Manual 17

ARIC Neurocognitive Exam (Stages 2 and 3)

October 14, 2011

(Updated July 2, 2012)

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

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List of Abbreviations

AD	Alzheimer's Disease
ARIC	Atherosclerosis Risk in Communities Study
CA	Community Affairs
CDI	Clinical Dementia Rating form - Informant
CDP	Clinical Dementia Rating Form - Subject
CDR	Clinical Dementia Rating
DEM	Dementia
DMS	Data Management System
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSS	Digital Symbol Substitution
DUI	Driving Under the Influence
DWR	Delayed Word Recall
FAQ	Functional Assessment Questionnaire
HH	Home and Hobbies
HIS	Hachinski Ischemic Scale form
HIV	Human immunodeficiency virus
JPS	Judgment and Problem Solving
LBD	Lewy body disease
LTCF	Long-term Care Facility
M	Memory
MCI	Mild Cognitive Impairment
MHX	Medical History form
MMSE	Mini-Mental Summary Exam
MRI	Magnetic Resonance Imaging
NACC	National Alzheimer's Coordinating Center
NCS	Neurocognitive Summary form
NFH	Neurologic Family History form
NHX	Neurologic History form
NIH	National Institutes of Health
NIHSS	National Institutes of Health Stroke Scale
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NPI	Neuropsychiatric Inventory form
O	Orientation
PC	Personal Care
PNE	Physical and Neurologic Examination form
PNE	Physical and Neurological exam form
QC	Quality Control
QxQ	Question by Question instructions
REM	Rapid Eye Movement pattern
RMSE	Root-Mean-Squared error
TIA	Transient Ischemic Attack
UDS	Uniform Data Set
UPDRS	Unified Parkinson's Disease Rating Scale
WF	Word Fluency

1. STAGE 2 AND 3 SELECTION

1.1. Overview

An overview of ARIC Neurocognitive Study and definitions of Stages 1, 2 and 3 are provided in Manual 16. In brief, Stage 1 is concurrent with ARIC Exam 5. Participants who require further cognitive evaluation and comparison are invited to Stage 2 for separate visits (clinical evaluation in Stage 2 and MRI in Stage 3). After Stage 1, participants are classified for selection as cognitively normal, or "typical", and as "not typical" for further study in Stages 2 and 3. The "not typical" classification is assigned when the participant has either:

- A low score on the MMSE, or
- A low Z score on any of five cognitive domains AND definite cognitive decline.

ARIC/NCS participants not meeting these criteria are classified as "typical."

"Low MMSE score" is defined as <21 if Caucasian or <19 if African American.

"Low domain Z score" is defined here. "Definite cognitive decline" is defined in the following paragraph. The five cognitive domains (and, in parentheses, their component tests) are Memory (Delayed Word Recall [DWR], Logical Memory II), Language (Animal Naming, Boston Naming), Visuospatial (Clock Reading), Attention (Trail Making Test A, Digit Span Backward), and Executive Function (Digit Symbol Substitution [DSS], Word Fluency [WF]). Each ARIC/NCS participant's test scores are compared to norms established using selected participants in the ARIC Brain MRI study in 2004-6 or, when not available in the ARIC Brain MRI study, using norms from NACC. Norms are based on mean scores estimated by linear regression for specific age, race and education subgroups. Z scores are calculated as the observed value minus the age, race, and education specific predicted mean divided by the root-mean-squared error (RMSE) from the linear regression models. There is one exception: a score of "0" on Logical Memory II is given a z score of -2.0, regardless of the individual's age, race or education. Then, domain z-scores are computed as the sum of test z-scores divided by the standard deviation of the sum. If one test in a domain is missing, the domain z-score is the z-score of the non-missing test. "Low domain score" is defined as a score of -1.5 or worse (or, in the case of Trails test, a score of 1.5 or greater). Since the Clock Reading Test is scored as pass/fail, a participant is defined as having a low Visuospatial domain score if there is failure on the Clock Reading Test. The 803 participants on whom norms were established were selected from among all 1134 ARIC Brain MRI participants after excluding those with prior stroke, doctor-diagnosed neurologic disorders (e.g. multiple sclerosis, Parkinson's disease, or brain tumor), or cognitive impairment (dementia, Alzheimer's disease, senility, or hardening of the arteries), brain surgery or radiation, an MMSE score of <21 or a Delayed Word Recall test score of "0", use of cholinomimetics (drugs used for Alzheimer's Disease), apoE44 genotype, or MRI evidence of cerebrovascular disease (white matter grade of 6 or greater, 2 or more lacunar infarcts). Exclusions were also made based on self-reported functional status, i.e., when participants reported often or constantly "misplacing or losing things around the house" or having "trouble remembering conversations that occurred just a few days earlier".

"Definite cognitive decline" is defined as substantial decline on DWR, DSS or WF (i.e. falling at or below the worst 20th percentile of change on more than 1 test or below the worst 10th percentile on at least 1 test; with change calculated as current score minus the highest prior score) using the 803 selected ARIC Brain MRI participants). The percentile values are:

	DWR	DSS	WF
20th percentile	-2	-12	-11

10th percentile	-3	-15	-15

As soon as Stage 1 cognitive testing is complete, exam staff will enter the cognitive test scores into the Neurocognitive Summary (NCS) form. The **Data Management System** will then provide exam staff with the following information about participants:

- Did he/she participate in the ARIC Brain MRI study?
- Did he/she have a low MMSE score?
- did he/she have low Z scores for one or more cognitive domains?, and
- Did he/she show definite decline on DWR, DSS or WF tests?

When Stage 1 testing is complete, the DMS will classify all participants as cognitively "typical" or "not typical" as follows:

- Participants whose MMSE scores are low are classified as "not typical".
- Participants without low MMSE or low domain Z scores are classified as "typical".
- For participants with adequate MMSE scores but one or more low domain Z scores:
    - If they have "definite decline" in scores on core tests (DWR, DSS, or WF), they are classified "not typical".
    - If they do not have "definite decline" on core tests, they are classified as "typical".

1.2. Selection for Stage 2 and 3, Clinic Examinees

This section describes selection for participants examined in clinic. The next section describes selection for participants examined at home or in a long-term care facility.

Stage 2 selection for ARIC Brain MRI exam participants

All 2004-6 ARIC Brain MRI participants, without regard to cognitive status, are scheduled for Stage 2.

