable to complete their visit in person or via phone within the timeline outlined in section 3.4, the missed visit and reason should be recorded on the Missed Visit Form.

A participant is considered lost to follow-up when all options suggested in the Participant Follow-Up Contact Schedule have been exhausted **and** the participant has not been successfully contacted for 2 consecutive follow-up visits. These participants should be designated as "Subject lost to follow-up" in the Subject Final Disposition form.

MarkVCID2 Participant Follow-up Contact Schedule



3.4.4 Site to Site Participant Transfer Procedures

If a participant is unable to return for in-person visits due to relocation, the enrolling MarkVCID site may transfer this participant to another active MarkVCID site to complete their in-person follow-up visit(s) upon PI and Coordinating Center (CC) approval. If there is no MarkVCID site local to the participant, the enrolling site should retain the participant and complete as many remote measures as possible (see section 3.4.3).

When the enrolling site becomes aware of a participant's plan to relocate and confirms the participant is willing to continue their participation in the study at another MarkVCID site, the site should contact the receiving site PI to discuss the possible transfer and confirm that they have the resources available to continue all remaining study visits with the participant. Examples of major resources include clinical and administrative personnel, MRI availability, biospecimen storage facilities, and supplies. Once confirmed, the enrolling site should email the receiving site PI and the CC for formal transfer approval.

Both sites must follow their site IRB and regulatory requirements to transfer or receive the participant and complete any other regulatory steps specific to their institutions. Once all regulatory requirements are met and the transfer is approved by the site IRBs, sites should notify the CC. Sites will then be prompted to complete the Participant Transfer Form in the MarkVCID electronic data capture system (EDC).

Please refer to the Participant Transfer Checklist for a detailed description of all required steps.

Location: MarkVCID2 Protocols & Resources | MarkVCID and **click** "Participant Screening, Registration, & Transfer" and **select** "Participant Transfer Checklist"

3.5. Clinical Data Collection

(Estimated duration 1.5 – 2 hours)
Location: MarkVCID2 Protocols & Resources | MarkVCID and **click** "Clinical & Cognitive Measures Collection Manuals"

- MarkVCID2 Comprehensive Clinical Data Measures
  (overview of clinical data elements collected across the consortium)

- Case Report Forms (CRFs)
  - Initial and Follow-up CRF Packages (printable data collection forms)
  - Initial and Follow-up CRF Completion Guidelines
- Neuropsychological (NP) Testing Battery
  - Evaluator's Instructions Manual
  - NP Testing Battery Worksheets
- Short Physical Performance Battery (SPPB)
  - SPPB Protocol and Scoring Guidelines
  - Wallchart and Supplementary Scoresheet

Please note that for the Laboratory Tests section of the CRF package, laboratory tests must have been conducted within 3 months of the research visit or at the time of the visit. Test results may be retrieved from the medical record. The following lab tests are required: HbA1c; Serum, HDL, LDL cholesterol (fasting); Triglycerides; and Serum creatinine.

The following lab tests are optional: HS-CRP; Blood Sugar (fasting); Homocysteine (fasting); Genetics; Serum Cystatin. Please note that if collected, cholesterol related labs, blood sugar, and homocysteine should be collected under fasting conditions when possible. If fasting conditions are unknown, mark "not fasting".

Please see section 3.2.3 for guidance on attempting to contact the informant as well as which CRFs to complete in the event that the informant is unable to accompany the study participant to the research visit.

3.5.1 CVLT, CVLT-SF, HVLT, SEVLT Guidance

MarkVCID research sites may choose to administer one of the following word list learning tests: CVLT, CVLT-SF, HVLT, or SEVLT. The Clinical Assessments In-Person Evaluator's Manual does NOT contain administration and scoring instructions for these tests. Please contact your site neuropsychologist for the test your site employs and additional instructions specific to your site's practices.

