1.0 RECRUITMENT AND FOLLOW-UP OF THE ARIC COHORT AT VISIT 4

1.1 Eligibility Requirements for Annual Follow-up Interviews

Participants who completed at least part of the baseline examination (Visit 1) are contacted annually and, if capable, are invited to subsequent ARIC examinations. Individuals excluded from annual follow-up and subsequent examinations at the beginning of the study are only those enumerated residents who completed the home interview, but did not sign the informed consent form at the first field center examination (Visit 1).

Unless requested otherwise by the participant, or a participant is lost-to-follow-up, an attempt is made annually to contact all surviving ARIC cohort members, regardless of whether they continue to participate in field center examinations. This includes participants who have moved away from the community in which they were recruited. Telephone AFU interviews can be conducted anywhere in the continental U.S. Addresses and telephone numbers of cohort members with multiple residences are kept on file to contact participants on their target anniversary date. Those who have moved are also invited to return for examinations, either at their recruitment or a sister field center. Reimbursement for long distance travel, however, is unavailable. See Section 1.5.5 for procedures for the scheduling of Visit 4 examinations of ARIC participants who have moved away from the community in which they were recruited and are willing to be examined in one of the other field centers.

1.2 Annual Follow-Up

1.2.1 Time Window for Annual Contacts Between Field Center Examinations

Study participants are recontacted annually on their initial (anniversary) examination date at approximately the same time each year. The target date for the AFU interview is the date of the baseline visit. Contact years are numbered sequentially, starting with the year of the baseline examination, i.e., Contact Year 01 was assigned to all participants at Visit 1, regardless of the year in which they completed their baseline exam (Table 1).
Table 1. Contact Years by Visit Dates

<table>
<thead>
<tr>
<th>All Visit Years</th>
<th>(86)</th>
<th>Year of 1st ARIC Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1987</td>
<td>1988</td>
</tr>
<tr>
<td>VISIT 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>CY01</td>
<td></td>
</tr>
<tr>
<td>1988</td>
<td>CY02</td>
<td>CY01</td>
</tr>
<tr>
<td>1989</td>
<td>CY03</td>
<td>CY02</td>
</tr>
<tr>
<td>VISIT 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td>CY04</td>
<td>CY03</td>
</tr>
<tr>
<td>1991</td>
<td>CY05</td>
<td>CY04</td>
</tr>
<tr>
<td>1992</td>
<td>CY06</td>
<td>CY05</td>
</tr>
<tr>
<td>VISIT 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1993</td>
<td>CY07</td>
<td>CY06</td>
</tr>
<tr>
<td>1994</td>
<td>CY08</td>
<td>CY07</td>
</tr>
<tr>
<td>1995</td>
<td>CY09</td>
<td>CY08</td>
</tr>
<tr>
<td>VISIT 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td>CY10</td>
<td>CY09</td>
</tr>
<tr>
<td>1997</td>
<td>CY11</td>
<td>CY10</td>
</tr>
<tr>
<td>1998</td>
<td>CY12</td>
<td>CY11</td>
</tr>
</tbody>
</table>

Because recruitment was done over a three year period, participants could be in any one of three ARIC contact years during the calendar year in which annual contact interviews are conducted. For example, in 1993, interviewers contacted participants in Contact Years 05, 06, and 07. Regardless of the contact year, the optimal time for placing the initial call each year for annual contact is generally not more than three weeks before the target (anniversary) date. A one year window, up to 6 months before and 6 months after the target date, is the maximum allowed for each annual contact.

When the contact window expires and no contact is made, a final result code for that window is entered on the Record of Calls (Appendix 1.5), and a new window begins.
The contact year to which a participant death is assigned is determined by two factors: the date of death and whether or not the participant had already been interviewed during the contact year in which the death occurred. For example, if the death is determined during or prior to the regularly scheduled AFU interview, the death is assigned to the contact year in which the AFU form was administered. If, however, a participant is interviewed during Contact Year 07, dies a short time thereafter, and the family notifies the field center of the death, the death is assigned to the next contact year, i.e., Contact Year 08.

1.2.2 Follow-up Procedures

Annual follow-up of cohort members is used to (1) maintain contact and correct address information on cohort participants, (2) update tracing information on two contact persons, (3) ascertain the participant's vital status, and (4) document interim medical events/hospitalizations, life events and functional status between the three-year comprehensive examinations.

There are five primary components to annual follow-up: (1) the generation of scheduling material by the ARIC Coordinating Center; (2) the scheduling of the AFU interview by field center staff; (3) the administration of the AFU interview; (4) the scheduling of a field center examination every third contact year; and (5) the ascertainment of medical information relating to hospitalizations for cardiovascular disease and documentation of fatal events. These steps are summarized in Figure 1 and described in the following sections.

![Figure 1.1 Contact Procedures Between Clinical Examinations in the ARIC Cohort Study](image)

Field centers initiate the AFU procedures by generating several times a year AFU materials for use in scheduling and conducting the AFU interview. These materials include the participant tracing information sheet (Appendix 1.1) and the verification of tracing information (UPD) form (Appendices 1.2 and 1.3). The list of participants includes the participant name, participant ID, date of Visit 1, and date of Visit 2 (optional), sorted in the order requested by the field center. The Participant Tracing Information Sheet includes the participant's name, address, telephone number(s); sex, race, date of birth, state of birth, social security number, driver's license state and number; employer's name and address; date of Visit 1; and the names, addresses and telephone numbers of two contact persons and the personal physician. The Verification of Tracing Information (UPD) form is available in long and abbreviated versions (depending on whether it is administered with the routine AFU interview or the AFU/Visit 4 scheduling interview) and lists the current data on file for the names and addresses of the participant and his/her two contact persons.
The scheduling of AFU interviews at the field centers is done year round and involves identifying the participants who require scheduling, determining the type of contact needed (routine AFU or AFU/Visit 4 scheduling), establishing contact, administering the AFU form, scheduling Visit 4, and recording participant-reported medical events to ARIC surveillance staff. The procedures for scheduling Visit 4 and event classification are described in sections 1.5 and Manual 3, respectively.

Using the list of participant anniversary dates, field centers identify participants for annual contact. The use of letters (Appendix 1.4) prior to the AFU interview reminding participants that they will be contacted by telephone by a staff member from the ARIC field center for their annual interview is optional. This letter contains:

1. A reminder that the addressee is in the study and that annual contact is involved.
2. A description of the purpose of the contact.
3. Information that the participant should obtain to assist with the interview (e.g., hospitalizations, physicians visits).
4. A request to call the ARIC Study office to set up a time to complete the Annual Follow-up Interview.

However, all participants who cannot be contacted by phone are sent this letter on ARIC Study stationery as a reminder and "forwarding and address correction requested" is stamped on the envelope. Participants who do not have phones, have trouble communicating by telephone, or have special needs are not contacted by telephone but are visited in-person. If these participants can be identified in advance, the letter indicates that an interviewer will visit the home, and annual follow-up and the scheduling of Visit 4 takes place there.

Participants found to have moved or who are otherwise lost to follow-up are traced using the tracing information obtained at Visit 1 and during subsequent annual follow-up contacts or other local sources of information, such as the telephone directory, city directory, etc. By using the Participant Tracing Information Sheet, field center staff can call or write to the family members, friends, employers, or physicians the participants identified as contact persons during previous interviews. By using social security numbers, periodic searches of the National Death Index are done. Every attempt is made to schedule and complete an AFU interview for each participant.

AFU interviewers telephone study participants at their homes at optimal times (i.e., late afternoons, evenings, or weekends) to conduct the annual follow-up interview (and during Contact Year 10, or subsequently if necessary, to schedule the fourth field center exam). When the timing of the initial contact is inconvenient for the participant, the interviewer reschedules the AFU interview. When a cohort member cannot be reached on the first call, the interviewer makes return calls as necessary, at varying times of the day and week until either the participant is contacted or a decision is made to initiate tracing procedures. On the Annual Follow-up Record of Calls (Appendix 1.5), a final contact status (result) code (and appointment status code in Contact Year 10) indicating the participant cannot be located (i.e., is lost to follow-up) is only assigned after all tracing avenues have been exhausted and supervisor approval has been obtained. Experience has shown that participants who are lost to follow-up in one year may be located in subsequent years of follow-up and only participants who die or insist on no further contact with the ARIC study should be considered irreparably lost to the study.
1.2.3 Annual Cohort Interview

In Contact Year 10, version "F" of the AFU form is administered, unless the one-time only version "E" with its companion AFU Medical History Form (AMHA) have not yet been administered. Question by question (QxQ) instructions for the Record of Calls and version "F" of the AFU form and prototype scripts for their administration have been prepared for the AFU interview (See Appendix 1.7). The interview includes the use of three forms (UPD, TRC and AFU) which update address and tracing information of cohort participants (See Appendix 1.2 or 1.3, UPDATE form); and ascertain their vital status (AFU, section A), death information (AFU, section B); perceptions of general health (AFU, section C); chest pain on effort (AFU, section D); possible infarction (AFU, section E); intermittent claudication (AFU, section F); TIA/stroke (AFU, section G); hospitalizations (AFU, sections H and K); and functional status, weight loss, and life events (AFU, section I) (See Appendix 1.6, Annual Follow-up form). The Record of Calls is used throughout the contacting process to log each participant's interim and final contact and appointment status (when applicable). At some point after the AFU interview, every participant-reported hospitalization is verified and the discharge diagnoses recorded. Potential cardiovascular events are reviewed further by the abstraction of participants' hospital records to document the presence/absence of ARIC Study endpoint criteria. Detailed information on diagnostic criteria and event determination of the cardiovascular events is provided in Chapters 4 and 5, respectively, of Manual 3, Surveillance Component Procedures.

The components of the AFU interview are usually done in the following order: (1) completion of the Record of Calls; (2) administration of the AFU questionnaire; (3) documentation of the participant's hospitalizations during the past year - section K of the AFU form; (4) scheduling of the appointment for Visit 4 (Contact Year 10); and (5) updating of the contact information (UPD form).

The Record of Calls (TRC form) is used to keep track of attempts to contact a participant and to schedule Visit 4 (Contact Year 10). The participant's name, ID, contact year, and contact year date ranges are pre-printed at the top of the form. Space is provided to document contact attempts, pertinent information for future contacts, and the outcome of the contact. There are ten contact RESULT CODES. The final result code is circled and entered into the data entry system. The paper copy of the form is kept in the participant's folder to assist in future contacts.

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*RESULT CODES (CIRCLE THE FINAL SCREENING RESULT CODE (AFUF Item 46)

01 No Action Taken
02 Tracing (Not yet contacted any source)
03 Contacted, Interview Complete
04 Contacted, Interview Partially Complete or Rescheduled
05 Contacted, interview refused
06 Reported Alive, Will Continue to Attempt Contact this Year
07 Reported Alive, Contact Not Possible this Year
08 Reported Deceased
09 Unknown
98 Does Not Want Any Future AFU Contact.
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Codes 01, 02, 04, and 06 are interim codes. Codes 03, 05, 07-09, 98 are final codes. See Appendix 1.7 for detailed instructions for completing the form, and a description of the Results Codes for contacts. It should be noted that...
these codes are required for all AFU contacts, in contrast to the APPOINTMENT CODES which are only used in the Contact Years in which the participant is scheduled for a clinic visit.

Once contact has been made, the entire AFU interview is administered to surviving participants. When a participant has expired prior to the annual contact, the relevant portions of the AFU form (Sections A, B, H and K) are administered to a member of the participant's household (or a contact person) in order to officially record the death and to obtain the date and location of death and other relevant medical information.

Section A of the AFU form documents the participant's vital status and the date on which the status determination was made. The criteria for establishing participant vital status are defined in the form's instructions.

Section B is completed on individuals who have died and records demographic information necessary for obtaining a copy of a death certificate. Sections C-G are administered to all surviving participants and document perceptions of health and interim (since the previous AFU interview) medical events; the majority of the questions were taken from the London School of Hygiene Questionnaire for chest pain on effort, possible infarction, and intermittent claudication. Guidelines for administering this section are provided below, in Section 1.2.3.1. Sections H and K on the AFU form are administered to all respondents (participants and proxies) to document overnight hospitalizations in acute or chronic medical care facilities. The surveillance staff is notified of every cohort hospitalization and an event investigation is initiated. Section I is administered only to surviving participants.

Tracing information listed on the pre-printed UPD form (Appendix 1.3) is verified at the conclusion of the AFU form. Instructions for administering the form and a prototype script are provided at the end of the annual follow-up instructions. Any changes to tracing information recorded on the paper form during the telephone interview are recorded on the computerized version of the UPD form by staff certified in the use of the ARIC Data Entry System.

1.2.3.1 Administration of London School of Hygiene Questionnaire

The questions in Sections D-F (CHEST PAIN ON EFFORT, POSSIBLE INFARCTION, and INTERMITTENT CLAUDICATION) of the AFU form are based on the London School of Hygiene Questionnaire. The purpose of the London School of Hygiene Questionnaire (generally referred to as the 'Rose Questionnaire') is to standardize the identification of 'angina on effort' as defined by Dr. Geoffrey Rose. It is not the purpose of the questionnaire to arrive at a medical diagnosis. The questionnaire will fail to identify angina pectoris in some participants whose pains are regarded by the physician as genuinely ischemic. It may categorize other cases as pain due to a quite different cause. Any special effort, however, to alter the conduct of the interview in such instances would destroy the basic purpose of the questionnaire technique, which is to insure uniformity in the eliciting of defined symptoms.

Questions must be put to the participant exactly as they are printed: small changes can make unexpectedly large differences in responses. Unequivocal answers must be recorded as such, whether they seem reasonable or not. Supplementary questions (probing) should rarely be used. When they have to be asked, they should depart as little as possible from the wording of the initial question, and must not be such as to suggest any one particular answer to the participant.

If serious doubt arises about the correct interpretation of a particular answer, it is recorded in such a way as to exclude the suspected condition. An example of this type of situation is demonstrated in the following question and hypothetical response.

(Question) "Do you get it when you walk uphill or hurry?"
(Response) "Well, I think I might, but I really can't remember."
This answer is recorded as NO and no probes are employed.

An exception is made to this rule only if a negative response to the lead-in question is an interpretation or denial of a positive response.

(Question) "Have you ever had any pain or discomfort in your chest?"

(Response) "No. Only indigestion."

The answer is recorded as YES, because the participant's interpretation of the symptom is disregarded.

A frequently made error in the administration of the Rose Questionnaire is to extrapolate the participant's response to similar, but not defined, situations in the question.

(Question) "Do you get it when you walk uphill or hurry?"

(Response) "Yes, the chest pain occurs when I cut the grass."

The answer to this question is recorded as NO, i.e., a strict interpretation is required. If pain is experienced only during some other form of exertion (e.g., cycling, stair climbing, lawn mowing, etc.), it must always be recorded NO. The response 'NEVER HURRIES OR WALKS UPHILL' can only be coded if the participant specifically denies walking uphill or hurrying.

For the remaining questions, unequivocal answers need not be probed. However, responses qualified by terms describing frequency of events, such as 'occasionally' or 'sometimes' should be probed by a question such as 'Does it happen on most occasions?'. Individual question by question instructions are provided in Appendix 1.7.

1.3 Linkage of AFU Ascertained Reports of Positive Cardiovascular Events and the Field Center Examination

The folders of ARIC participants to be scheduled for Visit 4 who report during their AFU interview symptoms of chest pain on effort or intermittent claudication, physician diagnosis of myocardial infarction or TIA/stroke, or hospitalization(s) for cardiovascular disease are flagged. These responses are subsequently confirmed during Visit 4 by a trained interviewer administering the Health History Form and the Medical Data Review.

1.4 Window for Visit 4

The scheduling of Visit 4 is made in conjunction with the annual contact in Contact Year 10. The optimal time frame for scheduling Visit 4 is within 30 days of the participant's annual contact target date, but can be made up to 4 months earlier to aid clinic scheduling. It is anticipated that most field center visits will be completed within 90 days of the target annual follow-up contact date. If the participant cannot complete Visit 4 within this time frame, it is still possible for Visit 4 to be completed at any time during Contact Years 10 through 12. For example, if the participant refuses or does not show for a visit in Contact Year 10, scheduling is attempted in Contact Years 11 and 12. The Visit 4 data are entered into the database as Contact Year 10 data, even if the field center exam occurs during Contact Years 11 and 12. This is in contrast to the recording of the actual contact year number (e.g., 11 or 12) of the AFU interview in which Visit 4 is successfully scheduled. For example, if a participant has an AFU interview and is scheduled for Visit 4 in Contact Year 10, does not come to the field center within the remaining time during Contact Year 10, is recontacted in Contact Year 11, and agrees to rescheduling and completes Visit 4 during Contact Year 11, the AFU contacts are listed as Contact Year 10 and Contact Year 11, but the Visit 4 contact year is listed as Contact Year 10.
There are 11 APPOINTMENT CODES which are completed on the Record of Calls (TRC), Version F in Contact Year 10. The appointment code is entered into the appropriate column on the Record of Calls form to describe the participant's (interim and) final appointment status. Like contact status (result) codes, final codes indicating permanent disenfranchisement from the study must be approved by the supervisor. The final appointment code is circled and entered into the data entry system.

** APPOINTMENT CODES (AFUF Item 47)**

- 00 Appointment scheduled (record date, time and special needs)
- 01 Clinic examination completed
- 02a Appointment deferred (by clinic staff)
- 02b Appointment pending due to sickness or other concerns/condition of the participant
- 03 Moved outside of the study area, will be contacted annually for follow-up
- 04 Rescheduled many times, unlikely to complete appointment
- 05a Appointment refused, permanently incapacitated
- 05b Appointment refused, other reason
- 06 Refused clinic visit and does not want any further contact
- 07 Unable to locate
- 08 Deceased

### 1.5 Scheduling of Visit 4 Field Center Examination

#### 1.5.1 Outline of Scheduling Procedures for Visit 4

The steps in the scheduling procedures for Visit 4 are similar to those for scheduling and conducting the AFU interview, but also includes recruitment for the Oral Glucose Tolerance Test (OGTT) and screening and recruitment for the dental examination.

1. The Participant Tracing Information Sheet is a list of participants to be contacted, their tracing information, the target contact date, and the six month time window around the target date which is provided to field centers by the Coordinating Center at least 4 months in advance of the contact date. The materials for identifying and scheduling participants for Visit 4 differ from the regular lists of annual follow-up, (the list of participants with anniversary dates for a minimum of three months, the participant tracing in formation sheet) only in that those printed for field centers in North Carolina and Mississippi identify which participants have been randomly selected for an ultrasound examination.

2. At the discretion of each field center, a letter is mailed to the participant indicating that the usual Annual Follow-up telephone call will take place, and at that time an appointment for Visit 4 will be set (Appendix 1.8). A brief description of Visit 4 is provided in the letter, as well as a request to have a calendar available to facilitate scheduling Visit 4.

