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Section 1: ARIC-NCS MRI Manual

October 18, 2010 - Draft

Section 2: MRI Technologist Procedures Manual for ARIC-NCS

November 24, 2010 - Draft

ARIC Neurocognitive Study

Study website - http://www.cscc.unc.edu/aricncs

ARIC-NCS MRI & MRI Technologist Procedures Manual

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SECTION 1: ARIC-NCS MRI MANUAL

1.1. AIMS

The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS) will add a neurocognitive assessment 24 years following the ARIC baseline exam conducted on 15,792 African-American and white residents aged 45-64. ARIC-NCS will use a 3-stage design to evaluate >7,000 survivors age 70+ years for dementia and MCI, and measure cerebral small vessel disease and regional brain volumes by MRI. Our broad objective is to evaluate the prediction of late-life cognitive impairment from midlife vascular risk factors and markers. Thus, we aim to help elucidate factors underlying ethnic disparities in dementia burden and provide the scientific basis for prevention strategies by identifying vascular therapeutic targets, optimal timing for interventions and useful intermediate outcomes.

1.2. SIGNIFICANCE

The overall vascular contribution to cognitive impairment in the population, though not accurately known, is substantial and is probably greater in African-Americans than whites. ARIC-NCS focuses on vascular cognitive impairment because of the benefits to be expected from risk factor modification. Prospective studies show strong prediction of cognitive impairment from vascular risk factors measured in midlife, but the evidence is from a small number of studies with some shortcomings which the proposed ARIC-NCS avoids. Also, ARIC-NCS (Aim 2) will provide unique information on mid-life prediction (1) in African-Americans, (2) from macro- and microvascular markers (and progression in these markers), and (3) from a broad range of vascular risk factors, including several never before studied in relation to cognitive change. ARIC-NCS will evaluate prediction of all dementia/MCI/cognitive decline cases together, without subdivision by clinical subgroups, but also of their clinical subtypes, and subgroups with and without concurrent MRI evidence of vascular insufficiency (Aim 3). Identification of an MRI-defined subgroup in which prediction is particularly strong may be useful in efforts to optimize future dementia prevention strategies. Also, by imaging participants with two prior cerebral MRI exams, ARIC-NCS will measure long term associations between specific cognitive changes and concurrent changes in brain structure (Aim 4). Finally, the availability in ARIC of the SNP database enables a powerful GWAS of cognitive change (Aim 5), with rigorous replication.

1.3. DESIGN OVERVIEW

The proposed ARIC-NCS visit will be a median of 24 years after the baseline ARIC examination. The figure below illustrates key design features of this study, the previous ARIC exams, and their relationship to ARIC-NCS study aims. Aim 1 assesses the prevalence of dementia and MCI, utilizing exams in the clinic, at home and in long-term care facilities, telephone interviews and hospital record reviews. Aims 2 and 3 utilize 4 previous exams with their rich collection of data on both vascular risk factors and vascular risk markers (both atherosclerosis and arteriolosclerosis), as well as cognitive test data spanning 20 years, which is lacking in most other large studies. Aim 4 benefits from inviting all participants of the ARIC Brain MRI Study to undergo a third brain MRI.

1.4. STUDY POPULATION

All African-American or white, male or female ARIC cohort members expected to be alive and ≥70 yo at the time of the examination (N=8,964) will be invited to participate in ARIC-NCS if they are available for study, i.e. currently in contact with the ARIC investigators and still residing in or near the four ARIC study communities (N=7,229). Appendix 3 shows recruitment projections. The available participants, 70-89 years of age at the time of the ARIC-NCS examination, 26%

African-American and 61% female, are similar to the 1,735 who are not available with respect to age group, gender, and most baseline risk factor levels (see Appendix 2).