3.6. Biosample Data and Sample Collection

Location: MarkVCID2 Protocols & Resources | MarkVCID and **click** "Biospecimen Collection Best Practices & Shipping Procedures"

- Fluid Sample Best Practices & Requirements
- Biosample CRFs
- Shipping Human Biospecimens Guidelines
- Research Site IDs for biosample entry coding and approved addresses
- Brain autopsy/brain tissue processing and biobanking *(coming soon)*

3.7. Imaging Data Collection

The MRI protocol consists of seven different scan types in addition to localizing scans. Each scan-type pulse sequence is listed below followed by the time required in parentheses. The times quoted are approximate as they will vary slightly between vendor and scanner operating system.

The total time of this protocol is approximately 38 minutes of scan time. Patient preparation and the preparation of the cerebrovascular reactivity (CVR) equipment will add additional time to the scan session.

1) Localizer (~0:12)
2) T1-weighted, (multi-echo MPRAGE, ~6:00)
3) Fluid Attenuated Inversion Recovery (FLAIR, ~6:30)
4) Diffusion-weighted imaging (PA, original data, ~7:00)
5) Diffusion-weighted imaging (AP, used for distortion correction, ~1:30)
6) T2-weighted (~4:00)
7) 3D Gradient-recalled echo (~5:30)
8) Localizer2 (~0:12)
9) Cerebrovascular Reactivity Scan (GRE, functional/BOLD scan, ~7:15)

Please see section 3.7.1 for guidance on repeat sequences.

In the scenarios listed below, the Coordinating Center will evaluate whether the participant should be removed from the study. Please email CC PM Herpreet Singh or the MarkVCID CC Imaging Team if a participant meets either of the below scenarios:

- The baseline MRI cannot be collected within the timeline outlined in section 3.4.
- The baseline MRI is missing at least one of the required scans (listed below) and cannot be collected within the timeline specified in section 3.4:
    - T1-weighted
    - Fluid Attenuated Inversion Recovery (FLAIR)
    - Diffusion-weighted imaging (PA and AP)
    - 3D Gradient-recalled echo

If the participant was enrolled and agreed to complete all scans, but at the time of the visit was unable to complete CVR, retain the participant data. The acquired data can still be uploaded; however, please indicate that the imaging protocol was not completed and record “CVR not completed”, along with the reason why, in the ‘Comments’ section of two forms: 1) Imaging CRF and 2) Imaging Data Registration Web Form on the website.

Refer to the comprehensive MarkVCID Imaging Manual for harmonized imaging protocols, data registration, data anonymization, and file transfer standard operating procedures.

Location: MarkVCID2 Protocols & Resources | MarkVCID (partners.org)

3.7.1 Repeat MRI Sequences

Please review all scans immediately after acquisition to ensure that the image quality is sufficient for analysis. If the data for a particular scan type has excessive motion, please repeat the scan during that scan session. If a repeated scan is not possible or the data is determined later to be unusable, you may be asked to rescan the participant. The chart below shows which sequences need to be completed (indicated by an "X") when a rescan is requested. For example, if the FLAIR scan is unusable and a rescan is requested, you should also acquire a T1-weighted scan during the rescan session. Note that a T1-weighted scan is required for all rescan sessions (except CVR) as this is needed for the registration step of the data processing. In addition, if either the PA or AP diffusion-weighted scans are missing or unusable, and a rescan is requested, please acquire both scans, as well as a T1-weighted scan. If multiple scans are unusable, repeat the sequences indicated by an "X" in the chart for both scans. For example, if the FLAIR scan and the CVR scan were both unusable, then the T1-weighted, FLAIR, and CVR sequences would need to be repeated.

During the scanner certification process, the Series Description (name) of each scan was specified and checked. Please do not modify the Series Description of the rescan as it is used in the automated scan-type identification pipeline at data upload. If a scan type acquisition must be repeated, please do not modify the Series Description to indicate that the later scan is a rescan. Repeated scans will be identified by the acquisition time. Please refer to section 5.1 of the Imaging Manual for more guidance.