3. The participant is telephoned, the Annual Follow-up Form is completed in the usual manner. Participants are reminded that it is time for their next clinical examination (Visit 4). The new procedures (oral glucose tolerance test, heart rate variability test, and the dental examination) which have been included in Visit 4 are reviewed, the dental screening form is administered to all cohort members and all eligible participants
are recruited for the dental examination. A prototype script for introducing the dental exam is provided in Appendix 2.6.c. An appointment for Visit 4 is scheduled. Some home interviews may be necessary for individuals unreachable by telephone or for special circumstances. After the appointment is set, basic instructions for Visit 4 are provided. The need for adequate hydration while maintaining fasting is stressed to facilitate venipuncture and the collection of a urine sample at the beginning of the examination.

4. Shortly before the appointment, field centers send a reminder letter indicating the appointment time.

5. A reminder telephone call also precedes the visit.

6. If a participant is unavailable during the usual time window for the Visit 4 appointment, additional efforts to schedule Visit 4 at a later date are made. If a participant refuses to return to the field center for the fourth examination, continued annual contact in subsequent years is attempted, as well as the scheduling of Visit 4, unless the supervisor considers it inappropriate.

1.5.2 Contacting Participants

The Coordinating Center generates from the ARIC database a list of participants to be contacted for Visit 4 and their target contact date. The list is similar to that provided for Annual Follow-up, and is generated well in advance of the contact window to allow field centers to schedule the lengthier interviews, and if necessary, to trace hard to find participants.

Field centers have the option of mailing a letter to all participants (or just those who cannot be contacted by telephone) indicating that the routine Annual Follow-up call is due and that the fourth field center examination (Visit 4) will be scheduled at that time. A prototype letter is provided in Appendix 1.8. Participant address files for producing mailing labels are routinely updated and distributed to the field centers by the Coordinating Center. These letters in envelopes stamped "forwarding and address correction requested" are sent, to assist in tracing participants who have moved.

Approximately one week after the letter is mailed, a telephone call is placed to the participant's home. Prior to initiating the joint AFU interview - Visit 4 scheduling telephone call, the interviewer has assembled (1) the AFU Record of Calls, (2) the AFU questionnaire, (3) calendar for scheduling the field center appointment and (4) the UPDATE form and (5) the DENTAL SCREENING form. Using the prototype scripts provided in the question by question instructions (Appendix 1.7, the AFU form; and Appendix 2.6.a, the Dental Screening Form), the interview is typically conducted in the order in which the forms are listed above. If a field center appointment is to be scheduled with more than one cohort member during a single call, it is often more expedient to conduct all AFU interviews first and then schedule appointments together. The short tracking information sheet (Appendix 1.2) is updated. More detailed information on contacts and primary medical care provider is updated during the clinic exam.

1.5.3 Making the Clinic Appointment

After completing the annual follow-up interview for all participants in a household, the interviewer describes the clinic visit, including the new components, and schedules the participant's Visit 4 appointment following the prototype script provided in the question by question instructions for the Annual Follow-Up form. A separate one page prototype Visit 4 Scheduling Script to standardize the scheduling of participant appointments is provided in Appendix 1.9. If there is more than one ARIC cohort member in a household, the interviewer has the option of completing the AFU and clinic scheduling portions of the interview with each cohort member, or completing
the AFU portion with each individual before jointly scheduling their field center appointments. The interviewer inquires about several items to assist in scheduling the appointment:

1. Preferred time and date of examination;
2. Any medical conditions (e.g., diabetes, dietary restrictions) which might affect the physical examination and/or type of snack provided;
3. Need for assistance getting to or moving about the clinic.

If possible, the interviewer schedules appointments for the examination during the 30 days following the telephone call. The interviewer notifies the clinic scheduler to set an appointment day and time. The appointment is recorded on a reminder sheet which is mailed to (or left with) the participant. When possible, cohort members are scheduled for appointments at their convenience, this includes scheduling all eligible members of a single household for examinations on the same day whenever possible.

1.5.4 Instructions for the Clinic Examinations

The instructions for clinic visits are specified on an information sheet (Appendix 1.10) prepared by each Field Center, and mailed (or delivered) to the participant soon after the appointment is made. The instructions include:

1. Appointment date and time.
2. Preparations:
   a) Instructions how to complete the 12-hour fast;
   b) Instructions on proper hydration while maintaining the fast;
   c) Instructions concerning restrictions on the use of tobacco and vigorous physical activity the morning prior to the visit;
   d) Appropriate clothing to wear for the examinations.
3. Things to bring:
   a) Eyeglasses for reading;
   b) Name and address of primary care physician and/or clinic;
   c) Name and address of dentist if participating in dental exam;
   d) Name, address, and phone number of contact persons;
   e) Medication Instruction Sheet: Instructions for bringing prescription and over-the-counter medications, including vitamins and mineral supplements, taken within the two weeks prior to the examination and a bag for bringing the medications to the field center.
4. Overview of Clinic Operations:
   a) A listing of the interviews and procedures for Visit 4 (optional);
   b) A reminder that a snack is provided during the exam;
   c) Clinic hours and phone number for questions or rescheduling appointment.
5. Directions to the clinic (e.g., a map) and to parking facilities:
   a) All Field Centers provide free parking or reimbursements.
6. Transportation:
   a) Some centers provide transportation and arrange for participant pick-up.
   b) In Jackson, those who drive are asked to record mileage for reimbursement.

1.5.5 Scheduling Appointments
Interviewers scheduling examinations report appointment information to their field center. Sufficient appointments are scheduled each day for Monday through Friday to meet the requirement of approximately 25 appointments per week.

Ultrasound B-mode examinations of the carotid arteries are scheduled for all Minneapolis and Washington County participants who did not have an ultrasound exam in Visit 3, and for approximately 50% of the participants from the Forsyth County and Jackson field centers. The collection of a urine sample is attempted from all participants and was implemented at the start-up of Visit 4. Eligibility to participate in the oral glucose tolerance test (OGTT) is determined during reception and all cohort members who are not diabetic on hypoglycemic medication are encouraged to participate. OGTT was implemented at start-up. The measurement of heart rate variability is performed on all participants and was implemented several months after start-up, beginning in May, 1996. The dental exam was implemented after start-up, and is performed on all eligible participants. Cohort members who completed their Visit 4 exam prior to implementation of the heart rate variability study and dental examination are invited to return for these procedures.

At a minimum, each field center maintains the following scheduling documentation:

1. Assignment record of ID labels for the clinics, generated and distributed by the ARIC Coordinating Center.

2. A listing of participants by ID, name, telephone number, anniversary date and earliest and latest dates during which to conduct the AFU interview and schedule the Visit 4 field center appointment (Participant Tracing Information Sheet).

3. Daily appointment log with participant name, ID number, appointment time, and special considerations such as health restrictions or child care requests. This schedule is used to structure that day's appointments and to check in participants as they arrive.

1.5.5.1 Guidelines for ARIC participants who relocate near another center

It is anticipated that over time, some members of the ARIC cohort will move far enough away from the community in which they were recruited to make the return for clinical follow-up impractical. Such individuals continue to be contacted annually. They are also offered the opportunity to have their fourth exam at a sister field center. In essence, however, they remain members of the original field center cohort. In spite of the fact that study data are collected 'off-site' (i.e., the alternate center), these data are entered and monitored at the original field center, and the original field center is responsible for preparing results reports and letters. The guidelines for implementing these procedures are as follows:

1. The original field center continues to perform all Annual Follow-up calls and the scheduling of field center examinations.

2. When participants are interested in completing their next clinic visit at another field center, the original field center contacts the closest ARIC field center (i.e., the alternate field center) and arranges for scheduling the appointment.

3. The original center sends the ARIC Coordinating Center and the alternate center written notification of the participant ID, as soon as the participant agrees to complete the exam at the new field center.

4. The original field center sends labels and a copy of the Participant Information Sheet (PIN), current Annual Follow-up form, and any other
pertinent information to the alternate center. Other pertinent information includes mention of any 'special needs', and copies of prior study results reports and letters to participants and physicians. All of this is treated as confidential information. Although the alternate centers does not prepare the equivalent materials for the current cohort visit, the person in charge of Medical Data Review needs to know about these items.

5. The Medical Data Review which occurs at the end of the clinic visit is performed by the alternate center. This includes any immediate follow-up to findings during the clinic visit. Subsequent notification of any alert values and the preparation of the report of study results and the accompanying letter(s) to the participant's provider of medical care are the responsibility of the original center.

6. The alternate center collects the study data on paper, assigning the original study ID. These forms are photo-copied; the originals sent to the original field center for data entry and a copy kept on file at the alternate center.

7. The original centers send the ARIC Coordinating Center and the alternate center a copy of the CXI once data entry of the forms collected at the alternate center are keyed. The alternate center verifies that all forms collected on paper were entered and then the photocopied forms can be discarded.
8. The alternate field center annotates all central agency sample inventory sheets, indicating the special situation. The central agencies (laboratories and reading centers) correspond with the original field center in the event of alert values or other special issues related to relocated participant data. The original center then sends a copy of the alert to the nurse/clinician at the alternate center for their information, since the participant may call either center with a question.

1.6 Retention of ARIC Participants

1.6.1 Introduction

Projected Visit 4 clinic re-examination rates (ranging from 80 to 90 percent) are dependent upon each field center's ability to contact eligible participants and schedule return appointments.

Every effort is made to make the field center visit as pleasant and burden free as possible. Additionally, the following features are part of the effort to maximize participation: (1) qualified interviewers, (2) pre-appointment contacts, (3) no show procedures, (4) reimbursement of transportation costs, and (5) publicity.

1.6.2 Certification of Annual Follow-up Interview Staff

Interviewers are trained and certified in general interviewing techniques and the administration of the Annual Follow-up form. This requires familiarity with the contents and procedures for administering the AFU form, assigning contact and appointment status codes on the AFU Record of Calls, scheduling a field center appointment, and verifying contact information on the UPDATE form. Staff are certified centrally in administering the Rose Questionnaire after review of a standardized protocol. Recertification is required annually with the recommendation of periodic refresher courses and retraining if quality assurance analyses indicate poor performance or inconsistent results.

1.6.3 Pre-appointment Contacts

To increase respondent participation following the Annual Follow-up/Visit 4 Scheduling telephone call by an ARIC interviewer, a pre-Visit 4 appointment packet is mailed at some centers prior to the scheduled appointment. This packet confirms the examination date and time and reviews the preparation procedures as listed in section 1.5.4.

Reminder calls are made to each participant one or two days prior to the examination. At this time, the information concerning the fasting requirements, medications bags, and other details is reviewed with the participant. Participants are asked if they have any special needs and every effort is made to answer participant's questions.

When appropriate, a letter is sent to the participant's employer explaining the ARIC Study and requesting time-off during work hours (see Appendix 1.11).

1.6.4 Contacts for No Shows

Eligible participants who fail to arrive for a scheduled appointment or who cancel their appointments are contacted by telephone to reschedule the appointment. At that time, the scheduler attempts to address any concerns or fears that the participant may still have.

Each no-show case is individually reviewed by the interviewer and when necessary by the supervisory staff. Conversion efforts include a combination of telephone contacts, in-person visits, and/or conversion letters. A participant is considered a refusal following three conversion contacts or
three broken appointments.

1.6.5 Reimbursement

Each center provides for, or reimburses, local transportation and/or parking. For those who are reimbursed, records are maintained for accounting purposes according to Office of Management and Budget (OMB) regulations and each university's guidelines.

1.6.6 Publicity

To enhance participation, the Field Centers maintain active contact with the media in their communities. Periodic attempts are made to provide them with updates of the study and to enhance community support.

1.6.7 Supervision

Throughout the entire process from initial interview to final examination or refusal, close supervision helps maximize the rate of response. Supervisors record reasons for non-response, and examine performance trends by interviewer and by area. When deemed appropriate, supervisors initiate re-contact with refusing participants to attempt their conversion. Detailed records of all contacts are maintained.
2.0 INTERVIEWS IN THE VISIT 4 CLINICAL EXAM

2.1 Introduction

During the annual follow-up interview, cohort members in the Contact Year 10 are invited to return for a fourth field center exam (Visit 4). As envisaged during the initial design of the ARIC study, a core component of the cohort examination has remained constant in Visit 4 to provide comparability. From the outset, each examination has included measurements of blood chemistries (glucose, lipids, hemostatic factors); blood pressure (sitting and supine blood pressure); body/frame size (anthropometry); resting electrocardiogram (ECG); and carotid artery B-mode ultrasound imaging. Core interviews have documented prevalent/incident cardiovascular disease, symptoms and medical care; fasting status prior to venipuncture; use of medications (prescription, over-the-counter, vitamins and mineral supplements and gonadal hormones in women); menstrual status in women (natural, pharmacological and surgical); and prevalent/incident cerebrovascular disease (stroke and TIA). In addition to the core elements, some ARIC procedures and interviews have been included with the intention of collecting data on a one-time-basis, and some at six year intervals. A test of cognitive function, originally administered to all participants in Visit 2 and to participants in Forsyth County, NC and Jackson, MS in Visit 3 who had cerebral MRI scans, is re-administered to all participants in Visit 4. The Spielberger Trait Anger interview, which was originally administered to all participants in Visit 2, is re-administered in Visit 4 as a measure of psychosocial status. New procedures in Visit 4 include the documentation of male pattern baldness; the collection of a urine sample for the assessment of microalbuminuria; and the administration of an oral glucose tolerance test. New interviews include medical histories of chronic inflammatory diseases, physical ability and socioeconomic status at birth and middle age (see Table 2.1.a). A repeatability study of the Visit 3 retinal exam is scheduled for the first few months of Visit 4 and its procedures and data collection forms are provided in Appendix 3.10, because it is only conducted on approximately 800 participants (200 per field center) and is not considered a primary component of Visit 4. Two ancillary studies, an oral examination to assess putative association(s) of chronic inflammation and the measurement of heart rate variability, have been integrated into Visit 4 and are conducted on all eligible participants (see Table 2.1.b).
<table>
<thead>
<tr>
<th>Work station</th>
<th>Description</th>
<th>Manual</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropometry</strong></td>
<td>Measure weight, height, waist and hips. In men, assess male pattern baldness.</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td>Obtain resting 12 lead ECG</td>
<td>2.3, 5</td>
</tr>
<tr>
<td><strong>Informed Consents</strong></td>
<td>Obtain informed consent for core Visit 4 exam including authorization for collection of DNA and other study data, access to medical records, release of study data and separate consents for ancillary studies</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Interviews</strong></td>
<td>Collect sociodemographic data; health care, and medical, personal and reproductive (women only) history; medication/vitamin use; physical ability; dental screening and history; history of chronic inflammation (two forms); OGTT screening; SES data; cognitive function</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Medical Data Review</strong></td>
<td>Ascertain the completeness of exam; verify abnormal results. Review results of medical history with participant, and provide a written clinic summary report. Refer participant for diagnosis or treatment elsewhere if needed. Return medication; answer questions; thank participants. Reschedule for missed procedures.</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>Microalbuminuria</strong></td>
<td>Collect urine sample at beginning of exam or any time prior to exit.</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Oral Glucose Tolerance Test</strong></td>
<td>Collect fasting and 2 hour post glucose load blood specimens</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Reception</strong></td>
<td>Greet the participant; obtain informed consents; determine fasting status; verify eligibility for OGTT; verify identifying information; obtain tracing data; collect medications.</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Sitting Blood Pressure</strong></td>
<td>Assess sitting blood pressure using random zero sphygmomanometer; average of 2 measurements</td>
<td>11</td>
</tr>
<tr>
<td><strong>Snack</strong></td>
<td>Provide snack with no stimulants to persons not doing the oral glucose tolerance test</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Ultrasound</strong></td>
<td>Obtain B-mode scan of extracranial carotid arteries. Record heart rate and blood pressure changes as participant arises from supine position.</td>
<td>6,11</td>
</tr>
<tr>
<td><strong>Venipuncture</strong></td>
<td>Obtain blood samples for laboratory tests and storage of specimens.</td>
<td>7</td>
</tr>
</tbody>
</table>
### Table 2.1.b Components of the Repeatability and Ancillary Studies in the Visit 4 examination, and the location of the procedures in the Manuals of Operation

<table>
<thead>
<tr>
<th>Work station</th>
<th>Description</th>
<th>Manual</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>REPEATABILITY STUDIES AT VISIT 4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinal</td>
<td>Repeatability study of procedures done in Visit 3 to photograph ocular fundus on 200–250 participants at each field center at the beginning of Visit 4.</td>
<td>App.3.10</td>
</tr>
<tr>
<td><strong>ANCILLARY STUDIES INTERFACING WITH VISIT 4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental Study</td>
<td>Collect history of periodontal disease on all pts; Screen all for eligibility in dental exam; Perform screening exam of oral hygiene; level of caries, missing teeth, plaque; collect gingival crevicular fluid; collect plaque; assess gingival inflammation; determine probing depth, cemento-enamel junction and bleeding on probing; provide summary of results of dental exam.</td>
<td>Manual 2-Chap. 3.6 DENTAL STUDY MOP</td>
</tr>
<tr>
<td>Heart Rate Variability</td>
<td>Assess cardiac autonomic activity by obtaining 6 min R-R interval data after 12 lead ECG on all participants prior to OGTT; performed after a 10 minute rest in the supine position when done on make-up participants</td>
<td>Manual 2-Chap 2.3 HRV MOP</td>
</tr>
</tbody>
</table>

Chapters 2-6 of this manual provide an overview of the fourth cohort examination, procedures for administering participant interviews and conducting exams, references to the pertinent manuals of the protocol for those examination procedures not covered in detail in Manual 2, and appendices of forms and question by question instructions for their administration. Chapter 2 provides an overview of the design, objectives and content of the fourth clinical examination (Visit 4), and describes the logistics for setting up the clinical examination. Chapter 3 provides the rationale and describes the procedures, the training and certification required to perform the procedure, the quality assurance activities, and the data collection instruments and procedures. Chapter 4 provides similar information for the interviews administered during Visit 4. Chapter 5 describes the activities associated with reporting results. Chapter 6 outlines the procedures at the field center to ensure participant safety.

Table 2.1.a lists the main components of Visit 4, identifying the activities at each work station and cross-referencing each procedure with its respective manual of operation. Table 2.1.b lists components from Visit 3 which are being repeated for quality control purposes and ancillary studies which have either been integrated into the clinical exam or for which additional blood samples are being drawn.

In general, the numbering of sections within chapters 2 – 6 follows a standard format: a description of and the rationale for the interview, procedure, or activity (.1), operational procedures (.2), training requirements (.3), the certification criteria (.4), routine quality assurance activities (.5), and data collection procedures (.6).
The rationale (.1) for core interviews, measurements and procedures briefly summarizes the major premise(s) for its inclusion in the ARIC study and its continued use in Visit 4. A more detailed rationale is provided for the new components in Visit 4.