1.5. EXAMINATION OVERIVEW

Each field center has an established clinic. At start-up, all personnel will be trained and certified centrally. When participants arrive, staff will review the goals, procedures, and potential risks of the study with them and obtain informed consent. Stage I assessment will include a structured interview to update medical history and medications, anthropometry, blood pressure, ankle-brachial index, specimen collection, and a 60 minute battery of neuropsychological tests to identify potential dementia and MCI cases. Stage II will include retinal photography, additional laboratory assays on specimens collected at Stage I, a neurological examination, and assessment of functional status and psychiatric symptoms, including an informant interview. Stage I and II assessments will be conducted at a single visit. Stage III includes neuroimaging. Participants who are unable to come to clinic will be offered the opportunity to be examined at home or in a long term care facility.

1.6. Stage I Assessment

Participants will be instructed by the recruiter and in written materials sent prior to the clinic visit to have nothing by mouth except clear liquids after midnight the evening prior to the visit and to abstain from alcoholic beverages for at least 24 hours before the visit. ARIC participants have complied well with this standard protocol in the past. After informed consent, trained technicians will perform anthropometry, measure blood pressure and ankle/brachial systolic BP and obtain blood and urine samples. Methods for risk factor measurements will be identical to those described in study manuals and used in previous ARIC exams. After phlebotomy, participants will be provided with a light breakfast. A trained interviewer will update the participant's medical history, which will include neurological diagnoses and family history of dementia, assess alcohol and smoking, and record all current prescription and over-the-counter medications.

1.7. Stage II Assessment

Stage II includes retinal photography, neurological examination and informant interview. The neurological assessment will be conducted by skilled nurses and will include an examination, assessment of mental status and functional status evaluated by semi-structured interview using the Clinical Dementia Rating Scale (CDR) administered to both the participant and an informant (family member or friend), and assessment of psychiatric symptoms using the Neuropsychiatric Inventory Questionnaire (NPI-Q) via informant interview. The Hachinski Ischemic Scale items that depend on historical information (i.e. history of stroke, abrupt onset of cognitive impairment) will be collected at the informant interview. Because of the cost of the neurological assessment, this component of Stage II will include only a sample (50 per center) of participants with normal cognitive function for validation purposes.

1.8. Stage III Brain MRI

MRI will be used to quantify cerebrovascular burden and signs of neurodegeneration associated with dementia using a standardized protocol across sites. This protocol is consistent with contemporary Alzheimer's research methods and includes methods sensitive to cerebrovascular disease as well.

1.8.1. MRI Acquisition Protocol:

The protocol will require <45 minutes. Sequences in the protocols are described here in "GE terminology", however vendor and platform specific protocols will be created by the Mayo Alzheimer's and Dementia Imaging Research (ADIR) Lab as was done for The NIA-funded Alzheimer's Disease Neuroimaging Initiative (ADNI) study. A specific electronic protocol will be created by the Mayo ADIR Lab for each scanner in the study, and distributed to each site. This obviates the need to create protocols manually on individual scanners, and eliminates the inevitable errors associated with protocol creation from a paper document. The following imaging sequences will be performed.

1) 3D-T1 SPGR
2) FLAIR
3) B0 Map
4) DTI
5) GRE
6) Vessel Wall Imaging
7) Time of Flight Imaging

1.8.2. Data Transfer and Storage:

All image data will be transferred to the Mayo ADIR Lab via LeapFILE from each scanner. The image data will be securely archived at the ADIR Lab with built-in redundancy. Appropriate database communication between the Mayo ADIR Lab and the ARIC Data Coordinating Center has been established for the ARIC Brain MRI study. All MRI interpretation results will be transmitted weekly to the ARIC Data Coordinating Center via the internet.

1.8.3. Site Qualification and Re-qualification:

Each MRI site will undergo qualification testing for MR prior to scanning subjects for the study.

1.8.4. Image Data flow and Quality Control:

Every week, the Mayo ADIR Lab will receive a list of subjects scheduled for MRI. Following exam completion, the image data will be immediately sent to Mayo for QC.

1.8.5. Phantom Scans:

Each site will receive an ADNI phantom and scan it bi-monthly throughout the study. The QC image data will be sent to Mayo. We will use these data to track scanner performance, particularly following upgrades, verify that appropriate geometry non-linearity correction is being applied, and verify that scanner performance is stable over time. Any significant deviation in stability of SNR or geometric calibration will result in notification to the site to have a system evaluation performed by the local service contractor.

