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National Institute of Neurological Disorders and Stroke
National Institute on Aging

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

MarkVCID Manual of Operating Procedures

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MarkVCID Consortium

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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.

MarkVCID Coordinating Center Key Personnel		
Name	Phone & Email	Role in Study
Steven M. Greenberg MD, PhD	617-724-1874 sgreenberg@mgh.harvard.edu	CC PI
Kristin Schwab	617-726-6227 kschwab@mgh.harvard.edu	Administrative Core Director
Karl Helmer, PhD	617-726-8636 helmer@nmr.mgh.harvard.edu	Data Core Director
Alexander Sherman	617-643-2935 asherman1@partners.org	Co-Investigator, Data Core
Herpreet Singh	617-643-3871 hsingh6@mgh.harvard.edu	Project Manager

MarkVCID Research Sites and PIs/MPIs	
Site	Name
Rush University & Illinois Institute of Technology	PI - Julie Schneider, MD, MS MPI - Konstantinos Arfanakis, PhD
University of Kentucky	PI - Donna Wilcock, PhD MPI - Gregory A. Jicha, MD, PhD
University of Southern California	PI - Danny JJ Wang, PhD, MSCE MPI - Amir Kashani, MD, PhD
University of California San Francisco, Davis, Los Angeles	PI - Joel Kramer, PsyD MPI - Charles DeCarli, MD
Johns Hopkins Medical Center	PI - Hanzhang Lu, PhD MPI - Marylin Albert, PhD
University of New Mexico Health Sciences Center	PI - Gary Rosenberg, MD MPI - Arvind Caprihan, PhD
CHARGE Consortium Boston University, University of Vermont, University of Texas-Houston/San Antonio	PI - Sudha Seshadri, MD MPI - Myriam Fornage, PhD MPI - Russell Tracy, PhD

2. Agreements and Regulatory Documentation

2.1. IRB Protocols and Informed Consents

Each site is responsible for obtaining IRB approval for its site-specific biomarker study and informed consent form. Site specific protocols and informed consent forms must allow for the collection of 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 and Operations Subcommittee developed template consent language that each site is to include in their 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:
https://markvcid.partners.org/consortium-protocols-resources
and **click** "Consent Language"

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

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 here:
https://markvcid.partners.org/charter-agreements, **click** "Research Agreement"

Signed research agreements are maintained by the Coordinating Center and are available upon request.

2.4. Agreements with External Investigators

External investigators requesting MarkVCID data and biosamples are required to submit a proposal, receive approval from the consortium, and sign a Data Use Agreement (DUA - data sharing) and/or Material Transfer Agreements (MTA - fluid biosample sharing).

DUAs will be executed electronically with the Coordinating Center through the website, and MTAs will be executed directly with the sites sharing biosamples from their MarkVCID collections.

Location: https://markvcid.partners.org/charter-agreements
and **click** "Data Use Agreement"

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.

Note: See section (7) for trainings and section (8) for specific biomarker kit protocols and associated procedural materials.

3.1. Clinical Data Collection

(Estimated duration 1.5 – 2 hours)
Location: https://markvcid.partners.org/consortium-protocols-resources
and **click** "Clinical/Cognitive Measures Collection Manuals"

- MarkVCID's Comprehensive Clinical Data Measures
  (overview of clinical data elements collected consortium-wide)

- 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

3.2. Biosample Data and Sample Collection

Location: 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

3.3. Imaging Data Collection

(Estimated duration 40-60 minutes)
Location: https://markvcid.partners.org/consortium-protocols-resources
and **click** "Imaging Standard Operating Procedures"

- MarkVCID Common Imaging Protocols
- Imaging Data Registration Standard Operating Procedure
- DICOM Data Anonymization Standard Operating Procedure
- Globus Installation & File Transfer Standard Operating Procedure

4. Prospective Site Recruitment and Procedures

Sites will maintain their UH2 IRB approved protocols and cohorts in the UH3 phase, 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).