Stage 2 selection for the "not typical" cognition group

"Not typical" participants who have low scores on the MMSE or on more than one cognitive domain are selected for Stage 2.

The remaining "not typical" participants (with only one low domain score), are also all selected for Stage 2. However, this 100% selection may need to be altered if actual experience is projected to deviate too greatly from the goal of approximately 1600 "not typical" examinees that consent to and show up for Stage 2 at the study end.

Stage 2 selection for the "typical" cognition group

Small percentage samples of the "typical" participants are selected for Stage 2. Sampling fractions are set for participants <80 and ≥80 years of age (targeting 10%, except in Forsyth where it will be 5% to compensate for recruitment of all Brain MRI Study participants; at Jackson the sampling fraction is not reduced since recruitment rates are expected to be lower than in other centers) to approximate the distribution of those selected from the "not typical" group. These percentages may need to be altered if actual experience is projected to deviate too greatly from the goal of approximately 1000 "typical" examinees that consent to and show up for Stage 2, including the "typical" ARIC Brain MRI participants at study end.

Stage 3 selection

Participants with contraindications to MRI are not invited for Stage 3. The contraindications are: cardiac pacemaker, defibrillator or valvular prosthesis, histories of meningioma, arachnoid cyst, craniotomy, with resection or radiation therapy involving the skull or brain, or normal pressure hydrocephalus, metal fragments in the eyes, brain or spinal cord, cochlear implant, spinal cord stimulator, or other internal electrical device, permanent eyeliner, or weight > 350 pounds. All Stage 2 participants without these exclusions are selected for Stage 3. This selection is made at the time of the Stage I exit interview and is scheduled at a time when the MRI facility has an opening. Sampling (i.e. <100%) can be implemented if needed to obtain, at study end, approximately 2000 persons (800 "typical" and 1200 "atypical") who have consented to and showed up to begin their Stage 3 MRI examination.

1.3. Selection for Stage 2, Participants Examined at Home or in a Long-term Care Facility (LTCF)

Participants seen at home or LTCF are classified as cognitively "typical" or "not typical" using the same procedures as for those seen in clinic. If informants are available at the time of the Stage 1 exam, they can be interviewed at that visit if needed.

All "not typical" participants and an approximately equal number of "typical" participants (balanced by age group to the age-group distribution of the "not typical" group) are selected for Stage 2. Stage 2 is performed, whenever possible, at the time of the home/LTCF visit. Note that the probability of selection for Stage 2 will be higher in participants seen at home if sampling fractions are reduced for "not typical" with only one low domain score. This reflects the expectation that true cognitive impairment is more frequent in the home-bound.

Stage 3 exams are not obtained on any home or LTCF examinees.

1.4. Random Selection

All random selections described must be masked to staff and participants until the selection is made. As noted above, all sampling fractions are subject to alteration during the course of the study to achieve target numbers of Stage 2 and Stage 3 examinees.

2. NEUROLOGICAL EXAM AND INTERVIEWS (STAGE 2)

2.1. Overview

Stage 2 examination can be conducted at any time between Stages 2 and 3. It seems most efficient to at least determine MRI eligibility with the Stage 1 exam (and probably obtain MRI consent) which then makes it possible to complete stages 2 & 3 with only one additional visit. Completing the CDR informant over the phone can reduce clinic exam time by an hour. Each of the measures described below are well-validated, standardized instruments that have been widely used in both clinical and epidemiologic studies of dementia and cognitive function, and include most of the measures recommended in the Uniform Data Set (UDS) implemented in 2005 across all National Institute on Aging-sponsored Alzheimer's Disease Centers. Sections that are part of the UDS include the UPDRS, CDR, HIS, and NPI.

2.2. Rationale

Neurologic assessment will be used in the classification process to help in subtyping cases of dementia and MCI. The combination of the Physical and Neurologic Examination – Other (PNE) form, which includes components of the National Institutes of Health Stroke Scale (NIHSS), and the Unified Parkinson's Disease Rating Scale (UPDRS) is a relatively complete neurologic examination. The NIHSS, not used in its entirety in this assessment, is a standardized neurological examination intended to describe the neurological deficits of vision, extraocular movements, facial palsy, limb strength, ataxia, sensation, speech and language. The UPDRS rates speech, facial expression, resting tremor, rigidity (4 limbs plus neck), posture, body bradykinesia, and gait. Many responses to questions on the UPDRS are determined by direct observation of the participant. This combination of tests would allow identification of Parkinsonian features, as might be found in a Lewy Body dementia or frontal signs consistent with frontotemporal dementia. In addition, certain findings could explain performance on particular cognitive tests: a significant peripheral neuropathy or slowing of rapid movements might explain slowing on the trail making tests.

2.3. Administration: Physical and Neurological Exam (Other)

This exam includes components of the NIHSS, in addition to other neurologic exam components. Participants will be examined by a study nurse in a seated position. All components are tested in the standard NIHSS sequence, with the exception of "language" (item #12) which will be based on previous interactions. The components that are excluded from this version of the NIHSS include components felt to be more relevant to acute stroke presentations, without relevance to an outpatient clinic (or home) evaluation.

Required equipment: chair, reflex hammer, safety pin (a different safety pin for each participant). When participants are examined at home, the latter two pieces of equipment will be brought by the study nurse, and the chair will be provided at the participant's home.

2.4. Administration: Unified Parkinson's Disease Rating Scale (UPDRS)

Participants will be examined by a study nurse in a seated position, although they will have to stand and walk for other parts of the assessment. The participant will need to lift his or her arms and perform movements from a seated position as instructed by the examiner. For "posture stability" (item #13), the participant will need to stand directly in front of a wall or closed door, so there will need to be in an area where there is an uncluttered space for this available. The interviewer examines rigidity by moving the arms and legs while the participant is in a comfortable seated position.

Required equipment: chair, no other equipment.

2.5. Quality Assurance

Study nurses are trained and certified at a central training session or at a local field centers by certified technicians prior to administering the neurologic exam on a participant. Training involves instruction on general interviewing techniques, review of each exam component (forms and QxQ instructions, the Neurologic Exam section of this manual), and discussion of challenges to data fidelity.