1.9. MRI Image Processing and Analysis

MRI scans from ARIC visit 3 (1993-5), the ARIC Brain MRI Study (2004-6) and in ARIC-NCS (2010-12) are referred to as Scan I, Scan II and Scan III respectively. We expect 858 persons with prior scans to be evaluated for cognitive outcomes in ARIC-NCS and 547 of them to receive all 3 MRI exams (see appendix 3).

1) SPGR image pre-processing to correct specific artifacts
2) Hippocampal volume measures for scan III MRI and change from scan II to III
3) Change in whole brain and ventricular volume from scan II to scan III
4) Voxel-based morphometry (VBM) to analyze cross-sectional voxel-wise associations with scan II and scan III structural MRI
5) Longitudinal voxel-based morphometry (LVBM) to evaluate associations with voxel-wise scan II to scan III GM change
6) Atlas-based Brain Parcellation for Quantitative ROI Analysis
7) Measurements of white matter hyperintensity (WMH) volume for associations with scan II and scan III MRI
8) DTI analysis for scan III MRI
9) Grading MRI scans for cerebrovascular disease (CrVD)
10) Scan grading bridging Scans I, II and III

SECTION 2: MRI TECHNOLOGIST PROCEDURES MANUAL FOR ARIC-NCS

2.1. Study Design:

Magnetic Resonance Imaging (MRI) scans of the brain will be acquired during 2011-2013. (MRI scans from ARIC visit 3 (1993-5), the ARIC Brain MRI Study (2004-6) and in ARIC-NCS (2010-12) are referred to as Scan I, Scan II and Scan III, respectively). We anticipate approximately 2000 subjects to receive Scan III. If for any time point scan quality is not acceptable the scans must be repeated as soon as possible.

2.2. Site Qualification:

Prior to site qualification, your MRI site will receive an electronic copy of the study MRI protocol (1) for human scans and (2) for phantom scans provided by Mayo. You will receive email notification and directions for installing these MRI protocols. This should be loaded onto the one and only 3T system that will be used for the study, labeled on the scanner directory, and not modified for the duration of the study. The one exception is in the case of a hardware/software upgrade of the system used for the study which is discussed below.

Prior to scanning any subject for the study at a particular site, that site must complete site qualification. Each site will be asked to scan a phantom with the approved study MRI Human and Phantom protocols. The Mayo QC team will perform a quality control check (including protocol compliance) on the site qualification scan data.

If the scan does not pass Mayo QC review, your site will be asked to re-scan the phantom after making the suggested changes by the Mayo QC team. Once qualified, an e-mail will be sent to the selected contacts for your site with a notification that your site has been approved and is ready to scan subjects.

Please Note:

- The same 3T MRI scanner must be used for site qualification and **ALL** subsequent subject scans during the trial. If the same MRI scanner is not used, the subject will need to be re-scanned on the qualified scanner.
- You will be supplied electronic protocols by Mayo. This can be installed by your physicist or engineer. This will ensure that you have the correct protocol for your MRI scanner. If you have any questions about this procedure please contact: aricmri@mayo.edu.

2.3. Subject Pre-screening:

All subjects must be screened by the study coordinator for standard MRI contraindications. However, subjects must also be screened for MRI contraindications immediately before the MRI scan using your local standard protocol. Contraindications include, but are not limited to:

- The presence of non-removable ferrous metal objects
- Aneurysm clips
- Pacemakers
- Other contraindications such as defibrillators, etc.

Consent: All sites will consent participants with the informed consent form approved by their institutional ethics committee.

Sedation: No sedation allowed for this study.

2.4. MRI Scanning:

2.4.1. Subject Safety and Monitoring:

All sites must follow the standard subject consent protocols as approved by their local IRB.

2.4.2. Subject Confidentiality:

Each site will be responsible for anonymizing all patient specific information according to their own local laws and regulations. Please follow the specific instructions for subject anonymization (Section 7).

