Manual 1
General Description and Study Management

Atherosclerosis Risk in Communities Study: Clinic Examination and Cohort Morbidity/Mortality Follow-Up

May 2, 2023 - Version 7.0

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

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FOREWORD

This manual, entitled General Description and Study Management is one of a series of protocols and manuals of operation for the Atherosclerosis Risk in Communities (ARIC) Study. The table below lists the current manuals, including those for the clinic visits and the associated neurocognitive ancillary study examination; participant follow-up; and cohort CVD events ascertainment. Gaps in the numbering correspond to manuals from earlier cohort examinations that are no longer a part of the clinic visits. The detailed Manuals of Operation, including those for the current and previous examinations, are available on the ARIC Website at https://sites.cscc.unc.edu/aric/aric-ncs-manuals.

ARIC Study Protocols and Manuals of Operations

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General Description and Study Management
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1. INTRODUCTION AND BACKGROUND

Cardiovascular Disease (CVD) mortality continues to decline but remains the leading cause of death in the US. Heart failure is a growing and costly condition. There have been few long-term US studies monitoring coronary and heart failure incidence and case fatality, and none other than ARIC have been conducted as multicenter studies in diverse communities. Information on the pattern of CVD trends is essential to guide public policy related to CVD. Yet, ARIC community surveillance, which was conducted from 1987 through 2015, has been costly and not geared to using electronic health records that are becoming widespread and have untapped potential for epidemiological research.

Much is known about lifestyle risk factors and the pathogenesis of CVD. However, there are still significant gaps in knowledge related to African Americans, women, and other population subgroups; about the relations of subclinical disease and its progression to clinical disease; about the role of genes and their interaction with environment in CVD causation, and about the role of novel biomarkers of atherosclerosis and its sequelae.

Heart failure epidemiology is particularly sketchy. There are gaps in understanding how heart failure progresses from subclinical to clinical stages, and data on heart failure outcomes in whole populations are lacking.

The ARIC Study cohort has a wealth of existing data and an effective and productive collaboration of experienced investigators. The latest renewal of ARIC will greatly increase numbers of cohort events, extending risk data to the current cohort of older adults (age >75 and >85 years who experienced the obesity epidemic), and permit more extensive subgroup analyses and interaction testing; allow the ARIC investigators to update risk factor information, medications, and medical history through a cohort exam; allow us to continue to analyze collected data on novel risk factors for CVD; and serve as a platform for new ancillary studies and collaborations to use existing data and stored specimens, potentially taking advantage of new developments in the fields of biochemistry and genomics to contribute to investigation of new risk markers for CVD and gene-environment interactions. The latest renewal also enables ARIC to contribute to methods for using electronic health records for CVD epidemiologic research.

