2.19.6 Data Collection

Raw echocardiographic data are directly digitized during data collection by an on-line system and stored on optical disks and super VHS videotapes. Individual echocardiograms are labelled and catalogued for subsequent reading, following standard ARIC data collection and identification protocols. Scans are read at the University of Mississippi Heart Station, data are stored on the image analysis system hard drive, and primary echocardiographic measurements are downloaded to ASCII files for transmission to the ARIC Coordinating Center.

2.20 Electrocardiogram

A resting 12-lead ECG is performed on each participant in Visit 3 using procedures and equipment identical to those employed in previous cohort examinations. Processing and coding at the Minnesota and Edmonton central electrocardiographic reading centers follows the same procedures used in the baseline visit. Full details are provided in Manual 5 of the ARIC Protocol.

2.20.1 Rationale

The main purpose of the electrocardiographic measurements is to provide information on (1) interim myocardial infarction; (2) changes in conduction pattern, ventricular hypertrophy and ischemia; (3) and other indicators of cardiac function. Hospital ECGs are also read and abstracted for all cohort participants hospitalized after their baseline visit, to determine if a cardiac end point event has occurred.

2.20.2 Procedures

Standard (12-lead) ECG operational procedures are provided in Manual 5, Electrocardiography.

2.20.3 Training

Central training of senior field center technicians was initially performed in Visit 1. Training for new ECG technicians is provided centrally and by the senior certified ECG technician at each field center, consisting of (1) electrode placement, (2) skin preparation, (3) MAC PC menus and data entry, and (4) self-evaluation techniques for technical performance.

2.20.4 Certification

Certification is required for ECG technicians performing 12-lead ECGs. Requirements and procedures are listed in Manual 5. The Minnesota ECG Reading Center serves as the certifier. Recertification is performed annually.
2.20.5 Quality Assurance

To maintain certification each technician is required to perform a minimum of three (3) ECGs per week over a two-month period; quality grades for each 12-Lead ECG are reported by the Edmonton ECG Reading Center to each technician on an ongoing basis; a monitoring/retraining visit by the local ECG trainer takes place annually; an ECG quality control checklists is administered quarterly (see Appendix Q of Manual 5).

Quality assurance of the ECG coding at each of the two central ECG reading facilities includes internal, and external quality control programs. These are detailed in manuals 5 (Electrocardiography) and 12 (Quality Control).

2.20.6 Data Collection

The standard electrocardiograph for the recording of 12-lead ECGs is the MAC PC Personal Cardiograph by Marquette Electronics, Inc. Data collection procedures are fully documented in Manual 5. Tracings are transmitted daily to the ECG Computer Center at Edmonton, Alberta via modem. Paper tracings are stored in the participant's folder.

2.21 Cerebral Magnetic Resonance Imaging

Age-eligible cohort participants at the Forsyth County and Jackson field centers who pass exclusion criteria are scheduled for brain MRI scans, either immediately following their ARIC exam, or for another more convenient time. These participants also repeat the Cognitive Function test they took during Visit 2.

2.21.1 Rationale

The goal of implementing the cerebral MRI into the ARIC study is to evaluate cerebral changes detected by MRI in a representative, biracial population, aged 56 to 70, and to evaluate the relationship of these changes to clinical stroke, coronary heart disease, cardiovascular risk factors, retinal microvascular changes, extracranial carotid atherosclerosis and changes in cognitive function. The MRI data are expected to supplement the clinical descriptors of cerebrovascular disease related hospitalizations by increasing the sensitivity of detecting subclinical disease and by distinguishing small-vessel from large vessel disease.

2.21.2 Procedures

Prior to the procedure at the MRI suite, the MRI technician confirms the absence of the exclusion criteria reported on the MRI Screening form, repeats an explanation of the procedure, its potential risks and benefits and administers a second hospital-required MRI consent form (Appendix 2.19.a). Prior to receiving the MRI scan, an ARIC staff member administers the ARIC Cognitive Function exam (see Appendix 2.2 for the form and instructions).

The participant is scanned according to the ARIC MRI scanning protocol and the technician completes the MRI Procedure Form. The form and their question by question instructions are located in Appendix 2.19.b and 2.19.c, respectively.

ARIC PROTOCOL 2. Cohort Component Procedures - Visit 3. VERSION 5.0 09/95
Although ARIC does not assume responsibility for the diagnosis and treatment of medical conditions, it assumes an obligation to identify abnormalities which may require further medical attention. The MRI technologist reviews each study for the presence of any condition identified by the ARIC protocol as an emergent alert. These include tumor without significant mass effect, AVM, aneurysm, obstructive hydrocephalus, cavernous angioma, venous angioma (urgent referral) and acute subdural or epidural hematoma, subarachnoid hemorrhage, acute intraparenchymal hematoma, acute infarct, subacute infarct, obstructive hydrocephalus, cerebral venous thrombosis, abscess and suspected tumor with significant mass effect (immediate referral). The ARIC neuroradiologist is contacted and established ARIC alert procedures are initiated (see section 2.28 in this manual and the MRI Manual of Operations, No.13).

2.21.3 Training

MRI technologists must have appropriate knowledge of cross-sectional anatomy, physiology, and pathologic processes with emphasis on neurologic imaging. The preferred level of education is completion of a two year AMA-approved program for diagnostic imaging and a minimum of 3 to 6 months MRI experience. The technologist must have a basic knowledge of MRI and knowledge of computer software applications, multi-format cameras, processors and video recording devices. The MRI technologist is trained by the study’s neuroradiologist to identify the anatomical location of the AC/PC Line, to implement the ARIC MRI pulse sequences, and to recognize conditions identified by the ARIC protocol as notification alerts.

2.21.4 Certification

MRI technologists are trained and certified by the local MRI/Neuroradiology Center. Certification of the readers is the responsibility of the MRI Reading Center.

2.21.5 Quality Assurance

Quality control procedures are described in detail in Manual 14. In summary, prior to the ARIC participant leaving the MRI suite, the MRI technologist reviews the scan for adherence to the ARIC MRI protocol and for technical quality. Using MRI calibration phantoms, MRI equipment is evaluated for field homogeneity, noise characteristics, spatial and contrast resolution. Masked, phantom quality control scans are sent to the MRI Reading Center for reading.

The acceptability of the MRI examination to the participants is monitored during the first three months of the study. Each week the Study Coordinator identifies two participants at random, who are contacted by an ARIC interviewer who administers the Post-MRI Acceptability Questionnaire. Results are reviewed by the Study Coordinator and Field Center PI. After 24 surveys are completed, copies are sent to the Chair of the ARIC Cohort Operations Committee for assessment.
2.21.6 Data Collection

Scans are recorded on magnetic tapes or optical disks, at the discretion of the ARIC MRI facility. Procedures for preparing, shipping and storing tapes and disks are fully described in Manual 13. Labelled tapes and disks are shipped via overnight carrier to the ARIC MRI Reading Center on a predetermined schedule, i.e., once a week (tapes) or once every two weeks (optical disks). Shipping containers include scans, log sheet, MRI Completion Forms and participant forms (refer to Manual 13).

Field centers are notified of study results, following the results reporting protocol. Summary results are transmitted electronically to the ARIC Coordinating Center for inclusion in the central database.

2.22 Retinal Photography

One 45 degree photograph is taken under non-mydriatic conditions (i.e., not requiring pharmacologic dilation of the pupil) of one eye of each participant during Visit 3. The photographs are sent to a central reading center for assessment of retinal status.

2.22.1 Rationale

Fundus photographs are used to evaluate changes in the retinal vasculature (presumed to be related to hypertension and/or arteriolar sclerosis) that may be prognostic for various cardiovascular outcomes. Generalized and focal narrowing of arterioles and changes in arterio-venous (A/V) crossings are evaluated. Signs of 'malignant' hypertension (hemorrhages and microaneurysms, 'cotton wool spots', and swelling of the optic nervehead), and other significant retinal conditions, (such as diabetic retinopathy or vascular occlusions) are assessed.

2.22.2 Procedure

Prior to photographing an eye, the Retinal Examination form (Appendix 2.20.a) is administered to each participant to document the general ophthalmic history, to record the method of selecting the eye photographed, or the reason photography cannot be performed. Question by question instructions for the form are located in Appendix 2.20.b. A Canon non-mydriatic, auto-focus fundus camera with 35 mm camera back is used to take a 45 degree retinal photograph (not requiring pharmacologic dilation of the pupil) of one eye of each participant in Visit 3. Photographs are sent to the Fundus Photograph Reading Center for assessment of retinal status. Procedural and operational detail is provided in Manual 14.

2.22.3 Training

Technicians are trained by personnel of the Fundus Photograph Reading Center during central training. Chief technicians are responsible for training newly hired staff.