2.4.3. Subject Positioning:

Proper subject positioning is crucial for successful reproduction of serial MRI exams. Therefore, it is important that each subject is positioned in the same manner for each and every MRI exam.

Please follow the procedures below for positioning the subject in the head coil:

- Place clean sheet on scanner table and coil cradle.
- In addition to standard room exclusions, ensure the subject has removed their dentures as well as any hair clips, combs, earrings, necklaces, etc.
- Remove all upper body clothing with metallic trim, such as zippers, buttons or embroideries that may cause artifacts in the MRI images.
- Tape stereotactic marker (vitamin E or fish oil capsule) on the subjects' right temple (RT) provided by the site.

Images Showing Placement of Stereotactic Marker

- Position the subject so their head and neck are relaxed, but without rotation in either plane. Proper placement in the head coil is crucial because scans are acquired straight, not in an oblique orientation. The subject should also be well supported in the head coil to minimize movement. Motion artifacts may result in data rejection and request for a re-scan.
- Support under the back and/or legs can help to decrease strain on the knees and back as well as assisting in the stabilization of motion in the lower body.
- **Once subject has been positioned, snugly place sponges along the sides of head and a Velcro strap across forehead (if available). This will decrease the possibility of patient motion and furthermore it will reduce the chances of a re-scan**.
- Align the centering crosshairs on the subject's nasion (directly between the eyebrows) at every scanning session.
- Center the head coil over the subject's head, making sure the subject is high enough in the coil to prevent signal loss at the inferior aspect of the brain.
- Remind subject to hold as still as possible and advance subject to the iso-center of the scanning bore.

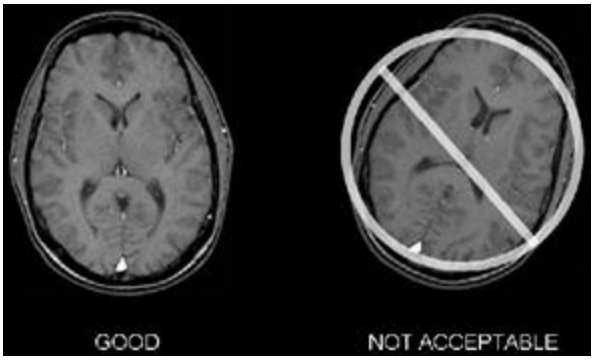
Please Note:

- It is extremely important that the subject is positioned in the same manner, at the nasion, for the MRI exam.
- If a deviation from these instructions is required to accommodate a subject, the MRI

2.5. MRI Acquisition Sequences:

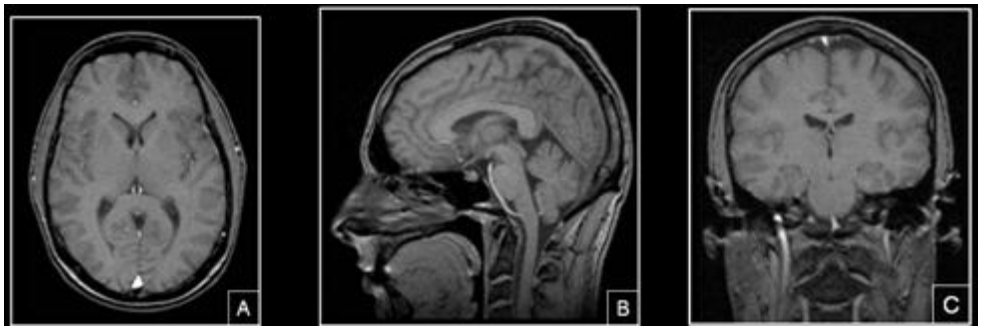
2.5.1. HUMAN Scan Sequences.

- If the subject is not positioned properly please adjust the subject in the head coil and re-scout. Continue repositioning and scouting until the subject is correctly centered in the head coil.