The section on operational procedures (.2) describes in detail the procedures for administering the interviews, conducting examinations or taking measurements, or gives a reference to the appropriate manual of operations for the procedures with their own separate protocols. Standardized definitions of terms for use by the interviewer or respondent in an interview or instructions for administering or filling in individual questions on the data collection forms for each interview, measurement or procedure are provided in the question by question (QxQ) instructions which are located in the Appendix, immediately following the individual data collection form.

Training requirements (.3) and certification criteria (.4) are listed separately from their traditional rubric of quality assurance to provide easier reference for study personnel. Training materials additional to those in this manual of operations on data management, general interviewing techniques, the administration of all interviews, the measurement techniques for procedures, informed consent, results reporting and referral guidelines were compiled for the Visit 4 central training workshop and are available in a separate notebook at each field center.

To reduce the use of repetitive statements for each procedure in the sections on training and certification for interviews and procedures, it is understood that the minimum training and certification requirements/criteria for all Visit 4 interviewers, technicians and clinicians are a command of the pertinent protocol sections and forms, and demonstrated proficiency on the ARIC direct Data Entry System or back-up procedures for data collection on paper forms. Detailed instructions for completing paper forms and for standardized interviewer techniques are found in appendices 2.1 and 2.2, respectively.

Table 2.2 lists the personnel responsible for the central and local training of each interview/procedure at the outset of Visit 4. The Quality Assurance section (.5) briefly summarizes and/or references the additional quality control activities that are carried out locally by field center personnel and globally by the Coordinating Center and other Central Agencies, see Manual 12, Quality Assurance and Quality Control.

The final section in each section is on Data Collection (.6) which briefly summarizes the standard and backup operating procedures for data collection using both the direct and delayed entry systems. A separate manual, The Data Management Manual, serves as the official reference document for all data collection and systems management procedures.

The appendices for this manual provide support material for Chapters 1-8, and include interviewing scripts, the data entry screen and paper versions of all forms, the detailed question by question instructions for administering each form, prototypes of all participant results reports and quality control checklists.
## Table 2.2 Certification Criteria: Visit 4 Cohort Exam Procedures and Interviews

<table>
<thead>
<tr>
<th>PROCEDURE OR INTERVIEW</th>
<th>CERTIFICATION REQUIREMENT</th>
<th>CERTIFIER OR REVIEWER</th>
<th>RECERTIFICATION REQUIREMENTS</th>
<th>RECERTIFIER OR REVIEWER</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFU (CY10-12) Annual Follow-up - typically done by telephone</td>
<td>Local review of AFU procedures</td>
<td>Supervisor or Lead Interviewer</td>
<td>Annual Rose Questionnaire Exercises Annually</td>
<td>G. Heiss-UNC</td>
</tr>
<tr>
<td>ANTHROPOMETRY</td>
<td>Lead Technician certified at central training; all others @ central training or by lead tech. @ field centers.</td>
<td>Central trainer or Lead Technician</td>
<td>Biannually (Jan/Jul) @ field centers; results sent to CC for documentation once a year.</td>
<td>Lead technician @ field centers</td>
</tr>
<tr>
<td></td>
<td>height</td>
<td></td>
<td></td>
<td>Monitor</td>
</tr>
<tr>
<td></td>
<td>weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>waist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>hip</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>baldness</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>1 cm of trainer</td>
<td></td>
<td></td>
<td>Lead technician @ field centers</td>
</tr>
<tr>
<td></td>
<td>1 cm of trainer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 cm of trainer</td>
<td></td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td></td>
<td>agreement w/trainer</td>
<td></td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Continuous</td>
</tr>
<tr>
<td>BLOOD PRESSURE, SITTING</td>
<td>Lead Technician certified at central training; all others @ central training or by lead tech. @ field centers.</td>
<td>Central trainer or Lead Technician</td>
<td>Biannually (Jan/Jul) @ field centers; results sent to CC for documentation once a year.</td>
<td>Lead technician @ field centers</td>
</tr>
<tr>
<td></td>
<td>2-replicate measures</td>
<td></td>
<td></td>
<td>Monitor</td>
</tr>
<tr>
<td></td>
<td>digit preference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>mean values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 4 mmhg/reading</td>
<td></td>
<td></td>
<td>Lead technician @ field centers</td>
</tr>
<tr>
<td></td>
<td>&lt; 3 mmhg/average</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>none</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coordinating Center</td>
<td></td>
<td></td>
<td>Continuous</td>
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<tr>
<td></td>
<td>Coordinating Center</td>
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<td>Continuous</td>
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<tr>
<td></td>
<td>Coordinating Center</td>
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<td></td>
<td>Continuous</td>
</tr>
<tr>
<td></td>
<td>Coordinating Center</td>
<td></td>
<td></td>
<td>Coordinating Center</td>
</tr>
<tr>
<td>COGNITIVE FUNCTION</td>
<td>Adequate technique on 5 taped interviews</td>
<td>Supervisor or Lead Interviewer</td>
<td>Annually, 1 taped interview (non-interviewer staff) included in round robin</td>
<td>4 field center interview supervisors monitoring round robin tapes</td>
</tr>
<tr>
<td>DENTAL HISTORY interview</td>
<td>Adequate technique on 5 taped interviews</td>
<td>Supervisor or Lead Interviewer</td>
<td>Annually, 1 taped participant interview included in round robin</td>
<td>4 field center interview supervisors monitoring round robin tapes</td>
</tr>
<tr>
<td>DENTAL SCREENING interview (phone or in-person)</td>
<td>Local review of interviews</td>
<td>Supervisor or Lead Interviewer</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>12 LEAD ECG</td>
<td>Adequate technique on 5 ECG tracings</td>
<td>Epicare reviews ECG quality</td>
<td>Monitored continuously @ Epicare with quarterly reports to field centers</td>
<td>Epicare</td>
</tr>
<tr>
<td></td>
<td>Review of procedures by Lead Technician</td>
<td>Biannual review of technique @ field center (Jan/July); results sent to CC once a year.</td>
<td>Lead Technician</td>
<td></td>
</tr>
<tr>
<td>HEALTH HISTORY interview</td>
<td>Adequate technique on 5 taped interviews</td>
<td>Supervisor or Lead Interviewer</td>
<td>Annually, 1 taped interview</td>
<td>4 field center interviewer</td>
</tr>
<tr>
<td>PROCEDURE OR INTERVIEW</td>
<td>CERTIFICATION REQUIREMENT</td>
<td>CERTIFIER OR REVIEWER</td>
<td>RECERTIFICATION REQUIREMENTS</td>
<td>RECERTIFIER OR REVIEWER</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------------</td>
<td>-----------------------</td>
<td>----------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Taped interviews</td>
<td>Interviewer</td>
<td>Participant interview included in round robin</td>
<td>Supervisors monitoring round robin tapes</td>
<td></td>
</tr>
<tr>
<td>HEALTH/LIFE PROFILE self-administered form</td>
<td>Adequate explanation on 5 taped introductions to participants</td>
<td>Supervisor or Lead interviewer</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>HEART RATE VARIABILITY</td>
<td>Adequate technique on 1 week of tracings, or 5 procedures</td>
<td>Ultrasound Reading Center</td>
<td>Monitored continuously @ URC with quarterly reports to field centers. Annual retraining and biannual review of technique w/ECG @ field center (Jan/July); results sent to CC once a year.</td>
<td>Ultrasound Reading Center</td>
</tr>
<tr>
<td>INFLAMMATION interview</td>
<td>Adequate technique on 5 taped interviews</td>
<td>Supervisor or Lead Interviewer</td>
<td>Annually, 1 taped participant interview included in round robin</td>
<td>4 field center interviewer supervisors monitoring round robin tapes</td>
</tr>
<tr>
<td>LETTERS/REPORTS Participant results reports</td>
<td>Local approval</td>
<td>Supervisor or PI</td>
<td>Methods reviewed annually during CC monitoring visit</td>
<td>Supervisor and Monitor</td>
</tr>
<tr>
<td>MEDICAL DATA REVIEW</td>
<td>Local approval</td>
<td>Supervisor or PI</td>
<td>Methods reviewed annually during CC monitoring visit</td>
<td>Supervisor and Monitor</td>
</tr>
<tr>
<td>MEDICAL HISTORY self-administered form</td>
<td>Adequate explanation on 5 taped introductions to participants</td>
<td>Supervisor or Lead interviewer</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>MEDICATION SURVEY Interview Transcription/coding</td>
<td>Adequate technique on 5 taped interviews</td>
<td>Supervisor or Lead Interviewer</td>
<td>Annually, 1 taped participant interview included in round robin</td>
<td>4 field center interviewer supervisors monitoring round robin tapes</td>
</tr>
<tr>
<td>MICROALBUMINURIA Urine collection and processing</td>
<td>Lead technician certified at central training; all others @ central training or by lead tech @ field centers</td>
<td>Central trainer or lead technician</td>
<td>Biannual (Jan/July) review of techniques Annual CC or central lab monitoring visit</td>
<td>Lead Technician Monitor</td>
</tr>
<tr>
<td>ORAL GLUCOSE TOLERANCE TEST</td>
<td>Lead technician certified at central training; all others @ central training or by lead tech @ field centers</td>
<td>Central trainer or lead technician</td>
<td>Biannual (Jan/July) review of techniques Annual CC or central lab monitoring visit</td>
<td>Lead Technician Monitor</td>
</tr>
<tr>
<td>PERIODONTAL EXAM Examiner</td>
<td>Examiners certified at central training and satisfactory performance of 5 exams</td>
<td>Dental Study PI Central trainer</td>
<td>Annual central refresher training Annual CC monitoring visit</td>
<td>Dental Study PI Monitors</td>
</tr>
<tr>
<td>PROCEDURE OR INTERVIEW</td>
<td>CERTIFICATION REQUIREMENT</td>
<td>CERTIFIER OR REVIEWER</td>
<td>RECERTIFICATION REQUIREMENTS</td>
<td>RECERTIFIER OR REVIEWER</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------------</td>
<td>-----------------------</td>
<td>-----------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Recorder</td>
<td>Certified at central training or by examiner at field centers</td>
<td>hygienist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PERSONAL HISTORY interview</td>
<td>Adequate technique on 5 taped interviews</td>
<td>Supervisor or Lead interviewer</td>
<td>Annually, 1 taped participant interview included in round robin</td>
<td>4 field center interviewer supervisors monitoring round robin tapes</td>
</tr>
<tr>
<td>PHYSICAL ABILITY self-administered form</td>
<td>Adequate explanation on 5 taped introductions to participants</td>
<td>Supervisor or lead interviewer</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>RECEPTION Informed consent Fasting/tracking form OGTT Screening</td>
<td>Adequate methods on 5 taped receptions</td>
<td>Supervisor or lead interviewer</td>
<td>Annual review</td>
<td>Supervisor or Lead Interviewer Monitor</td>
</tr>
<tr>
<td>UPDATE form</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>REPRODUCTIVE HISTORY interview</td>
<td>Adequate technique on 5 taped interviews</td>
<td>Supervisor or Lead interviewer</td>
<td>Annually, 1 taped participant interview included in round robin</td>
<td>4 field center interviewer supervisors monitoring round robin tapes</td>
</tr>
<tr>
<td>Transcription/coding</td>
<td>80% correct on coding exercises</td>
<td>Supervisor or Lead interviewer</td>
<td>Annual CC monitoring visit</td>
<td>Monitor</td>
</tr>
<tr>
<td>SES interview</td>
<td>Adequate technique on 5 taped interviews</td>
<td>Supervisor or Lead interviewer</td>
<td>Annually, 1 taped participant interview included in round robin</td>
<td>4 field center interviewer supervisors monitoring round robin tapes</td>
</tr>
<tr>
<td>TIA/STROKE interview</td>
<td>Adequate technique on 5 taped interviews</td>
<td>Supervisor or Lead Interviewer</td>
<td>Annually, 1 taped participant interview included in round robin</td>
<td>4 field center interviewer supervisors monitoring round robin tapes</td>
</tr>
<tr>
<td>Med review abn. symptoms</td>
<td>Local approval</td>
<td>Supervisor or PI</td>
<td>Annual review</td>
<td>Monitor</td>
</tr>
<tr>
<td>ULTRASOUND Scan and postural change</td>
<td>Attend central training @ URC Submit 10 acceptable B-mode scans</td>
<td>URC /Chief sonographer</td>
<td>Monitored continuously at URC</td>
<td>URC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Biannual QC review</td>
<td>URC and QC Committee</td>
</tr>
<tr>
<td>VENIPUNCTURE</td>
<td>Lead technician certified at central training; all others @ central training or by lead tech at field centers</td>
<td>Central trainer or Lead Technician</td>
<td>Biannual (Jan/July)</td>
<td>Lead Technician Monitor</td>
</tr>
</tbody>
</table>
2.2 Participant Flow

The participant flow is based on a paradigm used successfully since Visit 1, and modified to reflect study requirements in subsequent visits and the operational needs of the individual field centers. The schedule is divided into fixed and non-fixed sequences to accommodate legal requirements, scientific constraints of which measurements cannot precede another, the daily fluctuations in field center staffing patterns and unforeseen number of participants who keep scheduled appointments, the configuration of each field center's physical layout, equipment availability and function; the integration of ancillary studies, and so forth. Participant flow and the approximate time associated with each workstation are outlined in Table 2.3.

2.2.1 Rationale

The fixed components of scheduling participant flow are identical at all four field centers reflecting the requirement to initiate the examination with the administration of informed consent, the scientific constraints which establish the grouping of procedures which require fasting, and the logistical necessity of conducting medical data reviews after all other procedures have been completed. The flexible components reflect the advantages of having the separate field centers conduct the majority of the interviews and examinations in accordance with the physical layout and the scheduling patterns of the individual field centers. This approach is intended to minimize participant burden to approximately 4 hours and reduce variability in study measurements.

2.2.2 Fixed Sequences

The introduction of the oral glucose tolerance test (OGTT) and measurements of heart rate variability (HRT) in Visit 4 has substantially increased the number of components that must be conducted while the participant is fasting. An outline of the components, and the order in which they must be scheduled, is provided in Table 2.3. As has been done in Visits 1-3, Visit 4 always begins with the administration of the informed consent at the reception workstation and always ends with the reporting of preliminary study results to participants at the medical data review workstation. The collection of a urine sample from the participant is simplified when done in conjunction with the change from street clothes to a scrub suit and is therefore scheduled at the conclusion of the reception workstation and prior to the anthropometry/blood pressure workstation. (Note: a urine specimen can be collected at any time during the exam if the participant cannot void immediately after reception.) Because the measurement of sitting blood pressure requires knowledge of the circumference of the right arm in order to select the appropriate blood pressure cuff, anthropometry is
Table 2.3  Participant Flow in Visit 4

<table>
<thead>
<tr>
<th>PROCEDURES/WORKSTATIONS</th>
<th>Approximate Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIXED SEQUENCING</td>
<td></td>
</tr>
<tr>
<td>RECEPTION</td>
<td>15 min</td>
</tr>
<tr>
<td>Informed consent</td>
<td></td>
</tr>
<tr>
<td>Informed consent tracking</td>
<td></td>
</tr>
<tr>
<td>Update of contact information</td>
<td></td>
</tr>
<tr>
<td>Fasting status</td>
<td></td>
</tr>
<tr>
<td>OGTT Screening</td>
<td></td>
</tr>
<tr>
<td>CHANGE CLOTHES/</td>
<td></td>
</tr>
<tr>
<td>COLLECTION OF URINE SAMPLE</td>
<td>6 min</td>
</tr>
<tr>
<td>ANTHROPOMETRY</td>
<td>6 min</td>
</tr>
<tr>
<td>SITTING BLOOD PRESSURE</td>
<td>10 min</td>
</tr>
<tr>
<td>12 LEAD ECG</td>
<td>15 min</td>
</tr>
<tr>
<td>HEART RATE VARIABILITY</td>
<td>15 min</td>
</tr>
<tr>
<td>VENIPUNCTURE</td>
<td>6 min</td>
</tr>
<tr>
<td>GLUCOSE TOLERANCE TEST</td>
<td>5 min</td>
</tr>
<tr>
<td>FLEXIBLE SEQUENCING</td>
<td></td>
</tr>
<tr>
<td>DENTAL EXAM</td>
<td>35 min</td>
</tr>
<tr>
<td>STAFF ADMINISTERED INTERVIEWS</td>
<td>30 min</td>
</tr>
<tr>
<td>Cognitive Function</td>
<td>Medication Survey</td>
</tr>
<tr>
<td>Dental History</td>
<td>Personal History</td>
</tr>
<tr>
<td>Health History</td>
<td>Reproductive History</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Socioeconomic Status</td>
</tr>
<tr>
<td>TIA/Stroke</td>
<td></td>
</tr>
<tr>
<td>SELF-ADMINISTERED INTERVIEWS</td>
<td>10 min</td>
</tr>
<tr>
<td>Health and Life Profile (Self-Admin)</td>
<td></td>
</tr>
<tr>
<td>Medical History Questionnaire (Self-Admin)</td>
<td></td>
</tr>
<tr>
<td>Physical Ability Questionnaire (Self-Admin)</td>
<td></td>
</tr>
<tr>
<td>ULTRASOUND</td>
<td>40 min</td>
</tr>
<tr>
<td>Carotid arteries/Postural change in blood pressure</td>
<td></td>
</tr>
<tr>
<td>2ND VENIPUNCTURE</td>
<td>2 min</td>
</tr>
<tr>
<td>SNACK (After 2nd blood draw)</td>
<td>8 min</td>
</tr>
<tr>
<td>FIXED SEQUENCING</td>
<td></td>
</tr>
<tr>
<td>DATA INVENTORY</td>
<td>6 min</td>
</tr>
<tr>
<td>CHANGE CLOTHES</td>
<td>5 min</td>
</tr>
<tr>
<td>MEDICAL DATA REVIEW</td>
<td>10 min</td>
</tr>
<tr>
<td>Medical Data Review</td>
<td></td>
</tr>
<tr>
<td>TIA/Stroke Summary (not study data)</td>
<td></td>
</tr>
</tbody>
</table>
LAG TIME BETWEEN WORKSTATIONS

12 min

TOTAL FOR ULTRASOUND PROTOCOL 4 hours
TOTAL FOR OTHER 50 PERCENT 3 hrs 20 min

generally performed prior to sitting blood pressure, and is generally performed at the same workstation. Venipuncture must be done while the participant is in the fasting state, therefore venipuncture is always scheduled prior to the administration of the glucose load. The administration of the glucose load is known to affect heart rate variability. Therefore, the ECG/HRT sequence is always scheduled prior to venipuncture. A minimum of 5 minutes needs to elapse between a procedure in the supine position (such as the ECG and the measurement of heart rate variability) and the blood draw. The order in which anthropometry/sitting blood pressure and ECG/HRT, however, is a local option. The 2nd venipuncture of cohort members participating in the OGTT must be scheduled 2 hours after the ingestion of the glucose load. Interviews or the dental exam may be interrupted by the laboratory technician to perform the 2nd venipuncture if waiting would result in the post-glucose sample being drawn more than 10 minutes before or after than the target collection time.

