Atherosclerosis Risk in Communities Study

Visit 12 Manual 17

ARIC Neurocognitive Exam

2025

Study website - https://aric.cscc.unc.edu/aric9/

TABLE OF CONTENTS

Updates to Manual 17 Neuroclassification

This table describes any changes made to this manual regarding the neuroclassification process for Visit 12, if changes are made following visit start.

Modification Date	Modification

List of Abbreviations

ARIC	Atherosclerosis Risk in Communities Study
CA	Community Affairs
CSCC, CC	Collaborative Studies Coordinating Center
CDI	Clinical Dementia Rating form - Informant
CDP	Clinical Dementia Rating form - Subject
CDR	Clinical Dementia Rating
DEM, D	Dementia
DMS	Data Management System
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSS	Digital Symbol Substitution
DWR	Delayed Word Recall
FAQ	Functional Assessment Questionnaire
FS	Neurocognitive Factor Scores
HH	Home and Hobbies
JPS	Judgment and Problem Solving
LTCF	Long-term Care Facility
MEM	Memory
MCI, M	Mild Cognitive Impairment
MMSE	Mini-Mental State Exam
MRI	Magnetic Resonance Imaging
NACC	National Alzheimer's Coordinating Center
NCS	Neurocognitive Summary form
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NPI	Neuropsychiatric Inventory form
N	Normal cognition
O	Orientation
PC	Personal Care
QC	Quality Control
QxQ	Question by Question instructions
REM	Rapid Eye Movement pattern
RMSE	Root-Mean-Squared error
UDS	Uniform Data Set
WF	Word Fluency

1. OVERVIEW

The ARIC Visit 12 Neurocognitive Study (ARIC V12 NCS) is the 12th ARIC examination, to be completed in 2025-2026 on the survivors of the ARIC cohort. The design includes follow-up cognitive testing at ages where cognitive decline accelerates or manifests across several domains, allowing capture of a large number of both incident dementias and pre-dementia cognitive impairments. Its overall objectives are to determine the prevalence of cognitive impairments and the associations of mid-life vascular risk factors and markers with later-life cognitive impairments and cognitive change.

Participants are invited for exams in clinic or in their homes or long-term care (LTC) facilities. Additional information about participant's cognitive and functional status is sought from informants when necessary on a subset of the examined participants. An expert committee reviews data and classifies cognitive status (normal, mild cognitive impairment, or dementia).

This overview lists the ARIC NCS neurocognitive components with reference to corresponding Exam 12 Manual of Procedure (MOP) sections where the procedures are described in detail.

1.1. Eligibility

All surviving ARIC participants are eligible for ARIC NCS.

1.2. Recruitment

Recruitment begins during the ARIC Annual Follow-up interview. Details are found in V12 NCS Manual 2.

2. NEUROCOGNITIVE TESTING AND INFORMANT INTERVIEW (STAGE 2)

2.1. Overview

ARIC NCS has historically referred to two stages of neurocognitive testing. Stage 1 includes a cognitive test battery administered in-person. Stage 2 consists of informant interviews conducted by telephone shortly after the cognitive test battery is administered. A participant must attend Visit 12, attempt the cognitive test battery, and have given consent for an informant to be contacted to be selected for an informant interview (Stage 2). Participants with a ARIC NCS classification of level 1 dementia at prior visits are exempt from informant interview (Stage 2). An ARIC NCS classification of dementia carries forward to future visits.

Participants that exhibit one or more of the following characteristics are selected for the informant interview (Stage 2).

- Significant cognitive decline and at least *one* cognitive domain failure.
- Significant cognitive decline and an inability to complete any of the tests associated with *one* cognitive domain, i.e. missing *one* or more domain Z scores.
- An inability to complete any of the tests associated with *two* cognitive domains, i.e. missing *two* or more domain Z scores.

Detailed definitions are provided in the subsequent section. Participants who meet the criteria for Stage 2 selection are identified in CDART and contacted by the appropriate staff from the participant's site.

2.2. Definitions

2.2.a. Cognitive Decline

A confirmatory factor analysis model is utilized to compute a global cognition factor score based on all available cognitive tests administered in-person. Once a sufficient amount of data (N=100) has been collected to compute a reliable approximation of the sample mean for the current visit, a factor score is generated for each participant at each visit for each instance in which at least one neurocognitive test was completed. For details about this process please refer to Manual 30.

All global cognition factor scores from Visit 5 onward are incorporated into subject-specific regression models that calculate the annualized rate of decline. When the annualized rate exceeds -0.055 per year, the participant is categorized as exhibiting a ***significant cognitive decline***.

2.2.b. Cognitive Domains

Confirmatory factor analysis models are employed to compute factor scores for three cognitive domains designated executive function, language, and memory. Once a sufficient amount of data (N=100) has been collected to compute a reliable approximation of the sample mean for the current visit, a factor score is generated for each domain for every participant who completes at least one of the neurocognitive tests required by the domain-specific model. For details about this process please refer to Manual 30.