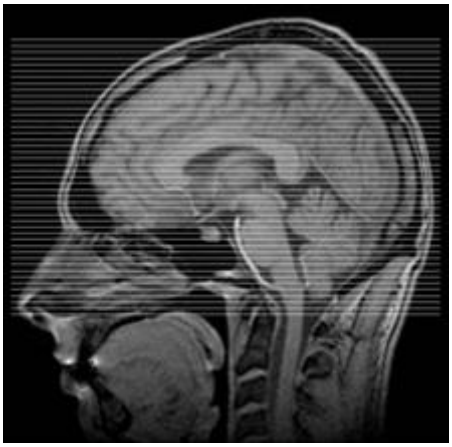
- Once the subject is positioned correctly, the following sequences are to be run.
    - 3 Plane Localizer
    - 3D-T1 Volumetric [9 min]
    - Axial FLAIR (Straight Axial – Not Oblique) [4 min]
    - B0 Map [2 min]

- DTI [7 min]
- Axial GRE [5 min]
- Vessel Wall Imaging [7 min]
- Time of Flight Imaging [8 min]
- TOTAL SCAN TIME: 42 min



Prescription of 3D-T1 Volumetric

- Box A – Axial image. FOV placed in center to avoid side-to-side wrap.
- Box B – Sagittal image. FOV placed anterior to avoid nose wrap.
- Box C – Coronal image. FOV placed to assure top of the brain is covered.



Prescription of Axial FLAIR

NOTE: Entire brain must be covered for all series

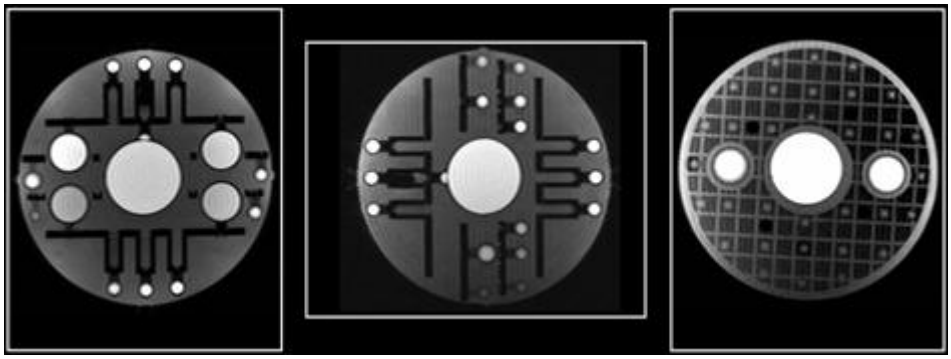
2.5.2. PHANTOM Scan Sequences

Phantom scans will be completed bi-monthly and after any hardware/software upgrades. These scans should be completed on the first business day of appropriate month. Email reminders will be sent out approximately one week prior.

Pre-scan and 3-plane localizer (A quick acquisition in 3 orthogonal planes for FOV placement)

- Make sure that 3D FOV is placed in center of phantom to avoid cropping.

  Example:



- 3D-T1 Volumetric Scan for quality control purposes.

2.6. Scan Discontinuation:

If the subject experiences discomfort in the MRI, every effort should be made to adjust the table, head coil, etc. to allow scan continuation. If the subject elects not to complete the scan, then the MRI must be abandoned and the Mayo MRI center as well as the Study Coordinator must be notified.

2.7. Anonymizing Data:

Each site will be responsible for anonymizing all patient specific information according to local laws and regulations. At a minimum, the following DICOM fields will be replaced:

1) Patient name: must be replaced with the anonymized subject ID described below

2) Patient ID: must be replaced with the anonymized subject ID described below

Mayo will use the following nomenclature which will be entered into the name field and will be generated by the Coordinating Center using the following algorithm:

Nomenclature = CLLLMFFGBB

C = Field Center identifier (F, M, J, W)

LLL = first three letters of last name

M = first letter of middle name

FF = first two letters of first name

G = gender (M or F), and BB is the day component of the birth date.