2.2.3 Flexible Sequences

The staff- and self-administered interviews, oral exam, ultrasound scan of the carotid arteries, and 2nd venipuncture are scheduled in the non-fixed portion of the exam.

The Participant Information (PIN) Sheet (Appendix 2.16) is prepared by the Coordinating Center and serves as a summary of clinically relevant data from previous ARIC exams for use during reception, interviews and medical data review. The participant’s record of data collection is documented on the ARIC Cohort Inventory (CXI, Appendix 2.3.a) form within the Data Entry System, and manually on the Sample Inventory Record (SMP, Appendix 2.3.b) in the DES. The CXI is completed as a function of the DES software as each interview or procedure is completed and monitors the completion of data collection forms. The SMP serves as the summary of procedures performed during the clinic visit is entered into the DES following the participant's visit. The Participant Itinerary Sheet (Appendix 2.17) is prepared by the individual field center and is attached to a participant's folder. It has several purposes: to monitor the amount of time it takes to complete each component of the examination; to provide staff with information about where the participant is in the process, or to establish the participant's sequence of procedures and interviews based on daily staffing patterns.

2.3 Reception

The reception workstation initiates the Visit 4 interviews and clinical measurements at the field center. Prior to the participant's arrival, a Visit-4 folder is assembled which contains labelled data collection forms: the most recent Annual Follow-up (AFUF) and Record of Calls and Scheduling (TRCF) forms (these may also be filed in a separate, recruitment folder at the discretion of the field center, but are available for use during the ARIC exam), the Update (UPDB) form, the Participant Itinerary Sheet (PIN), the Dental Screening (DSRA) Form, and blank copies of the ARIC Visit 4 and Dental Study Informed Consent forms, the Fasting/Tracking (FTRD) form, the Oral Glucose Tolerance Test screening (GTSB) form, the Venipuncture (LABB) and Oral Glucose Tolerance Administration (GTAA) forms (data are collected on paper for delayed data entry), the Cognitive Function Test (CNFC) form (data are collected on paper for delayed data entry), and the Health and Life Profile (HPCB), Medical History (MHQA), and Physical Ability (PAQA) forms (self-administered forms completed by participants between work stations). Folders also contains previously completed Report and Referral forms and ALERT/REFERRAL logs and blank copies for use in Visit 4. The Itinerary Sheet is attached to the outside of the clinic visit folder.
On arriving at the field center, the participant is greeted and welcomed. Informed consent for the full ARIC exam (Appendix 2.11.a) is obtained before administering any other ARIC interviews. The ARIC Dental Study informed consent (Appendix 2.11.b) is administered in conjunction with or after the ARIC study informed consent, at local discretion. Participant questions are answered. Demographic and tracking information (Update Form, Appendix 2.22) are updated. Fasting status (Fasting/Tracking form, Appendix 2.7) is determined. The person's eligibility (OGTT Screening Form, Appendix 2.15 and previous status of treated diabetes on the PIN sheet) and consent to participate in the oral glucose tolerance test are ascertained. Consent to tape interviews for quality assurance assessment is requested and documented on the Itinerary sheet (Appendix 2.17). The Informed Consent Tracking form (Appendix 2.12) is completed either during or after the participant has left the reception work station. Medication bags are logged and labelled.

General instructions on how to administer each interview are given in the text of Chapter 2 under the name of the data collection form. Specific instructions for completing each item on the data collection form are given in the question by question (QxQ) instructions which follow the form in the Appendix.

When screening for the Dental Study has not been done prior to the Visit 4 exam, the Dental Screening form (Appendix 2.6) is administered at the reception work station, and eligible cohort members are recruited to have a dental exam, the same day if possible, and the Dental Study informed consent is administered.

The schedule for reporting the participant's study results can be reviewed with the participant at the reception work station as a local option. The interviewer explains that some of the study results are reported at the conclusion of the exam before the participant leaves the field center. All study results done during the visit are reviewed with the ARIC clinician after the participant has left the field center (Appendix 5). A final summary report is mailed to the participant and his/her physician (with his/her permission) 6 - 8 weeks after the clinic visit date, as described in Chapter 7 (RESULTS REPORTING). Referral letters are mailed to participants and their physicians in conjunction with their final summary report when study results are out-side of the study's reference ranges, or prior to that when study results are found to be an alert value (Chapter 7, Appendix 6 and 7).

When informed consent and the Update, Fasting and OGTT Screening forms have been administered, and eligibility to do the glucose tolerance test confirmed, the participant is shown where to change into an examination gown/robe, asked to remove all jewelry, and to place clothing and valuables in a secured locker. The participant is requested to provide a urine sample, if possible, and then empty the bladder prior to beginning the examination. Specific instructions on how to collect the urine sample are given in Chapter 3.5.

Staff are trained for the reception work station at central training and locally by the Study Coordinator at each field center. Certification requirements include the successful completion of training on general interviewing techniques, Informed Consent, the Fasting/Tracking form, Direct Data Entry System, and OGTT Screening. Although no formal certification schedule has been established, interviewers working at the reception work station are observed by the local study coordinator for quality assurance and standardization.
2.4 Cognitive Function

In Visit 4, a standardized test of Cognitive Function (CNFC) is administered to all participants (Appendix 2.4). The blank data collection form (Appendix 2.4.a) is filed in the participant's folder. The three components (Delayed Word Recall, Digit Symbol Substitution Task, and the Word Fluency Task) are those administered to all participants in Visit 2, and the participants in Forsyth County, NC and Jackson, MS who had cerebral MRI scans. The administration and scoring instructions, and the data entry system (DES) screen are unchanged from previous visits. This includes a prohibition of the taping of the procedure.

2.4.1 Rationale

The main objective of cognitive function testing in Visit 2 was to establish a baseline for future comparison. Although the ARIC study population continues to be too young in Visit 4 to focus on frank dementia, the repeated measurement of cognitive function provides the opportunity to investigate changes in cognitive function over time. This in turn can be correlated with specific risk factors.

The three measures used in Visit 2 are repeated: the Delayed Word Recall, Digit-Symbol Substitution and Word Fluency tests. None of these tests have an upper limitation on performance, and can be expected to allow small changes in mental performance to be detected longitudinally.

The Delayed Word Recall is a test of short term memory. This test has the added feature of allowing participants to encode the words to be recalled (use each word in a sentence) to enhance retrieval. Ten words are given which in effect removes the ceiling or upper limit of performance.

The Digit Symbol Substitution Test requires response speed, sustained attention, and visual-spatial skills. It is part of the Wechsler Adult Intelligence Scale. This test requires that the participant fill in a series of symbols within 90 seconds.

The Word Fluency Test measures verbal function. This too requires speed and sustained attention, but measures mental agility in retrieving words.

2.4.2 Administration

A trained ARIC interviewer administers the cognitive function tests, one right after the other, in a quiet room which is sheltered from distracting noises and has sufficient work space for the participant to place the Digit Symbol Substitution form on a table and fill in the blanks on the form. The purpose of the tests is briefly explained to each participant. The tests are administered following the instructions printed on the Cognitive Function paper forms (Appendix 2.4.a) and QxQ instructions (Appendix 2.4.c). Responses to Parts A and C are recorded on a paper form by the interviewer. Part B is completed by the participant. Test results are tabulated by the interviewer after the participant has completed the tests and left the room. Test results are entered on the Cognitive Function DES screen (Appendix 2.4.b) by the interviewer.

2.4.3 Training

Interviewers are trained centrally prior to Visit 4. The field center interviewer supervisor is responsible for the training and certification of new field center interviewers.

2.4.4 Certification

Certification for administering the Cognitive Function form is achieved by the demonstration of adequate technique on interviews on non-ARIC participants,
and approved by the supervisor or lead interviewer. Recertification is done annually, and requires the successful completion of one interview reviewed by the local interviewer supervisor.

2.4.5 Quality Assurance

Technique and adherence to protocol are monitored by Coordinating Center Monitors; data quality is monitored by the Quality Control Committee semi-annually.

2.4.6 Data Collection

Results of the Delayed Word Recall and the Word Fluency Task are recorded by the interviewer on the Cognitive Function form. Symbols for digits are recorded on the form by the participant. Test scores are calculated and entered by the interviewer on the last page of the form for delayed data entry (Appendix 2.4.b), after the participant has left the work station.

2.5 Dental History

The Dental History (DHSA) form is included in Visit 4 as part of the initiative to study the association of chronic inflammation, as measured in individuals with periodontal disease, with atherosclerosis and its sequelae (Appendix 2.5.a). The Dental History form is administered to all ARIC participants, regardless of whether they are scheduled for the dental examination. The questions are designed to document aspects of the participant's dental status, which may be related to a history of chronic inflammation. The form includes questions on the cause(s) of tooth loss, loose teeth, false teeth, root canal(s), dental implant(s), frequency of brushing and flossing, and the use of dental care.

2.5.1 Rationale

During Visit 4, data on chronic inflammation are being collected to explore its association with atherosclerosis and thrombo-embolic events. During the interviews at the field center, self-reported medical histories of chronic infections are recorded on the Inflammation Form and the Medical History Questionnaire. Periodontal disease also represents a form of chronic inflammation which can be assessed both by recording a person's history of periodontal disease, as is done in the Dental History form (see below), and by performing a non-invasive clinical examination of the mouth, which is done in the dental exam (see the ARIC Dental Procedures Manual of Operations). By administering the Dental History form to all study participants, it is possible to collect a history of conditions which may reflect or result in periodontal disease as a surrogate measure of chronic inflammation.

2.5.2 Administration

The Dental History form is designed to be administered to all ARIC participants by trained and certified ARIC interviewers as part of the standard battery of interviewer-administered interviews. Like other ARIC forms, the questions on dental history are written using lay terminology, and are supported by QxQ instructions (Appendix 2.5.c) for the interviewer. Participant responses are either entered on a paper form for delayed data entry or entered directly into the DES (Appendix 2.5.b).

2.5.3 Training

The field center interviewer supervisor is responsible for the training and certification of new field center interviewers.

2.5.4 Certification
Certification for administering the Dental History form is identical to that required for the administration of the other ARIC interviewer-administered forms, and is achieved by the demonstration of adequate technique on 5 taped interviews on non-ARIC participants, reviewed and approved by the supervisor or lead interviewer. The dental examiner or hygienist performing the dental examination may administer the Dental History and record participant responses on a paper form for delayed data entry only when certified to administer the form. Recertification is done annually, and requires the successful completion of one taped interview of an actual ARIC participant. With participant approval, all interviews are taped for quality control. This tape is included in the round robin which is reviewed by the four interviewer supervisors selected to monitor each year's round robin tapes.

2.5.5 Quality Assurance

With participant approval, most staff-administered interviews are taped for quality control. A non-systematic sample of the taped Dental History interviews are reviewed by the supervisor. Technique and adherence to protocol are also monitored by Coordinating Center Monitors; data quality is monitored by the Quality Control Committee semi-annually.

2.5.6 Data Collection

The Dental History form data are collected by direct data entry on a data entry screen (Appendix 2.5.b) unless the computer is not operational.

2.6 Dental Screening

The Dental Screening (DSRA) form is usually administered during the recruitment/scheduling call (Appendix 2.6.a). It can also be administered at the reception work station if eligibility to participate in the dental exam has not been established prior to the clinic visit. However, delayed determination of eligibility compromises the efficient scheduling of dental exams of eligible participants. Screening determines whether the participant has any teeth or whether the person would be placed at risk if a dental examination were performed without coverage by an antibiotic. See Section 3.2 for a description of the procedures in the Dental Study.

2.6.1 Rationale

Screening of ARIC participants prior to their clinic visit is done to identify persons in whom an oral examination is not informative, and as a safety precaution, following American Heart Association guidelines.

2.6.2 Administration

The Dental Screening form is a new form in Visit 4, and is designed to be administered as part of the Annual Follow-Up interview and Visit 4 scheduling call. An introductory script is provided in the QxQ instructions (Appendix 2.6.c) to aid the interviewer in providing a standardized explanation that a dental exam has been added to the procedures in Visit 4. The script is read to participant prior to administering the form. A table of definitions and synonyms of the medical terms used in the questions is also included in the QxQ instructions to assist interviewers in interpreting participant responses or defining terms to participants who are unsure as to whether or not they have had one or more of the medical conditions which would result in exclusion from the dental exam. As soon as an exclusion criterion is identified, the interviewer skips to the end of the form and informs the participant that he/she is not eligible to participate, either because (1) the person does not have any of his/her natural teeth; (2) the person has been told by a dentist that he/she needs to take antibiotics before every dental exam; or (3) the person reports having had a medical condition which requires the person to have antibiotics before a dental exam or procedure, according to American Heart Association guidelines. When no exclusion criteria are identified, the
interviewer, using the script printed on the form, explains what takes place during the dental exam and attempts to recruit the participant. When a participant is uncertain about the need to have an antibiotic prescribed for all dental exams or procedures, or is uncertain whether he/she has one of the medical conditions on the form, the interviewer selects the response category of UNKNOWN, does not exclude the person, and encourages the person to contact his/her doctor or dentist and resolve the uncertainty prior to coming to the ARIC exam. In situations where the participant indicates that he or she does not have a doctor/dentist with whom to consult, the interviewer can volunteer to discuss the situation with the local ARIC physician. When the person comes to the field center and the uncertain status of an exclusion criterion has not been resolved, the UNKNOWN status is changed to YES, and the person is excluded from the dental examination, unless the ARIC physician has indicated otherwise.

When a participant meets an American Heart Association exclusion criterion, AND REQUESTS the dental examination, the person can be recruited into the study if he/she agrees to take the antibiotics required for a dental examination. These antibiotics have to be prescribed by a dentist or physician, with the knowledge of the date of the ARIC exam. A special note is made and initialed on the Dental Exam Informed Consent that the participant has an exclusion criterion and is taking the required antibiotics.

2.6.3 Training

The field center recruitment interviewer supervisor is responsible for the training and certification of new field center interviewers.

2.6.4 Certification

Certification for administering the Dental Screening form is identical to that required for the administration of the other ARIC interviewer-administered forms, and is achieved by the demonstration of adequate technique and adherence to protocol, reviewed and approved by the supervisor or lead interviewer.

2.6.5 Quality Assurance

Routine quality assurance is provided at each field center by means of observation by the local study coordinator and recruitment supervisor. Administrative techniques and adherence to protocol are also monitored by Coordinating Center and Dental Study Monitors; frequency distributions of consent preferences recorded on the Dental Screening Form are routinely monitored by the Dental Study investigators and by the ARIC Quality Control Committee semi-annually.

2.6.6 Data Collection

In general, data are recorded on the paper version of the form during the AFU/Visit 4 Scheduling interview for delayed data entry into the ARIC DES. When necessary, the form can be administered (1) during an extra telephone when it is necessary to call back a participant who has already attended his/her Visit 4 exam, or (2) it can be administered to the participant at the reception work station when the person arrives at the field center without having had his/her eligibility ascertained. In all cases, the paper version of the form is completed for delayed data entry into the ARIC DES (Appendix 2.6.b).

2.7 Fasting/Tracking

The Fasting/Tracking (FTRD) form (Appendix 2.7.a) is a core data collection form which is unchanged since Visit 2. The form is administered at reception and documents the participant's fasting status, confirms one of the criteria for participation in the OGTT (minimum fasting for 10 hours), and establishes
the participant's official visit date for Visit 4.

2.7.1 Rationale

The participant's fasting status affects the measurement of glucose, and the lipid and hemostatic profiles. To standardize measurements, participants are requested to take nothing by mouth except water for 12 hours prior to arriving at the field center.

2.7.2 Administration

QxQ instructions for administering the Fasting/Tracking form are provided in Appendix 2.7.c. The participant's fasting status is verified. Strict fasting is defined as nothing taken by mouth, except water, for the preceding 12 hours. However, for purposes of results reporting of the clinical chemistries, participants can be considered fasting if they have fasted for at least 10 hours or if they have ingested no more than one cup of black, unsweetened coffee/tea within the past 10 hours. Ingestion of more substantive liquids or solids constitutes breaking the fast. The participant's fasting status is recorded in number of hours on the Fasting/Tracking form, but the consumption of coffee/tea is recorded in a note log. Likewise for determining eligibility for the OGTT, participants who have fasted for at least 10 hours are considered fasting (see Section 2.15 for further instructions on determining OGTT eligibility).

Blood samples are drawn on all participants, regardless of fasting status. If the participant has not fasted for 10 hours, the participant is also offered the opportunity to repeat blood drawing in the fasting state at a later date. The Fasting/Tracking Form is completed; the non-fasting state and rescheduled date of venipuncture are noted on the Participant Inventory Form. When the participant returns in the fasting state for venipuncture, the questions concerning fasting status and recent blood donation on the Fasting/Tracking form are updated, and the Lipid and Hemostasis laboratories are notified that replacement samples are being shipped (See Section 3.9).

The Fasting/Tracking Form also documents whether the participant has given blood within the last 7 days. It is assumed that very few cohort members will have donated blood within the last week as they are reminded during both the scheduling calls not to do so, or to reschedule their clinic visit if they have had to give blood. Recent donors are not rescheduled once they come for Visit 4; the response to question 5 on the Fasting/Tracking form is recorded to reflect the recent blood donation and the individual is sent to the venipuncture workstation.

2.7.3 Training

Staff are centrally trained before Visit 4 and the study coordinator is responsible for providing training for new staff.

2.7.4 Certification

Certification for administering the Fasting/Tracking form is achieved by the observation of reception procedures by the Study Coordinator or interviewer supervisor. Recertification is done annually, and requires the successful completion of one taped interview. With participant approval, all interviews are taped for quality control. This reception tape is included in the round robin which is reviewed by the four interviewer supervisors selected to monitor each year's round robin tapes.

2.7.5 Quality Assurance

Routine quality assurance is locally provided by observation of the study coordinator. Protocol adherence and interviewing techniques are reviewed at least biannually by Coordinating Center field center monitors. Deviations from protocols and possible remedial actions are discussed with study
coordinators and staff at that time. Major deviations are brought to the attention of the ARIC Cohort Operations Committee.

2.7.6 Data Collection

The Fasting/Tracking form is collected by direct data entry on a data entry screen unless the computer is not operational. Computed fasting time is calculated by the Data Entry System (DES). A paper version of the form is available for back-up and subsequent data entry. Computed fasting time may be hand calculated, or obtained from a precalculated chart in the Fasting/Tracking form question by question instructions, and written in the margin to assist in determining the need to reschedule the participant for venipuncture. The computed fasting time is calculated by the data entry system when the data are batch entered into the data entry system (Appendix 2.7.b).