2.22.4 Certification

ARIC PROTOCOL 2. Cohort Component Procedures - Visit 3. VERSION 5.0 09/95
Photographer certification is conferred after training, either at the central training session the beginning of Visit 3 or by a field center certified photographer. Practice on local volunteers, and the submission of satisfactory photographs of ten eyes to the Fundus Photography Reading Center are required. Satisfactory quality includes proper field definition, exposure, alignment and focus. Photographs must be completely labeled and mounted according to protocols and accompanied by Photography Log Form(s) and completed shipping manifest.

2.22.5 Quality Assurance

The quality of photographs is monitored throughout the study. For new technicians all photographs are reviewed by the reading center and feedback provided to the photographers in cases that warrant critique. Data on quality of the photographs are routinely generated by the readers on all photographs and reported to field centers, via the ARIC Coordinating Center. A small percentage of the photographs is reviewed by the Reading Center and feedback provided to individual field center photographers when appropriate. One to two participants per week at each field center are asked to volunteer for a repeat photograph (same eye), which is sent to the reading center under a (blinded) quality control ID number.

2.22.6 Data Collection

Data for the Retinal Examination Form (Appendix 2.20.a) are routinely collected on paper for delayed data entry. Question by question instructions for completing the form are located in Appendix 2.20.b. A daily Photography Log Form (Appendix 2.20.c) is maintained at the field center for use by the reading center for each roll of film which includes the film roll number, date, photographer code, participant ID, eye (right or left) and the photographer’s comments. A film processing log (Appendix 2.20.d) is maintained at the field center to track the local development of film prior to film mounting and mailing to the reading center. A shipping manifest is prepared by the field center for inclusion in each film shipment to the reading center.

2.23 Ultrasound

Ultrasound B-mode imaging of the carotid arteries is a core study measurement performed at each examination on all, or a sample of participants, to detect early changes in arterial walls. It represents a non-invasive, standardized measurement of thickening of the intima-media area of the arterial wall, a marker of atherosclerosis. The presence of atherosclerotic lesions is also recorded. These measurements in ARIC make it possible to study the natural history of atherosclerosis, factors associated with its distribution in populations and temporal progression, in addition to its clinical manifestations as is the case for traditional studies of overt clinical disease.
2.23.1  Rationale

Thickening of the arterial wall, attributable to atherosclerotic arterial disease, precedes significant stenosis and clinical manifestations of coronary heart disease. Its prevalence in the study population and its change over time represent a dependent variable for major study questions in ARIC. These ultrasonographic indices of atherosclerosis continue to be collected to test their ability to predict incident cardiovascular events in the ARIC cohort. During Visit 3, the B-mode ultrasound examination consists of imaging of the carotid arteries in the neck and monitoring of arterial blood pressure in the supine, seated and standing positions.

2.23.2  Procedures

Procedural and operational detail is provided in manuals 6-A (Ultrasound Scanning), 6-B (Ultrasound Reading).

2.23.3  Training

Central training for ARIC sonographers is provided by the Ultrasound Reading Center (URC), and described in Manual 6-A.

2.23.4  Certification

Certification of experienced sonographers is based on the ability to visualize arterial walls, consistent with the process average of all sonographers certified in Visits 1 and 2 and adherence to the scanning protocol. The process average for visualization is monitored using statistical process control techniques at the Ultrasound Reading Center. Certification remains in effect as long as visualization is consistent with the overall sonographer process average.

New sonographers read training materials, observe certified sonographers, attend a central sonographer training course at the URC and practice scanning volunteers at their local field centers. Practice scans are reviewed by chief sonographers at the field centers. When practice scans conform to protocol and are approximately equivalent to the study average, the trainee produces videotapes of scans of volunteers, of the same ages as cohort members, for review at the URC by certified readers. Certification is conferred when the trainee’s average number of paired points meet or exceed that of current certified sonographers.

Loss of certification occurs when a sonographer’s average monthly visualization falls significantly below the process average for one site, by a small amount for a number of sites, or the visualization reports reveal any trend toward a loss of visualization, or if the scans deviate from the ARIC protocol, or if the sonographer does not meet the minimum number of scans per month.

ARIC PROTOCOL 2. Cohort Component Procedures - Visit 3. VERSION 5.0 09/95
2.23.5 Quality Assurance

Quality assurance of the ultrasound scan is supported by annual retraining of chief sonographers, visits by URC experts to field centers, a preventive maintenance program of the ultrasound equipment, monitoring by the URC of equipment performance, repeat scanning of a randomly selected arterial segment for each participant, and monitoring of data at the URC and the Coordinating Center. The ultrasound system is monitored by scanning of tissue-equivalent phantoms on a schedule determined by the performance characteristics of the systems.

The URC monitors sonographer adherence to protocol, as well as the quality of arterial wall boundary images contributed by each sonographer. At the Coordinating Center periodic reports are prepared for the Quality Control Committee, to monitor the rate of success in the acquisition of data, comparability between repeated scans, by sonographer, by field center, and over time. Equivalent reports are prepared by the Coordinating Center to monitor ultrasound reader performance.

2.23.6 Data Collection

A microcomputer assists the sonographer during the standardized examination sequence and data collection. The B-Mode examination is recorded on 4 inch SVHS videotape and read at the URC; a back-up ½ inch tape remains at the field center. Data on blood pressures, beat-to-beat heart rate, and their timing are sent to the URC on diskette.

2.24 Venipuncture

Venipuncture, which strictly follows a standardized protocol at each field center, permits the measurement of associations of atherosclerotic manifestations and new coronary heart disease with clinical chemistries (glucose), plasma lipid, lipoprotein cholesterol, and plasma apolipoprotein levels and hemostatic factors which are known or suspected to be risk factors for coronary heart disease.

2.24.1 Rationale

The objective in ARIC continues to be having blood samples for various blood chemistries drawn and processed locally at each field center, but analyzed and reported by central laboratories. Because the venipuncture itself can affect study results, the need for strict interpretation of the standardized venipuncture methods outlined in manuals 7-9 is paramount.

2.24.2 Procedures

Venipuncture is performed in a fixed sequence in the participant flow, after anthropometry and sitting blood pressure measurements on all cohort members who have met fasting requirements (or who are medically unable or indicate an unwillingness to adhere to fasting). The venipuncture protocol is a separate document, Manual 7: Blood Collection and Processing. The Venipuncture form (Appendix 2.21.a) documents blood drawing and blood processing procedures. Question by question instructions for completing the form are located in
Appendix 2.21.b. A Venipuncture Incident Record (Appendix 2.21.c) is completed if one or more blood samples are not drawn, the tourniquet is reapplied, there is inappropriate fist clenching by the participant or there is needle movement during the procedure. Shipping problems, such as broken tubes, clotting, hemolysis, lipemia, etc., are also recorded on this form.

2.24.3 Training

Prior to the first cohort visit, phlebotomists were trained centrally. Subsequently, technicians performing venipuncture and processing blood samples have been trained and certified locally by the chief ARIC laboratory technician. Refer to Manual 7 for further details.

2.24.4 Certification

Recertification is required annually and is performed by the chief ARIC technician at the Central Hemostasis Laboratory or by trainer/certifiers from two of the ARIC field centers. Criteria are described in Manuals 7 and 12.

2.24.5 Quality Assurance

Data quality monitoring includes periodic review by the Quality Control Committee of (1) tube filling time, (2) number of venipuncture attempts, (3) condition of specimens on arrival at the central laboratories, and (4) selected markers of lack of adherence to protocol during phlebotomy and/or processing of specimens at the field center laboratory.

2.24.6 Data Collection

Venipuncture data are collected on a hard copy of the Venipuncture Form (see Appendix 2.3.g). Notes reflecting blood drawing or processing problems are recorded on the accompanying Venipuncture Incident Log which is forwarded as hard copy to the central laboratories and Coordinating Center.

2.25 Snack

A light snack is scheduled as soon as possible after venipuncture. Caffeine-free refreshments are provided, including decaffeinated coffee and tea. Menus are locally determined.

2.26 Data Inventory

The data inventory step initiates the second fixed component of the field center examination sequence, and is done after all interviews and examination procedures have been completed in preparation for the Medical Data Review. Participant data are collected by various means during the course of Visit 3 and require summarization and placement in the participant’s folder for nurse/clinician review.

2.26.1 Rationale

Although the ARIC study does not diagnose or treat any medical condition, the participant’s safety is of paramount concern. Therefore, data collected
during the examination that could indicate the need for emergent or immediate referral for medical care are put together into one document, the Medical Data Review Printout (Appendix 2.22), and reviewed with the participant prior to the completion of the examination. Data inventory is the data management process by which the Medical Data Review Printout is produced.

2.26.2 Procedures

A staff person reviews the participant's itinerary sheet and folder for completeness. After completeness of examination and quality control procedures have been confirmed, participants are invited to change back into street clothes while the data are being prepared for the medical data review. Medical data review may be conducted in street clothes.

2.26.3 Training

At each field center the Data Coordinator and/or the Study Coordinator is responsible for training the personnel charged with data inventory, and the assembly of study materials for the Medical Data Review.