Missing or Unusable Sequence	T1-weighted (multi-echo MPRAGE)	Fluid Attenuated Inversion Recovery (FLAIR)	Diffusion-weighted imaging (PA)	Diffusion-weighted imaging (AP)	T2-weighted	3D Gradient-recalled echo	CVR
T1-weighted	X	X	X	X	X	X	X
FLAIR	X	X					
Diffusion-weighted (PA)	X		X	X			
Diffusion-weighted (AP)	X		X	X			
T2-weighted	X				X		
3D Gradient-recalled echo	X					X	
CVR							X

4. Data Management

The secure internal MarkVCID website https://markvcid.partners.org/ allows trained users to enter data in the following portals. You can also navigate to these portals through the website's "Data Portals" dropdown menu.

- Patient Registration (register a patient and receive a patient ID)
https://markvcid.partners.org/consortium-protocols-resources

- Imaging Data Registration (register patient scan sessions)

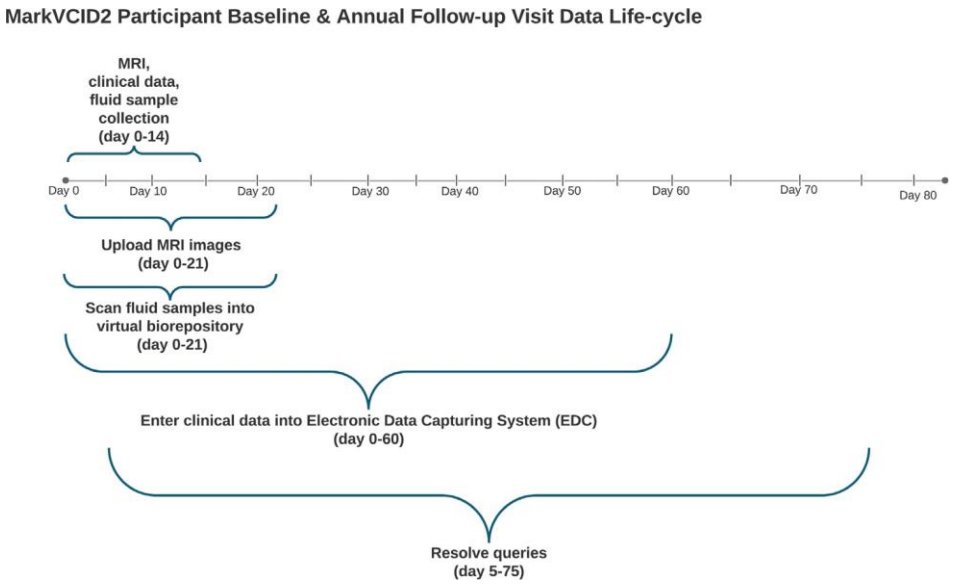
- Clinical Data Entry (enter patient clinical data)

- Virtual Biorepository (register and track patient biosamples)

-Subject Deletion Request (delete a subject entered in the system)

See training section (2.4) for data management overview.

Research sites are asked to adhere to the life cycle of study procedures and data entry depicted below. The CC will review the timeliness of data collection and data entry on a regular basis as part of its data quality control efforts.



4.1. Handling of Data and Confidentiality

MarkVCID participant's clinical data, images and biosample data are stored in the MarkVCID data system at Massachusetts General Hospital. Registered patient data including imaging and biosample data will be assigned randomly generated IDs by the MarkVCID data system. Dates relating to research visits and clinical care will be stored in the data system and shared with participating MarkVCID sites that have signed the Research Agreement. No other health information (PHI) will be shared with sites or with the Coordinating Center.

Logs connecting the MarkVCID IDs to the subject's identity will be maintained at the recruiting sites following their site confidentiality policies, and only IRB approved site staff will have access to the logs.

De-identified biosamples and data may be shared with other researchers at universities, hospitals, commercial companies and not-for-profit organizations if approved by the consortium.

4.2. Patient Registration and Tracking

The MarkVCID Patient ID is used to identify MarkVCID participants entered in the data system. A Patient ID is obtained by registering a participant through the Patient Registration portal page on the MarkVCID internal website. Participants must first be registered before any data is entered.