Trainees must complete the online training and certification for the NIH Stroke Scale (http://learn.heart.org/ihtml/application/student/interface.heart2/nihss.html); even though the entire test is not being used (the neurologic exam includes most components of the NIHSS, however). During the central training, practice exams will be conducted in the presence of the lead neurologist trainer who will provide feedback to reach criterion performance. Following central training, study nurses will submit 3 audio-taped Stage 2 assessments for review and approval by a study neurologist. The lead study neurologist trainer will perform site visits annually to ensure each certified staff person continues to follow the protocol.

General feedback pertaining to all examiners will be provided on monthly conference calls involving field center staff and study coordinators. These calls will provide an opportunity to discuss and problem-solve any exam issues that arise.

3. CLINICAL DEMENTIA RATING (CDR)

3.1. Rationale

The CDR scale includes the CDR Informant and CDR Subject interviews, and two scores: the standard CDR summary score and the standard CDR sum-of-boxes. Since subject and informant responses must be recorded in categories of severity which unavoidably require subjective judgment, interviewers need good training and adequate QA to assure adequate standardization. The CDR gives important information about daily functioning, and it is a required element in the determination as to whether an individual is demented or has mild cognitive impairment, or is normal.

3.2. Administration: CDR Subject

The CDR Subject form is administered by the study nurse while the participant is seated, and requires no equipment for administration. It should be administered in a quiet private area.

3.3. Administration: CDR Informant

The CDR Informant form is also administered by the study nurse while the informant is seated, in a quiet private area without the subject present, whether in the clinic or at home, LTC facility. No equipment is required for administration. In the event that the informant does not accompany the subject in person, the CDR informant can be administered by the study nurse over the telephone, as is standard for this portion of the CDR.

3.4. Administration: CDR summary score

The study nurse will score the CDR after completion of these two components (subject and informant), and will not score them in the presence of the subject or informant. A scoring algorithm will be taught to study nurses based on the responses to the questions on both the CDR subject and the CDR informant; this will be completed in the event of a missing informant, as well.

The study nurses will be primarily responsible for generating the CDR box scores, ranging from 0 (normal) to 3 (severe impairment) for each of the following 6 areas, for the standard CDR:

memory (M), orientation (O), judgment and problem solving (JPS), community affairs (CA), home and hobbies (HH), and personal care (PC). In addition, the areas of behavior/ comportment, and language are each rated for the supplemental CDR, using the same scale. The online training module described above teaches how to translate a participant's responses into box scores, with the following basic guidelines: 0=no impairment; 0.5= questionable impairment; 1= mild impairment; 2= moderate impairment; 3=severe impairment. The standard CDR sum-of-boxes is simply a sum of the first 6 CDR box scores (with total possible range from 0 to 18). The standard Global CDR is calculated based on a formula generated at Washington University, where the CDR online training is administered. This standard Global CDR will only be used for publication purposes and will not be part of the classification or selection process. This website: http://www.biostat.wustl.edu/~adrc/cdrpgm/index.html generates a global CDR score based on individual box scores, and the same formula used to generate scores from this website are used to generate Global CDR scores based on box scores in the ARIC-NCS study.

The basic formula to generate a global CDR score is as follows: memory is considered the primary category, with others considered secondary. The global CDR is the same as the M score if at least 3 secondary categories are given the same score as M; however, if 3 or more secondary categories have a score greater or less than the M score, the global CDR score equals the score of the majority of secondary categories on whichever side (scores below or scores above) of M has the greater number of secondary categories. If three of these secondary categories are scored on one side (below or above) of M and two are on the other side of M, CDR=M. When the M score is 0.5 (or greater); the global CDR cannot be 0. Instead, when M=0.5, the global CDR can be 1 if 3 or more of the other categories are scored at a 1 or greater. I M=0, the global CDR=0 unless there is a score of 0.5 or greater in two or more secondary categories (in which case CDR=0.5).

3.5 Administration: Functional Assessment Questionnaire (FAQ) Score

Although the Functional Assessment Questionnaire (FAQ) score is not administered as a distinct scale, the items for the FAQ are embedded within the CDR, and scoring ranges from a 0 (normal function) to 1 (has difficulty, but does by self), to 2 (requires assistance, to an FAQ of 3 (dependent), depending on the specific response. There are 9 items from the CDR which are also FAQ questions (there are 10 FAQ questions; one CDR question encompasses two FAQ questions). The following items on CDR are used for the FAQ: CDR informant items 17, 18, 22, 25, 26, 31, 35 (scored twice: covers two FAQ questions), 36, and 37. The total FAQ score, used for classification, is the sum of the 10 individual scores.

3.6. Quality Assurance

Online training and certification for the CDR is required (www.adrc.wustl.edu). After selecting "Begin CDR Training", the user will be asked to register after which they will have access to 9 videos, each approximately 30 minutes in duration. The trainee should plan to review these videos over several days. Two audio-taped recordings of the CDR interviews (Informant and Subject interviews) per trainee will be reviewed by a study neurologist for certification.

During the first 6 months of the study, 2 audiotaped sessions of the CDR interviews (CDR-Subject [CDP]; CDR-Informant CDI]) and associated documentation (PDF file from DMS for CDP, CDI, and CDR-Summary [CDS]), for each interviewer will be reviewed by a neurologic expert. After the initial 6 month period, the neurologic expert will review one session per interviewer, noting deviations from the standardized protocol. General feedback that pertains to all examiners will be provided on QC Committee conference calls. These calls will also provide an opportunity to discuss and problem-solve various exam issues that may arise.

4. NEUROLOGIC AND NEUROPSYCHIATRIC SCALES

4.1. Rationale: Hachinski Ischemic Scale (HIS)

This scale is used to determine the relative vascular contribution to a potential case of dementia. By giving points based on focal neurologic signs and symptoms as well as history of stroke, how abrupt or stepwise the onset of symptoms has been, the likelihood of a vascular contribution can be estimated. Although a standard part of the UDS, and the only validated scale currently used for estimation of vascular contribution to cognitive impairment and dementia, this scale is limited to the detection of clinically apparent vascular disease.

4.2. Rationale: Neuropsychiatric Inventory (NPI)

The NPI consists of questions relating to personality and behavioral changes. Certain types of dementia (such as frontotemporal dementia) may be more likely based on the presence or absence of some of these behavioral changes, or the presence of significant depression in combination with a high CES-D score (from Stage 1) might increase the likelihood that apparent memory or other cognitive problems are actually due to depression, rather than dementia.