2.8 Health History

The Health History (HHXD) form (Appendix 2.8.a) is a core data collection form which is administered during the flexible component of the exam. In Visit 4, it serves as a follow-up to participant-reported chest pain on effort reported by the participant during the previous year (i.e., ascertained during the most recent AFU interview). The occurrence of the participant-reported chest pain is confirmed as positive angina and/or myocardial infarction by London School of Hygiene criteria. The questionnaire also documents the occurrence of procedures to diagnose or treat cardiovascular disease since the last ARIC exam, records information on the life time occurrence of head injuries which either resulted in loss of consciousness or required medical care and the age of the first blood transfusions and the source(s) of the first and any subsequent transfusions any time prior to the interview, and whether the participant requires aid in walking or standing.

2.8.1 Rationale

A major objective of the ARIC Study is the assessment of coronary heart disease (CHD) in the study population at each clinical examination and across time since the baseline examination. This is done, in part, by the documentation of the symptoms of heart disease and exposure to diagnostic and therapeutic procedures of each participant at each Visit. Another objective is a similar assessment of cerebrovascular disease (stroke). Questions on the life-time history of serious head injuries, defined as those which resulted in a loss of consciousness or required medical care, help evaluate other information collected symptoms of TIA or stroke. Information on the receipt of blood transfusions may help in the assessment of the associations of infections with atherosclerosis.

2.8.2 Administration

The Health History form is administered by trained and certified interviewers with an understanding of the medical terms and diagnostic procedures referred to in this instrument. The frame of reference for questions in Section A (chest pain on effort) and Sections B and C (invasive/non-invasive diagnostic and therapeutic cardiovascular procedures) is the time period between the 3rd and 4th ARIC examinations. Detailed procedures for administering the form are provided in the question by question instructions immediately following the form in Appendix 2.8.c and in the central training manual. Interviewers refer to the PIN sheet in the participant’s folder to determine whether chest pain reported during the most recent AFU interview meet diagnostic criteria for Rose positive angina.

2.8.3 Training
Field center staff are centrally trained before Visit 4; they are responsible for providing training to new staff in interviewing techniques, technical terminology, and the question by question instructions for the Health History form.

2.8.4 Certification

Certification for administering the Health History form is achieved by the demonstration of adequate technique on 5 taped interviews, reviewed and approved by the supervisor or lead interviewer. Recertification is required annually, and requires the successful completion of one taped interview. With participant approval, all interviews are taped for quality control. This tape is included in the round robin which is reviewed by the four interviewer supervisors selected to monitor each year's round robin tapes.

2.8.5 Quality Assurance

With participant approval, most staff-administered interviews are taped for quality control. A non-systematic sample of taped Health History interviews are reviewed once a month by the supervisor. Technique and adherence to protocol are also monitored at least semi-annually by Coordinating Center Monitors; data quality is monitored by the Quality Control Committee on a semi-annual basis.

2.8.6 Data Collection

Data from the Health History form are collected by direct data entry unless the work station computer is inoperable. A paper version of the form is available for back-up and delayed data entry (Appendix 2.8.b).

2.9 Health and Life Profile

The Health and Life Profile (HPCB) form in Visit 4 (Appendix 2.9.a) repeats one portion of the form (Part C) which was originally administered during Visit 2. Part C is the Spielberger Trait Anger form and was designed to measure personality traits. The form is self administered. Although a brief explanation of the hypotheses to be tested is given below, no explanations, other than those provided on the form, are given to participants if they inquire as to why they need to respond to the statements on the form.

2.9.1 Rationale

Several components of Type A behavior, such as anger and hostility, have been shown in some studies to be associated with the risk factors and the expression of heart disease and stroke. This portion of the Health and Life Profile is administered to test many of the current hypotheses, and is being re-administered to assess consistency or changes over time in this putative measure of anger as a personality trait at the population level.

2.9.2 Administration

The Health and Life Profile form is designed to be self-administered, but can be interviewer administered if necessary. QxQ instructions are in Appendix 2.9.c. The form begins with printed instructions, is followed by ten statements (Items 1-10) to which the participant selects a response of ALMOST NEVER, SOMETIMES, OFTEN, ALMOST ALWAYS, and ends with an administrative section (Items 11-13) which is completed by the interviewer. The interviewer records in Item 12 of the Administrative Section whether the form was self-administered (A), interviewer-administered (B), both (C), or not done (D). Because the majority of participants will use this as a self-administered form, the option for no response and the definitions of type of administration are not printed on the form. Detailed instructions for self- or interviewer-administration are provided in the QxQ instructions in Appendix 2.9.c.
Prototype scripts which can be read to introduce and explain how to complete the self- or interviewer-administered versions of the form and are also included at the end of the QxQ instructions (2.9.d).

2.9.3 Training

Staff are centrally trained and the study coordinator is responsible for providing training for new staff.

2.9.4 Certification

Certification for administering the Health and Life Profile form is achieved by the demonstration of adequate technique in administering the instructions on how to complete the form and approved by the supervisor or lead interviewer. Recertification is required annually, and requires the successful completion of an explanation, observed by the interviewer supervisor.

2.9.5 Quality Assurance

Routine quality assurance is locally provided by observation of the study coordinator. Protocol adherence and interviewing techniques are reviewed by Coordinating Center field center monitors. Deviations from protocols and possible remedial actions are discussed with study coordinators and staff at that time. Major deviations are brought to the attention of the ARIC Cohort Operations Committee.

2.9.6 Data Collection

The Health and Life Profile form is designed to be self-administered, and even though it can be interviewer administered, it is always completed on paper. Data are subsequently keyed by the interviewer into the DES (Appendix 2.9.b). The HPCB data entry screen is one of the few DES screens that is different from the paper version of the form in that an additional response category, "E" for "no response" is available in Items 1-10 for the interviewer to document the participant did not respond to the statement.

2.10 Inflammation

The Inflammation (INFA) form is a new interview in Visit 4 to collect information on the participant's prior history of a series of chronic infectious diseases, treatment with antibiotics, and a history of periodontal disease (Appendix 2.10.a). The introductory script of the interview serves as a brief explanation to the participant as to why questions on a history of chronic infectious diseases and periodontal disease is being collected, and tangentially, why the periodontal exam is also being performed.

2.10.1 Rationale


2.10.2 Administration

The Inflammation Form is administered by a study-certified nurse/nurse
practitioner, licensed practical nurse or an equivalently trained field center staff member with a general understanding of the medical terminology referred to in this interview. The time frame during which these conditions were diagnosed varies, requiring careful administration of each question. The exact wording and order of the questions are followed to ensure standardization. QxQ instructions and a table of standardized definitions and synonyms for the use of the interviewer are provided in Appendix 2.10.c. As a positive response to most (note, not all) of the lead-in questions of the diseases and conditions covered in the interview requires the diagnosis by a physician, the name of the disease/condition should be familiar to the participant. As with the administration of all other interviews, the definition of a term is only provided if the participant requests clarification.

2.10.3 Training

Interviewers are trained centrally prior to Visit 4. The field center interviewer supervisor is responsible for the training and certification of new field center interviewers.

2.10.4 Certification

Certification is achieved by the demonstration of adequate technique on 5 taped interviews, reviewed and approved by the supervisor or lead interviewer. Recertification is required annually, and requires the successful completion of one taped interview of an actual participant. With participant approval, all interviews are taped for quality control. This tape is included in the round robin which is reviewed by the four interviewer supervisors selected to monitor each year's round robin tapes.

2.10.5 Quality Assurance

With participant approval, most staff-administered interviews are taped for quality control. A non-systematic sample of Inflammation forms are reviewed by the supervisor. Technique and adherence to protocol are also monitored by Coordinating Center Monitors; data quality is monitored by the Quality Control Committee semi-annually.

2.10.6 Data Collection

The Inflammation form is designed to be interviewer-administered and collected by direct data entry (Appendix 2.10.b) unless the work station system is inoperable. A paper version of the form is available for back-up and delayed data entry. The format for most of the conditions is a lead-in question in which the time frame is a life time history and the disease must have been diagnosed by a doctor, followed by a question on the frequency of episodes within the past 10 years and concluding with a question as to whether the person has had at least one episode in the 12 month's prior to the interview. Negative or equivocal responses to lead-in questions trigger a skip to the next disease/condition.

2.11 Informed Consent

Administration of informed consent precedes all other activities at the field center. The core content and consent options of the Visit 4 (Appendix 2.11.a) and the Dental Study (Appendix 2.11.b) informed consent documents comply with the National Institutes of Health and the National Heart, Lung, and Blood Institute guidelines on the protection of human subjects, the American Society of Human Genetics' statement on informed consent for genetic research and the approval of the ARIC Steering Committee. The wording of the consent forms administered at the individual field centers, however, has been tailored to meet the specific requirements of their local Institutional Review Board, which reviews and approves all human research sponsored by their university.
2.11.1 Rationale

The primary objective of re-administering the Visit 4 informed consent is to reaffirm that the participant understands (1) the purpose of the research; (2) what data collection procedures are used; (3) the risks and benefits of participation; (4) what procedures are in place to protect confidentiality; (5) he/she is free to participate, refuse any procedure or answer any question, and to withdraw at any time; (6) and that withdrawing carries no penalties. The updated informed consent has a record of the project director and a contact person. Signing permits the participant to indicate his/her current preference for the use and disposition of study data, including genetic materials, and to change his/her preference at a future date; reaffirms permission to release clinically relevant study data to the physician of his/her choice, and updates the participant's permission to abstract his/her medical records in the event of hospitalization or death. Because the dental study is funded as an ancillary study in ARIC, separate informed consent is obtained to have the dental examination. This second informed consent document more clearly identifies for each participant the exclusion criteria specific to the dental examination, which do not apply to the regular ARIC exam.

2.11.2 Administration

The goals of the ARIC study at the fourth exam and the dental study are reviewed with the participant prior to the administration of any other data collection instrument. Consent to participate in the regular ARIC examination (Visit 4) and the periodontal examination (ARIC Dental Study) is documented on two separate informed consent forms. (In general, eligibility and willingness to participate in the dental study will have been determined prior to the participant's arrival at the field center. Refer to Section 2.6, Dental Screening.) Time is allowed for the person to read and ask questions about the informed consent documents in a confidential setting. If the participant is visually handicapped or otherwise incapable of reading the study description and informed consent page, the narrative portion is read to him/her and then the person is asked to sign the document. The original Informed Consent documents are filed in the participant's ARIC study folder. At local option, a copy of each informed consent can be given to the participant.

2.11.3 Training

Interviewers are centrally trained in general interviewing techniques and the goals and objectives of informed consent. Study coordinators or interviewer supervisors are responsible for providing local staff training for new staff.

2.11.4 Certification

Although there is no formal certification schedule, interviewers who administer informed consent are observed by the local study coordinator or interviewer supervisor.

2.11.5 Quality Assurance

Routine quality assurance is provided at each field center by means of observation by the local study coordinator. Administrative techniques and adherence to protocol are also monitored at least semi-annually by Coordinating Center Monitors; frequency distributions of consent preferences recorded on the Informed Consent Tracking form (ICTA) are monitored by the Quality Control Committee on a semi-annual basis.

2.11.6 Data Collection

Descriptions of the study and the signature pages acknowledging informed consent for Visit 4 and the Dental Study are paper forms. The participant has the option of receiving a copy of the full informed consent document or the
signed consent statement. In all cases, the original signature page must be kept at the field center and stored in the participant's ARIC study folder.

2.12 Informed Consent Tracking

The Informed Consent Tracking (ICTA) form is an internal form that applies to the consent given by cohort members to participate in the regular ARIC study (Appendix 2.12.a). It tracks each participant's type of consent (full or partial), restrictions on use or storage of DNA (yes or no), type of restrictions on DNA use or storage (CVD research, ARIC only, no use/storage of DNA, other), other restrictions on procedures or use of study data (yes or no), type of restrictions on procedures or use of study data (CVD research, ARIC only, other), restrictions on release of results to participant's physician and permission to access medical records. The form is completed by ARIC staff, and NOT administered to participants.

2.12.1 Rationale

The purpose of the form is to document and track in the ARIC central database the initial level of, and subsequent (if any) changes to, participants' restrictions on the use of their DNA or other study data by ARIC investigators.

2.12.2 Administration

Items 1-8 on the Informed Consent Tracking form are completed by an interviewer at the reception workstation, and participants have read and signed the Visit 4 Informed Consent form. Items 9 through 14 are completed when a participant notifies the study of a desire to either change his/her type of consent or access to medical records, or to withdraw from the study. QxQ instructions are provided in Appendix 2.12.c.

2.12.3 Training

Staff are trained locally by the study coordinator or interviewer supervisor.

2.12.4 Certification

No certification is required.

2.12.5 Quality Assurance

Frequency distributions of consent preferences recorded on the Informed Consent Tracking form (ICTA) are monitored by the Quality Control Committee on a semi-annual basis.

2.12.6 Data Collection

Data for the Informed Consent Tracking form can be directly entered into the DES (Appendix 2.12.b) or collected on the paper version of the form for delayed data entry.

2.13 Medical History Questionnaire

The Medical History Questionnaire (MHQA, Appendix 2.13.a) is a new self-administered form in Visit 4 to document a life-time medical history of clinically diagnosed or symptoms of arthritis, hay fever, cataracts, thyroid diseases, systemic lupus, gout, stomach or duodenal ulcers, adenoma or polyp of the colon, deep vein thrombosis, pulmonary embolus, Parkinson's disease, gallbladder diseases, fractured hip/wrist/spine, urinary frequency, or for males, prostate surgery for reasons other than cancer.

2.13.1 Rationale
The collection of a medical history on each participant permits the assessment of overall health, and various non-cardiovascular morbid conditions.

2.13.2 Administration

The Medical History Questionnaire is a self-administered questionnaire given to each participant to complete between work stations or during snack. Usually, the form is attached to a clip board with a cover sheet for confidentiality to allow participants to carry it with them. The type of presentation, however, is left to local option. Each participant is instructed on how to complete the Medical History Questionnaire using a demonstration form (Appendix 2.13.c). Interviewers explain and administer the demonstration form, watch the participant complete the demonstration form, answer questions and determine whether assistance in completing the Medical History Questionnaire is requested or required. If assistance is needed, the Itinerary sheet is annotated, and the three self-administered forms (Medical History, Physical Ability and Health/Life Profile) are added to the interviews for staff-administration. If no assistance is requested, the participant is invited to work on the forms between work stations and return the clip board (or other carrying mechanism) to any ARIC staff upon completion. The forms are reviewed for completeness prior to the medical data review, and if incomplete, the participant is asked if assistance to complete the forms is needed. The administration date, type of administration (self (A), staff (B), both (C), not done (D)) and staff ID code are entered in Items 27-29 on the form.

One of the objectives of this form is to determine in a standardized fashion whether a doctor ever diagnosed the participant as having any of the medical conditions mentioned. Because the questions in the Medical History Questionnaire are phrased as "has a doctor ever told you that you had (name of condition)" , the response requires the participant to have heard the name of the condition from the doctor. Therefore, a table of definitions has not been provided for this form. For persons who request a definition of a medical term, respond by saying

"If you don't recognize (or understand the meaning of) a medical term, mark NO or DON'T KNOW on the form and go on to the next question".

Note, lack of familiarity with a medical term is different from not being able to read the name of the disease or condition on the form. For persons who cannot read the form, offer to do the form with them at some point during the visit.

2.13.3 Training

ARIC staff are locally trained by study coordinators or interviewer supervisors in the explanation and monitoring of self-administered forms.

2.13.4 Certification

No certification is required.

2.13.5 Quality Assurance

Routine quality assurance is locally provided by observation of the study coordinator or interviewer supervisor. Protocol adherence and interviewing techniques are reviewed by Coordinating Center field center monitors. Deviations from protocols and possible remedial actions are discussed with study coordinators and staff at that time. Major deviations are brought to the attention of the ARIC Cohort Operations Committee. Frequency distributions of the medical conditions recorded on the Medical Health Questionnaire by field center and interviewers are monitored by the Quality Control Committee on a semi-annual basis.
2.13.6 Data Collection

The Medical History Questionnaire is designed to be self-administered, and even though it can be interviewer administered, it is always completed on paper. Data are subsequently keyed by the interviewer into the DES (Appendix 2.13.b).

2.14 Medication Survey

The Medication Survey (MSRD, Appendix 2.14.a) is part of the core data collection instruments which was introduced during the first examination and continues to be administered to all participants during Visit 4. The survey covers the use of any prescribed or over-the-counter medications, including vitamins or mineral supplements, used within the two weeks prior to the participant's interview, and has been updated to ascertain the epidemiology of the current and regular use of aspirin and non-steroidal anti-inflammatory drugs in the ARIC population.

2.14.1 Rationale

As in previous examinations, the goal of the Medication Survey is to ascertain medication usage by coding both prescription and nonprescription drugs used by the respondent within the two weeks preceding the interview. This information assists in measuring patterns of medication use in the study communities, temporal changes in medical care practice, diagnostic classification of cardiovascular diseases, interpretation of laboratory results, and predictors of study end points.

2.14.2 Administration

The Medication Survey questionnaire is divided into three major sections. Question by question instructions are located in Appendix 2.14.c. During reception, the interviewer determines and records in Part A of the form whether the participant has brought in all medications taken within the last two weeks. Identification labels are placed on the participant's medication bag and Medication Survey form. If the participant has not brought in any (all) medications, inquiries are made to differentiate between non-compliance with pre-visit instructions or non-use of medications in the prior two weeks. In case of inadvertent omissions, arrangements are made for obtaining the information, usually by telephone interview. The deliberate omission to bring medications to the Field Center is recorded on the Medication Survey and on the Participant Itinerary Sheet (Appendix 2.17) and conversion is attempted later with the participant during the review of medical data. Subsequent parts of the Medication Survey can be administered during reception (if the area affords the opportunity for maintaining confidentiality) or later, by trained interviewers or the ARIC nurse/clinician in areas in the field center usually designated for conducting interviews.

Before starting Part B of the Medication Survey, the name on the medication bag is checked against the name on the Medication Survey form. Medication containers are removed from the participant's medication bag and the medication name and concentration are transcribed into column (a) of Section B on the form. Medications that are not in a container are examined only in front of the participant, with his/her permission. When there are more than 17 medications, recording the name and concentration is continued on the back of the page if a paper form is used. If the Medication Survey DES (Appendix 2.17.b) is used and more than 17 medications need to be entered, the name and concentration of the additional medications are written on a piece of paper labelled with the participant's ID, and filed in the participant's folder for future coding. See below for coding instructions. If the name of the medication exceeds the number of fields in the DES, the name is abbreviated on the screen.
When more than 17 medications have been recorded, the priority algorithm for
data entry and coding of the medications is as follows: prescription
medications first; aspirin and aspirin containing medications (aspirin, Alka
Seltzer, headache powders, cold medications, medication for arthritis, etc.);
anti-inflammatory drugs (ibuprofen, motrin, nuprin, etc.); then over-the-
counter-medications, followed by vitamins and food supplements.