The Patient ID will be displayed on the screen and will also be emailed to the registering user.

Save this ID in the provided MarkVCID Patient Enrollment Log.

Location: MarkVCID2 Protocols & Resources | MarkVCID (partners.org)

4.3. Clinical Data Entry

Once the patient ID is generated through the MarkVCID website, clinical data can be entered in the data system.

Detailed instructions and links for training documents can be found in section 2.4. Clinical Data Collection and Entry.

4.4. Imaging Data Registration and Tracking

Patient scan sessions must be registered in the Imaging Data Registration page. An Imaging Data ID will be generated for each scan session and will appear on the screen and be emailed to the registering user.

Save this Imaging Data ID in the MarkVCID Imaging Data Log (excel sheet locally stored at each site).

4.5. Fluid Biosample Registration and Tracking

Participant biosamples (plasma, serum, and packed cells) will be stored locally at the sites and tracked using a Virtual Biorepository system that connects biosample data to other data contained in the data system via the MarkVCID patient ID. Sites will scan biosamples in (when collected/stored) and out (when used/shipped) of the Virtual Biorepository. The data system will track this and provide a current inventory when an investigator queries the data system.

4.6. Postmortem Brain Donation

MarkVCID sites must adhere to local state law and IRB policies for brain donation consent. Regulations as to who is legally authorized to consent to brain autopsy following the death of the individual and whether such consent can be provided prior to death varies by state.

Regardless of a particular state's policies, brain autopsy is best accomplished through early educational initiatives with patients. All research participants enrolled into MarkVCID should be informed of the rationale for and value of brain autopsy and provided with relevant information for them to consider at their convenience.

A clinician should engage the participant in the brain autopsy discussion and answer any questions from the participant about brain autopsy and emphasizes these points:

1. The immense research value of the neuropathological assessment.

2. No added costs to the family (other than the costs the family would bear if there was no autopsy, such as the costs of transportation of the decedent from the place of death to the funeral parlor or crematory).

3. No delay in plans for funeral services.

4. No facial disfigurement, thus permitting open casket viewing during funeral services should the family wish.

5. A copy of the neuropathological report of the brain autopsy findings will be provided to the next of kin.

6. We are happy to answer any questions now and after you have a chance to digest the additional informational material that we will provide to you.

Please refer to the Postmortem Procedures Best Practices Guideline on the MarkVCID Protocols & Resources web page (under the Case Report Form Packets dropdown menu) for additional guidance.

5. Approved MarkVCID2 Biomarker Kits

Kit protocols/trainings are located on the MarkVCID Protocols & Resources web page under the MarkVCID2 Biomarker Kit Protocols dropdown menu.

5.1. MRI Cerebrovascular Reactivity (CVR)

Research contact: Hanzhang Lu, PhD | hanzhang.lu@jhu.edu

5.2. MRI Peak Skeletonized Mean Diffusivity (PSMD)

Research contact: Claudia Satizabal, PhD | satizabal@uthscsa.edu

5.3. MRI Arteriolosclerosis (ARTS)

Research contact: Konstantinos Arfanakis, PhD | Konstantinos_Arfanakis@rush.edu

5.4. MRI Free Water (FW)

Research contacts:
Pauline Maillard, PhD & Arvind Caprihan, MD | acaprihan@mrn.org | pmaillard@ucdavis.edu

5.5. Plasma Neurofilament Light (NfL)

Research contact: Sudha Seshadri, MD & Claudia Satizabal, PhD | satizabal@uthscsa.edu | seshadri@uthscsa.edu

For MarkVCID1 biomarker kits, please navigate to https://markvcid.partners.org/consortium-protocols-resources

Document History

Summary of Changes
MarkVCID2 Manual of Operating Procedures (MOP)

Version	Description of Changes	Reason for Change	Version Date
1.0	N/A – original version	N/A	4.7.22
2.0	Additional guidance added re: eligibility criteria	N/A	4.18.22