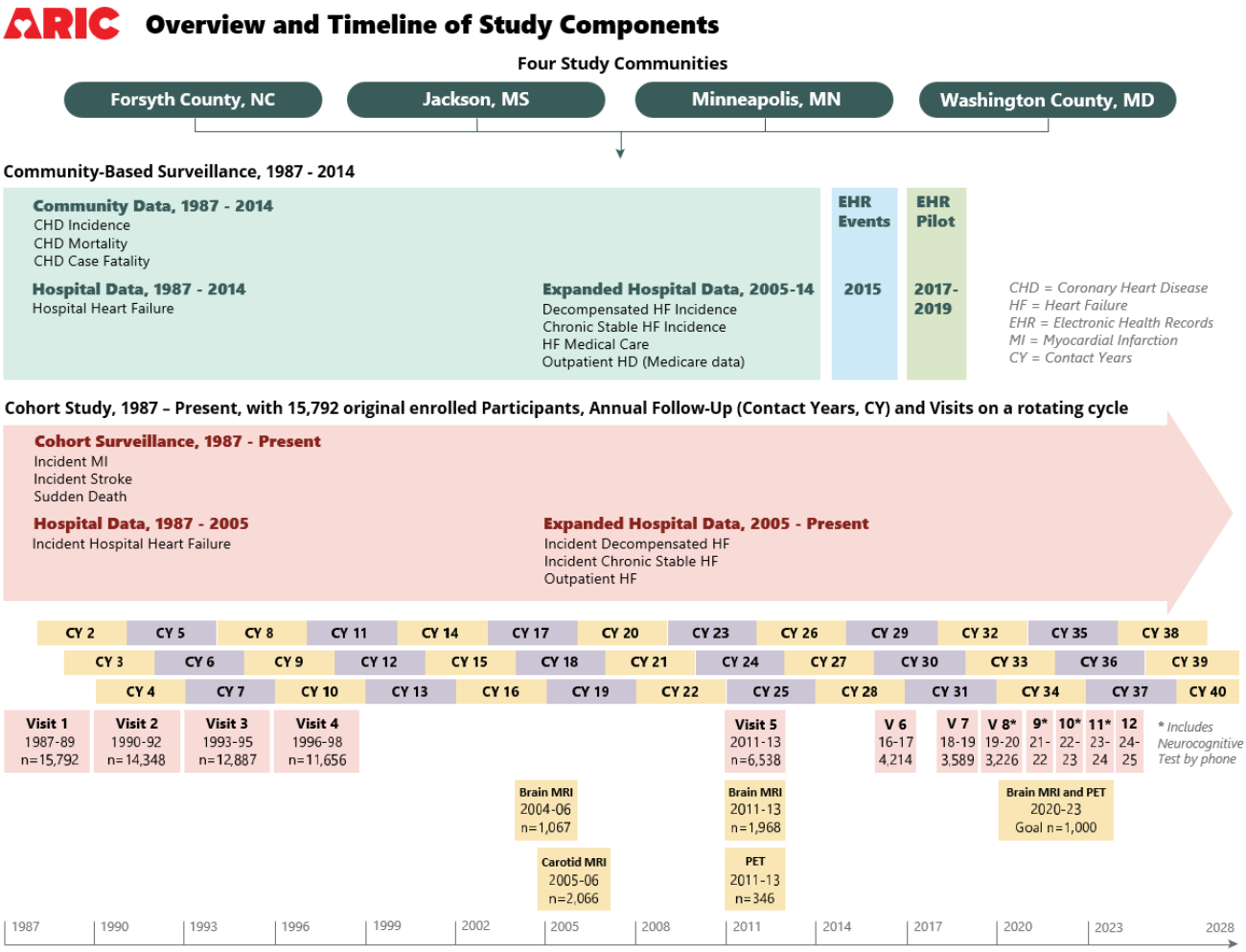
This renewal of ARIC includes a re-examination of the cohort to update risk factor levels. At ARIC Visit 7, an ancillary study expanded its characterization of HF progression via an echocardiogram performed in the same fashion as ARIC Visit 5 (2011-13). Using echo measurements and novel biomarkers, the study documented progression of HF stages in the cohort and identified genetic and environmental factors leading to ventricular dysfunction and vascular stiffness. In conjunction with the neurocognitive ancillary study, data continues to be collected on cognitive function and decline, as well as dementia. Other ancillary studies have been added at ARIC Visit 9 and 10, approved by the ARIC Steering Committee and NHLBI staff and funded by various sponsors. Ancillary studies offered at ARIC Visit 10 include ambulatory and home blood pressure monitoring, peripheral neuropathy, and devices to monitor glucose levels and heart arrythmias in patients with diabetes.

2. STUDY DESIGN

The ARIC study is a prospective study initiated in 1987 to investigate the etiology and natural history of atherosclerosis and its clinical manifestations, and to measure variation in cardiovascular risk factors, medical care and disease by race, gender, place and time. The

study has included cohort and community surveillance components. See Table 1 below for an overview and timeline of the ARIC study components.

Table 1.



2.1 Cohort

For the cohort component, population samples were randomly chosen from four US communities, totaling 15,792 persons aged 45-64 at baseline (1987-89). The four communities are Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland. The Jackson sample includes African Americans only; in the other field centers samples are representative of the populations in these communities, i.e., mostly white in Minneapolis and Washington County, and about 15% African American in Forsyth County. During a baseline home interview, persons were invited to participate in the study, and information was collected on health status, selected risk factors, family medical history, employment and educational status, diet, and physical activity. Cohort members completed six clinic examinations, conducted three years apart, in 1987-89 (baseline Exam 1), 1990-92, 1993-95, 1996-98, 2011-13, and 2016-17 (Exam 6, supported largely by the ARIC Neurocognitive Study). The components for each visit (Visits 1-10) are included in a separate document with this manual on the ARIC website (**Available ARIC Data by Exam**).