Example: John Doe Smith; Date of Birth 08/15/1950; scanned at Wake Forest

WSMIDJOM15

2.8. Data Transfer:

Data transfer must be electronic in DICOM format in order to meet turn around requirements. In order to allow rescheduling of repeat scans, data must be uploaded to Mayo within 24 hours of the exam. Data transfers will occur via a secure upload site. Sites will connect to http://mayomri.leapfile.com. All DICOM files for a specific exam will be uploaded to this secure site following the detailed instructions found in “ARIC-NCS_upload-instructions.pdf”.

Additional data transfers or copies will be requested by the coordinating center in the event that a data transfer is interrupted or incomplete.

2.9. On-site Clinical Reads:

1) **Every subject must receive a clinical read by an on-site radiologist at each MRI facility.** The clinical read should follow standard local practice and a clinical dictation of the read should be transferred to the study coordinator at the referral site. This read must also be sent to Mayo via email (aricmri@mayo.edu).

2) Scan interpretations for diagnostic clinical purposes will **not** be provided by Mayo.

2.10. Archive Procedures:

Every MRI for the study must be archived at the MRI facility following their own standard local practice in addition to the data transfer to Mayo immediately after the MRI scan. Additional data transfers or copies will be requested by the coordinating center in the event that a data transfer is interrupted or incomplete.

2.11. Request for Repeat MRI Scans:

2.11.1. Reasons for MRI Repeats:

- A request for a repeat MRI may be required in the event that the scans are found to be unacceptable due to subject motion or an incomplete/incorrect MRI acquisition. Your site will be asked by Mayo within 3-5 calendar days of receipt of data to schedule a repeat study.
- Mayo QC will check all study exams to be sure the correct, electronically loaded sequences have been used to scan each subject. Repeat exams may also be required if the incorrect scan sequence, orientation, or angulations are used. It is imperative to use the precise study protocol stored on your MRI system for every subject.

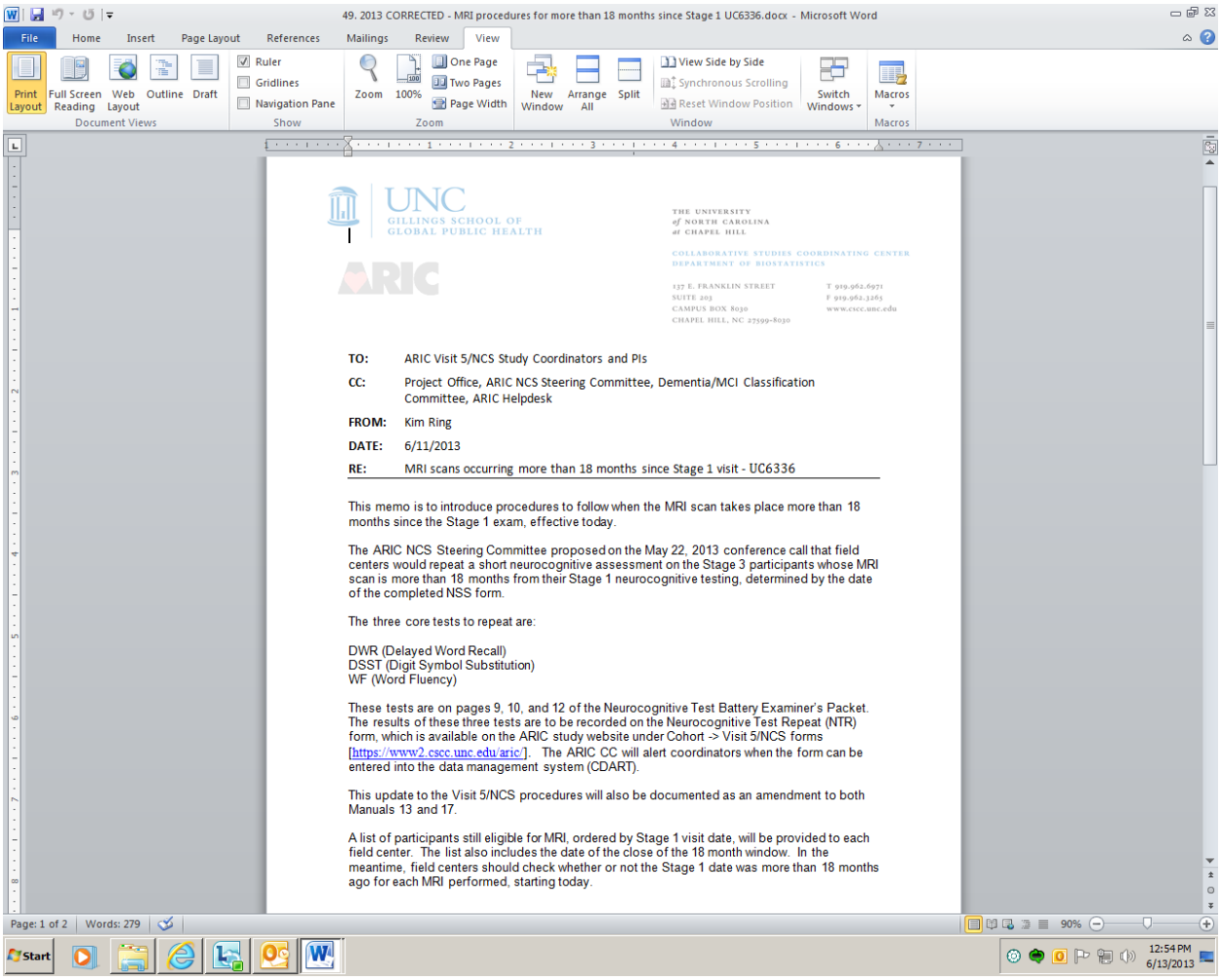
2.11.2. Procedures for MRI Repeats:

- Upon receipt of a request from Mayo for a repeat MRI scan, the scan should be scheduled to be performed as soon as possible. Detailed information regarding the reason for the repeat as well as suggestions for improvement will be communicated to both sites.

2.12. Anticipation of Scanner Software and/or Hardware Upgrades:

The Mayo team requires at least 2 weeks or more notification prior to any software and/or hardware upgrades for any scanner involved in the imaging study. The site will be required to scan a phantom prior to resuming scanning study subjects.

Appendix 1: Procedures When MRI is More Than 18 Months Since Stage 1



49. 2013 CORRECTED - MRI procedures for more than 18 months since Stage 1 UC6336.docx - Microsoft Word

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TO: ARIC Visit 5/NCS Study Coordinators and PIs

CC: Project Office, ARIC NCS Steering Committee, Dementia/MCI Classification Committee, ARIC Helpdesk

FROM: Kim Ring

DATE: 6/11/2013

RE: MRI scans occurring more than 18 months since Stage 1 visit - UC6336

This memo is to introduce procedures to follow when the MRI scan takes place more than 18 months since the Stage 1 exam, effective today.

The ARIC NCS Steering Committee proposed on the May 22, 2013 conference call that field centers would repeat a short neurocognitive assessment on the Stage 3 participants whose MRI scan is more than 18 months from their Stage 1 neurocognitive testing, determined by the date of the completed NSS form.

The three core tests to repeat are:

DWR (Delayed Word Recall)
DSST (Digit Symbol Substitution)
WF (Word Fluency)

These tests are on pages 9, 10, and 12 of the Neurocognitive Test Battery Examiner's Packet. The results of these three tests are to be recorded on the Neurocognitive Test Repeat (NTR) form, which is available on the ARIC study website under Cohort -> Visit 5/NCS forms [https://www2.cscc.unc.edu/aric/]. The ARIC CC will alert coordinators when the form can be entered into the data management system (CDART).

This update to the Visit 5/NCS procedures will also be documented as an amendment to both Manuals 13 and 17.

A list of participants still eligible for MRI, ordered by Stage 1 visit date, will be provided to each field center. The list also includes the date of the close of the 18 month window. In the meantime, field centers should check whether or not the Stage 1 date was more than 18 months ago for each MRI performed, starting today.

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