Cognitive domain norms were established using a robust Normative Sample of participants who completed visit 5. For details about the selection of participants for the robust Normative Sample please refer to ARIC Visit 7 Manual 17. Using the robust Normative Sample, race-specific linear regression models were developed that utilized age (continuous), education (< HS, HS, >HS) and WRAT score at Visit 5 (continuous) to predict a normal domain factor score. The parameter estimates from these models are depicted below.

Coefficients and 95% CI for Linear Regression Model of Domain Scores

Domain	Race	Intercept	Education: < HS	Education: HS	Age (yrs) -75	WRAT - 45	RMSE
Memory	African Am.	0.294 (0.219, 0.369)	-0.349 (-0.509, -0.189)	-0.150 (-0.276, -0.025)	-0.030 (-0.040, -0.019)	0.022 (0.014, 0.029)	0.583
	Caucasian	0.448 (0.402, 0.494)	-0.304 (-0.417, -0.192)	-0.158 (-0.217, -0.100)	-0.035 (-0.040, -0.030)	0.029 (0.024, 0.034)	0.593
Language	African Am.	0.129 (0.052, 0.206)	-0.332 (-0.497, -0.167)	-0.299 (-0.428, -0.169)	-0.029 (-0.040, -0.018)	0.041 (0.033, 0.049)	0.601
	Caucasian	0.449 (0.405, 0.494)	-0.338 (-0.446, -0.229)	-0.209 (-0.266, -0.153)	-0.030 (-0.036, -0.025)	0.046 (0.041, 0.051)	0.570
Executive Function	African Am.	-0.129 (-0.204, -0.055)	-0.489 (-0.649, -0.330)	-0.265 (-0.390, -0.139)	-0.037 (-0.048, -0.026)	0.041 (0.033, 0.048)	0.580
	Caucasian	0.599 (0.553, 0.645)	-0.434 (-0.548, -0.320)	-0.144 (-0.203, -0.085)	-0.049 (-0.054, -0.043)	0.028 (0.023, 0.034)	0.598

A predicted domain factor score is generated for each participant. A small percentage of participants have missing values for education or Visit 5 WRAT score. In these situations, when applying the prediction formula from the race-specific linear regression models, education is set to < HS and WRAT was set to the median WRAT score according to age (70-74, 75-79, 80+), race, and education level (< HS, HS, > HS). Predicted scores for Asian or Native American participants are calculated using the Caucasian-specific formula.

A domain Z score is computed for each participant by taking the domain factor score, subtracting the predicted domain factor score, and dividing by the root-mean-squared error (RMSE). ***Cognitive domain failure*** is defined as a domain Z score less than -1.5.

2.2.c. Discontinued Tests

When administering the cognitive test battery, each test is attempted but may be discontinued by the examiner due to participant refusal, physical impairment (e.g. hearing loss), cognitive impairment, etc. In these instances, the test is classified as missing and the reason the test was discontinued is documented.

3. NEUROLOGICAL INTERVIEWS (STAGE 2 – INFORMANT INTERVIEW)

3.1. Overview

The neurologic interviews completed as part of Stage 2 include the Clinical Dementia Rating Scale (CDR) and the Neuropsychiatric Inventory (NPI). The CDR includes the CDR Participant (CDP, administered to all participants, is described in MOP 2), the CDR Informant (CDI), and the CDR Summary (CDS). The CDI and CDS are described in this MOP. In addition, the Functional Activities Questionnaire (FAQ) is used in determining a participant's level of daily functioning, but does not have a dedicated interview or form- rather, all FAQ items are embedded within the CDR interview and recorded on the CDI. 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 some of the measures recommended in the Uniform Data Set (UDS) implemented in 2005 across all National Institute on Aging-sponsored Alzheimer's Disease Centers.

3.2. Clinical Dementia Rating (CDR)

3.2.1. Rationale

The CDR scale includes the CDR Informant and CDR Participant 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. The CDP is administered to all participants and is described in MOP 2. This form (CDP) will need to be referred to, along with the CDI, when the CDR scoring is being completed (on the CDS form). Because some subjective assessments are needed in order to make the CDR scoring determinations, only staff members who have experience in neurocognitive testing, who have previously undergone CDR certification, or who have a nursing degree would be considered for CDR certification.

3.2.2. Administration: CDR Informant

The CDR Informant form is administered by a certified staff member while an informant, usually identified by the participant, 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. The CDR informant (CDI) is administered by the psychometrist.

3.2.3. Administration: CDR Summary Score

The certified staff member will score the CDR after completion of these two components (participant (CDP) and informant (CDI)), and will not score them in the presence of the subject or informant. A scoring algorithm will be taught to study staff 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 staff member 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).

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 (M) 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. If 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).

3.2.4. 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.

3.2.5. Quality Assurance

Online training and certification for the CDR is required (https://knightadrc.wustl.edu/cdr-training-application/). After selecting "Access CDR Training Application 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 the neurologic QC reviewer with oversight by a study neurologist for certification. See ARIC Visit 7 Manual 12 for additional details on neurologic quality assurance and quality control.