4.3. Administration: HIS

This scale is completed by the interviewer (study nurse) after completion of the other parts of the neurologic examination and CDR administration, and will not be completed while in direct interaction with the participant, but will be based on the responses during the previous interactions with the participant and the informant. No special equipment is needed.

4.4. Administration: NPI

This scale is completed after the CDR with the informant only, and is done with the informant, seated, in a quiet private space (either in clinic or at home, depending on the remainder of the visit). The participant should not be present. No special equipment is needed.

4.5. Quality Assurance

Certification and recertification are performed as described above. The NPI should be audio recorded with the CDI. The HIS is not recorded, but the forms are reviewed during the on-site neurocognitive exam QC visits.

5. EXIT INTERVIEW

The following script will be given to participants at the end of Stage 2:

“Thank you for participating in this part of the study. Because the measurements done in ARIC are sent to specialized laboratories we do not have any results to give you today. In about six weeks we will send you a report with your test results, and will let you know if any of these tests are abnormal. This report will be sent to you and/or the person you have designated.”

Although most Stage 2 participants will go on to participate in Stage 3, staff will not still be available (after the MRI) so this script will be given at the end of Stage 2.

6. DIAGNOSIS AND ADJUDICATION OF MCI AND DEMENTIA

6.1. Rationale

The diagnosis of cognitive impairment is the centerpiece of the ARIC-NCS project. Using a variety of sources of information, our diagnostic reviewers will review data on each ARIC-NCS participant and render a diagnosis of normal cognition, mild cognitive impairment (MCI) or dementia (DEM). Following the establishment of the syndromic diagnosis, an etiological diagnosis will be made for participants with MCI or DEM diagnoses.

The bases for the syndromic diagnoses of MCI and DEM are well-established. New criteria for MCI (Albert, 2011) and dementia (McKhann, 2011) were published recently, and prominently included ARIC investigators. The new MCI criteria are a considerable advance in clarity and flexibility compared to prior versions of MCI criteria. In the case of DEM, the new criteria for all-cause dementia are based on DSM-IIIR and the dementia criteria of the 1984 NINCDS-ADRDA criteria (McKhann, 1984), but reflect the advances of the past 25 years in the field.

The bases for the etiologic diagnoses are the known clinical features that have relevance for linkage to the underlying cause of the cognitive disorder. The diagnosis of AD dementia will be a clinical one in ARIC-NCS, but will be aided by information from imaging, history and examination that will facilitate non-AD diagnoses. Many of our MCI and DEM subjects will have imaging studies to allow us to detect relevant cerebrovascular disease. We will also have neurological examinations to allow us to detect extrapyramidal signs, and therefore enable a diagnosis of Lewy Body Dementia. Under any circumstances diagnoses of behavior variant frontotemporal dementia and primary progressive aphasia require the direct involvement of a behavioral neurologist and neuropsychologist, so it may be possible that cases with these syndromes could be missed. However, their prevalence (1 in 10,000 in a 45-65 year old sample, and probably lower in the next oldest decade) is such that only a very few cases would be anticipated in our cohort. Diagnoses of cognitive impairment secondary to depression, other psychiatric conditions or major medical illnesses are difficult and uncertain under any circumstances and will be challenging here, but we will have the medical history and depression inventory data to address these diagnostic possibilities.

6.2. Personnel

Drs. McKhann, Gottesman, Knopman, Mosley, Selnes, Albert and Windham will serve as diagnostic reviewers. Diagnoses of all subjects will be reviewed by two diagnostic reviewers.

Diagnosis will be assigned independently by 2 of these diagnostic reviewers. When possible, one reviewer will be a physician and one will be a neuropsychologist. Discordant cases will be assigned to a 3rd independent adjudicator (either Albert or Knopman). Substantive differences will be discussed by conference call with the entire Classification Committee for final diagnosis. Discordant cases will be settled by consensus. If a committee member cannot agree, the case will be tagged as discordant, with the primary diagnosis being the one agreed on by 2 of 3 reviewers.

For training of diagnostic reviewers, a set of standard cases will be generated, and some cases will be re-adjudicated for verification of the diagnoses. A training session for diagnostic reviewers will take place in person. Thereafter, a telephone conference call will occur 3 months after adjudication activities begin, in order to address issues that have arisen. A teleconference for the diagnostic reviewers will take place every 3 months over the course of the ARIC-NCS recruitment.

The Classification Committee will have access to the following materials on each subject:

6.3. Information and Tools available to Members of Classification Committee

1. Neuropsychiatric information (from clinic, home, long-term care)

    A. Current neurocognitive tests: Raw scores and age, race and education adjusted Z scores and age, race and education adjusted domain Z scores.

    B. Previous neurocognitive tests: Raw scores (without adjustment), for comparison with current raw scores. Note: included are DSS, DWR, WFT test scores from all previous occasions and other tests first administered in the ARIC Brain MRI study.

    C. CES-D. If 11-item CES-D $\geq$ 8 (major depression), cognitive disorder could be attributed to depression.

    D. DSS, DWR, WFT change: Change from highest previous score, categorized as in the lowest 10%ile, 11-20th%ile, or other.

    E. Psychometrist comments, verbatim.

2. Medical/ family history (clinic, home, long-term care)

    A. Responses to ARIC medical history questionnaire *only* for: TIA, Stroke, (distinguish between self-report and adjudicated strokes), arthritis; TIA/Stroke questionnaire past visits; MHX form (from sAFU): need compiled questions and answers for the following items (and if applicable, sub items): 1; from AFU form: Stroke/ TIA item [questions 7-9b (hospitalization), question 48 (self-report), and questions 49-50b (was participant hospitalized)

    B. "Neurologic" history ARIC NCS form results (includes Parkinson's, head trauma, MS, brain tumors, etc.): NHX form, need compiled questions and answers for the following items (and if applicable, sub items):1, 2, 3, 4a, 4b, (stroke/TIA item), 5

    C. Family history form results (limit to relevant areas, e.g., exclude vascular): NFH form; all compiled questions/ answers/ sub items for items with "yes" response (if answer is No don't need to list that item at all).

    D. Demographic information: race, sex, age

3. Study partner/ subjective memory (clinic, home, long-term care)

    A. CDR informant, including FAQ questions embedded; scanned complete CDI (should be given on paper) Also, any CDI "notes" from the DMS.