2.26.4 Certification

Certification for data inventory is the responsibility of the field center Data Coordinator.

2.26.5 Quality Assurance

Quality assurance consists of observation by the supervisor and retraining or corrective action, as required.

2.26.6 Data Collection

Please refer to the Manual of Operations for Data Coordinators.

2.27 Medical Data Review

2.27.1 Rationale

Although it is made clear to all cohort participants and their providers of medical care that the interviews and clinical exams which they undergo are not a substitute for regular medical care, one of the benefits to participants is the summary of results distributed by the field center at the conclusion of, and also several weeks following the clinical exam. At the end of the field center visit, participant interview and examination data are reviewed by the nurse/clinician to provide the participant with a preliminary summary of study results: weight, blood pressure and preliminary ECG reports. (Please refer to the results reporting sheet, Appendix 2.23.a).

From the perspective of the investigators, the primary objective of the medical data review, is to safeguard participant safety. Clinical interview data are reviewed with the participants to confirm selected positive symptoms reported during the interviews/exams and to determine if these appear to warrant immediate or additional medical follow-up. When all laboratory data
reported by the central agencies (laboratories and reading centers) have been received, all data are again reviewed prior to producing summary reports for participants and their physicians. As part of this review, ARIC clinical personnel again may recommend follow-up if symptoms/conditions appear to warrant further medical attention.

At the field center, participant Visit 3 data are reviewed at three levels. The first is designated the Medical Data Review (see below, section 2.27.2), which is conducted by the nurse/clinician after all interviews and physical exams have been completed and all data have been assembled as part of the Data Inventory step (section 2.26). The second and third levels of medical data review are described in sections 2.29 (Physician Review) and 2.30 (Results Reporting), respectively.

2.27.2 Procedures

The nurse/clinician conducts the medical data review to (1) summarize the results of selected measurements obtained during the exams/interviews and to answer participant questions, (2) determine whether a reported stroke/TIA symptom(s) constitutes a possible cerebrovascular event(s), and (3) identify potential medical problems. Prior to meeting with the participant, the Annual Follow-up Form (to document reported positive Rose Angina symptoms), the interview note logs, ECG, blood pressure, TIA/Stroke form, weight, demographics, major medical problems on the Medical Data Review printout (Appendix 2.11) are examined.

During the Medical Data Review, the participant’s data are reviewed for positive findings during Visit 2 (i.e., alert values and referral letters), positive findings during any of the three Annual Follow-up interviews between Visit 2 and Visit 3 (such as positive Rose Angina, cardiac procedures or hospitalizations), or comments on the participant’s current itinerary form made by interviewers or technicians. A networked program within the ARIC data entry system is concurrently run on the participant’s data to generate a printout of selected items pertinent for the Medical Data Review, including:

1. Blood Pressure
   a. Historical data annotated on Itinerary Form and PIN;
   b. Abnormal values from previous exams on Alert/Referral Log;
   c. Current values on clinic visit report, prepared by DES;
   d. Use of antihypertensive medications;
   e. Physician diagnosis of hypertension reported by participant and date of most recent medical care.

2. Electrocardiogram
   a. Historical tracings filed in participant folders;
   b. Abnormal values from previous exams on Alert/Referral Log;
   c. Current tracing filed in participant’s folder;
   d. ECG interpretation printed on tracing (optional by field center);  
   e. Preliminary reading written on Clinic Visit Report.

ARIC PROTOCOL 2. Cohort Component Procedures - Visit 3. VERSION 5.0 09/95
3. Physician Diagnosed Medical Problems Reported by Participant
   a. Physician diagnosis of diabetes reported by participant;
   b. Physician diagnosis of high cholesterol reported by participant;
   c. Physician diagnosis of cancer reported by participant;

4. Participant Reported Medical Conditions Consistent with:
   a. Uterine bleeding not associated with normal menstruation or 
      hormone replacement therapy on Reproductive History form;
   b. Rose Questionnaire Angina on AFU or Health History forms;
   c. Possible congestive heart failure on Personal History form;
   d. Stroke/TIA reported on TIA/Stroke form;
   e. Intermittent claudication reported on AFU form.

5. Invasive Cardiovascular Procedures
   a. Coronary bypass or other heart procedures on Health History form;
   b. Carotid endarterectomy or other arterial revascularization on 
      Health History form;
   c. Balloon angioplasty at any site on Health History form.

6. Cardiac Diagnostic Procedures
   a. Echocardiogram on Health History form;
   b. ECG on Health History form;
   c. Treadmill or cardiac stress test on Health History form;
   d. Carotid artery ultrasound on Health History form;
   e. MRI of the brain on Health History form;
   f. CAT scan of the brain on Health History form.

7. Weight
   a. Historical data annotated on Itinerary Form and PIN;
   b. Current weight from Anthropometry form.
   c. Current height from Anthropometry form.

8. Demographics
   a. Date of birth and age from UPD form;
   b. Name/source of medical care from UPD form.

Responses I, 0, or D of item 4 (uterine bleeding) of the Female Reproductive 
History form are followed-up as part of the Medical Data Review. The 
participant’s response to item 4 is printed on the Medical Data printout; the 
back-up procedure in case of computer failure or incomplete data collection is 
to identify this item on the paper form for review during the Medical Data 
Review. When a referral takes place for this condition, it is identified on 
the Alert/Referral form under Other Conditions, Specify.

If the response to Item 4 is either I, O, or D, ask whether the participant 
has seen a physician for this. If the answer is no, a referral should take 
place. If the bleeding has occurred during the 6 months preceding the clinic 
visit, the participant is encouraged to see her physician within one month, as 
a consult for this bleeding. If the bleeding has not recurred in the six 
months preceding the clinic visit, the participant is encouraged to mention 
the uterine bleeding to her physician at the next convenient appointment.

When the letter to the physician reporting the participant’s study results is
prepared, it should include mention of uterine bleeding and the referral made at the time of the participant's clinic visit. If there is another condition that merits an urgent referral (to the same physician) at the time of the clinic visit, the bleeding should also be mentioned.

Access to data from previous examinations (Visits 1 and 2) by field center staff during Visit 3 is limited to two purposes: (1) to prepare the Visit 3 folder, and (2) to conduct the medical data review. Visit 1 and 2 data should not be accessed for other purposes during the course of the Visit 3 exam to avoid the possibility of biasing.

The data coordinator, or staff member designated by the study coordinator to prepare participant folders, should be the only person accessing Visit 1 or 2 information prior to the follow-up visit. During folder preparation, the chart is reviewed for any incidents and special participant needs that may have been recorded during previous visits, as well as factors that could affect participant and staff safety (infectious disease, syncopal episodes, etc.) The latter is the only Visit 1 or 2 information to be brought to the attention of the entire staff. It is to be noted on the Visit 3 Participant Itinerary Sheet or the PIN Sheet. The person performing the medical data review has access to all previous ARIC findings relevant to the medical review, immediately prior to discussing the participant’s clinic visit report (Appendix 2.23.a).

If during the course of the Visit 3 examination the participant asks about changes in laboratory values/clinical procedures since Visit 2, staff members defer the questions to the Medical Data Review. A prototype response by ARIC staff is: "I do not have access to the results from your previous exam, but if you hold your questions until the completion of your visit, Ms/Mr. will answer them." During the Medical Data Review, an attempt is made to address all questions that may arise. Care must be taken not to over-emphasize changes between visits, because some differences may be random variability or measurement error and in order not to 'intervene' on the cohort. Changes may be pointed out, but health education recommendations, are to be avoided unless contained in the referral guidelines.

Below are guidelines for Visit 3 recommendations.

1. Changes in anthropometrics should be focused on weight gained or lost. These are summarized in the participant results reports.