The cohort is followed-up by semi-annual phone interviews, and search of death certificates and hospitalizations. Events (e.g., deaths, hospitalized MIs, heart failure) have been ascertained through cohort surveillance activities. ARIC also has linked to Medicare and Medicaid records, which provide additional cohort endpoints after age 65. To test hypotheses, traditional cohort analyses are used as well as nested case-cohort analyses. These involve the ARIC laboratories and stored specimens, to relate novel risk factors to clinical endpoints.

ARIC is conducting a tenth examination (Visit 10) of the cohort in 2023. The exam components include the core visit components as well as ancillary studies including ePatch/CGM, blood pressure monitoring, and peripheral neuropathy. The details of this examination are provided in Manual 2, with more information about specific procedures in various other manuals.

2.2 Community Surveillance

The aim of this component was the assessment from 1987-2015 of geographic and time variation in incidence rates of fatal CHD and of hospitalized (fatal or nonfatal) myocardial infarction, and other summary statistics (e.g., proportions receiving various treatments, case fatality) in persons aged 35-74 in the four communities. Beginning in 2005, community surveillance of hospitalized heart failure (ages 55 and older) was added and the age window for CHD was expanded to include ages 75-84. More recently, the Coordinating Center has been obtaining CMS records for the study communities to help describe community CVD rates and trends.

Active monitoring of CHD surveillance events in the ARIC communities started in January 1, 1987, and per NHLBI decision will end in its present form with events through 2015. Hospital surveillance for heart failure will have covered January 1, 2005 through 2015. The most recent ARIC renewal also includes a pilot study to document whether community surveillance using algorithms to extract data from electronic health records is feasible and accurate, compared to ARIC's prior methods.

Even though NHLBI has decided to end ARIC's community CVD surveillance, cohort follow-up for CVD events will continue using similar established procedures. The standardized ARIC surveillance process involves three components: 1) identification of possible events; 2) investigation by abstraction, interviews, or other means; and 3) endpoint classification. Endpoint classification has been performed by computer algorithm at the Coordinating Center or by the Morbidity and Mortality Classification Committee (MMCC), comprised of physicians from each field center. Since 2005, ARIC also has obtained Medicare and Medicaid records from CMS for the ARIC communities, to further identify cohort events and describe trends in CVD in the communities. In addition to fatal CHD and hospitalized MI and heart failure, cohort events of interest include stroke, atrial fibrillation, diabetes, chronic kidney disease, hypertension, peripheral artery disease, and others.

2.3 Central Agencies

In addition to the four Field Centers, the ARIC study includes a coordinating center and several other central agencies. The protocols for the procedures performed by each of these agencies are contained in separate manuals on the ARIC website from the ARIC cohort examinations, including: echocardiography, retinal photography, magnetic resonance imaging, clinical chemistry, hemostasis, lipids, electrocardiography, pulmonary function, carotid ultrasound, and quality control. The roles of the agencies which continue in the study are summarized in this section.

2.3.1 Central Lipid Laboratory

Central Lipid Laboratory at Baylor University develops and performs laboratory analyses of blood and urine samples collected from ARIC Visits 1-10 to test new hypotheses regarding biochemical markers and their associations with development and progression of atherosclerosis, heart failure, and other cardiovascular diseases. The laboratory also serves as a repository for the biological samples from ARIC Visits 1-10.

2.3.2 The DNA Laboratory

The DNA Laboratory at the Human Genetics Center, University of Texas-Houston evaluates the ability of genetic variation to predict the occurrence and progression of atherosclerosis and onset of clinical CVD. It uses genomic laboratory and statistical methods to identify and localize novel gene regions contributing to the occurrence and progression of atherosclerosis and CVD. The laboratory also serves as a repository for DNA samples from the ARIC clinical examinations.

2.3.3 Central Clinical Chemistry Laboratory

The Central Clinical Chemistry Laboratory at the University of Minnesota performed clinical chemistry measurements at exams 1, 2, 5, and 6. Frozen serum remains available at the Clinical Chemistry Lab for future analysis.

2.3.4 ECG Reading Center at Wake Forest University

This ECG Reading Center oversaw the acquisition and reading of ECGs on several ARIC cohort visits. The Wake Forest ECG Reading Center now reads hospital ECGs to help with classification of MI in ARIC cohort participants.

