ARIC Manuscript Proposal # 1554

PC Reviewed: 09/08/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: **Determining the accuracy of a semi-automated method for measuring white matter hyperintensity volume on cranial MRI**

b. **Abbreviated Title (Length 26 characters): Volumetric Analysis of WMH**

2. Writing Group: from the MGH Stroke Research Center and ARIC
Writing group members: Natalia Rost, Jonathan Rosand, Dean Shibata, Tom Mosley

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _NSR_ **[please confirm with your initials electronically or in writing]**

First author: **Natalia S Rost, MD**
Address: 175 Cambridge Street, Suite 300, MGH, Boston, MA 02114

Phone: 617-643-3877 Fax: 617-643-3939
E-mail: nrost@partners.org

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
Name: **Tom Mosley, PHD**
Address: University of Mississippi Medical Center

Phone: 601-984-2763 Fax: 601-815-3422
E-mail: tmosley@medicine.umsmed.edu

3. Timeline: data analysis completed – by February 15 2010; manuscript drafted – by April 15 2010

4. Rationale: White matter hyperintensity (WMH) is the most common manifestation of cerebrovascular disease in the elderly. Presence and severity of WMH contributes to risk of symptomatic stroke, as well as cognitive decline, gait deterioration and late-life

depression. Furthermore, individuals with higher volumes of WMH have greater functional disabiity following acute ischemic stroke.

Studies of WMH require accurate measurement of the volume of brain affected. Accurate automated and semi-automated methods have been successfully applied to research MRIs that have been rigorously performed according to a set protocol. Patients with known history of cerebral infarction or other cerebral lesion, however, are generally excluded from such studies because of the challenge of distinguishing WMH from other brain lesions. Because of this limitation to established quantitative measurement approaches, an enormous resource for investigations of WMH has not been made fully available. This resource includes patients with stroke admitted to the hospital, who undergo MRI scans for clinical indications.

We have developed a semi-automated method of measuring WMH volumes from clinical MRI scans. Highly reliable, with excellent correlation with the standard semi-quantitative (visual grading) scales applied to WMH on clinical MRI scans, this method has enabled us to demonstrate the relationship between increasing volume of WMH and poor outcome from stroke. Furthermore, it is the basis of a genome-wide association study of WMH volume in patients with stroke, funded by the American Heart Association-Bugher Foundation.

While our semi-automated method for measuring WMH is reliable, its accuracy remains to be assessed. Taking advantage of unique resources of ARIC, we propose to evaluate the accuracy of semi-automated volumetric measures of WMH by comparing it to "gold standard" measurements in the ARIC cohort. In addition to providing a vital assessment of what is, at present, the only available method of directly measuring WMH volume from clinical MRI scans, this study could facilitate reconciling methodological differences among various WMH databases and allow for data integration and interchange for future joint studies of WMH.

5. Main Hypothesis/Study Questions: Our main hypothesis is that the semi-automated method for measuring WMH is highly accurate when compared to "gold standard" measurements in the ARIC cohort.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present). Using 120 electronically available, previously-evaluated MRI scans from subjects enrolled in the ARIC study, we will (a) identify scans randomly, equally sampled from the individuals whose WMH grade was designated as mild, moderate, and severe (40 scans per group), and send these scans, de-identified, to MGH; (b) at MGH, we will measure the severity of the WMH on all 120 scans using semi-automated volumetric analysis; (c) calculate correlations between WMH volumes (measured in cm^3) using the MGH method vs. the "gold standard," as well as WMH grade.

MGH volumetric analysis procedures. MRI images will be transferred in DICOM format and under the full HIPAA restrictions to MGH for volumetric analysis. Scans will be converted to Analyze format using *MRIcro (*www.mricro.com *)* for computer-assisted determination of WMH volume without knowledge of clinical or neuroimaging grading information associated with each scan. All scans will be stored on a secure MGH server

and will be analyzed under the supervision of Dr. Natalia Rost, who is also responsible for quality assurance and training in the MGH Stroke research neuroimaging program.

We will preferentially segment the areas of supratentorial WMH on FLAIR images in the axial plane. Then, using a semi-automated technique based on intensity thresholding by setting individually determined intensity thresholds, the first layer of ROIs corresponding to WMH will be created. A second layer of ROIs will then be manually outlined on each slice by gross contouring of all WMHs**.** The intersection of first and second layers of ROIs to serve as a WMH map for volume calculation by *MRIcro* will finally be manually inspected and corrected, if needed. In order to normalize WMH volumes to correct for differences in head size, a validated method for calculating ICA as a surrogate measure of intracranial volume will be used. nWMH was calculated by dividing the subject's WMH volume by the ratio of the subject's ICA to the mean ICA of the study population (153 cm^2). To avoid the possibility that the ischemic infarct might distort the underlying white matter, WMH volume for these subjects will be calculated in the hemisphere without the lesion, and the amount of WMH will be doubled for final record. This method has high inter-rater reliability for WMH (ICC=0.98) and ICA (ICC=0.92) measurement.

MGH neuroimaging quality assurance procedures. WMH volume measurements will be carried out by research staff the direct supervision of Dr. Rost. All readers will have undergone 6 hours of didactic instruction on brain and cerebrovascular anatomy, principles of MRI and the use of software involved in image processing and determination of WMH volume and midline cross-sectional sagittal ICA. These individuals must then measure nWMH volume on a standard set of 20 MRI scans with subsequent review and feedback by Dr. Rost. When adequate technical ability is demonstrated the potential reader performs nWMH segmentation on an additional set of 10 MRI and the results are compared, by calculation of the intra-class correlation coefficient for total nWMH volume and mid-sagittal ICA, to previously performed gold-standard segmentations. If adequate performance, defined as an intra-class correlation co-efficient of >0.9, is demonstrated then the reader is certified. Continuous quality checks are performed for all readers. For each reader, a random sampling of 10 out of every 100 nWMH volumes is independently confirmed by another certified reader. Readers are permitted to move on to the next 100 scans if inter-rater reliability is maintained (ICC>0.9).

Inclusion/Exclusion criteria. Inclusion criteria are availability of MRI in digital format (including T2 FLAIR, DWI, and saggital T1 sequences) and availability of the WMH severity score based on the ARIC criteria.

Statistical Methods. Scale comparison, inter-rater agreement, and correlations with quantitative measurements will be obtained in order to determine accuracy of the MGH method.

Potential Limitations. Anticipated methodological limitation could be related to the quality of the MRI images and presence of cerebral infarcts which may obscure WMH available for analysis. However, this issue is routinely addressed using our semi-automated method and will be accounted for by the volumetric measurement protocol.

7.a. Will the data be used for non-CVD analysis in this manuscript?

____ Yes __X__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used?

____ Yes ____ No

(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?

____ Yes __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?

____ Yes ____ No

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?

____Yes ____No

9.The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

_____ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

None related.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

__XX__ Yes ____ No

11.b. If yes, is the proposal

XX__ A. primarily the result of an ancillary study (list number* = ARIC Brain MRI study; 1999.01**)**

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. **Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.**