2. The blood pressure readings, based on the average of the second and third measurements, are discussed at the Medical Data Review according to the categories listed in Table 2.27.1.a and in the Clinic Visit Report. The referral guidelines published from the fifth report of the Joint National Committee (Table 2.27.1.b) are made for adults aged 18 and older. A caveat to this algorithm is provided by the Committee with the statement that "the scheduling of follow-up should be modified by reliable information about past blood pressure measurements, other cardiovascular risk factors, or target-organ disease" (The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med:153;154-183,1993). Because of the clinical judgment required to operationalize the referral guidelines
Table 2.27.1.a Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC V): Blood Pressure Classifications for Adults Aged 18 and Older, Not Taking Antihypertensive Drugs

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic (mm Hg)</th>
<th>Diastolic (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 130</td>
<td>&lt; 85</td>
</tr>
<tr>
<td>High normal</td>
<td>130-139</td>
<td>85-89</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1 (mild)</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2 (moderate)</td>
<td>160-179</td>
<td>100-109</td>
</tr>
<tr>
<td>Stage 3 (severe)</td>
<td>180-209</td>
<td>110-119</td>
</tr>
<tr>
<td>Stage 4 (very severe)</td>
<td>≥ 210</td>
<td>≥ 120</td>
</tr>
</tbody>
</table>

Table 2.27.1.b Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC V): Recommendations for Follow-Up

<table>
<thead>
<tr>
<th>Systolic Pressure (mm Hg)</th>
<th>Diastolic Pressure (mm Hg)</th>
<th>Explanations to Participants and Follow-up Recommendations¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 130</td>
<td>&lt; 85</td>
<td>Your blood pressure is normal²; recheck in 2 years (no ARIC referral)</td>
</tr>
<tr>
<td>130-139</td>
<td>85-89</td>
<td>Your blood pressure is high normal; recheck in 1 year (no ARIC referral)</td>
</tr>
<tr>
<td>140-159</td>
<td>90-99</td>
<td>Your blood pressure is elevated; confirm or refer to source of care within 2 months</td>
</tr>
<tr>
<td>160-179</td>
<td>100-109</td>
<td>Your blood pressure is elevated; evaluate or refer to source of care within 1 month</td>
</tr>
<tr>
<td>180-209</td>
<td>110-119</td>
<td>Your blood pressure is high; evaluate or refer to source of care within 1 week</td>
</tr>
<tr>
<td>≥ 210</td>
<td>≥ 120</td>
<td>Your blood pressure is very high; evaluate or refer to source of care immediately</td>
</tr>
</tbody>
</table>

¹ If the systolic and diastolic categories are different, follow recommendations for the shorter-time follow-up (eg, 160/85 mm Hg should be evaluated or referred to source of care within 1 month).
² If unusually low readings should be evaluated for clinical significance.

ARIC PROTOCOL 2. Cohort Component Procedures - Visit 3. VERSION 5.0 09/95
Figure 2.27.1 Report on Your Blood Pressure and Follow-up Recommendations
(Based on the Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure)

Name: ____________________________ Your blood pressure is: ___/___ mmHg

Please follow the recommendation panel highlighted for you. Health Care Provider: ____________________

Average systolic blood pressure (mmHg)

If on anti-hypertensives, see §

Average diastolic blood pressure

(in millimeters of mercury)

<85
85-89
90-99
100-109
110-119
120 or over

<130 130-139 140-159 160-179 180-209 210 or over

Recheck in 2 years
Recheck in 1 year
Refer within 2 months
Refer within 1 month
Refer within 1 week
Refer immediately

§If the participant is on anti-hypertensive treatment and blood pressures are in the range identified by the interrupted line, follow the schedule recommended by the participant's physician.

Appointment needed: Yes____ No____
Appointment Scheduled: _______ _______
Staff ID _________
Date _____/____/____
of individuals with a previous history of high blood pressure, other CVD risk factors, or target-organ disease, the ARIC referral guidelines (Figure 2.27.1), adapted from the fifth Joint National Committee recommendations, are followed for all participants, unless the study physician recommends otherwise.

3. Action on ECG findings depends on the severity of the findings. The previously unrecognized appearances of a major abnormality warrants consultation with the ARIC medical staff and possible referral. In contrast, a previously referred ECG abnormality that demonstrates no change in Visit 3 in an asymptomatic participant does not warrant repeat referral.

4. It is unlikely that participants will ask about changes in other factors. However, these should also be considered in the context of measurement variability before labelling them real changes.

During the Medical Data Review, selected affirmative answers to the standardized questions in the interviews and exams are confirmed through additional, non-standardized, clinically-oriented questions. The participant's responses to selected items of the various questionnaires administered during the field center examination are printed on the Medical Data printout for ease of review by the clinician performing the Medical Data Review. This printout is a compilation of participant responses with potential medical care impact or participant safety implications. The back-up procedure in case of computer failure or incomplete data collection is to identify such items on the paper form for review during the Medical Data Review. Referral guidelines and alert values are listed in Section 2.28.

The TIA/Stroke Worksheet is completed when participants have reported positive symptoms on the TIA/Stroke form to document (1) the presence of noncerebrovascular causes for an event(s), (2) the impression of a TIA or stroke, and (3) the most recent date of a putative event. Should this event(s) be attributable to cerebrovascular symptoms within the last six months, the field center medical director is consulted for recommendations on referral for medical care.

In summary, factual information (the First Participant Report, Appendix 2.24.c) is given to participants about their results during the Medical Data Review, identifying any abnormalities and recommending referral as needed, but avoiding medical advice about prognosis, prevention or therapy. Physician back-up is available at all times.

2.27.3 Training

Nurse/clinicians are trained by the ARIC medical director and/or field center principal investigator. The medical director of one of the field centers serves as the central trainer.

2.27.4 Certification

The central trainer is responsible for certification of the physician assistants, and nurse practitioners/clinicians responsible for medical data
review. This certification is obtained after review of procedures with the
central trainer; it is acceptable to do this over the telephone.

2.27.5 Quality Assurance

It is the responsibility of the medical director of each ARIC field center to
ensure that the medical data review, referrals and reporting of results are
done according to the procedures in the ARIC protocol.

2.27.6 Data Collection

The study data generated during the Medical Data Review include confirmation
of positive symptoms identified on the TIA/Stroke Form, and occasionally
critically important notes. These data are stored as hard copy in the
participant’s folder, and referrals are coded on the Report and Referral Form.

2.28 Referrals and Review Guidelines

2.28.1 Rationale

Participants are referred based on the guidelines for referral listed below.
For participant safety, the nurse/clinician is alerted prior to the Medical
Data Review that the participant has provided affirmative responses to key
items indicative of hypertension, diabetes, ischemic heart disease,
hypercholesterolemia, cancer, uterine bleeding, chest pain on effort,
congestive heart failure, TIA/stroke, and intermittent claudication.
Guidelines for the staff conducting the medical data review are provided in
the Medical Data Review instructions. Referrals for initial care, as well as
follow-up care, can be made at the Medical Data Review or in subsequent
communications. Uniform criteria for emergency, immediate, urgent and routine
referrals have been established for use at all ARIC field centers. Sources of
medical care for participants who do not have a physician are identified by
each field center in consultation with the representatives of the local
medical community. All referrals are documented on a separate Report/Referral
Form and the ARIC Alert/Referral Log, Appendices 2.23.a and 2.23.b,
respectively.

2.28.2 Procedures

Referrals made during the Medical Data Review follow the criteria listed
below.

1. Emergency Referral. Transportation to the nearest emergency care
facility is provided or an emergency squad is called.

2. Immediate Referral. The participant is urged to see his/her physician
within one day.

The nurse/clinician consults with the ARIC physician, and the
participant’s physician is called. The participant’s physician is sent
a letter of explanation (Appendix 2.25, REFMD.a)
3. **Urgent Referral.** The participant is asked to see his/her physician within one week.

The nurse/clinician confirms the decision with the ARIC physician, and explains the reason(s) for an urgent referral to the participant. The ARIC physician calls the participant’s provider of care, and sends a referral letter. (Appendix 2.25, REFMD.a)

4. **Routine Referral.** The participant is asked to see his/her physician within one month, or at the first convenient appointment.

The nurse/clinician advises a visit to the participant’s physician. A referral letter is sent to the participant’s physician. Referral letters are sent to participants and their providers of medical care (Appendices 2.26-2.29).

5. **No Referral.** The study results are summarized for the participant and held for a routine results letter. Letters indicating no abnormal findings are sent to participants and their physicians (Appendices 2.26-2.28)

Procedure/symptom specific guidelines are summarized in Table 2.28.1. Certain interview items or measurements (identified with an asterisk) require confirmation. Referral guidelines for blood pressure differ based on a prior history of an elevated blood pressure during the second examination. The reviewer determines the acuteness of the findings, and whether or not the condition is being monitored by the participant’s physician. If the participant is aware of and being followed medically for a condition, judgement is exercised about whether to refer, and the degree of urgency. The types of participant and physician referral and normal results letters used for each of the five referral categories are summarized in Table 2.30.2; examples of the texts of these letters are provided in Appendices 2.25-2.28.
### Table 2.28.1 Medical Care Referral Guidelines.