2.3.5 Echocardiography Reading Center

The Echo Reading Center oversees the acquisition and reading of echocardiograms on ARIC cohort participants. The major responsibilities of the Echo Reading Center includes: 1) developing protocols for the acquisition, reading, information abstraction, and quality control and assurance of the echocardiography (M-mode and 2-D echocardiography with tissue Doppler and speckle tracking), 2) providing training and guidance of Field Center echocardiography staff, and 3) performing readings and information abstractions of echocardiograms. The ARIC Echo Reading Center is at the Brigham and Women's Hospital, Harvard University Medical School.

2.3.6 Coordinating Center (CC)

The CC provides centralized administration, planning, and management for all components of the ARIC Study. Its administrative functions include supporting the Project Office and the chairman of the Steering Committee and Executive Committee in convening meetings, documenting decision and action items, preparing and distributing meeting minutes and coordinating the work of the various subcommittees. Technical support for the installation, use and maintenance of local equipment and software is provided by CC staff. The CC serves as the official repository for all ARIC Steering Committee records, manuals of operations, data collection instruments, research data and publications.

The CC supports the Morbidity and Mortality Classification Committee in monitoring the status of each study endpoint, preparing documentation of events to be verified and creating a final diagnosis file.

The CC also supports the design, management, and analysis of the ARIC cohort examinations and nested case control studies, and the publication of results of the collaborative study.

The Coordinating Center's responsibility for the centralized management of the study includes the provision and tracking of training and certification; monitoring protocol adherence in the Field Centers and Central Agencies; the design, implementation and monitoring of quality assurance programs in the field centers, laboratories and reading centers; and data management, including the development of a computerized data collection system, on-site and centralized data processing and data analysis. The specific procedures for the distributed data management systems and data analysis are described in the following section of this manual.

The CC implements closure of the data. The closed data files are prepared in SAS transport format for distribution to Field Centers, Central labs and NHLBI. Documentation of the distributed data files is sent with the data.

The CC prepares study data in SAS transport format for submission to the NHLBI's Data Repository. Datasets for the Data Repository are submitted no later than 3 years after the completion of each examination or follow-up cycle or 2 years after the follow-up, genetic, ancillary study, or other data set is finalized within the study for analysis for use in publications, whichever comes first.

The Coordinating Center also manages the ECG Reading Center at Wake Forest University. In addition, the Coordinating Center establishes and manages two expert teams: a Pulse Wave Velocity (PWV) team and a Pulmonary Function Test (PFT) team. The expert teams oversee the training, acquisition, and quality control and assurance of PWV and PFT measurements.

3. STUDY MANAGEMENT

3.1 Introduction

The ARIC Study is funded primarily by a contract from the National Heart, Lung, and Blood Institute, and directed by the Epidemiology Branch of the Prevention and Population Science Program, Division of Cardiovascular Sciences. In addition, investigator initiated ancillary studies fund important components. ARIC operations are directed by the ARIC Study Steering Committee.

The Steering Committee is supported by committees responsible for the details of study design and implementation, and a Morbidity and Mortality Classification Committee (MMCC). These committees report and make recommendations to the Steering Committee. The committees and their charges are listed in the section below. In addition, there are parallel committees for the ARIC Neurocognitive Study, which is a major ancillary study contributing to ARIC.

3.2 ARIC Study Committees and Charges

3.2.1 Steering Committee

The Steering Committee comprises the Principal Investigators of the Field Centers, Coordinating Center, Lipid Laboratory, DNA Laboratory, and the NHLBI Project Officer. The Steering Committee meets monthly to oversee all operations of the study including clinic visits, follow-up, and cohort surveillance activities.

3.2.2 Executive Committee

The Executive Committee comprises the Field Center PIs and Coordinating Center PI and the NHLBI Project Officer. The committee meets monthly to manage the study, approve manuscripts and ancillary study proposals forwarded from those respective committees, and consider pertinent study activities that arise interim to the Steering Committee meetings.

3.2.3 Surveillance Committee

The Surveillance Committee comprises the Field Center PIs, a representative of NHLBI Project Office, and members from the Coordinating Center. The Committee meets monthly to discuss progress toward meeting annual closure deadlines, quality control, changes in medical care and diagnostics, and events ascertainment. In matters pertaining to events outcomes, the Surveillance Committee is responsible for training for interviewers, and abstractors; quality control; data interpretation; and monitoring and protocol adherence.

The Heart Failure Committee is a subcommittee of the Surveillance Committee and comprises scientists and physicians with expertise in heart failure. The HF subcommittee is charged with developing the scientific rationale and study protocol for case ascertainment, classification/validation, quality assurance, instrument development and testing, and data management.