3.3. Neuropsychiatric Scale

3.3.1. 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 visit 7 exam) might increase the likelihood that apparent memory or other cognitive problems are actually due to depression, rather than dementia.

3.3.2. Administration: NPI

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

3.3.3. Quality Assurance

Certification and recertification are performed as described above. The NPI should be audio recorded with the CDI.

4. DIAGNOSIS AND ADJUDICATION OF MCI AND DEMENTIA

4.1. Rationale

The diagnosis of cognitive impairment is the centerpiece of ARIC-NCS. Using a variety of sources of information, our diagnostic reviewers will review data on each ARIC-NCS participant and render a syndromic diagnosis of normal cognition, mild cognitive impairment (MCI), or dementia (DEM).

The basis for the syndromic diagnoses of MCI and DEM are well-established. Current criteria for MCI (Albert, 2011) and dementia (McKhann, 2011) prominently included ARIC investigators. Current 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.

4.2. Personnel

Drs. Albert, Knopman, Albert, Gottesman, Mosley, Walker, Windham, and Yasar 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 (Knopman). Cases with substantive differences may be discussed during the Neurocognitive Classification Committee teleconferences. Agreement tables are also reviewed during Committee teleconferences.

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

4.3. Information and Tools Available to Members of Classification Committee

1. Demographic information: race, sex, age
2. Table containing historical algorithmic and syndromic diagnoses since visit 5.
3. Neuropsychiatric information (from clinic, home, long-term care)
   A. Current neurocognitive tests: Raw scores, (adjusted) cognitive domain (Z) scores, and the reason for any missing tests (i.e., recorded by the examiner at the visit as due to physical disability, etc.).
   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 as well as the more detailed cognitive battery administered in the ARIC Brain MRI study and visit 5.
   C. Cognitive Decline: Decline in General Cognitive Performance from visit 6 to 7 (or V5 to V7 in the absence of V6 data) (defined in 2.2.b).
   D. Psychometrist comments, verbatim.
   E. BLESSED items.
4. 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 score sheet; CDS: need each box score, as well as total scores.
   C. 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.” The NPI is included in the packet to provide information to the reviewer about the participant. No item on the NPI is used for determining the syndromic diagnosis.
   D. 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

4.4. Operational Criteria

An algorithmic diagnosis is assigned to each participant automatically as depicted in the table in the column *Algorithm Dx*. Members of the Dementia/MCI Classification Committee review the information associated with each participant including the algorithmic diagnosis as documented in the column *Requires Review*. A reviewer designated diagnosis of dementia (Dem), mild cognitive impairment (MCI), or normal (NL) is assigned. This definitive diagnosis may align with or override the algorithmic diagnosis. In situations where one or more of the diagnostic elements are missing or discordant, the reviewer will use their best judgment to make a diagnosis.

Table 4.1. Computer Generated Algorithmic Diagnoses

Stratum	Decline[1]	Failed domain[2]	CDR sum of boxes	FAQ	Algorithm Dx[3]	Selected to Stage 2	Requires Review
1	PPT diagnosed with dementia at a prior visit				Dem	No	No
2	Prorated MMSE score less than 21 for white participants ***or*** prorated MMSE score less than 19 for black participants				Dem	No	No
3	No	Any	uncollected	uncollected	NL	No	No
4	Yes	0 failed	uncollected	uncollected	NL	No	No
5	Yes	1 failed or missing	0 or missing	≤5 or missing	MCI	Yes	Yes
6	Yes	1 failed or missing	0	>5	Prob MCI	Yes	Yes
7	Yes	1 failed or missing	>0 but ≤3	≤5 or missing	MCI	Yes	Yes
8	Yes	1 failed or missing	>0 but ≤3	>5	Prob MCI	Yes	Yes
9	Yes	1 failed or missing	>3	≤5	Prob Dem	Yes	Yes
10	Yes	1 failed or missing	>3	≤5 or missing	Prob Dem	Yes	Yes
11	Yes	>1 failed	0 or missing	≤5 or missing	MCI	Yes	Yes
12	Yes	>1 failed	0	>5	Prob MCI	Yes	Yes
13	Yes	>1 failed	>0 but ≤3	≤5	MCI	Yes	Yes
14	Yes	>1 failed	>0 but ≤3	≤5 or missing	Prob MCI	Yes	Yes
15	Yes	>1 failed	>3	≤5	Prob Dem	Yes	Yes
16	Yes	>1 failed	>3	≤5 or missing	Dem	Yes	Yes

1 Definitions of cognitive decline and domain failure are provided in section 2.2.

2 The algorithmic diagnosis will be assigned according to the following hierarchy: 1) PPTs diagnosed with dementia at a prior visit, 2) PPTs with low, race specific prorated MMSE, 3) according to the PPTs cognitive decline, domain failure, CDR sum of boxes, and FAQ.

Appendix 1. 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.
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