To administer Parts B and C, a trained interviewer or the ARIC nurse/clinician
shows each container of medication to the participant, transcribes its name in
column (a) of Section B (MEDICATION RECORDS), records medication's
concentration in column (b), and asks and records in column (d) whether the
medication was used within the last 24 hours.

When preparing to ask the participant about each medication, the interviewer
removes all containers from the bag and sets them in front of the participant.
As each medication is reviewed, it is shown to the participant while keeping
the other medications in view. After the participant answers the questions
for each medication, its container is placed back in the carrying bag to
minimize confusion and to assure that all medications are returned.

The interviewer verifies the transcription of medication names and makes
corrections on the paper (or DES) form as required. Use the American Drug
Index and Physician's Desk Reference for unknown and incomplete names.

Part C of the Medication Survey ascertains (1) whether any of the participant-
reported medications were used to treat cardiovascular diseases or symptoms
(high blood pressure; high blood cholesterol; angina; arrhythmia; heart
failure; blood thinning; diabetes; stroke; intermittent claudication) or (2)
whether aspirin or aspirin containing medications were used in the last two
weeks and the reason for their use; current, regular use (at least once per
week for several months) of aspirin or other non-steroidal anti-inflammatory
drugs.

2.14.3 Training
Interviewers and medication coding specialists are centrally trained and are
responsible for providing local staff training in the transcription and coding
of medications.

2.14.4 Certification
Certification to administer the Medication Survey is achieved by the
demonstration of adequate technique on 5 taped interviews, reviewed and
approved by the supervisor or lead interviewer. Recertification is required
annually, and requires the successful completion of one taped interview of an
actual participant. This tape is included in the round robin which is
reviewed by the four interviewer supervisors selected to monitor each year's
round robin tapes.

Separate certification is required for medication coding, based on a minimum
of 80% correct responses on the certification test provided by the
Coordinating Center and administered at central training or by the local
medication coding specialist. Recertification for medication coding is also
required annually. For the medication coding specialist, this includes
coding a set of selected medication names circulated for this purpose and
adequate performance on blinded re-coding of medications recorded during the
previous year. Recertification criteria for field center medication coders
require meeting minimum standards of coding repeatability (by
interviewer/transcriptionist) and a review at the Coordinating Center of the
accumulated performance on quality control repeat medication coding.

2.14.5 Quality Assurance
With participant approval, most staff-administered interviews are taped for
quality control. A non-systematic sample of Medication Survey forms are reviewed by the supervisor. Technique and adherence to protocol are also monitored by Coordinating Center Monitors; data quality is monitored by the Quality Control Committee semi-annually.

For each person certified to code medications a ten percent sample of medication coding records is identified by the Coordinating Center for blinded repeat coding at the field center.

2.14.6 Data Collection

The Medication Survey is designed to be interviewer-administered and collected by direct data entry (Appendix 2.14.b) unless the work station system is inoperable. A paper version of the form is available for back-up and delayed data entry. The six digit medication code numbers are listed in a hard copy or DES version of the Medication Coding Dictionary. The Medispan code in part (c) can be matched to the drug name while transcribing the name of the drug in part (a) into the DES screens, or can be ascertained later. Drug names are listed alphabetically. The medication code of a drug not listed in the dictionary is left blank, and its status code is always set to "Q" (questionable) so that the pharmacist at the Coordinating Center can develop a code number and update the dictionary. Detailed instructions for coding medications are provided in the QxQ instructions for the Medication Survey (Appendix 2.14.c).

2.15 Oral Glucose Tolerance Screening

The Oral Glucose Tolerance Screening (GTSB) is a new interview in Visit 4, administered at the reception work station, to document cohort members' eligibility and willingness to participate in a test of their ability to process glucose during the fourth clinical exam (Visit 4). See Chapter 3.6 for a discussion of the rationale and procedures for administering the oral glucose tolerance test.

2.15.1 Rationale

Although the OGTT could be performed safely on all ARIC participants, data obtained from diabetics taking insulin or oral hypoglycemic medication would be difficult to interpret, and thus these diabetics are excluded from the OGTT. Persons treating their diabetes by diet alone are encouraged to participate. Persons who have not fasted for at least 10 hours or who have a history of diabetes treated by oral or injectable hypoglycemic medication are ineligible to participate in the OGTT.

2.15.2 Administration

The OGTT Screening form (GTSB, Appendix 2.15.a) is administered during reception, after the fasting form. (QxQ instructions and prototype scripts for the OGTT Screening form are provided in Appendix 2.15.c. Eligibility criteria are discussed below in Section 2.15.2.1.) The PIN sheet is reviewed to select the response to Item 1 on the OGTT Screening form to determine whether the person was being treated for diabetes in Visit 3. In Item 2, participants are asked about current regular treatment of diabetes with medication. The interviewer verifies a participant's denial of the current treatment of diabetes by reviewing the medications brought in to the field center to determine whether insulin or oral hypoglycemic medication have been used within the past two weeks. This can be done with the participant or while the participant is changing clothes. The Fasting/Tracking form is reviewed to select the response to Item 3 to determine whether the person has fasted for a minimum of 10 hours. Items 4 and 5 cover medical conditions that could subject the participant to undue risk and positive responses result in ineligibility. When a participant is ineligible, the interviewer reads the appropriate exclusion statement using a standard introduction and conclusion and selecting one of the statement's four exclusion options. Eligible
participants are then asked if they are willing to participate. Eligibility status is also documented on the Itinerary Sheet.

2.15.2.1 Eligibility

Scheduling information during the Annual Follow-up interview and the appointment material mailed prior to the date of the ARIC exam need to remind all participants to come to the field center in the morning after a 12-hour fast on the date of their appointment. The inclusion of the OGTT as one of the new procedures for Visit 4 is mentioned during the telephone interview and participants are asked if they have diabetes which is being treated by oral or injectable medications. Although the OGTT could be performed safely on all ARIC participants, data obtained from diabetics taking insulin or oral hypoglycemic medication would be difficult to interpret, and thus these diabetics are excluded from the OGTT. Persons treating their diabetes by diet alone are encouraged to participate.

During reception, participant eligibility (the absence of diabetes treated by oral or injectable hypoglycemics and fasting for at least 10 hours) and willingness to participate are determined and documented on the OGTT Screening Form. Responses are keyed into the DES and eligibility for the OGTT is determined by means of a pre-established algorithm. At the Jackson center, individuals whose PIN sheet indicates a fasting blood glucose value of > 300 mg/dL at Visit 3 and who are not on hypoglycemic treatment at the time of their Visit 4 examination are asked an additional set of questions on polydypsia and polyuria.

Fasting in ARIC is defined as the abstinence from all food and drink (except water or one cup of black, unsweetened, decaffeinated coffee or tea) for a minimum of 10 hours prior to the clinic visit. Note: as has been done in Visits 1-3, participants are told to fast for 12 hours prior to their clinic visit when Visit 4 is scheduled. When a participant comes to the field center having fasted for less than 10 hours, the initial blood samples are drawn with the caveat to the participant that his/her non-fasting state may affect the values of some of the studies. The minimum fasting requirement for participation in the OGTT is 10 hours. Participants who have not fasted for a minimum of 10 hours are not offered the OGTT. A return appointment for the OGTT in the fasting state, however, should be scheduled if the participant agrees. The participant's fasting status is recorded on the Fasting/Tracking form.

Hypoglycemic medications are one of two classes of medications that lower blood sugar: insulin, which is administered by injection, and oral hypoglycemics. Participants taking these medications are automatically excluded from the OGTT and the OGTT Screening form coded accordingly.

Fasting and Use of Medications. During the Annual Follow-up and Visit 4 scheduling call (and in the mailed appointment material) participants are told they cannot drink nor eat anything during the period between the administration of the glucola and the 2-hour blood drawn, nor take any medications that can be postponed for two hours. If in doubt, participants are encouraged to verify with their physician how best to rearrange their a.m. medication schedule.

Because there are many misconceptions regarding the OGTT, ARIC staff should reassure participants that the OGTT is safe and has few, if any, side effects. This is particularly relevant prior to documenting a person's willingness to participate. Participants who are unwilling to participate are excluded from the OGTT and the OGTT Screening Form is marked accordingly.

2.15.3 Training

Interviewers are trained centrally prior to Visit 4. The field center interviewer supervisor is responsible for the training and certification of new field center interviewers.
2.15.4 Certification

Certification is achieved by the demonstration of adequate technique on 5 taped interviews, reviewed and approved by the supervisor or lead interviewer. Recertification is done annually, and requires the successful completion of one taped interview. With participant approval, all interviews are taped for quality control. This tape is included in the round robin which is reviewed by the four interviewer supervisors selected to monitor each year's round robin tapes.

2.15.5 Quality Assurance

A non-systematic sample of OGTT Screening forms is reviewed by the supervisor. Technique and adherence to protocol are also monitored by Coordinating Center Monitors; data quality is monitored by the Quality Control Committee semi-annually.

2.15.6 Data Collection

The OGTT Screening form is designed to be interviewer-administered. It can be collected by direct data entry (Appendix 2.15.b) or by hand using the paper version of the form for delayed data entry. It is imperative that the participant's OGTT eligibility status is documented on the Itinerary Sheet, particularly if the data are collected by direct data entry and the paper form is not available in the participant's folder.

2.16 Personal History

The Personal History (PHXB, Appendix 2.16.a) form collects current information on the participant's access to and use of medical care for general medical complaints and conditions related to cardiovascular disease, and updates information on smoking, passive smoking, and alcohol consumption.

2.16.1 Rationale

The re-administration of questions on access to/payment for medical care, occurrence of medical conditions related to cardiovascular disease, exposure to active and passive tobacco smoke, and use of alcoholic beverages is to document current practices within the cohort and changes since the baseline exam which may in part explain differences in cardiovascular diseases and their treatment by such factors as age, ethnicity, gender and socioeconomic factors.

2.16.2 Administration

The Personal History form is administered by certified interviewers within the flexible sequence of the participant examination. Detailed instructions for administering each question are provided in the QxQ instructions (Appendix 2.16.c). Questions on smoking and alcohol consumption may be considered sensitive by participants and care must be exercised to administer each section in a non-judgmental format.

2.16.3 Training

Interviewers are centrally trained before Visit 4. Study coordinators and interviewer supervisors are responsible for providing training to new staff in interviewing techniques and the question by question instructions.

2.16.4 Certification

Certification to administer the Personal History form is achieved by the demonstration of adequate technique on 5 taped interview and approved by the supervisor or lead interviewer. Recertification is done annually, and requires the successful completion of one taped interview of a participant.
This tape is included in the round robin which is reviewed by the four interviewer supervisors selected to monitor each year's round robin tapes.

2.16.5 Quality Assurance

With participant approval, the majority of the staff-administered interviews are taped for quality control. A non-systematic sample of interviews is reviewed by the study coordinator or interviewer supervisor. Technique and adherence to protocol are monitored by the Coordinating Center monitors; data quality is monitored by the Quality Control Committee.

2.16.6 Data Collection

Data from the Personal History form are collected by direct data entry (Appendix 2.16.b) unless the work station computer is inoperable. A paper version of the form is available for backup and delayed data entry.

2.17 Physical Ability

The Physical Ability (PAQA) Questionnaire is a new self-administered form in Visit 4 to document current physical ability to stand, walk, sit down, bend, lift, and perform activities of daily living (e.g., cook, clean house, eat, dress, manage personal finances, etc.).

2.17.1 Rationale

The collection of a measure of physical ability and activities of daily living on each participant permits the assessment of pre-symptomatic (e.g., atherosclerosis) and symptomatic cardiovascular disease (e.g., clinically diagnosed heart attacks and stroke) within the context of the cohort's overall health.

2.17.2 Administration

The Physical Ability Questionnaire is a self-administered questionnaire and is given to each participant along with the Health and Life Profile and the Medical History Questionnaire to complete between work stations or during snack. Usually, the form is attached to a clip board with a cover sheet for confidentiality to allow participants to carry it with them. The type of presentation, however, is left to local option.

The interviewer instructs each participant in how to complete the Physical Ability Questionnaire by reading the text in the instruction box at the top of the form (Appendix 2.17.a). Because this is a self-administered form, there are no additional QxQ instructions. Interviewers explain that the selection of the response category (no difficulty, some difficulty, much difficulty, unable to do, don't know or do not do) should be based on the level of difficulty that best describes the person's ability to do the activity by him(her)self and without the use of aids. Participants' questions are answered and the interviewer determines whether assistance in completing the Physical Ability Questionnaire is requested or required. If assistance is needed, the Itinerary sheet is annotated, and the three self-administered forms (Medical History, Physical Ability and Health/Life Profile) are added to the interviews for staff-administration. If no assistance is requested, the participant is invited to work on the forms between work stations and return the clip board (or other carrying mechanism) to any ARIC staff upon completion. The forms are reviewed for completeness prior to the medical data review, and if incomplete, the participant is asked if assistance to complete the forms is needed. The administration date, type of administration (self (A), staff (B), both (C), not done (D)) and staff ID code are entered in Items 18-20 on the form. Note, the type of administration is not annotated on the form and must be memorized by the interviewer prior to administration.

2.17.3 Training
ARIC staff are locally trained by study coordinators or interviewer supervisors in the explanation and monitoring of self-administered forms.

2.17.4 Certification

No certification is required.

2.17.5 Quality Assurance

Routine quality assurance is locally provided by observation of the study coordinator or interviewer supervisor. Protocol adherence and interviewing techniques are reviewed by Coordinating Center field center monitors. Deviations from protocols and possible remedial actions are discussed with study coordinators and staff at that time. Major deviations are brought to the attention of the ARIC Cohort Operations Committee. Frequency distributions of the medical conditions recorded on the Medical Health Questionnaire by field center and interviewers are monitored by the Quality Control Committee.

2.17.6 Data Collection

The Physical Ability Questionnaire is designed to be self-administered, and even though it can be interviewer administered, it is always completed on paper. Data are subsequently keyed by the interviewer into the DES (Appendix 2.17.b).

2.18 Reproductive History

The Reproductive History form (RHXC) is unchanged since Visit 3 and is administered to female cohort members during the flexible component of the exam. The objective of this questionnaire is to update the menopausal status, the use of exogenous gonadal hormones since the last field center examination, and to update her history of gynecological surgery since Visit 3.

2.18.1 Rationale

The questions on menstrual patterns and hormone use have been expanded slightly to help establish with more certainty whether menopause has taken place. Questions addressing exogenous gonadal hormone exposure are used because of the belief that they may play a role in the development of atherosclerosis.

2.18.2 Administration

The Reproductive History form (Appendix 2.18.a) is administered by certified interviewers within the flexible sequence of the participant examination. Detailed instructions for administering each question are provided in the question by question instructions (Appendix 2.18.c). Questions on menstrual history and the use of female hormones may be considered sensitive by participants and care must be exercised to administer each section in a non-judgmental format.

The questionnaire is divided into 3 sections: (1) recent menstrual history and onset of menopause; (2) the use of exogenous hormones since Visit 3; and (3) a history of gynecological surgery since Visit 3.

Item 1 is not read aloud. The response category is based on information printed on menopausal status on the PIN sheet. The majority of the questions on the form are closed-ended or pre-coded questions designed for direct entry into the computer by the interviewer. Open-ended questions are to obtain names of female hormones being used, age, or some other concept of time.

The exact wording and order of the questions is followed to ensure
standardization. Questions are not skipped unless indicated by the skip pattern.

2.18.3 Training

Interviewers are trained centrally prior to Visit 4. The field center interviewer supervisor is responsible for the training and certification of new field center interviewers.

2.18.4 Certification

Certification is achieved by the demonstration of adequate technique on 5 taped interviews, reviewed and approved by the study coordinator or interviewer supervisor. Recertification is done annually, and requires the successful completion of one taped interview of an actual participant. With participant approval, all interviews are taped for quality control. This tape is included in the round robin which is reviewed by the four interviewer supervisors selected to monitor each year's round robin tapes.

2.18.5 Quality Assurance

A non-systematic sample of Reproductive History forms is reviewed by the supervisor. Technique and adherence to protocol are also monitored by Coordinating Center Monitors; data quality is monitored by the Quality Control Committee.

2.18.6 Data Collection

Data from the Reproductive History form are collected by direct data entry (Appendix 2.18.b) unless the work station computer is inoperable. A paper version of the form is available for backup and delayed data entry.

2.19 Socioeconomic Status

The Socioeconomic Status (SESA) form is a new data collection instrument in Visit 4 to track participant's socioeconomic status (SES) at different stages of development, using birth weight, education, income and occupation as measures of SES. The administration of this form in Visit 4 increases the information on SES during each participant's infancy and early adulthood, and updates information on marital status, employment or retirement status, occupation, and annual household income.

2.19.1 Rationale

SES is a known predictor of coronary heart disease worldwide. Several studies have suggested that a person's SES at birth may be equally or more important in predicting morbidity and mortality. These data permit a longitudinal assessment of SES at birth, youth, young and middle adulthood.

2.19.2 Administration

The Socioeconomic Status form (Appendix 2.19.a) is administered by certified interviewers within the flexible sequence of the participant examination. Detailed instructions for administering each question are provided in the QxQ instructions (Appendix 2.19.b). Questions on marital status, income, parents' SES status may be considered sensitive by participants and care must be exercised to administer each section in a non-judgmental format. The first portion of the form updates each participant's current marital status, employment/retirement status, occupation if it has changed since Visit 3, and annual household income for the 12 months prior to Visit 4. These questions are repeated from previous interviews. Subsequent sections collect information which may help classify each participant's socioeconomic status at birth and between ages 25 to 45.
2.19.3 Training

Interviewers are trained centrally prior to Visit 4. The field center interviewer supervisor is responsible for the training and certification of new field center interviewers.

2.19.4 Certification

Certification is achieved by the demonstration of adequate technique on 5 taped interviews, reviewed and approved by the supervisor or lead interviewer. Recertification is done annually, and requires the successful completion of one taped interview of an actual participant. With participant approval, all interviews are taped for quality control. This tape is included in the round robin which is reviewed by the four interviewer supervisors selected to monitor each year's round robin tapes.

2.19.5 Quality Assurance

A non-systematic sample of the SES form is reviewed by the supervisor. Technique and adherence to protocol are also monitored by Coordinating Center Monitors; data quality is monitored by the Quality Control Committee.

2.19.6 Data Collection

Data from the Socioeconomic Status form are collected by direct data entry (Appendix 2.19.b) unless the work station computer is inoperable. A paper version of the form is available for backup and delayed data entry.

