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

V7.8.22
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).

Table of Contents

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	PI - Joel Kramer MPIs – Pauline Maillard, Jason Hinman
Johns Hopkins University School of Medicine	PI - Hanzhang Lu MPI - Marylin Albert
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: 1. Regulatory 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 is available in the MarkVCID2 website: 1. Regulatory Resources | MarkVCID (partners.org)

Signed research agreements 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.

Sites are encouraged to utilize the training checklist provided by the CC to keep track of their trainings.

All trainings are located on SkyPrep (please contact hsingh6@mgh.harvard.edu for an account)

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 training located in SkyPrep. 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 training slides on SkyPrep, the trainee must complete and pass a series of test sets.

Imaging Data Management

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

The trainee is expected to conduct a mock scan anonymization and data-upload to confirm knowledge of the process and identify any technical issues.

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.

When 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).

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.

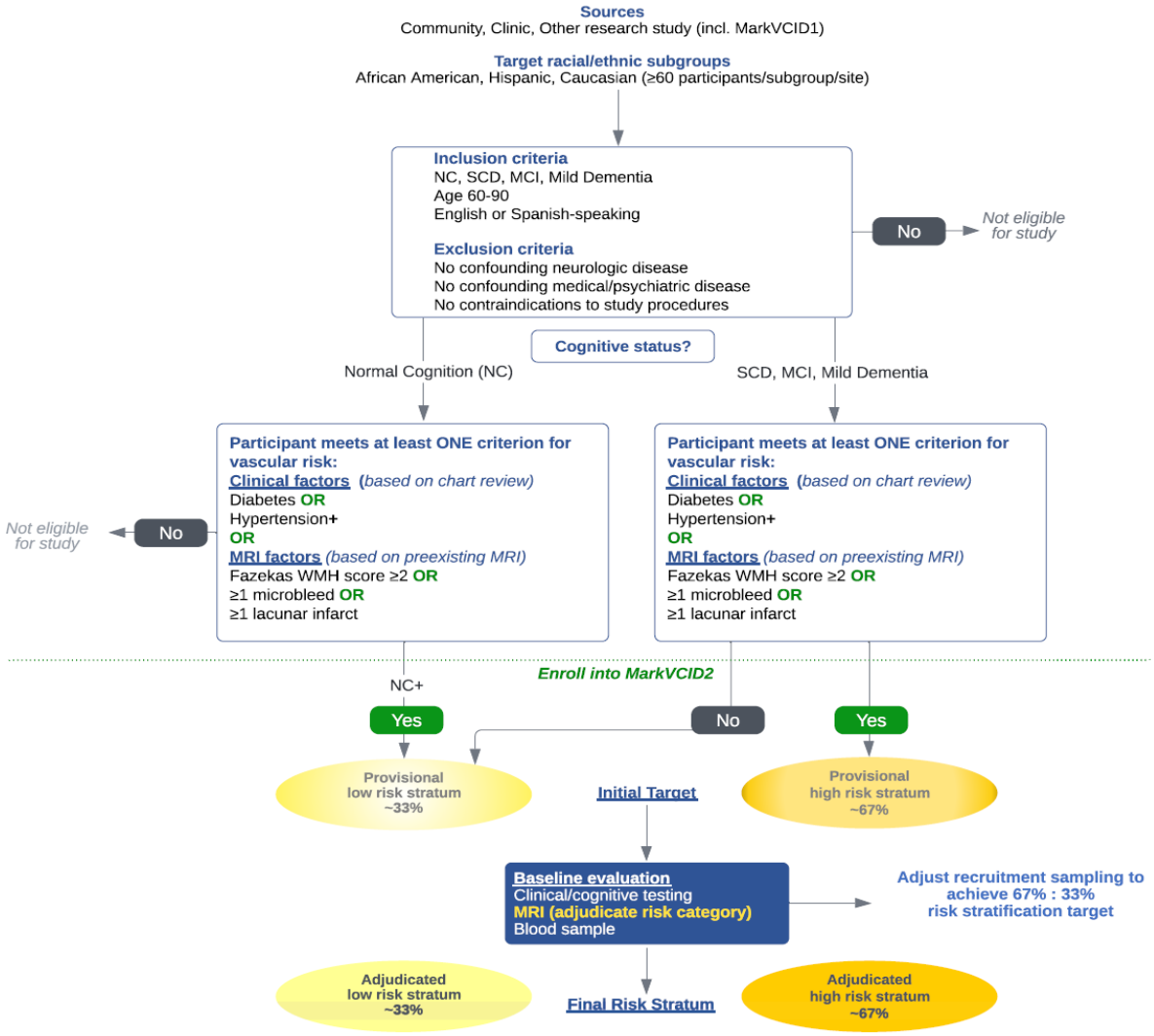
3.2. Eligibility Requirements

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.