<table>
<thead>
<tr>
<th>Referral Classification</th>
<th>Examination Findings</th>
<th>Recommendation to Participant</th>
<th>Explanation to Participant</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMMEDIATE REFERRAL</td>
<td>*SBP ≥ 210 mm Hg or DBP ≥ 120 mm Hg</td>
<td>See M.D. today.</td>
<td>BP very high.</td>
</tr>
<tr>
<td></td>
<td>*Unstable angina</td>
<td>&quot;</td>
<td>Your chest pains may be important</td>
</tr>
<tr>
<td></td>
<td>*Neurologic symptoms in past week</td>
<td>&quot;</td>
<td>Your symptoms may be important.</td>
</tr>
<tr>
<td></td>
<td>*Other severe symptoms or findings</td>
<td>&quot;</td>
<td>Your symptoms may be important.</td>
</tr>
<tr>
<td>URGENT REFERRAL</td>
<td>*Angina, stable but untreated/not being followed</td>
<td>See M.D. within a week.</td>
<td>Your chest pains may be important</td>
</tr>
<tr>
<td></td>
<td>*Neurologic symptoms, untreated, one week to six months ago</td>
<td>&quot;</td>
<td>Your symptoms may be important.</td>
</tr>
<tr>
<td></td>
<td>*Acute congestive heart failure</td>
<td>&quot;</td>
<td>Your symptoms may be important.</td>
</tr>
<tr>
<td></td>
<td>*Other acute, but less severe symptoms</td>
<td>&quot;</td>
<td>Your symptoms may be important.</td>
</tr>
<tr>
<td></td>
<td>*SBP ≥ 180-209 mm Hg or DBP ≥ 110-119 mm Hg</td>
<td>&quot;</td>
<td>BP high.</td>
</tr>
</tbody>
</table>

* Interview items or measurements require confirmation during Medical Data Review
Table 2.28.1 Medical Care Referral Guidelines, continued

<table>
<thead>
<tr>
<th>Referral Classification</th>
<th>Examination Findings</th>
<th>Recommendation to Participant</th>
<th>Explanation to Participant</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROUTINE REFERRAL</td>
<td>*Old MI (Rose Questionnaire), previously unrecognized</td>
<td>See M.D. within month or at first convenient appointment.</td>
<td>Your chest pain may be important.</td>
</tr>
<tr>
<td></td>
<td>*Neurologic problem (stroke, TIA exam findings) &gt;6 months ago, unrecognized</td>
<td></td>
<td>Your symptoms may be important.</td>
</tr>
<tr>
<td></td>
<td>*Claudication, previously unrecognized</td>
<td></td>
<td>Your leg pain may be important.</td>
</tr>
<tr>
<td></td>
<td>*Other symptoms or findings needing evaluation/not being followed</td>
<td></td>
<td>Your symptoms may be important.</td>
</tr>
<tr>
<td></td>
<td>*Uterine bleeding; response I,O,D on Reproductive Hx form.</td>
<td></td>
<td>Your symptoms may be important.</td>
</tr>
<tr>
<td></td>
<td>*SBP 160-179 mm Hg or DBP 100-109 mm Hg</td>
<td>See MD within one month.</td>
<td>BP elevated.</td>
</tr>
<tr>
<td></td>
<td>*SBP 140-159 mm Hg or DBP 90-99 mm Hg</td>
<td>See MD within two months.</td>
<td>BP elevated.</td>
</tr>
<tr>
<td>NO REFERRAL</td>
<td>*Angina, stable on treatment/being followed</td>
<td>None.</td>
<td>Confirm only.</td>
</tr>
<tr>
<td></td>
<td>*MI, previously documented</td>
<td>None.</td>
<td>Confirm only.</td>
</tr>
<tr>
<td></td>
<td>*SBP 130-139 mm Hg or DBP 85-89 mm Hg</td>
<td>Recheck in 1 year</td>
<td>Your reading is high normal.</td>
</tr>
<tr>
<td></td>
<td>*SBP ≤ 140 mm Hg and DBP ≤ 90 mm Hg</td>
<td>Recheck in 2 years</td>
<td>Your reading was normal.</td>
</tr>
<tr>
<td></td>
<td>Height, weight</td>
<td>None.</td>
<td>Report only.</td>
</tr>
</tbody>
</table>

* Interview items or measurements require confirmation during Medical Data Review
Table 2.28.1 Medical Care Referral Guidelines, continued

<table>
<thead>
<tr>
<th>Referral Classification</th>
<th>Examination Findings</th>
<th>Recommendation to Participant</th>
<th>Explanation to Participant</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG Findings</td>
<td>Acute pattern</td>
<td>Would like to review with M.D.</td>
<td></td>
</tr>
<tr>
<td>Requiring abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review by M.D.</td>
<td>MI, ischemia...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before Participant leaves Field Center.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any other ECG finding, alone or in conjunction with symptoms, causing concern.*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other ECG Findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or Normal ECG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinal photos</td>
<td>Acute abnormalities.#</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormalities requiring routine referral.+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal results.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral MRI</td>
<td>Acute pattern abnor- malities. @</td>
<td>Would like to review with MD.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minor chronic findings.%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 2nd or 3rd degree block, ventricular tachycardia, R on T, atrial fibr/flutter with ventricular rate < 60 or > 110, sinus bradycardia < 50, sinus tachycardia > 110, PR interval > 0.26 sec.
# Immediate/urgent referrals: Vascular occlusions; malignant hypertension; papillary swelling; high risk diabetic retinopathy; central macular edema; retinal detachment; advanced maculopathy; active chorioretinitis; possible melanoma/tumor.
+ Routine evaluations: Mild to moderate diabetic retinopathy; questionable diabetic retinopathy; glaucoma.
@ Urgent referral: Tumor without significant mass effect; AVM, aneurysm, obstructive hydrocephalus; cavernous angioma, venous angioma. Immediate referral: Acute subdural, epidural, intraparenchymal hematoma; subarachnoid hemorrhage; acute or subacute infarct; hydrocephalus.
% Old infarct greater than 5mm or old hematoma.
2.29  Physician Reviews

2.29.1  General Policies

The second level of medical data review is a review of the participant's data within one week of the visit by the field center medical staff. This procedure includes the information initially reviewed by the nurse/clinician at the Medical Data Review; optional hematology results received from local laboratories; clinical chemistry, hemostasis or lipid alert values reported by telephone or electronic mail from one or more of the central laboratories; and ultrasound alert values if the URC ultrasound clinician has reported a finding meeting the criteria of an alert criteria.

This general medical review provides a medical staff interpretation of the study results and an overview of referrals and reports from the field center.

2.29.2  Procedures

The physician review is an ongoing activity at the field center. Once a week a physician reviews the data of participants seen in the preceding week. After examination of the participant's medical data review printout and ECG, the physician records the interpretation on the Medical Data Review printout and reviews the preliminary interpretation by the nurse/clinician. The physician also confirms the optional hematology results for alert values, and assumes responsibility for any referrals. Any referrals made during Medical Data Review are reviewed.

2.30  Results Reporting

2.30.1  Rationale

This activity concludes a process which extends over 4 to 12 weeks after the participant completes Visit 3. When all study results are received from the central laboratories, reading centers, and the Coordinating Center, they are summarized for final disposition by field center medical staff. Final summaries of study results are compiled, according to the criteria in section 2.30.6, and mailed to participants and physicians.

As alert values (see Section 2.27.2) are returned from the central laboratories and reading centers, the medical staff reviews them and assumes responsibility for referrals (see Table 2.30.1). Routine results may bypass physician review until the final report is generated. The ARIC physician or clinic director reviews all letters and reports sent to participants and their physicians.
<table>
<thead>
<tr>
<th>Test</th>
<th>Alert Value</th>
<th>Reference Range ARIC Laboratory*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL CHOLESTEROL (mg/dL)</td>
<td>--</td>
<td>&lt; 200 Desirable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200-239 Mildly elevated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 240 Markedly elevated</td>
</tr>
<tr>
<td>LDL CHOLESTEROL (mg/dL)</td>
<td>--</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>HDL CHOLESTEROL (mg/dL)</td>
<td>--</td>
<td>&gt; 35</td>
</tr>
<tr>
<td>TRIGLYCERIDES (mg/dL)</td>
<td>&gt; 1,000</td>
<td>&lt; 220</td>
</tr>
<tr>
<td>GLUCOSE (mg/dL)</td>
<td>&lt;60, &gt;200</td>
<td>70 - 130</td>
</tr>
</tbody>
</table>

* Laboratory notifies field center; field center MD takes referral or notification action.
** Reference ranges are provided on ARIC reports to participant and their physician.

Reporting of Visit 3 values is made in the context of Visit 2 results. Specifically, all alert values, such as those in Table 2.27.1, are reported. However, if an abnormal result is noted to be similar or identical to one that resulted in a referral at Visit 2 (an electrocardiogram for example), a repeat referral in Visit 3 is not automatic and is only initiated at the discretion of the medical director. A copy of the abnormal study result, however, is included in the summary of results sent to the participant and his/her medical care provider.

With participant approval, results of all the standard medical tests (normal and abnormal) are reported to the participant’s physician. Standard medical tests are differentiated from those with strictly research value as being of empirical value for diagnosis and/or treatment. Whenever the therapeutic implications of results are not known, a statement to that effect is included in the report to the physician. Copies of all reports and letters concerning examination results sent to participants and physicians are kept on file at each field center.