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. Data collected using different collection protocols/best practices (UH2 phase data), should not be entered into the consortium data system, but can be shared directly with other MarkVCID centers when requested.

Each enrolled patient should have a baseline visit followed by up to 2 annual follow-up visits. At each visit, clinical data, imaging, and biosamples should be collected in accordance with the common protocols and best practices.

Time windows for baseline and annual follow-up assessments are as follows:

- For each timepoint, all imaging, clinical/cognitive data, and blood samples must be collected within **14 days** and CSF must be collected within **30 days**
- Annual follow-up window for imaging, clinical/cognitive data, and blood samples is **1 year ± 30 days** from the subject's prior study procedure visit

Deviations from these time windows must be approved by the Coordinating Center prior to scheduling the visit. Please email deviation requests to the CC Project Manager.

If a patient was enrolled in the UH2 phase and returns for a follow-up visit, sites can collect the common clinical data, imaging, and biosamples and register the patient in the MarkVCID data system. This visit will be considered their baseline visit in the data system and subsequent annual visits will be considered follow-up visits.

Additional Procedures Required for Instrumental Validation (Test-Retest of Subjects)

Each site must collect the following data and biosamples on a limited number of subjects at multiple timepoints for instrumental validation:

- Common MRI scan protocol on at least 6 patients at 2 timepoints on separate days and within 14 days of each other
- Common OCTA scan protocol on at least 6 patients at 2 timepoints with the first scan on the same day as the baseline/follow-up scan and second retest scan within 14 days
- Common biosamples (including plasma, PPP, and serum) at the same time of day on 10 subjects at 3 timepoints at least 5 days apart from one another and completed within 30 days.
- Subjects should be a minimum of 50% diseased patients. Remaining can be healthy controls or additional patients.

Schedule of Events

The chart below provides an overview of required MarkVCID events/procedures and visit timepoints.

Events	Baseline (0-14 days except CSF)	Fluid test-retest (within 30 days)	MRI/OCTA test-retest (2 weeks)	Follow-up (12-month ± 30 days)	Follow-up (24-month ± 30 days)
Clinical data collection	X			X	X
CDR	X			X	X
Neuropsych Battery	X			X	X
Short Physical Performance Battery	X			X	X
Clinical Labs	X			X	X
Plasma, serum, PPP	X	X X Two draws at least 5 days apart from one another & completed within 30 days at the same time of day on 10 participants		X	X
Packed cells collection	X				
CSF collection	X day 0-30				
MRI scan protocol	X		X day 1-14 6 participants	X	X
OCTA	X Baseline & test-retest scan same day 6 participants		X day 1-14 same 6 participants	X	X
Fazekas *(scored after MRI obtained)*	X			X	X

5. Handling of Data and Confidentiality

MarkVCID patient's clinical data, images and biosample data are stored in the MarkVCID data system at the Massachusetts General Hospital. Registered patient data including imaging and biosample data will be de-identified and assigned randomly generated IDs by the MarkVCID data system. No protected health information (PHI) will be stored in the data system or shared amongst 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.

6. Data Entry & Logs

The secure internal MarkVCID website allows trained users to enter data in the following portals. You can also navigate to this portals through the website's "Data Portals" dropdown menu.

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

- Imaging Data Registration (register patient scan sessions)
  https://markvcid.partners.org/data_registration_form

- Clinical Data Entry (enter patient clinical data)
  https://ncri0.partners.org/MarkVCID/PE/

- Virtual Biorepository (register and track patient biosamples)
  https://ncri0.partners.org/MarkVCID/BR/

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

See training section (7) for data management overview.

6.1. Patient Registration, Data Entry and Tracking

The MarkVCID Patient ID is used to identify MarkVCID patients entered in the data system. A Patient ID is obtained by registering a patient through the Patient Registration portal page on the MarkVCID internal website. Patients 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: https://markvcid.partners.org/consortium-protocols-resources and **click** "Clinical/Cognitive Measures Collection Manuals" > *"Patient Enrollment Log Template (v10.23.18)" See training section (7).*

6.2. 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 7.2. Clinical Data Collection and Entry.