3.0	Revised manual to reflect updated guidance including:
	• Section 2.4: Clarification regarding requirement that a physician completes neurological exam
	• Section 3.1: Screening information, handling ineligible participants, and timeline to complete Enrollment and Vascular Risk Criteria CRFs
	• Section 3.4: Collection of clinical lab results
	  ○ Subsection 3.4.1: Guidance regarding CVLT, CVLT-SF, HVLT, SEVLT administration.
	• Section 3.7: Screening column to Schedule of Events
	  ○ Subsection 3.7.1: Guidance on study visits and collecting information from informants
	• Section 4: Visual representation of the participant baseline and annual follow-up visit life cycle
		To describe study procedures in more detail	6.8.22

4.0	Revised manual to reflect updated guidance including: • Section 2.4: Information on training for the Fazekas scale and Microbleed/Lacunar Infarct Rating • Section 3.1: Clarification on enrolling participants with informants • Section 3.2: Eligibility Requirements regarding patient exclusion if there's contraindication to CVR ○ Subsection 3.2.3: Guidance regarding informants • Section 3.4: Guidance regarding visit data collection from the participant's informant • Section 3.6: Guidance on retaining participant if CVR could not be completed at the time of MRI collection • Section 3.7: Addition of Microbleed/Infarct Rating data collection to the Schedule of Events	Clarification of study procedures	7.8.22
5.0	Revised manual to reflect website updates including: • Section 2.2: Updated website link to reflect organizational changes on the study website • Section 2.3: Updated guidance on where to find the Research Agreement template to reflect changes from website reorganization	Update links to the study website as needed due to website edits	11.3.22
6.0	Revised manual to reflect updated guidance including: • Section 2.4: Addition of Research Site Staff Form link and information on staff training for CVR • Section 3.1: Clarification regarding the timing of when a participant can be registered or added to the data system ○ Subsection 3.1.1: Guidance regarding participant co-enrollment in other studies • Section 3.2.1: Eligibility requirements for CVR • Section 3.2.3: Guidance regarding attempting to contact the informant after the visit window • Section 3.6: Guidance that participants who have not completed the baseline MRI, or at minimum, completed the critical sequences within 3 months of the baseline visit must be withdrawn; how to document when CVR is not collected • Section 3.7: Guidance added to bring participants back for study activities not collected in the 14-day baseline visit window	Clarification of study procedures	3.13.23

7.0	Revised manual to reflect updated guidance including: • Section 3.4: Clarification that the Coordinating Center will review extenuating circumstances if a participant cannot complete all study procedures within 90 days of their baseline visit. • Section 3.7: Language updates including clarification that the Coordinating Center will review all cases where required MRI sequences are not collected within 90 days of baseline; clarification of when localizer scans are completed. • Section 3.7.1: Addition of section to provide rescan guidance.	Clarification of study procedures	9.8.23

8.0	Revised manual to reflect updated guidance including:
	• Section 3.2.1: Enrollment and anti-amyloid immunotherapy.
	• Section 3.4: Out-of-window follow-up visits.
	  • Section 3.4.1: Remote baseline NP testing. Removal of redundant information regarding informants.
	  • Section 3.4.2: Participants missing baseline study procedures and when study withdrawal is necessary.
	  • Section 3.4.3: Remote follow-up visit procedures and participants missing follow-up visit procedures.
	• Section 4.6: Added reference to the Postmortem Procedures Best Practices Guideline and a hyperlink to the location on the MarkVCID website.
	• Section 5: Added hyperlink to MarkVCID web page containing biomarker kit protocols and training.
		Clarification of study procedures	1.26.24

9.0	Revised manual to reflect updated guidance including: • Section 2.4: Imaging Acquisition training. • Section 3.4.3: Participant Follow-up Contact Schedule and lost to follow-up guidance.	Clarification of study procedures	6.7.24
10.0	Revised manual to reflect guidelines for transferring participants: • Section 3.4.4: Site to Site Participant Transfer Procedures	Addition of study procedures	1.9.25