All reports to participants or physicians are factual. If verification or follow-up is needed, the participant is advised to discuss the results with the provider of medical care. ARIC study personnel provide no specific medical advice or interpretation of results. This type of medical practice is felt to be the prerogative and responsibility of the participant’s physician. Consistent with this policy, clear instructions are given to all ARIC staff to avoid interpreting study results. Even though ARIC is an observational study, the recommendation to participants for additional tests and procedures to be performed by participant’s physician as a result of ARIC reporting is considered an acceptable and necessary consequence of study participation.
2.30.2 Overview of Results Reporting

Figures 2.30.1 and 2.30.2 (Summaries of Review of Results, Reporting, and Referral) provide an overview of this process and illustrate the interface between the review of medical data, the referral process, and the notification of study results. The figures also illustrate that certain results are reported on a routine basis, whereas potentially abnormal study results are reported to participants and their physicians on an expedited basis.

The reports to the participant and/or the physician provide a minimum, standard set of study results. Reports to participants include a statement indicating either that all study results are within ranges considered normal, or that a study result requires confirmation or further investigation. Normal ranges and brief explanatory statements are provided. Physicians receive a letter of explanation (Table 2.30.2 and Appendices 2.25-.29) and a copy of the participant's results report, and are thus aware of any results flagged as being outside of the ARIC reference range, and the wording and explanations provided to their patients.

1. At reception, the participant is given the document Schedule of ARIC Results Reporting (Appendix 2.24.c), describing the tests to be reported to the participant and the physician, and their timing.

2. At Medical Data Review, a Participant Medical Data Review Printout is generated summarizing findings for the Medical Data Review. Items flagged for review are automatically retrieved from the data base and printed on this form. The nurse/clinician conducts the Medical Data Review with the participant, as described in section 2.27. A preprinted Summary of Visit 3 Report (Appendix 2.24.a) is given to the participant to summarize exam results.

3. At the Medical Data Review, a referral may be necessary. Three levels of referral are designated: Immediate, Urgent, Routine, and the corresponding referral letters are sent to the participant's physician (Appendix 2.25.a). In some cases, a phone call may be indicated.

4. Once a week, a physician review occurs during which the ARIC physician reviews participant data and interprets ECG tracings, as described in section 2.29.2. If an abnormality is detected at this time, a report or referral letter is sent to the participant and his/her physician (Appendix 2.26-2.28).

5. Subsequent to the exam, results are received from the central laboratories and reading centers as described below. If there are "alert values", the participant is notified using a Alert Value Referral Letter (Appendix 2.26.e and f) and the medical care provider is notified (Appendix 2.26.b and c). If there are no "alert values", the results are entered in the database for final Results Letters.

6. A record is kept of all alert values and referrals on the Alert/Referral Log (Appendix 2.23.b) and a copy of all referral letters is filed in each participant's folder.
7. When all results are available, the Summary Report to the Participant and Physician and accompanying cover letters are generated. The types of cover letters are summarized in Table 2.30.2.

8. The field center director or a field center physician reviews all results and takes responsibility for letters before they are mailed. If the ARIC participant is also a participant in another medical research project, possible unblinding by reporting ARIC results is considered.
ARIC Referral/Notification Procedures

Blood Pressure
Electrocardiogram

Field Center (Nurse / PA)
Select Type of Report

Alert | Routine

MD Review / Sign

Alert Letter | Routine Report

Participant MD | Participant MD

Lipids
Glucose

Central Lab

Alert | Routine

Field Center Nurse / PA / MD

Alert Letter | Routine Report

Participant MD | Participant MD

Ultrasound

Field Center Sonographer

Suspicious | Routine

Clinical Evaluation at URC

Alert Cutpoint

Field Center MD

Alert Letter to MD | Routine Report

Participant MD

Figure 2.30.1 ARIC Referral/Notification Procedures

ARIC PROTOCOL 2. Cohort Component Procedures - Visit 3. VERSION 5.0 09/95
ARIC Referral/Notification Procedures

Retinal Photography

Field Center

Retinal Photography Reading Center

Alert Routine

Field Center MD Coordinating Center

Referral Letter to MD

Cerebral MRI

Clinical MRI Center

Suspicious Routine

Local Clinical Reading MRI Reading Center

Alert Routine

Field Center MD

Referral Letter to MD Coordinating Center

Figure 2.30.2 ARIC Referral/Notification Procedures
Table 2.30.2  Cover Letters for the Reports to Participants and Physicians

<table>
<thead>
<tr>
<th>RECIPIENT</th>
<th>TYPE OF RESULTS LETTERS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>REFERRAL LETTERS FOR ALERT VALUES</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Physician</strong></td>
<td>REFMD.a) referral at clinic visit</td>
</tr>
<tr>
<td></td>
<td>b) referral post clinic visit</td>
</tr>
<tr>
<td><strong>Participant</strong></td>
<td>REFPPT.a) referral at clinic visit (N/A)</td>
</tr>
<tr>
<td></td>
<td>b) referral post clinic visit (with MD)</td>
</tr>
<tr>
<td></td>
<td>c) referral post clinic visit (no MD)</td>
</tr>
</tbody>
</table>

| **COVER LETTERS FOR SUMMARY VISIT 3 RESULTS REPORT** |
| **Physician** | V3MD.a) Normal results |
| | b) Abnormal results, no previous referral made |
| | c) Abnormal results, previous referral made |
| **Participant** | V3PPT.a) Normal results |
| | b) Abnormal results, no previous referral made |
| | c) Abnormal results, previous referral made |
| | d) Normal results, no MD designated |
| | e) Abnormal results, no MD designated |

| **INSURANC.LTR** Study results sent to third party |

| **COVER LETTERS REPORTING RESULTS FOR MRI** |
| **Physician** | MRIMD.a) Normal results |
| | b) Minor abnormal findings, no referral indicated |
| | c) Abnormal results |
| | d) Abnormal results, participant not informed |
| **Participant** | MRIPPT.a) Normal results |
| | b) Minor abnormal findings, no referral indicated |
| | c) Abnormal results, referral recommended |
| | d) Normal or abnormal results, no MD designated |

| **COVER LETTERS REPORTING RESULTS FOR RETINAL PHOTOGRAPHY** |
| **Physician** | RETINMD.a) Abnormal results |
| **Participant** | RETINPPT.a) Abnormal results, referral recommended |
| | Abnormal results, no MD designated |

| **COVER LETTERS REPORTING RESULTS FOR ULTRASOUND** |
| **Physician** | USMD.a) Abnormal results |
| **Participant** | USPPT.a) Abnormal results, referral recommended |
| | Abnormal results, no MD designated |

**ARIC PROTOCOL 2. Cohort Component Procedures - Visit 3. VERSION 5.0 09/95**
The ARIC ultrasound examination is oriented toward the detection of early atherosclerotic changes in the arterial wall and does not provide clinical documentation of the extent of lesions which might be of medical importance. Portions of the internal carotid artery, which may have disease, are not visualized at all. Some of the early arterial changes documented for ARIC (changes in arterial distensibility, for example, or non-lumen encroaching wall thickness) are not, at present, of known medical value and are of research interest only. Such results are not routinely reported to the participant and his/her physician. In the process of obtaining consent, the participant is informed of this fact. Neither the ARIC ultrasound examination protocol, nor the training of the ARIC sonographers, provide an adequate capability to detect clinically significant arterial lesions in the study participants. If in the course of the highly standardized ultrasound scanning procedures a lesion(s) is found of potential clinical importance, the ARIC sonographer sends the study to the URC for expedited review by an expert neurologist. If a minimum residual lumen of 2 mm or less is present, and/or if in the opinion of the neurologist an ultrasound scan according to a clinical protocol is indicated, this is communicated to the field center as an alert value. If during the reading process at the Ultrasound Reading Center an arterial wall thickness of 2 mm or more is found, the study is forwarded to the neurologist for evaluation. Field centers then contact the study participant and their provider of medical care by phone and by a letter signed by the medical director (Appendix 2.29.a-c). If in the course of routine readings a minimal residual carotid artery lumen of 2 mm or less or an arterial wall thickness of 2 mm or greater is detected, this is also reported to the field center. Records of this notification are kept at the Reading Center and the field center. The Ultrasound Reading Center's clinical expert reviews all studies identified in this manner, suspected to contain an alert value.

The medical and ultrasound experts of the ARIC Study agree that the alert value cutpoints criteria are consistent with local medical practice for each of the ARIC study communities. It is an explicit requirement of the participant safety criteria of the ARIC Study that this section of the protocol be reviewed periodically, and modified as needed according to advances in the state of the science and evolving medical practice.

The Retinal Reading Center sends notification of retinal abnormalities to each field center for participants with conditions where referral to an ophthalmologist or other pertinent provider of medical care may be advisable. A letter is prepared both for conditions where prompt referral to a clinician is suggested and for conditions where routine evaluation by an ophthalmologist may be advisable (Appendix 2.28.a-c). The immediate referral alerts are sent to the field center via FAX with a follow-up phone call to ensure that the alert was received. The notifications for routine evaluation are also sent via FAX, but the follow-up phone call is not required. In both cases, the original report is mailed to the field center secondary to the FAX.
20.30.4.1 Retinal alert notifications

Retinal alert notifications for referral to an ophthalmologist or other provider of medical care are sent for the conditions listed below.