6.3. 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).

Location: https://markvcid.partners.org/consortium-protocols-resources and **click** "Imaging Standard Operating Procedures" > *"MarkVCID Imaging DocID Log Template (v10.23.18)"*

6.4. Biosample Registration and Tracking

Patient biosamples (plasma, serum and CSF) 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.

7. Trainings

Site staff must take several consortium trainings prior to conducting the common clinical data, imaging and biosample collection protocols with subjects. 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.

Sites are encouraged to utilize the training checklist provided by the CC to keep track of their trainings: https://markvcid.partners.org/3-site-certification-trainings

7.1. Data Management System Overview

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

Location: https://markvcid.partners.org/0-markvcid-data-system-overview

7.2. Clinical Data Collection and Entry

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

Location: https://markvcid.partners.org/1-electronic-data-capture-edc-system-training

7.3. Virtual Biorepository

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

Location: https://markvcid.partners.org/4-virtual-biorepository-training

7.4. Neuropsychological Testing Battery

(Applies to staff administering the battery including MoCA and GDS. 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 online, the trainee must conduct three practice administrations, one of which must be observed by a neuropsychologist or psychometrician. Observer must send an email to the Coordinating Center confirming they observed the trainee in at least one practice administration and that the trainee is qualified to administer the NP tests.

The Coordinating Center will be conducting a quality control check on NP Battery scoring. Site coordinators are required to scan and email their first three subjects' neuropsychological battery forms and worksheets to hsingh6@mgh.harvard.edu. A neuropsychologist at the Coordinating Center will review scoring and provide feedback.

Please redact other study or participant information including IDs and replace them with the MarkVCID ID.

Location:
https://markvcid.partners.org/2-neuropsychological-testing-battery-cdr-gds-training

7.5. Short Physical Performance Battery

(Applies to staff administering the short physical performance battery)

Location:
https://markvcid.partners.org/3-short-physical-performance-battery-sppb-training

7.6. Fazekas Scale

(Applies to staff responsible for rating scans)

Location: https://markvcid.partners.org/5-fazekas-score-training

7.7. OCTA Site Certification

(Applies to staff responsible for screening, conducting scans, and data entry)

The trainee is expected to review a series of documents and submit test eye scans to confirm knowledge of the process and identify any technical issues.
Location: https://markvcid.partners.org/6-octa-vsd-biomarker-kit-training

7.8. 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.

Location: https://markvcid.partners.org/consortium-protocols-resources
and **click** "Imaging Standard Operating Procedures"

8. Approved Biomarker Kits

Note all kits are posted here: https://markvcid.partners.org/consortium-protocols-resources

8.1. MRI White Matter Hyperintensity Volume

Research contact: Charles DeCarli, MD | cdecarli@ucdavis.edu

8.2. MRI Cerebrovascular Reactivity

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

8.3. MRI Peak Skeletonized Mean Diffusivity

Research contact: Claudia Satizabal | clausati@bu.edu

8.4. MRI Arteriolosclerosis

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

8.5. MRI WMH Growth/Regression

Research contact: Greg Jicha, MD, PhD | gajich2@email.uky.edu

8.6. MRI Free Water

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

8.7. OCTA Vessel Skeleton Density

Research contact: Amir Kashani, MD, PhD | ahkashan@med.usc.edu

8.8. Plasma Endothelial Signaling

Research contact: Jason Hinman, MD, PhD | jhinman@mednet.ucla.edu

8.9. Plasma Exosome Endothelial Inflammation

Research contact: Fanny Elahi, MD, PhD | fanny.elahi@ucsf.edu

8.10. Plasma Neurofilament Light

Research contact: Sudha Seshadri, MD | seshadri@uthscsa.edu

8.11. CSF Placental Growth Factor

Research contact: Donna Wilcock, PhD | donna.wilcock@uky.edu