    B. CDR participant; scanned complete CDP. Also, any CDP "notes" from the DMS.

    C. CDR score sheet; CDS: need each box score, as well as total scores.

    D. NPI: study partner; NPI form: list each item that has a "yes" along with its severity score. No need to list items with a "No."

    E. FAQ compiled score: CDI25 + CDI26 + CDI31 + CDI35 + CDI36 + CDI37 + CDI37 + CDI18 + CDI17 + CDI22 where CDI numbered items are questions on the CDR – Informant (CDI) form

4. Neurologic / physical examination / labs:

    A. Physical and Neurologic Exam (PNE): Itemized list of all findings. For example:

        A1. Right leg: 0 normal;

        A2. Left leg: 2 abnormal moderate weakness (3/5)

        Etc. for all items- don't need actual form, just printed list of all items.

    B. UPDRS (clinic): UPR form, each item displayed in the same way as for PNE.

    C. ARIC lab results *only*: TSH, B12

    D. Hachinski scale with the exclusion of "hypertension" item and "emotional incontinence" item: from HIS, itemized list of score: e.g.

        abrupt onset: absent (0);

        stepwise deterioration: present (1)

        Total summed score listed.

5. Imaging information

    A. NCS Brain MRI report/ infarct rating/ white matter rating/ atrophy- the MRI Report and Referral (MRR) Form contains this information in summary format.

    B. Prior imaging report from ARIC Brain.

    C. Selected slices from NCS MRI – for cases of MCI or DEM, diagnostic reviewers will request images from Mayo Reading site, with expectation of receiving a PDF of selected sections with 7-10 days, to complete etiological diagnostic algorithm.

6. Medications

    A. Yes/No response for use of certain medications (medications known to impact cognition/alertness).

6.4. Operational criteria

Participants with suspected dementia or MCI evaluated in clinic or home/LTC visit, and a sample of cognitively-normal examined controls are reviewed by the Dementia/MCI Classification Committee. Reviews will be structured such that syndromic and etiologic diagnoses are performed in separate stages. Regardless of the review type, reviewers will be blinded to all factors which may limit our ability to test hypothesized relationships (e.g., associations with vascular risk factors or markers).

Step ONE - Syndromic Diagnosis

Mild Cognitive Impairment (MCI).

An MCI diagnosis is assigned in persons without dementia who meet the 3 criteria below:

1. FAQ $\leq$ 5 or CDR Sum of Boxes $\leq$ 3 (Note the FAQ data is based on an analysis of NACC database by Teng et al 2010, and CDR Sum of Boxes based on unpublished analysis of NACC data), and
2. At least one neuropsychological cognitive domain Z score < -1.5 Z or clock reading failure, and
3. Documented decline in ARIC serial cognitive test battery of three tests: DWR, DSST and WF (i.e. falling at or below the worst 20^{th} percentile of change on more than 1 test or

below the worst 10th percentile on at least 1 test; with change calculated as current score minus the highest prior score).

(Subjective complaint by subject not necessary.)

Note that we will not ask diagnostic reviewers to distinguish MCI subtypes. That can and will be accomplished through the neuropsychological test results.

Also note that the above criteria are the "ideal." In actual practice there will be cases that are close to but not strictly adherent to the above criteria that will be diagnosed with MCI. As shown in Table 6.1 below, an MCI diagnosis may also be assigned in specific instances where some of the four diagnostic elements (decline, domain failures, CDR and FAQ) might conflict.

Dementia

Diagnosis can be made either:

A. By a low MMSE score (<21 for Caucasians or <19 for African Americans, even in the absence of more complete cognitive testing, if, in the judgment of the Classification Committee, any prior DWRT, DSST and WFT scores were not indicative of dementia, or

B. By meeting all three of the following criteria:

   1. FAQ > 5 or CDR SUM OF BOXES > 3, and
   2. At least two neuropsychiatric cognitive domain scores < -1.5 Z. and
   3. Documented decline in ARIC serial cognitive test battery (as defined above).

As with MCI; there may be instances where subjects are diagnosed with dementia whose data does not strictly conform to the above criteria. As shown in Table 5.1, a dementia diagnosis may also be assigned in specific instances where four diagnostic elements might conflict.

Normal

Participants failing to meet criteria for MCI or dementia are classified "normal".

Conflicting data and computer diagnoses

The table below shows the 36 possible combinations of decline (yes/no), number of failed domains (0, 1, or >1), CDR sum of boxes (0, >0 but ≤3, >3) and FAQ (≤5, >5). Where the criteria above are met, a diagnosis will be assigned by computer, and the table designates these cases as automatic diagnoses. In all other instances, which are expected to occur infrequently, data may be inconsistent, and the computer will provide only a "probable" or "uncertain" diagnosis. In all cases the Classification Committee will assign its own preferred diagnosis, which might differ from the computer diagnosis.

Most "typical" persons, i.e., those who do not show decline or fail any domains, will not be selected for Stage 2 exams, so CDR and FAQ scores will be not available. As indicated in the table, they will be assigned a "normal" diagnosis. However, for the sample of "typical" persons who are selected for Stage 2, including all ARIC Brain MRI participants, CDR and FAQ data will be available. For them, diagnoses based the table below will provide for estimation of the proportion of all "typical" participants who would have had diagnoses other than "normal" had the data been available.