MarkVCID2 Adaptive Enrollment Strategy



[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)
- Other neurologic conditions that interfere with test performance or biomarker analysis

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 study procedures (Claustrophobia, cardiac pacemaker, intracranial clips/metal implants etc.

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 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. Clinical Data Collection

(Estimated duration 1.5 – 2 hours)
Location: MarkVCID2 Protocols & Resources | MarkVCID (partners.org)https://markvcid.partners.org/consortium-protocols-resources
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 the informant isn't able to accompany the study participant to the research visit.

3.4.1 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.

3.5. Biosample Data and Sample Collection

Location: MarkVCID2 Protocols & Resources | MarkVCID (partners.org)https://markvcid.partners.org/consortium-protocols-resources
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)*

3.6. Imaging Data Collection

The MRI protocol consists of seven different image-contrast scan types. 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) T1-weighted, (multi-echo MPRAGE ,~6:00)
2) Fluid Attenuated Inversion Recovery (FLAIR, ~6:30)
3) Diffusion-weighted imaging (PA, original data, ~7:00)
4) Diffusion-weighted imaging (AP, used for distortion correction, ~1:30)
5) 3D Gradient-recalled echo (~5:30)
6) T2-weighted (~4:00)
7) Cerebrovascular Reactivity Scan (GRE, functional/BOLD scan, ~7:15)

If the participant was enrolled and agreed to complete all procedures, but at the time of the visit was not able to complete CVR, retain the participant and data and mark “CVR not completed”.

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)
https://markvcid.partners.org/consortium-protocols-resources

3.7. 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 must be collected within **14 days.**
- 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.

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					

3.7.1 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.

An informant is required to gather information about the study participant during the course of the study. 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 either by phone or by electronic survey to collect the necessary information. If after significant effort the site is still unable to contact an informant, the administrator must mark 'not collected' and a 'reason for not collecting' on the informant case report forms.

Please see the Clinical Assessments Remote Administration Evaluator's Manual on the MarkVCID2 website for guidance on completing the neuropsychological battery remotely.

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)

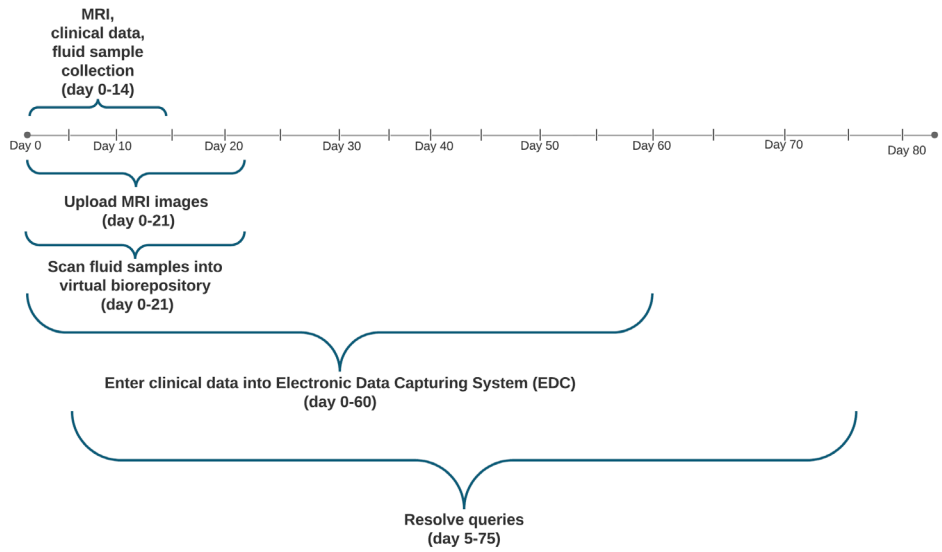
- Virtual Biorepository (register and track patient biosamples)

-Subject Deletion Request (delete a subject entered in the system)
https://markvcid.partners.org/consortium-protocols-resources

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.

MarkVCID2 Participant Baseline & Annual Follow-up Visit Data Life-cycle



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 answers 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.

5. Approved MarkVCID2 Biomarker Kits

Kit protocols and trainings are located here: MarkVCID2 Protocols & Resources | MarkVCID (partners.org) and **click** "MarkVCID2 Biomarker Kit Protocols"

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	4.7.2022
2.0	Additional guidance added re: eligibility criteria	N/A	4.18.2022

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	6.8.2022

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	7.8.2022