1. Recent, fresh vascular occlusions, including both arteriolar and venous.

2. Signs suggestive of malignant hypertension, such as extensive flame-shaped retinal hemorrhages, with soft and/or hard exudates. The alert for these findings includes a disclaimer that the lesions could reflect hypertensive retinopathy, diabetic retinopathy, or some other disease process.

3. Severe papillary swelling accompanied by retinal hemorrhage and/or exudates.

4. Presumed diabetic retinopathy with an overall retinopathy level characterized as:
   a. High risk characteristics (retinal levels 71, 75, 81 or 85);
   b. Proliferative retinopathy (levels 61 and 65); or
   c. Severe non-proliferative retinopathy (level 53).

5. Macular edema threatening or involving the center, as inferred from hard exudates, hard exudate rings or changes in retinal transparency.

6. Retinal detachment.

7. Advanced maculopathy characterized by evidence of subretinal neovascularization.

8. Active chorioretinitis.

9. Possible melanoma or choroidal tumor.

Possible alert conditions observed by the grader are confirmed by an ophthalmologist (the Reading Center director) prior to initiating alert notification procedures. The grader also initiates alert procedures if a condition not listed above is of medical concern and the consulting ophthalmologist concurs. The Reading Center director suggests an appropriate time to referral, either immediate or urgent within a stated time frame, for inclusion in the alert notification. Retinal alerts are completed at the time the photos are read or, if time is needed for consultation, within two working days.

20.30.4.2 Retinal abnormality notifications

Retinal abnormality notifications advising routine evaluation by a clinician are sent for the following conditions:
1. Presumed diabetic retinopathy characterized as early, mild to moderate, background retinopathy (retinal levels 20, 31, 43 and 47). The letter includes a disclaimer that the lesions could be due to diabetes, hypertension, or some other disease process.

2. Questionable diabetic retinopathy, characterized by diabetic lesions without microaneurysms (retinal levels 14 and 15). The letter includes a disclaimer that the lesions could be due to diabetes, hypertension, or some other disease process.

3. Signs suggestive of glaucoma, such as hemorrhage on the disc or crossing the disc margin, or a cup to disc ratio greater than or equal to .7, accompanied by disc pallor, notching of the rim or undercutting of retinal vessels at the edge of the cup.

These notifications recommending routine evaluations are either sent at the time the photo is read or deferred for up to seven working days until a larger group of photos are read.

20.30.4.3 Retinal notification status: batch reports to the field centers

The Retinal Reading Center provides each field center with a cover letter and a batch report on the retinal notification status of all participants concurrent with its routine transmission of data to the ARIC Coordinating Center (See Manual 13). The batch report contains the following retinal notification status codes and the date of the FAX notification letter (if applicable), which were entered in the grading database at the Retinal Reading Center from the grading form.

0 = no retinal notification
2 = retinal notification sent, and
8 = cannot grade for retinal notification conditions.

The report first lists all participants who had no abnormalities prompting either an alert for referral or routine evaluation, followed by participants who previously received a retinal notification letter, and ending with those whose photographs could not be read due to technical problems. The cover letter provides explanations on the photographic problem(s) or other items of special interest in the report.

2.30.5 Report of Cerebral MRI Measurements

Study participants with certain MRI scan abnormalities may require further medical attention. ARIC does not assume responsibility for diagnosis and management of its participants, but has assumed an obligation to refer such individuals to their local source of medical care. Alert conditions requiring urgent or immediate referral (see Section 2.30.5.1) can be identified either at the imaging center or the MRI reading center.

The MRI technologist at the local MRI Center reviews each study for the presence of any condition identified as an emergent alert. When found, the
ARIC neuroradiologist is notified, and the occurrence recorded on the MRI Procedure Form. After review of the potential urgent or immediate alert by the MRI Center neuroradiologist, a brief report is prepared within 24 hours, the field center is notified, and the notification process is recorded on the MRI Procedure Form. The field center is responsible for contacting the participant.

When a condition identified as an emergent alert (i.e., requiring immediate or urgent referral) is noted at the MRI Reading Center, the alert status is recorded on the participant’s result file. If the alert has previously been identified at the local MRI Center, no further action is taken by the MRI Reading Center. If the MRI Procedure Form does not identify an alert, or refers to an alert condition different from that detected at the MRI Reading Center, the Reading Center physician prepares a brief report which is included with the participant’s file, the Reading Center sends the MRI results data file to the field center by electronic mail or FAX, and a hard copy of the MRI scan film to the field center by overnight delivery.

2.30.5.1 MRI scan alert notifications

MRI scan abnormalities which require urgent referral for possible further medical attention are defined as

1. tumor without significant mass effect, AVM, aneurysm, obstructive hydrocephalus;

2. cavernous angioma, venous angioma.

Those requiring immediate referral are:

1. acute subdural or epidural hematoma, subarachnoid hemorrhage, acute intraparenchymal hematoma, acute infarct, subacute infarct, obstructive hydrocephalus (less severe than those requiring urgent referral), cerebral venous thrombosis, abscess and suspected tumor with significant mass effect.

Conditions not listed which require referral in the opinion of an MRI technologist are triaged and reported accordingly, per the judgement of the field center or MRI center neuroradiologist. Doubtful cases are triaged to the more severe category.

2.30.5.2 MRI scan routine notifications

MRI scan abnormalities classified as old infarcts, old hematomas, and exceptionally, other chronic abnormalities result in letters to participants indicating that there were minor chronic findings ‘which are often seen on MRI’ for which referral to a physician is optional. Corresponding letters to physicians indicate that an old infarct greater than 5 mm or an old hematoma was visualized, but the clinical significance of these findings is not known. When there are no clinically significant findings, this is indicated in a letter to the participant.
2.30.6 Routine Notification of Study Results

Results of routine medical examinations, normal or abnormal, are reported to the participant and his/her physician, unless the participant has not identified a personal physician or has specifically asked to receive all study results. (Refer to Appendix 2.26-2.29 for prototype letters.) This is explained to the participant during the visit to the ARIC field center, and the participant is provided a schedule for results reporting (see Appendix 2.24.c).

2.30.6.1 Results routinely reported to the participant

Results reported to the participant during the clinic visit (ARIC CLINIC VISIT 3 REPORT, Appendix 2.24.a) include current weight and weight at the previous examinations, current height and height at Visit 1, current blood pressure and blood pressure measurements from the previous two examinations, a statement that the ECG tracing will be read for inclusion in the summary report, and a statement that only abnormalities on the carotid artery scan will be reported.

Within two months after Visit 3, the following report (SUMMARY OF ARIC VISIT 3 RESULTS FOR PARTICIPANTS AND THEIR PHYSICIANS, Appendix 2.24.b) is mailed to the participant. This report includes the following confirmed study results from Visit 3: weight and height; blood pressure; summary report of electrocardiogram; summary report of echocardiogram (Jackson participants); summary report of the retinal photograph of one eye; summary report on the cerebral MRI (Forsyth County and Jackson participants); and blood tests (total cholesterol, LDL cholesterol, total HDL cholesterol, triglycerides, and glucose).

2.30.6.2 Results routinely reported to the physician

Participants' physicians receive a copy of the reports sent to their patients, as indicated in Section 2.30.2. In addition, physicians are notified of any important symptoms reported by the participant and they are provided with the participant's electrocardiogram.

2.30.7 Results Reported Only by Request

All other study measurements, i.e., those not routinely reported to the participants and/or their physicians, are considered to be of research value only. If a participant requests them, these values are provided on an ad hoc basis.

On the rare occasion that a field center receives a request for a participant's study results from a third party medical care payor, a results report can be released according to the following steps.

1. A signed statement of release must accompany the request from the participant and is kept in the participant's folder.

2. The report contains only the information that was released to the participant's physician (or the participant), i.e., an exact copy of the cover letter, the results report and the ECG tracing.

ARIC PROTOCOL 2. Cohort Component Procedures - Visit 3. VERSION 5.0  09/95
3. This information is sent with a cover letter (Appendix 2.26.1) from the field center's medical director stating that the ARIC study does not provide diagnostic services or treatment.

4. The information is sent directly to the third party with an exact copy to the study participant, indicating the date on which the information was sent.

2.30.8 Study Results Requiring Special Notification

The ARIC protocol identifies certain potentially abnormal findings that require expedited notification to the participant or his/her physician. These include flagged responses to the medical history questionnaire. These items, and the corresponding referral and notification criteria, are described in section 2.27. Similarly, "alert value" levels have been defined for the functional tests and laboratory measurements.

Laboratory and ultrasound results are not available at the time of the clinic visit. Local (and optional) hematology results are reviewed at the Field Center for alert values within several days of the clinic examination. Notification in response to an alert value in hematology results occurs after review of the participant's record. The central laboratory, the Ultrasound Reading Center, the MRI Reading Center, and the Fundus Photograph Reading Center notify field centers directly of "alert values". Notification of alert values to field centers is by telephone, electronic mail or FAX; confirmation and acknowledgment is required. The laboratory alert values are in Table 2.30.1.