Table 6.1. Computer Generated Algorithmic Diagnoses

Row	Decline[1]	Fail domain[2]	CDRsb	FAQ	Algorithm Dx	Adhering
0	MMSE score less than 21 for white participants ***or*** MMSE score less than 19 for black participants				Prob Dem	
1	N	0	0, missing	≤5, missing	NL	yes
2	N	0	0	>5	Prob NL	
3	N	0	>0 but ≤3	≤5, missing	Prob NL	
4	N	0	>0 but ≤3	>5	Uncert, rvu	
5	N	0	>3	≤5, missing	Uncert, rvu	
6	N	0	>3	>5	Uncert, rvu	
7	N	1	0, missing	≤5, missing	Prob NL	
8	N	1	0	>5	Prob MCI	
9	N	1	>0 but ≤3	≤5, missing	Prob MCI	
10	N	1	>0 but ≤3	>5	Prob MCI	
11	N	1	>3	≤5, missing	Prob Dem	
12	N	1	>3	>5	Prob Dem	
13	N	>1	0, missing	≤5, missing	Prob NL	
14	N	>1	0	>5	Prob MCI	
15	N	>1	>0 but ≤3	≤5, missing	Prob MCI	
16	N	>1	>0 but ≤3	>5	Prob MCI	
17	N	>1	>3	≤5	Prob Dem	
18	N	>1	>3	>5, missing	Prob Dem	
19	y	0	0, missing	≤5, missing	NL	
20	y	0	0	>5	Uncert, rvu	
21	y	0	>0 but ≤3	≤5, missing	Prob NL	
22	y	0	>0 but ≤3	>5	Prob NL	
23	y	0	>3	≤5, missing	Uncert, rvu	
24	y	0	>3	>5	Uncert, rvu	
25	y	1	0, missing	≤5, missing	MCI	yes
26	y	1	0	>5	Prob MCI	
27	y	1	>0 but ≤3	≤5, missing	MCI	yes
28	y	1	>0 but ≤3	>5	Prob MCI	
29	y	1	>3	≤5	Prob Dem	
30	y	1	>3	>5, missing	Prob Dem	
31	y	>1	0, missing	≤5, missing	MCI	yes
32	y	>1	0	>5	Prob MCI	
33	y	>1	>0 but ≤3	≤5	MCI	yes
34	y	>1	>0 but ≤3	>5, missing	Prob MCI	
35	y	>1	>3	≤5	Prob Dem	
36	y	>1	>3	>5, missing	Dem	yes

1 Documented decline on DWRT, DSST or WFT as defined above.

2 Number of failed domains as defined above.

Step TWO - Etiologic Diagnoses for both MCI and DEM

Diagnoses will be recorded as PRIMARY or SECONDARY. Primary diagnoses and all vascular diagnoses, whether primary or secondary, will be adjudicated.

1. Alzheimer Disease MCI/Dementia – The diagnosis of Alzheimer's disease as an etiologic diagnosis of MCI or Dementia in ARIC NCS as a primary diagnosis is a clinical one and is based on the presence of the cognitive syndrome that is not of abrupt onset and includes memory impairment, and the absence of features of other specific diagnoses sufficient to cause the cognitive impairment, such as those detailed below. The criteria are those of McKhann et al 2011.
2. Cerebrovascular disease (CVD) related MCI/Dementia – The elements ARIC will use for this diagnosis include (1) History of stroke temporally related to an abrupt onset of the cognitive disorder, (2) bilateral or multiple infarcts or extensive white matter hyperintensities on imaging and (3) physical examination evidence of a typical stroke pattern. These elements are defined below:

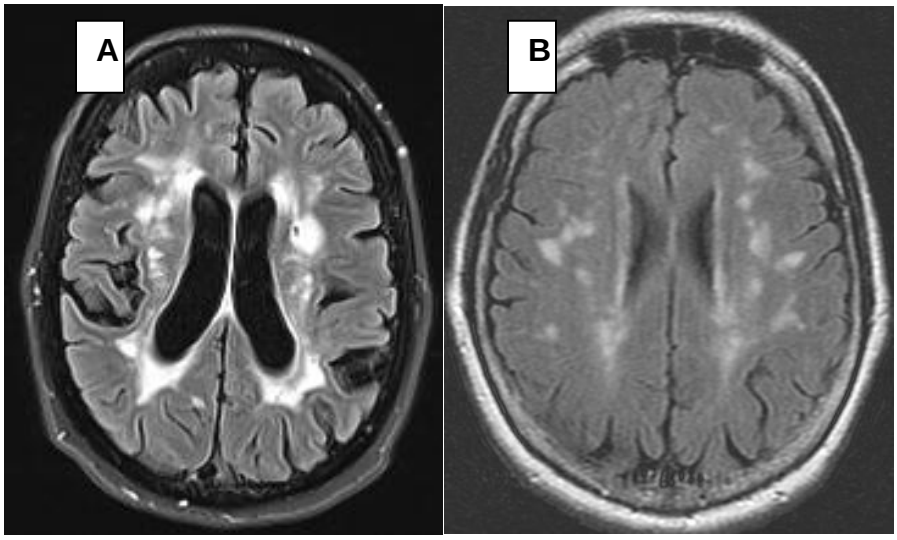
    a. As per NINDS-AIREN criteria, the lag between the onset or stepwise decline in cognition and the stroke event should be <6 months to diagnose cognitive impairment temporally related to a stroke. We will not have that level of detail, but "history of stroke" plus "abrupt onset" of cognitive impairment as recorded in the Hachinski Ischemic Scale.

    b. The criteria for "bilateral or multiple" infarcts is unfortunately not easy to define further, but erring on the side of conservatism, only the most flagrant cases (at least 2 distinct large or lacunar infarcts) plus a history of stroke will be considered as per the Table on the next page.

    c. Similarly, the NINDS-AIREN criteria for severe white matter hyperintensity (WMH) burden is neither precisely defined nor empirically validated. To be conservative, we will require the amount of WMH to involve >50% of the circumference of the coronal radiata – see Figure below. Note that we have classified WMH in the same category as a "single" infarct for the purposes of classification in the Table on the next page

    d. Positive physical examination findings are those that demonstrate an asymmetric corticospinal tract pattern of weakness + reflex changes, or another pattern typical of cerebrovascular disease.

    Case (A) as an example of WMH (plus an infarct in white matter) that should be the minimum to consider cerebrovascular disease as a primary diagnosis. In contrast case (B) could support a diagnosis of cerebrovascular disease as a secondary diagnosis.



Cases with MCI or dementia and any evidence of cerebrovascular disease are reviewed to determine whether the cerebrovascular disease is the likely sole cause or is contributory to the impairment. The table below shows the etiologic diagnosis to be given when Diagnostic Reviewers determine that the pattern of diagnostic elements falls in specific rows. Exam, history and imaging categories shown in the table are defined in sections 2 a, b, c and d above.