2.20 TIA/Stroke

The TIA/Stroke (TIAE/TIBE) form is one of the core data collection instruments which was introduced during the first examination and continues to be administered to all participants during Visit 4 to assess the prevalence and incidence of stroke and transient ischemic attack. The interview is administered during the flexible component of the ARIC exam.

2.20.1 Rationale

Stroke and transient ischemic attack (TIA) are identified as end points in the ARIC study. A baseline history of TIA/stroke was collected during Visit 1. New occurrence(s) of cerebrovascular disease is updated by repeating all questions in the TIA/Stroke form, but restricting the response period to the interim between Visit 3 and Visit 4.

2.20.2 Administration

The TIA/Stroke Form (Appendix 2.20.a) is administered by certified interviewers. Positive symptoms are recorded during the standardized interview along with their speed of onset, duration, and co-morbid manifestations. QxQ instructions are in Appendix 2.20.c). Section A of the form documents the participant's medical history of a TIA or stroke since the last ARIC exam. The subsequent sections cover six neurologic symptoms which are associated with strokes and TIAs and are administered in a standardized format. Descriptors of the neurologic symptoms (earliest, longest and worst) often require probing, but the definitions are left to the respondent.

2.20.3 Training

Interviewers are centrally trained before Visit 4 and study coordinators and chief interviewers are responsible for training new staff, based on a standardized interview techniques (Appendix 2.1), question by question instructions for the TIA/Stroke Form, practice scripts, and role playing.

2.20.4 Certification
Certification is achieved by the demonstration of adequate technique on 5 taped interviews, reviewed and approved by the supervisor or lead interviewer. Recertification is done annually, and requires the successful completion of one taped interview of an actual participant. With participant approval, all interviews are taped for quality control. This tape is included in the round robin which is reviewed by the four interviewer supervisors selected to monitor each year's round robin tapes.

2.20.5 Quality Assurance

With participant approval, most staff-administered interviews are taped for quality control. A non-systematic sample of the taped TIA/Stroke interviews is reviewed by the supervisor. Technique and adherence to protocol are also monitored by Coordinating Center Monitors; data quality is monitored by the Quality Control Committee.

2.20.6 Data Collection

Data from the TIA/Stroke form are collected by direct data entry (Appendix 2.20.b) on two data collection forms (TIAE and TIBE) unless the work station computer is inoperable. A paper version of the form is available for backup and delayed data entry.

2.21 Update

The Update (UPDB) form is the primary source of tracking information for each participant and is administered yearly to all cohort members. During Visit 4, it is administered at the Reception Workstation.

2.21.1 Rationale

The previously collected name, address and telephone number of the participant and two contact persons, permission to send study results to the participant's physician updated and the physician's mailing address are verified on the Update form. This form is generated by the Coordinating Center from information stored in the study's central database, and sent to the field centers.

2.21.2 Administration

After greeting the participant and obtaining his/her informed consent, the information on the Update (UPD) Form screen (Appendix 2.21.a) is verified by reviewing with the participant the information which was filled out on the form sent to his/her home in the Visit 4 information packet (see Appendix 1.10) or is listed on the UPD data entry screen. For example, names or addresses which could have multiple/unusual spellings are verified and missing information is completed. If the social security number has not been collected previously, the social security disclosure statement (Appendix 2.21.b) is given to or read to the participant prior to requesting the number. This form also includes mailing information for the health care provider designated to receive the participant's study results. Question by question instructions are located in Appendix 2.21.b.

In recognition of the confidential nature of the information collected on the Update form, the information sheet that was brought in is either returned to the participant or torn up and disposed of in front of the participant.

2.21.3 Training

Staff are centrally trained before Visit 4 and study coordinators are responsible for providing local training for new staff.

2.21.4 Certification
Certification is required, provided by the study coordinator.

2.21.5 Quality Assurance

Routine quality assurance is provided locally by the study coordinator, by observing staff performance. Protocol adherence and interviewing technique are reviewed by Coordinating Center monitors. Deviations from protocols and possible remedial actions are discussed with study coordinators and staff. Major deviations are brought to the attention of the ARIC Cohort Operations Committee.

2.21.6 Data Collection

The Coordinating Center provides an Update Form for each participant with demographic and tracking information from the most current information on the consolidated database. During reception, data in this form are modified using Change Mode of the DES (Appendix 2.21.a).
3.0 PROCEDURES IN THE VISIT 4 CLINICAL EXAM

3.1 Anthropometry

Height, weight and body size are measured during Visit 4 following the same procedures used during Visit 3. Male pattern baldness in male participants is assessed for the first time in Visit 4. All measurements are recorded on the Anthropometry form (Appendix 3.1.a). Procedures for measuring the height, weight, waist and hip girths, and hair patterns are provided below. Separate instructions for completing the data collection form are provided in the Anthropometry form QxQ instructions (Appendix 3.1.c). At the option of the field center, the circumference of the right upper arm (to determine blood pressure cuff size) can also be measured at this work station and recorded on the sitting blood pressure form.

3.1.1 Rationale

The same anthropometric measurements as measured during Visit 3 are obtained in Visit 4 to assess height, weight and body fat distribution cross-sectionally and prospectively. In addition, a new set of procedures to classify male pattern baldness in male participants has been added to assess the recently reported, putative association(s) between certain patterns of male pattern baldness and coronary heart disease.

3.1.2 Procedures

Anthropometry is performed before the clinic snack and after the participant has changed into a scrub suit or examination gown and been given the opportunity to empty his/her bladder. All measurements are made with the participant wearing light-weight, non-constricting underwear. Participants wearing nylon hose or other forms of constricting undergarments are instructed to remove them. Each field center determined at the beginning of the study whether hip measurements were to be taken over or under the scrub suit and has followed that procedure consistently for the duration of the study. Weight and height are measured without shoes. Technicians complete the procedures on every participant by following the general checklist for performing anthropometric measurements (Appendix 3.1.d).

All anthropometric measurements are taken by either a team of two persons (one serving as observer; the other as recorder) or by one technician using a full length mirror to aid in the appropriate placement of the tape measure to record the girths. Using the team approach, the observer calls out the name of the next measurement, takes the measurement, and keeps the measuring instrument in place until the recorder repeats the number. The recorder checks the position of the examinee and verifies the horizontal placement of the measuring instrument during each procedure, and records the result. When a single technician performs the measurements, she verifies the horizontal placement of the measuring instrument (using the mirror when appropriate) for each measurement and records each measurement immediately after it is taken. Values are rounded down to the unit indicated for each measurement.

3.1.2.1 Standing height

The participant stands erect on the floor or the horizontal platform with his/her back against the vertical metal centimeter ruler mounted on the wall. The heels are placed together and positioned against the vertical ruler. The participant is instructed to stand as straight as possible, but with feet flat on the floor. The participant looks straight ahead with his/her head in the Frankfort horizontal plane (i.e., the horizontal plane which includes the lower margin of the bony orbit -- the bony socket containing the eye -- and the most forward point in the supratragal notch -- the notch just above the anterior cartilaginous projection of the external ear) (Figure 3.1). The right angle is brought down snugly, but not tightly, on the top of the head.
A foot stool is used if the examiner is shorter than the participant, such that the examiner's view is level with the point of measurement on the head of the participant. The certified technician follows a checklist for height measurement (Appendix 3.1.f) which outlines the procedures for checking the equipment and measuring the participant's height and enters study data on the Anthropometry form. The participant's height is recorded to the centimeter, rounding down. A chart converting centimeters to inches is available for use in informing the participant of his/her height in inches (Appendix 3.1.k).

The height rule is observed weekly to see that it (a) touches the hard-surfaced floor or platform on which measurements are done, and (b) is perpendicular to the floor. This weekly check is recorded on the Anthropometry Equipment Calibration Log (Appendix 3.1.e).

Figure 3.1 Frankfort Plane for Measuring Body Height
3.1.2.2 Body weight

Before a participant is weighed, the scale is balanced so that the indicator is at zero when no weight is on the scale. The scale must be level and on a firm surface (not a carpet). The participant is instructed to stand in the middle of the platform of the balance scale (Detector, model #437) with head erect and eyes looking straight ahead. Weight is adjusted on the indicator until it is balanced. Results are recorded to the pound, rounding down.

To maintain accuracy, the scale is zero balanced daily and calibrated with a known weight (50 lbs) every week or whenever the scale is moved. The daily zero balance and the weekly scale calibration are documented on the Anthropometry Equipment Calibration Log (Appendix 3.1.e). The scale is professionally calibrated and serviced annually. The certified technician follows a checklist for weight measurement (Appendix 3.1.g) which outlines the procedures for checking the equipment and measuring the participant's weight and enters study data on the Anthropometry form.

3.1.2.3 Abdominal girth

The participant is instructed to stand erect and relaxed with the feet approximately 6 inches apart and the weight equally distributed on both feet. The participant is asked to lift the scrub suit top just high enough to make the area visible (hands must not go above waist level). An anthropometric tape is applied at the level of the umbilicus (navel) and the participant is instructed to breathe quietly. The tape should be snug, but not so tight as to compress tissue. (Figure 3.2). The full length mirror or recorder verify that the participant is standing erect and that the tape is horizontal. The measurement is recorded to the nearest centimeter, rounding down at the point of relaxed end exhalation. The technician follows a checklist for the measurement of the maximal abdominal girth (Appendix 3.1.h).

3.1.2.4 Hip girth

The participant stands erect, yet relaxed, with weight distributed equally over both feet and with the feet together. The hip girth is measured at the level of the maximal protrusion of the gluteal muscles (hips). (Figure 3.2). The tape is placed horizontally level around the participant's gluteal muscles (hips) at the level of maximal protrusion. The position is verified by passing the tape measure above and below the observed maximum. The tape is kept horizontal at this level and the measurement is recorded to the centimeter, rounding down.

A checklist for maximal hip circumference measurement (Appendix 3.1.i) is used for measuring each participant. The most common source of error for this measurement is due to not having the tape horizontal and not verifying that the maximum width is being measured. The position of the tape is checked from both the front and the back.

The tapes used for measuring girth are calibrated monthly against the metal height rule, as indicated on the Anthropometry Equipment Calibration Log. Tapes that show damage or wear or that do not measure within the required range are replaced.
Figure 3.2.a    Location of Waist Girth Measurement
Figure 3.2.b Location of Hip and Upper Arm Girth Measurements and the Subscapular Skinfold
Figure 3.3  Bony Landmarks for Anthropometric Measurements
3.1.2.5  Arm Circumference

The participant stands facing away from the technician with the right arm flexed at 90 degrees at the elbow, hand across midsection. The observer determines and marks the tip of the olecranon (elbow). Bony landmarks for measuring the circumference of the right arm are depicted in Figure 3.3. The participant straightens the arm, allowing it to hang loosely at the side. The technician then determines and marks the posterior tip of the acromion process (shoulder bone). Using a centimeter tape, the technician measures the length of the upper arm between the two marks and marks the midpoint (+).

The technician wraps the tape around the arm at the midpoint mark, making sure that the tape is level. The arm circumference is measured to the nearest centimeter, rounding down, and is recorded in Item 6 (SBPD) or on the participant's itinerary sheet as a reference for the subsequent completion of the sitting blood pressure form.

3.1.2.6  Male Pattern Baldness

After the anthropometric measurements have been taken, the technician briefly explains to the male participants why male pattern baldness is being assessed at Visit 4 and requests their permission to observe their natural hair pattern. A standardized explanation is included in the introductory script which is printed on the data collection form (Appendix 3.1.a). This is read to each male participant and his willingness to participate is recorded in Item 5.a (ANTD). If the participant agrees, the technician first observes the person's natural hair patterns from the right and left sides and from above, and selects the diagrams on the modified Hamilton Baldness Scale (Figure 3.4, and Appendix 3.1.l) which most closely resemble the person's hair patterns as observed from the three angles. The technician then inquires about the age of onset of hair loss (if any) and a history of treatment for hair loss. The instructions for completing the data collection form are provided in Appendix 3.1.c.

Typically male pattern baldness affects two parts of the head: the forehead (frontal baldness) and the vertex (top of the head). Using the Hamilton Baldness Scale (Figure 3.4), technicians assess the person's natural hair pattern. There are 12 baldness patterns, each shown from 2 views. In general, the extent of baldness increases from Figure 1 to Figure 12, but there are more subtle differences between categories. When the vertex is not involved (e.g., when there is no hair loss from the vertex), the technician chooses from among Figures 1-5 or Figure 8. When the vertex is involved, the choice among Figures 6, 7 and 9-12 depends upon the extent of vertex baldness and the extent and type of frontal baldness. Complete baldness (not shown in the diagram) is coded as "13" in Item 5.b (ANTD).

FIGURE 1 on the scale shows little or no hair loss in the frontal area and no vertex baldness.

FIGURE 2 shows some (or a little) hair loss in the frontotemporal areas. Areas tend to be triangular and symmetrical and the hair loss stops well before the ear. There is no vertex baldness.

FIGURE 3 shows midfrontal hair loss; the hairline lies high on the forehead; there is no vertex baldness.

FIGURE 4 shows somewhat the same hair loss pattern as Figure 2, but is more severe. There are deep frontotemporal recessions; there is no vertex baldness and the midfrontal area is relatively spared.

FIGURE 5 shows midfrontal hair loss that has progressed further back than in Figure 3; there is no vertex baldness.
FIGURE 6 shows some vertex baldness. There may also be some frontal recession.

FIGURE 7 shows vertex baldness that is more severe than in Figure 6. Frontal baldness is also more severe. The two areas are separated by a band of moderately dense hair.

FIGURE 8 shows recession from the front has progressed beyond that in Figure 5. There is no vertex baldness.

FIGURE 9 shows both vertex and frontotemporal baldness and hair loss is more severe than in Figure 7. The areas of loss are now larger but still separated by a narrower, sparser band of hair, so separation is not as distinct.

FIGURE 10 appears to have less vertex baldness than Figures 9 and 11.

FIGURE 11 shows a large area of baldness, but not as extensive as Figure 12.

FIGURE 12 shows all that remains is a narrow, horseshoe-shaped band of hair.
Figure 3.4 The Hamilton Scale (modified by Norton) of Male Pattern Baldness
The goal is to identify the "natural" pattern and not the cosmetic appearance. For example, vertex baldness may sometimes be "disguised" by cosmetic combing. The natural pattern is observed to the best of the technician's ability without asking the person to recomb his hair. Unless the participant volunteers that he has a toupee, he is not asked. The following guidelines are followed when selecting the diagram which best depicts the hair pattern.

1. Always classify each participant according to the best matching figure, even if none matches exactly.
2. Ask the participant to turn his head to the right and to the left. If one side shows more baldness than the other, classify according to the side that has the more severe baldness.
3. If there is difficulty deciding between two classifications, choose the one with the LESSER baldness.
4. Vertex baldness is thought to be more significant than frontal baldness. If there is difficulty selecting a figure that resembles both the vertex and frontal baldness, classify the participant according to the vertex baldness.

3.1.3 Training

Technicians are trained centrally and are responsible for the local training of newly hired technicians (observers) and recorders. Training includes an (1) introduction to the rationale for body size measurements and male pattern baldness, the expected limits of reproducibility, and usual errors; (2) a demonstration of proper and improper procedures; (3) practice on volunteers and (4) testing on volunteers with four different body types - lean, obese, athletic and aged - and on men with as many different types of patterns of baldness as is practical.

3.1.4 Certification

Common criteria are used for initial certification and recertification for anthropometry. Field center anthropometry supervisors and technicians are certified after participating in central training or locally by the chief technician, and all observers are recertified bi-annually (January and July) by the local expert. Each technician practices on volunteers with a variety of body shapes and male pattern baldness, and for the assessment of certification and re-certification, measures one volunteer, meeting the following criteria:

1. The standing height measurement must agree within 1.0 cm of the trainer/certifier.
2. The waist and hip circumference measurements must agree within 1.0 cm of the trainer/certifier.
3. Weight must agree within 1 lb of the trainer/certifier.
4. Selection of hair pattern must agree with trainer.

Recertification is performed locally every 6 months at the field centers. The following additional certification criteria for each type of measurement need to be met:

1. Absence of end digit preference for more than 6 months during one year;
2. Absence of systematic differences in mean values;
3. Adequate performance on replicate measurements.
3.1.5 Quality Assurance

In addition to annual recertification, protocol adherence in the performance of each procedure is reviewed at least annually by the by Coordinating Center field center monitors. Deviations from protocol and possible remedial actions are discussed with study coordinators and staff at that time. Quality control observations of technicians by an observer are also performed biannually by field center staff in January and July of each year and documented on the Report on Use of Observation and Equipment Checklist (Appendix 3.1.j). These are sent to the ARIC Coordinating Center for review. Major deviations from the protocol are brought to the attention of the Cohort Operations Committee.

Anthropometry equipment is calibrated frequently and results are recorded on an Anthropometry Equipment Calibration Log (Appendix 3.1.d). Scales are zero balanced daily and calibrated weekly, or when moved. Measuring tapes are checked monthly and replaced as needed. The number of above measurements are recorded on the 'Report on Use of Observation and Equipment Checklist' and sent to the Coordinating Center biannually.

Digit preference, systematic differences in location statistics, completion of checklists/logs according to schedule are analyzed by the Coordinating Center and reviewed by the Quality Control Committee. Refer to Manual 12 for a detailed description of quality assessment procedures.

3.1.6 Data Collection

The Anthropometry Form is collected by either the technician (observer) or recorder by direct data entry on a data entry screen (Appendix 3.1.b) or on a paper form for delayed data entry.

3.2 Dental Study

The ARIC Dental Study is an ancillary study to Visit 4, funded by the National Dental Institute, and jointly conducted by the University of North Carolina (UNC) School of Dentistry and current UNC ARIC Study investigators under the auspices of the ARIC Steering Committee. At the field centers, the dental study consists of dental screening and dental history interviews and a blood serum sample from all participants. An oral exam, based on a standardized study protocol performed by trained and certified dental hygienists, is done on all eligible cohort members to identify problems in dental hygiene (as a courtesy to participants); assess levels of plaque; collect and store crevicular fluid and plaque; record a gingival index; measure probing depth and cemento-enamel junction (CEJ), and record the extent of bleeding on probing.

The UNC School of Dentistry serves as an ARIC Study central agency for (1) the preparation of standardized protocols for the dental examination; (2) the creation and maintenance of a data entry system; (3) the training and certification of dental examiners and recorders; (4) the analysis of gingival and crevicular fluid and serum samples and (5) collecting, analyzing and transmitting study data to the ARIC Coordinating Center.