3.2.4 Ancillary Study Committee

The Ancillary Studies Committee comprises representatives from Field Centers and the CC with expertise in laboratory methods, and examination methodologies, and a representative of NHLBI Project Office. They are charged with reviewing proposals for ancillary studies and making recommendations to the Steering Committee. See the link to the Ancillary Study website for information on policies and procedures: https://sites.cscc.unc.edu/aric/ancillary-studies-pfg.

3.2.5 Publications Committee

The Publications Committee is described in Section 3.4.

3.2.6 Follow-up Committee

This committee comprises one PI and all follow-up coordinators from the ARIC field centers, the Coordinating Center PI and pertinent staff, and a representative of NHLBI Project Office. The Committee meets monthly to monitor follow-up operations, quality control, and annual training and certification of interviewers.

3.2.7 Operations Committee

This committee comprises one Field Center PI, the Coordinating Center PI and pertinent CC staff, Field Center clinic coordinators, and a representative of NHLBI Project Office. The Committee meets monthly to plans for and monitor all data collection activities related to clinic visits, including training and certification of technicians, pilot study, data collection operations, quality control, and assurance.

3.2.8 Laboratory/Genetics Committee

The Laboratory Committee comprises the Laboratory PIs and pertinent staff, the Coordinating Center PI and staff, a representative of NHLBI Project Office, and interested Field Center PIs. The Committee proposes and monitors laboratory analyses using ARIC's stored specimens and the appropriate study design.

3.2.9 Echocardiography Committee

The Echocardiography Committee is led by the Echocardiographiy Reading Center PI and includes representatives from the CC and Field Centers, and the NHLBI Project Officer. This committee is charged with refining the protocol, conducting training, and monitoring quality of data collection for the echocardiographic measurements acquired during clinic visits.

3.2.10 Quality Control Committee

The Quality Control (QC) Committee comprises a Field Center PI, a CC representative, a representative of the Annual Follow-up Interviewers, a representative of the Surveillance Abstractors and a representative of the NHLBI Project Office. The Committee meets monthly during the data collection period for the clinic visits and quarterly thereafter to discuss protocol adherence and quality control issues for the lab and follow-up.

3.2.11 Morbidity and Mortality Classification Committee

The Morbidity and Mortality Classification Committee (MMCC), comprising physicians from the Coordinating Center and each Field Center, is responsible for the process of assigning all medical events of interest in the ARIC Study into diagnostic classes defined by the study.

The MMCC operates by assessing medical information received from each Field Center. In most cases this involves independent assessment by two committee members with differences adjudicated by the full committee. Problems in classification may result from lack of clarity in the study diagnostic criteria. Under these circumstances the committee recommends appropriate modifications to the criteria.

3.3 Communications

3.3.1 Periodic Reports

The Field Centers and Central Agencies prepare routine periodic reports to the ARIC Study Project Office, which document the progress to date in each major activity, administrative matters, staffing changes, and current or anticipated problems. The Coordinating Center also provides reports on recruitment and data collection at the Field Centers, data received from Central Laboratories and Reading Centers, quality control findings on examinations, re-abstracted records, recertification, and protocol adherence. Quality control reports are also sent to the Central Laboratories and Reading Centers.

3.4 Publication Policy

Overall responsibility for manuscript and abstract generation and approval for the ARIC Study lies with the Steering Committee and Publications Committee. The Steering Committee and Publications Committee have developed procedures for generating manuscripts and abstracts as well as the formal requirements for manuscript approval prior to submission for publication or prior to abstract submission for presentation, detailed on the ARIC web site in the Publications section (https://sites.cscc.unc.edu/aric/pubs-policies-and-forms-pg).

The overall aim of this process is to encourage the preparation of manuscripts and abstracts while also providing appropriate control over their quality and content. The process also serves to avoid inappropriate duplication.

Central to all of these activities is the Publications Committee referred to above. The Publications Committee is composed of at least four members, all of whom are active in the ARIC Study. One member serves as chair and another as the Committee's editor. The Committee holds monthly conference calls to review manuscript proposals and discuss

operational issues. Abstracts and manuscripts are reviewed on an ongoing basis through e-mail.