Row	**Physical Exam** typical stroke pattern (yes/no)	**History of stroke** (Sx Abrupt or not)	**Imaging** (1) multiple large infarcts; (2) single infarct or extensive white matter hyperintensities, or (3) neither	**Etiologic Diagnosis** (Prim/Sec)
1	no	No Hx	neither	Not CVD
2	no	Hx, not abrupt	neither	AD/CVD
3	no	Abrupt	neither	CVD/AD
4	no	No Hx	single	AD/CVD
5	no	Hx, not abrupt	single	CVD/AD
6	no	Abrupt	single	CVD/AD
7	no	No Hx	multiple	CVD/AD
8	no	Hx, not abrupt	multiple	CVD/AD
9	no	Abrupt	multiple	CVD
10	yes	No Hx	neither	AD/CVD
11	yes	Hx, not abrupt	neither	CVD/AD
12	yes	Abrupt	neither	CVD/AD
13	yes	No Hx	single	CVD/AD
14	yes	Hx, not abrupt	single	CVD
15	yes	Abrupt	single	CVD
16	yes	No Hx	multiple	CVD/AD
17	yes	Hx, not abrupt	multiple	CVD
18	yes	Abrupt	multiple	CVD

Note: The AD diagnoses indicated in the table are made only in the absence of evidence for other causes sufficient to explain the cognitive impairment.

3. Lewy Body Disease – A diagnosis of Lewy Body disease as a primary diagnosis should be made when there are at least 2 of the following: Diagnosed Parkinson's disease (by history or exam; or on anti-Parkinson medications), REM sleep behavior disorder or excessive daytime sleepiness, or hallucinations. If only one of the features is present a diagnosis of AD primary and Lewy Body disease secondary should be made.
4. Depression - If 11-item CES-D > 8 (major depression), cognitive disorder could be attributed to depression (See Kohout FJ, Berkman LF, Evans DA, Cornoni-Huntley J. Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. J Aging Health 1993; 5:179-193.
5. Other major psychiatric disorders – if clinician believes that schizophrenia, bipolar disease could be the cause of cognitive disorder
6. Alcohol-related: although this diagnosis is notoriously difficult, instances of documented Wernicke encephalopathy or Korsakoff syndrome would fit this diagnosis. Heavy alcohol use with documented complications of DUI, alcoholic blackouts, withdrawal seizures, as well as a DSMIV diagnosis of chronic alcohol abuse would be the minimum features necessary to apply this diagnosis.
7. Medication-related – if reviewing clinician believes that a medication could be contributing to or the sole cause of cognitive impairment
8. Other Neurodegenerative disorder. This should be reserved for cases with certain diagnoses such as PSP, corticobasal syndrome, Huntington disease, HIV dementia, i.e. other than AD or LBD.
9. Trauma related – In situations where the history reveals a major instance of head trauma with loss of consciousness and clear documentation of cognitive decline coincident with the trauma, this diagnosis could be used.
10. Systemic disorder with major impact on brain function - e.g. severe heart failure, active cancer, severe connective tissue disease
11. Cognitive disorder of uncertain etiology.

6.5. Case Law

Clarifications to diagnostic criteria made after initiation of the review process will be documented in this section as case law.

6.6. Classification process

ARIC-NCS will have as many as 3000 Stage II participants, including 1000+ "typical" and 1600+ "atypical." Details of the classification process sketched out in Section 6.2 are provided below. The procedure described here will be re-evaluated by the committee three months after initiation of the review process. At that time, the committee will consider discontinuing review of cases where neurocognitive status is "typical" and CDR Sum of Boxes is 0.

Primary Review

Participants are selected for primary review if they meet the operational criteria (see Section 6.4), have had an MRI (or have refused or been determined ineligible), and meet the following additional data criteria:

- CDR Sum of Boxes non-missing.
- The presence of at least 4 of the following forms: CDR Summary, Neurologic/Physical Exam, Unified Parkinson's Rating, Hachinski Ischemic Scale, Neuropsychiatric Inventory, CDR – Informant, CDR-Participant.
- MRI images in PDF format received from Mayo

Reviewers are assigned as follows:

- One reviewer for cases where neurocognitive status is "typical" and CDR Sum of Boxes is 0.
- Two reviewers (one physician and one neuropsychologist) for cases where either the neurocognitive status is "typical" and CDR Sum of Boxes > 0 or Neurocognitive status is "atypical."

Reviewers examine the participant case packet and determine:

- Whether the participant is syndromically normal, MCI, or demented.
- If the participant is MCI or demented, the primary etiologic diagnosis and (if applicable) any secondary etiologic diagnosis(es).

The reviewers enter a "Primary Review" Diagnostic Classification Form (DCF) for each case they review. Once primary review is complete and the DCF(s) locked by the reviewer(s), for cases with two reviewers (one physician and one neuropsychologist) agreement between reviewers is assessed by the CC. Agreement is assessed for each of the following:

- Syndromic diagnosis
- Primary etiologic diagnosis
- The presence of "CVD" as either a primary or secondary etiologic diagnosis.

If the reviewers agree with respect to Syndromic diagnosis, Primary etiologic diagnosis or the presence of "CVD" as either a primary or secondary etiologic diagnosis. Review is considered complete for cases with only one reviewer (defined above) or when agreement with algorithmic diagnosis ("typical") is assessed by the CC. Cases diagnosed as MCI or dementia will be reviewed by the committee. Otherwise, the review is considered complete.

Re-review

Cases are selected for re-review if reviewers disagree on either the Syndromic diagnosis, Primary etiologic diagnosis or the presence of "CVD" as either a primary or secondary etiologic diagnosis.

- A list of cases needing re-review is sent to the original reviewers by the CC; after examining each other's DCF and (if necessary) re-examining the case packet data, the reviewers enter a "Re-review" DCF. Reviewers may consult with each other by phone or email if desired.
- Once re-review is complete and the DCF(s) locked by the reviewers, the CC checks the "Re-review" DCFs for agreement between reviewers using the same criteria outlined in the above section.

If the reviewers agree with respect to the criteria above, the review is considered complete.

Adjudication Review

Cases are selected for adjudication review if the original reviewers do not reach agreement after re-review of the case. A list of cases and a set of case packets for cases needing adjudication is sent to one of the two adjudication reviewers (**note:** if either of the two adjudication reviewers served as a primary reviewer for a case requiring adjudication review, the case is sent to the other adjudication reviewer). The adjudication reviewer examines the case packet and the DCFs of the original reviewers and determines the syndromic, primary etiologic, and secondary etiologic diagnoses; two outcomes are possible, either singly or in combination:

- The adjudicator records his/her diagnoses in an "Adjudication" DCF; and/or
- If the adjudication reviewer feels that diagnostic classification is too complex, s/he refers the case to the full committee by entering a DCF in the Full Committee event.