2.31 Participant Safety

The safety and welfare of the ARIC participants is protected by (1) specific measures taken in the design or conduct of the examination for their safety, (2) the mechanisms established for handling potential emergencies, (3) routine notification of participants and their physicians regarding the results of the examination and (4) the procedures ARIC staff use to review all potentially medically important results and make the appropriate referrals.

An important factor in participant welfare involves their expectations regarding the examination. If they believe the ARIC examination is a substitute for a clinical examination, delay in seeking needed medical care could occur. Therefore, the provision of adequate information is a requisite to the ARIC informed consent procedures (described in section 2.3.1).

2.31.1 Measures to Protect the Participant

Examination procedures which convey potential risk to participants include the fasting requirement, venipuncture, and measurement of postural changes in blood pressure. Methods by which participant risk is minimized (more fully described elsewhere in ARIC Manuals) include the following.

The possibility of hypoglycemia with a 12-hour fast is diminished by routine inquiry about reasons which should exempt the participant from fasting during the scheduling of Visit 3. Other medical conditions or dietary restrictions
which may be incompatible with the snack provided in the clinic are also ascertained.

Hematomas or prolonged bleeding may result from venipuncture. These are usually avoided if well-trained technicians follow the procedures for blood drawing and take the precautions described in ARIC Manual 7. Prior to venipuncture, the participant is asked the question "Do you have any bleeding disorders?" If the participant answers affirmatively or is uncertain, he/she is asked about whether he/she has had blood drawn previously and if so, whether there were any problems such as swelling or continuing to bleed at the venipuncture site. If the answer to this question is "yes", the clinic supervisor is summoned to approve the venipuncture. Occasionally, with any participant, bleeding persists after venipuncture. Procedures described in Manual 7 are followed. If the measures taken have not stopped all bleeding within 30 minutes, and there is no obvious explanation for the prolonged bleeding, a medical referral is made. Also, the participant is instructed to seek medical care promptly if bleeding recurs after leaving the ARIC clinic. Participants may experience syncope during the venipuncture. Methods for handling minor and major emergencies are described in section 2.31.2.

The ARIC ultrasound exam involves no more ultrasound exposure than is usually the case when examining superficial arteries clinically. See ARIC Manual 6 for details. The American Institute for Ultrasound in Medicine has issued the following statement concerning the safety of ultrasound.

Safety Statement for Training and Research

Diagnostic ultrasound has been in use for over 25 years. No confirmed adverse biological effects on patients resulting from this usage have ever been reported. Although no hazard has been identified that would preclude the prudent and conservative use of diagnostic ultrasound in education and research, experience from normal diagnostic practice may or may not be relevant to extended exposure times and altered exposure conditions. It is therefore considered appropriate to make the following recommendations:

In those special situations in which examinations are to be carried out for purposes other than direct medical benefit to the individual being examined, the subject should be informed of the anticipated exposure conditions, and of how these compare with conditions for normal diagnostic practice.

Following the 45 minute ultrasound examination, the participant is asked to sit and then stand so that postural changes in blood pressure and pulse rate can be measured. These procedures are described in ARIC Manual 11. The precautions against adverse effects of orthostatism are summarized here.

Before beginning, the procedures for measuring postural changes are explained to the participant. The participant is asked whether or not he or she ever feels faint on standing. If the question is answered in the affirmative, permission to make the measurement (postural change) is still sought. Should the patient decline, the procedure is not performed. In the absence of a reason not to continue, however, the participant is asked if he or she is
taking medications that produce postural effects. When the postural changes are measured, the sonographer is positioned closely behind the patient as a protective measure should he or she become faint. A sturdy chair is close at hand so that the participant may sit down promptly should s/he feel the need. Furthermore, examinees are advised to notify staff immediately if not feeling well and to ask for the chair. Clinic staff are instructed to watch the participant for signs of distress. In the event that the participant faints, the procedures described in section Manual 11 are followed.

2.31.2 Methods for Handling Emergencies

While all life threatening emergencies (eg. acute MI) require immediate evaluation of the participant at an acute care facility, some emergency measures may be required in the clinic before departure (e.g., cardiac arrest). In addition, there are minor emergencies (hypotension, fainting, etc.) which may require treatment in the clinic only. Although most emergencies are of the less severe nature, ARIC Field Center clinics are prepared for both types.

2.31.2.1 Major emergencies

In a serious event the primary concern of the clinic staff is to implement pre-established procedures to get the participant to the nearest medical facility. All ARIC clinics are located within a few city blocks of a large general acute-care hospital. At every clinic session a staff person with certification in basic life support is on duty and physically present. Needed life support procedures are continued until emergency care arrives or the participant is transported to a hospital. Each ARIC clinic, depending on its location and staffing patterns, has specific emergency procedures, which define:

1. Who is in charge during the emergency.
2. Who is to administer treatments.
3. Who is to be notified.
4. What action clinic staff is to take.
5. Which reports are to be filed.

Each clinic has, in addition to trained personnel and emergency equipment, posted in a conspicuous place (e.g., the reception area): phone number of police and fire stations; ambulance services; and specific phone numbers or codes to alert medical teams, if applicable.

In each participant's folder, the name and phone number of his/her physician or usual source of health care is available on a standard ARIC form. The home and work telephone numbers of the next of kin are also listed. Each field center clinic is required to have on site at all times during which participants are interviewed and examined either a physician, a physician assistant or a registered nurse.
All emergency situations are coordinated by the staff person designated, a priori, or by a physician if present. Each center has a designated physician on duty for each clinic session. If not physically present in clinic, he or she is within immediate reach by phone or paging system and within a short distance to the clinic. The physician duty roster is posted with the clinic secretaries and in the office of the nurse/clinician so that the name of the responsible physician is readily accessible. However, in no case is emergency referral and/or care deferred while staff is attempting to locate a clinic doctor.

All personnel are trained to carry out their specific responsibility during an emergency. Retraining is conducted at least yearly.

All emergencies, whether serious or minor, are documented. This requires filling out an institutionally-approved form identifying the type of emergency. This is done by the person in charge at the time, and all reports are co-signed by a clinic physician and are filed at each clinic.

2.31.2.2 Minor emergencies

The most common minor emergency is simple syncope (fainting) and near syncope. These events may occur during the postural blood pressure measurements or venipuncture. Management of simple syncope or near syncope is the same whether associated with measuring postural blood pressure changes or drawing blood.

Many syncopal episodes can be prevented if clinic staff are alert to early signs. In any situation in which syncope is likely, e.g., before the venipuncture, staff verify that the participant does not look or feel faint.

If the participant looks faint or feels faint in the venipuncture area:

1. Have the person remain in the chair and sit with head between the knees or recline if the appropriate chair is used at the field center.
2. Crush an ampule of smelling salts and wave it under the participant's nose for a few seconds;
3. Provide the participant with a basin and a towel if he/she feels nauseous;
4. Have the participant stay in the chair until he/she feels better and the color returns.

If the participant continues to feel sick, recline the chair, place a cold wet towel on the back of the person's neck, and notify the supervisor. If a participant faints, he/she is cautiously lowered to the supine position on the floor and one attendant immediately calls for an in-house nurse/clinician to assist the patient. The remaining attendant raises the patient's legs above the plane of the body to increase venous return. Prior to this, the staff member momentarily palpates for a carotid pulse and checks to be sure the subject is breathing. If life support measures are needed, the procedures outlined in section 2.31.2.1 are followed.
2.31.3 Emergency Equipment

A basic first aid kit is maintained at each Field Center. The kit contains a reference guide of its contents, and is checked every year and immediately after each use. At each Field Center the Study Coordinator identifies a person responsible for this task.

2.31.4 Notification of Study Results

Before the informed consent is administered, the ARIC participant is told about each component of the examination. It is emphasized that the ARIC examination is not a substitute for clinical examination. The participant is told, however, that one of the benefits of participation is possible early detection of warning signs of certain diseases.

As described in section 2.30, the ARIC notification mechanism is designed to provide a clear statement to the participant to seek medical care, when confirmation or further investigation of study results indicates this course of action. An additional criterion built into the notification mechanism is to avoid anxiety in the study participants when presented with medical information, and any unnecessary consultation to practitioners.

All letters of notification conform to common procedures stipulated in the ARIC protocol. Appendix 2.25 of this Manual includes prototype letters of notification. The wording of these letters can be modified by the principal investigators of the ARIC Field Centers, to conform to the referral practices of each ARIC study community.

Section 2.30 of this Manual identifies the minimum set of significant findings and the alert values of laboratory results to be reported to participants and/or their physicians. It also specifies the schedule followed by the ARIC central agencies and field centers in notifying study participants, according to an expedited and a routine notification procedure. Section 2.27 describes the medical data review mechanisms that generate a referral, and the report to the participant and his/her the physician.