Publications committee procedures are summarized in the following documents in the Policies and Forms section of the Publications page on the ARIC web site (link provided above):

- Procedure for Submitting a Manuscript Proposal and/or Abstract
- Procedure for Submitting an Abstract for ARIC review
- Manuscript Proposal Form (to be used for all manuscript proposals except when the proposal is part of a parent consortium which has its own form; for some studies affiliated with ARIC the original study/consortium form can be used instead, please check with aricpub@unc.edu for specific studies)
- Publications Committee Overview (a brief summary of the logistics for submission and review)
- Information for New Investigators (summary describing opportunities and procedures in welcoming new investigators to ARIC)
- Acknowledgement Statement: ARIC (to be used in all ARIC papers, unless using one of the more specific versions below; support for ancillary studies can be added to these statements)
- Acknowledgement Statement: Neurocognitive (ARIC-NCS)
- Acknowledgement Statement: ARIC OMICS
- Acknowledgement Statement: ARIC Cancer Funding
- Acknowledgement Statement: Carotid MRI Study
- Expedited Manuscript Review Policy (describes the procedures for a LIMITED review by the editor only for letters and consortium papers – goal of 1 week approval – and EXPEDITED review of time sensitive papers – goal of completing a full review in 2-3 weeks or less – as well as policies for the editor's handling of overdue reviews)
- NIH Public Access Policy Notification (describes the availability of ARIC data to non-ARIC investigators)
- Withdrawn ARIC Manuscript Proposals (topics from this list of withdrawn manuscripts can be used for new proposals)

3.5 Ancillary Studies Policy

The ARIC ancillary studies policy is laid out in a document in the "Ancillary Studies" section of the ARIC website at https://sites.cscc.unc.edu/aric/ancillary-studies-pfg. In general, ancillary studies require external (non-ARIC) funding. Funding must be sufficient to cover any costs relating to the ancillary study that will be incurred by the field centers or central agencies. The policy document describes the process for obtaining approval of an ancillary study as well as reporting and data sharing requirements. The "Ancillary Studies" section of the web site also contains additional documents and information, including a Data and Materials Distribution Agreement (DMDA).

For ancillary studies needing biospecimens, the password-protected section of the ARIC web site has inventories of the biospecimens at the central laboratories.

4. STRATEGY FOR ORGANIZING AND MANAGING ARIC DATA SETS

4.1 Data

Create a directory called “ARIC”.

Create the following sub-directories under the ARIC directory:

SUBDIRECTORY	DESCRIPTION
V1FINAL	Visit 1 data
V2FINAL	Visit 2 data
V3FINAL	Visit 3 data
V4FINAL	Visit 4 data
V5PRELIM	Any visit 5 data distributed before the final versions of the visit 5 datasets are distributed
V5FINAL	Visit 5 data
C_CNTRL1	Visit 1 case/control data
C_CNTRL2	Visit 2 case/control data
INCIDENT	Incident CHD and stroke data
SURVALL	Surveillance data

The CSCC will send ARIC data in the format of SAS transport files or SAS version 7/8/9 datasets.

Transport files should be converted to SAS data sets that are formatted appropriately for a user’s operating system. For example, if using Microsoft Windows, transport files should be converted to SAS data sets for Windows.

The SAS data sets created should be stored in the relevant subdirectory. For example, all visit 1 files should be stored in the V1FINAL subdirectory, visit 2 files should be stored in the V2FINAL subdirectory and so on.

If you received an updated version of a file that you already have:

a) You can move the older version of the file to a backup medium.

b) Create a subdirectory called “OLD” under each of the subdirectories listed above. Move the old version of the data set to the appropriate “OLD subdirectory. For example, if you receive an updated version of the visit 1 HOM file, move the older version of HOM to \V1FINAL\OLD. Files in the “OLD” subdirectories can be stored in compressed format to conserve space.

a) One exception to the above rules is for visit 5 data. If preliminary versions of visit 5 datasets are distributed before the final versions, keep these in a separate directory (V5PRELIM) so that it is clear that they are not the final versions. Once the final versions are distributed, V5PRELIM can be archived or moved to a subdirectory of V5FINAL.

4.2 Documentation

A notebook should be maintained with documentation for ARIC data. The notebook should be divided into sections similar to the ARIC data (visit 1, visit 2, ……) . When datasets are distributed by the CC, accompanying documentation will be provided. The documentation will be in the form of file contents, listing of the first 10 observations, and descriptive statistics. When documentation is received it should be stored in the appropriate section of the ARIC data notebook.