If the adjudication reviewer does not refer the case to the full committee, review is considered complete and the DCF locked by the adjudicator.

Full Committee Review

Cases are selected for full committee review based on the adjudicator's opinion.

- The committee reviews the case packet material and determines a syndromic, primary etiologic, and secondary etiologic diagnoses.
- The adjudicator records the committee's diagnoses in a "Full Committee" DCF
- Review is complete

Appendix 1: Normal ranges

1. WRAT:

Score	Grade
0-12	Pre-school
13-18	K
19-23	1
24-28	2
29-31	3
32-34	4
35-36	5
37-38	6
39	7
40-41	8
42-47	HS
48+	post-HS

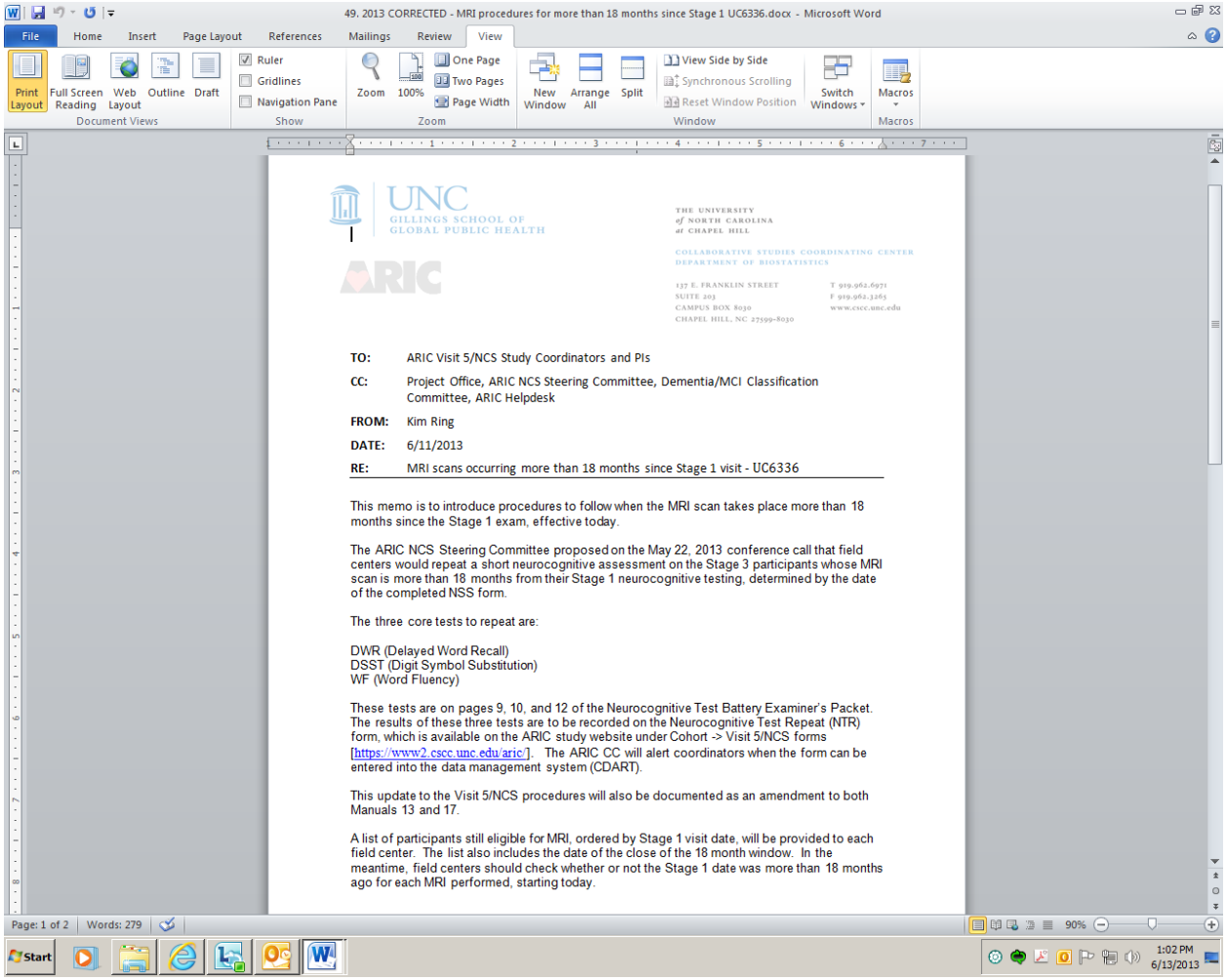
2. TSH: normal 0.4- mU/L
3. B12: normal 200- 911 pg/ml

Appendix 2: CDR: 0/0.5/1/2/3: Level of impairment

	0 (None)	0.5 (Questionable)	1 (Mild)	2 (Moderate)	3 (Severe)
Memory	No memory loss, or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss, more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment and problem solving	Solves everyday problems, handles business and financial affairs well; judgment good in relation to past performance	Slight impairment in these activities	Moderate difficulty in handling problems, similarities and differences; social judgment usually maintained	Severely impaired in handling problems, similarities and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Life at home, hobbies and intellectual interests slightly impaired	Unable to function independently at these activities, although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside the home; appears well enough to be taken to functions outside the family home	No pretense of independent function outside the home; appears too ill to be taken to functions outside the family home
Home and Hobbies	Life at home, hobbies and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned.	Only simple chores preserved; very restricted interests; poorly maintained	No significant function in the home.

	0 (None)	0.5 (Questionable)	1 (Mild)	2 (Moderate)	3 (Severe)
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence
Behavior, comportment and personality	Socially appropriate behavior	Questionable changes in comportment, empathy, appropriateness of actions	Mild but definite changes in behavior	Moderate behavioral changes, affecting interpersonal relationships and interactions in a significant manner	Severe behavioral changes, making interpersonal interactions all unidirectional
Language	No language difficulty or occasional mild tip-of-the-tongue	Consistent mild word finding difficulties; simplification of word choice; circumlocutions; decreased phrase length; and/or mild comprehension difficulties	Moderate word finding difficulty in speech; cannot name objects in environment; reduced phrase length and/or grammatical speech; and/or reduced comprehension in conversation and reading	Moderate to severe impairment in either speech or comprehension; has difficulty communicating thoughts; writing may be slightly more effective	Severe comprehension deficit; no intelligible speech

Appendix 3: 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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ARIC

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.