The specific aims of the ARIC Dental Study are to (1) determine the prevalence, extent, and severity of periodontal conditions in the ARIC population and describe the associations between those conditions and prevalent CHD, carotid artery wall thickness, and atherosclerotic risk factors, and (2) determine whether the local gingival crevicular fluid levels of prostaglandin E$_2$, thromboxane B$_2$, interleukin-1B, and tumor necrosis factor-alpha are elevated in cases of severe carotid atherosclerosis, and whether elevated levels of these mediators are associated with atherosclerosis risk factors, including elevated serum lipid values and fibrinogen. Although the dental study was implemented 4 to 6 months after the start-up of Visit 4, all cohort members are screened and recruited to participate in the
dental study. The majority of ARIC participants are screened during their Contact Year 10 Annual Follow-up interview and Visit 4 scheduling telephone call. Those participants who were examined prior to the implementation of the Dental Study are recontacted, screened and offered the opportunity to return to the field center at a later date for the dental exam. The dental study serum sample is not drawn on participants returning to the field center for a dental exam.

3.2.1 Rationale

Periodontal diseases, which are chronic gram-negative infections, represent a possible risk factor for both atherosclerosis and thromboembolic events. Previous studies have demonstrated an association between periodontal disease severity and a risk for CHD and stroke. These associations may be due to a chronic, underlying inflammatory response that places an individual at higher risk for developing both periodontal disease and atherosclerosis.

3.2.2 Procedures

The protocol for administering the dental screening (Section 2.6) and history (Section 2.5) interviews is in Chapter 2; their respective data collection forms and question by question instructions are in Appendix 2.5 and 2.6.

A brief description of the procedures for collecting the dental study serum sample and completing its data collection form (LABB) is provided in Section 3.9 of this manual and Appendix 3.9. The Dental Study serum sample is drawn during the routine ARIC venipuncture, is processed along with the other ARIC blood samples and shipped to the UNC School of Dentistry according to the study protocol. Further details are provided in Manual 7 (Blood Collection and Processing).

The specific procedures for performing and collecting the data for the oral exam are described in separate manuals, The ARIC Dental Procedures Manual, and the Dental ARIC Data Entry System Users Manual, respectively. The Dental Study data collection forms and results report are located in the ARIC Dental Procedures Manual.

In general, the participant's eligibility and willingness to have a oral exam are established prior to the visit, and the oral exam is scheduled in advance, allowing the dental examiner to have the pre-packaged specimen data collection packets labelled and set out prior to the participant's arrival. The oral exam takes approximately half an hour and is conducted during the flexible component of the ARIC exam. See Table 2.3.

The oral exam is performed by a trained and ARIC certified dental examiner, usually a dental hygienist, and data and sample collection are collected by a trained and certified recorder who assists the dental examiner. Data collected in the Dental Study data entry system and samples are stored and shipped to the UNC School of Dentistry according to the procedures in the Dental ARIC Data Entry System Users Manual and the ARIC Dental Procedures Manual, respectively.

The participant's eligibility is confirmed by the hygienist prior to the oral exam by briefly reviewing the responses on the Dental Screening form (not re-administering the form) and determining whether an interim event(s) since the administration of the screening form now requires prophylactic antibiotic coverage.

The oral exam can be briefly interrupted when a participant is scheduled to have the 2 hour post-load glucose sample drawn during the time the oral exam is being done. The participant is escorted by a laboratory technician to the
venipuncture workstation (unless the dental workstation meets OSHA
venipuncture regulations and the blood can be drawn according to the ARIC
venipuncture protocol), the second OGTT sample is drawn, and the participant
is returned to the dental workstation to complete the oral exam.

A Dental Study results report which summarizes the hygienist's findings and
recommendations (if any) for further follow-up with a dentist is generated at
the conclusion of the oral exam and given to study participants as a courtesy.
ARIC participants are informed that the oral examination, like the interviews
and procedures in the ARIC Study, is not the same as a dental examination
performed by one's personal dentist, and does not provide diagnosis, treatment
or medical advice.

3.2.3 Training

Training for the dental examiner and the dental recorder is done centrally at
the UNC School of Dentistry. Training for new dental recorders can be done
locally by certified dental examiners. Training, however, for dental
examiners is always provided by the UNC School of Dentistry. Refresher
courses are provided annually.

3.2.4 Certification

Certification is required for dental examiners. Certification is done by the
Dental Study principal investigator (PI), based on reviews of data submitted
on five people. Clinical exam data are reviewed for completeness and unusual
patterns and entries. Samples are assayed in the laboratory to determine if
cytokines are present and within expected parameters. Recertification is
performed annually after the annual retraining sessions.

3.2.5 Quality Control

Quality control starts with the Dental Study computerized examination data
entry system (DES), which directs the examination procedure, requires
consistency throughout the exam, and allows only a certain range of entries to
be made. When examination data are received at the Dental School, they are
checked for completeness of the examination, expected patterns of entries, and
the examinations are matched with the screening and history forms to look at
acceptance rates and patterns of refusals and exclusions.

3.2.6 Data Collection

Data from the periodontal exam and sample storage and shipping procedures of
dental study participants' samples are listed in their respective manuals of
procedures. Data from the periodontal exam that are recorded in the Dental
Study DES (the clinical exam form) are stored on diskette and shipped to the
School of Dentistry every two weeks. Participant samples are stored at the
field centers and also shipped to the School of Dentistry (separate location).

In contrast, screening and dental history data are collected on all
participants. The Dental Screening and History forms are entered into the
ARIC data entry system and transferred to the ARIC Coordinating Center,
according to the ARIC study protocol.

3.3 Electrocardiogram

A resting 12-lead ECG is performed on each participant in Visit 4 using
procedures and equipment identical to those employed in previous cohort
examinations. Processing and coding at the Minnesota and EPICARE centers
follow the same procedures used in the baseline visit. Full details are
provided in Manual 5 of the ARIC Protocol.

3.3.1 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.

3.3.2 Procedures

Standard (12-lead) ECG operational procedures are provided in Manual 5, Electrocardiography, and the central training manual.

3.3.3 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, with attention to (1) electrode placement, (2) skin preparation, (3) MAC PC menus and data entry, and (4) self-evaluation techniques for technical performance.

3.3.4 Certification

Certification is required for ECG technicians performing 12-lead ECGs. Requirements and procedures are listed in Manual 5 and summarized in Table 2.2. The EPICARE ECG Reading Center serves as the certifier. Recertification is performed bi-annually by the field center senior technician (January and July), but technician performance is monitored continuously by EPICARE with quarterly reports to the field centers.

3.3.5 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 EPICARE Center to each technician on an ongoing basis; an ECG quality control checklist is administered biannually (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).

3.3.6 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. Paper tracings are stored in the participant's folder. Electronic records of the 12-lead ECGs are transmitted daily by modem to the ECG Computer Center at EPICARE with next day verification of receipt to the field centers.

3.4 Heart Rate Variability

Heart rate variability (HRV) is collected on all ARIC Visit 4 participants, immediately after the 12-lead ECG or as soon as the participant has been supine for at least 10 minutes. In order to derive HRV indices, R-R interval data over a specified period (6 minutes) are collected and stored following a standardized protocol. These R-R interval data are processed at a central location by trained technicians to derive HRV indices from the R-R interval variations.
HRV data are collected on individuals regardless of fasting status or participation in the OGTT. However, for persons doing the OGTT test, HRV data must be collected prior to the administration of the glucose load, i.e., 9HRV is never collected after the glucola is administered.

In all instances, the HRV technician verifies fasting status according to the ARIC QxQ instructions of the Fasting/Tracking form. This information is recorded on the HRV log and the HRV screen per instructions found in the HRV protocol manual.

3.4.1 Rationale

HRV has been used as a non-invasive measure of cardiac autonomic activity, and has been found to be associated with the prognosis of acute myocardial infarction in clinically-based studies.

3.4.2 Procedures

Standard HRV procedures are provided in a separate manual (Heart Rate Variability Data Collection Manual).

3.4.3 Training

Lead HRV technicians are centrally trained by the central HRV technician in conjunction with the ARIC Ultrasound Reading Center staff. Other ECG technicians and new staff are trained locally by the designated local expert at each field center.

3.4.4 Certification

Certification is based on the adequate performance of five procedures observed by the trainer. Retraining is conducted annually. Technician performance is monitored continuously, with deterioration of quality indices being brought to the attention of the technician by the Ultrasound Reading Center. Satisfactory performance over the course of one year leads to recertification.

3.4.5 Quality Control

Quality control procedures for technicians are described in the HRV Data Collection Manual. Quality control procedures for the reading center technicians are described in the HRV Data Processing Manual.

3.4.6 Data Collection

HRV data are collected using ART HRVECG system installed on a dedicated PC. Details are in the HRV Data Collection Manual. HRV data are backed up weekly and shipped to the Ultrasound Reading Center with the weekly shipment of the ultrasound tapes. A copy of the data is also stored on diskettes at the field centers.

3.5 Microalbuminuria study

A urine sample is collected on all ARIC participants at Visit 4 in order to perform assays for microalbuminuria. Procedures for the collection of the urine sample is provided below. Procedures for the processing, storage, and shipping of urine samples are provided in Manual 7. Instructions for completing the urine section of the Laboratory form (LABB, Appendix 3.6.c) are provided following the data collection form in Appendix 3.6.a.
3.5.1 Rationale

A primary focus of Visit 4 is the assessment of the putative association(s) of chronic inflammation to atherosclerosis and other aspects of coronary heart disease and stroke.

3.5.2 Procedures for Collecting the Urine Specimen

A urine sample is collected from each participant (preferably) at the beginning of the clinical exam. The specimen is divided into three separate sample tubes and frozen at the field centers until shipping. Aliquots for creatinine and albumin on each participant are shipped to the Minneapolis ARIC Field Center. The 50 ml conical tube (one per participant) for the hemostatic metabolites are shipped to the ARIC Hemostasis Laboratory.

3.5.2.1 Participant Instructions

After participants complete the reception work station activities and are taken to change clothes, they are informed about the urine collection by saying something like:

*During your exam, we hope to collect a urine specimen. You may do that as you change clothes for the exam. Or, if you wish to do it later, please notify us when you need to use the bathroom.*

The urine specimen is collected at the field center whenever the participant needs to void. If the participant has not voided by the time of the exit interview, the participant is asked to void at that time.

When the participant is ready to void, a specimen cup (labeled with his/her ID) and lid and a TIME VOIDED label are provided by the staff member working with the participant at that time. The participant is instructed to:

1. void in the cup, filling it if possible, and place the lid securely on top of the container
2. record the time of voiding on the label, and
3. bring the specimen cup back to the staff member, OR
4. place the sample container in a refrigerator designated for urine samples, and report to a staff member that the specimen has been collected, depending on locally approved OSHA regulations.

Bathrooms are equipped with a wall clock and pencils for participants to use in recording the time of voiding on the label. The staff member verifies the participant has written the "time voided" on the label, and assesses the adequacy of the sample for processing. If insufficient, the participant is requested to void again in a clean container prior to leaving the field center. A note is made on the participant's Itinerary Sheet that a second sample is needed by the ARIC staff person who observes the placement of the participant's urine specimen in the refrigerator. A note can also be made on the participant's first sample that a second sample is needed. The optimal time for the collection of the second specimen is after the snack when the participant is changing back in to street clothes. The instructions for providing the urine sample are repeated to the participant at that time.

Prior to processing, the laboratory staff records whether a urine sample was obtained and transcribes the collection time of the urine void from the ID label onto each participant's LABORATORY (LABB) form (Appendix 3.6.a).
3.5.3 Training

Training in the provision of instructions to participants for the collection of urine specimens is provided centrally, or locally for new staff by a certified laboratory technician, the interviewer supervisor or study coordinator at each field center.

3.5.4 Certification

No certification is required.

3.5.5 Quality Control

Techniques and adherence to protocol are observed by Coordinating Center monitors; the quality of the urine specimens and missingness are monitored by the Quality Control Committee.

3.5.6 Data Collection

Information on the collection and processing of urine samples is recorded on the paper version of the Laboratory (LABB) form for delayed data entry. When the first urine sample is insufficient for processing, the participant is asked to provide a second sample, which is mixed with the first. The time of the urine sample, however, is recorded on the Laboratory form as the hour and minutes of the last voided specimen. The assessment of volume adequacy for the Laboratory form is made immediately prior to processing.

3.6 Oral Glucose Tolerance Test

In population surveys of middle-aged individuals, approximately 50% of diabetics and almost all individuals with impaired glucose tolerance will not have been diagnosed. Although measurement of fasting glucose identifies some diabetics (fasting glucose levels have been obtained on all ARIC participants at each clinical examination), this measurement alone misses approximately 75% of the population with abnormal glucose tolerance. The oral glucose tolerance test (OGTT) is the standard test to determine whether diabetes or a milder abnormality of glucose tolerance is present. The OGTT is necessary to document mild, asymptomatic abnormalities in glucose clearance. It is required to distinguish between individuals with normal glucose tolerance and those with abnormal glucose tolerance (who have not yet developed fasting hyperglycemia).

3.6.1 Rationale

Diabetes is a metabolic disease characterized by abnormally high blood sugar and an increased risk of several chronic complications, including heart, vascular, eye and kidney diseases. In the middle aged and the elderly, diabetes is associated with increased cardiovascular disease (CVD) and is an especially strong risk factor for heart disease in women. Many people with diabetes are asymptomatic, but remain at increased risk of complications. Impaired glucose tolerance is defined as an abnormal glucose tolerance level between normal and diabetes. People with impaired glucose tolerance also appear to have an increased risk of CVD, but little or no increased risk of eye and kidney disease.

Until a few years ago, larger doses of glucose were commonly administered during the OGTT and some individuals complained about the fluid volume and/or subsequent GI distress. During the last 10 years, the use of a lower dose of glucose has greatly reduced this problem. In a study performed by the National Institute of Aging, only 0.3% (3 per thousand) participants complained of side effects, all of which were mild and transient. Between 1990 and 1992, National Heart, Lung, and Blood Institute investigators have performed over 10,000 OGTTs, like those to be done in ARIC, with no serious
side effects and less than 0.5% of mild side effects. Because the ARIC study screens the individuals invited to take part in the OGTT, participants can be reassured that this is a safe, widely used, and informative test.

3.6.2 Procedures

The OGTT has several components which are all fixed within the context of the participant flow. Note that heart rate variability, and therefore ECG, as well as the fasting venipuncture must be done prior to administering the glucose load. And, the post glucose load venipuncture must be scheduled 2 hours, plus or minus 10 minutes, after ingestion (see below for details).

Participants are optimally scheduled at the field center by 10:30 am. Their eligibility and willingness to participate in the OGTT is determined during reception. The OGTT Screening Form (GTSB) is administered to all participants (see section 2.6). Persons taking medications to control their diabetes, those with prior surgery to remove part of the stomach or intestines, on kidney dialysis, and those declining to participate are excluded from the OGTT. Exclusion from OGTT (for either medical reasons or personal preference) is also marked on the Itinerary Sheet.

Before administering the glucose load, the technician verifies the participant's eligibility, as recorded on the OGTT Screening Form. Blood samples to measure participants' initial fasting blood sugar are drawn as part of the routine ARIC venipuncture. The glucose load (75 grams of glucola) is administered immediately following venipuncture. Two hours after the participant began to drink the glucola, a second blood sample is obtained for measurement of glucose and insulin. A snack is provided soon after the drawing of the two hour blood sample.

3.6.2.1 Venipuncture for Fasting Glucose Samples

Fasting glucose samples are drawn as part of the regular ARIC procedures. Detailed instructions are outlined in Manual 7. Either prior to or during venipuncture, the phlebotomist verifies the participant's eligibility to participate on the OGTT Laboratory Form. Administration of the glucola is scheduled immediately following venipuncture.

3.6.2.2 Administration of Glucose

All eligible participants receive a standard 75 gram glucose load as a flavored drink. Commercially available preparations for the OGTT made from 75 grams of glucose monohydrate only contain 68 grams of glucose, and are not to be used. The preferred means of serving the glucola to the participant is to remove the cap and serve the bottle with a straw. If requested by the participant, the contents can also be poured into a paper cup and served with or without a straw. Participants are instructed to consume the contents of the container (bottle or glass) in its entirety in less than 10 minutes. Most individuals consume the full amount in 3 to 5 minutes quite easily.

The timing for the 2 hour post load venipuncture begins as soon as the participant starts to drink the glucose solution. The time the participant began drinking the glucola is recorded in Item 1 of the Oral Glucose Tolerance Administration (GTAA) form (Appendix 3.6.a). (Instructions on how to complete the form are in Appendix 3.6.b.) The time the participant should have the 2 hour post load venipuncture is recorded on the Itinerary Form.

Study participants are encouraged to drink the full amount of glucola; otherwise they will not get the full benefit of the test. If the individual does not consume the full amount of glucola, the technician measures the residual amount and records it in Item 2 of the OGTT Administration (GTAA) form. The measurement of the residual glucola is not necessary if only a few drops are left. If the residual amount is 145 ml or more, the 2 hour blood
draw is NOT performed, and the OGTT Administration Form is completed accordingly. Based on the experience in many epidemiologic studies in the U.S. and elsewhere, this should be a very uncommon event.

3.6.2.3 Two Hour Post Glucose Load Venipuncture

The two hour blood sample is obtained for measurement of glucose and insulin two hours after the start of the test. The blood sample is drawn as close to the two hour time as possible. The phlebotomist records that the post-load blood glucose sample was drawn, and the actual time it was drawn (or the reason(s) for non-collection) in the OGTT Administration (GTAA) Form (Appendix 3.3.a).

Every scheduling effort is made to allow participants to go to the venipuncture work station for the 2 hour blood sample. The Itinerary Sheet needs to be checked frequently as a guide to scheduling interviews and procedures, especially towards the end of the examination. In a complex study such as ARIC, it is inevitable that some participants will be busy with other parts of the examination. If the participant is available within a 10 minute window of the scheduled 2 hour post-load venipuncture, the overlapping interview or procedure does not need to be rescheduled or interrupted. However if the 2 hour blood sample is due and the participant cannot come to the venipuncture work station within the 10 minute window, the phlebotomist, if possible, goes to the participant to obtain the sample.

3.6.2.4 Snack

OGTT study participants should neither drink nor eat anything in the period between the glucose administration and the 2-hour blood draw. After the post-load venipuncture, participants are given the regular snack, as soon as possible. OGTT study participants will have been reminded to ask their physicians whether they can postpone taking the medications they usually take first thing in the morning until they have their 2 hour post-load venipuncture (see Eligibility, above).

3.6.2.5 Documentation of Side Effects

If participants complain of any problems during the test, they should be reported to the Study Coordinator or the Study Nurse and documented on the field center's Incident Log. Based on previous studies similar to ARIC, side effects are very infrequent, and vomiting was reported only on 0.1 percent of tests (diarrhea is not a side effect of the OGTT). However, if vomiting has occurred, the 2-hour blood draw should not be done, and the reason for the incomplete test recorded as 'other' in Item 4 of the OGTT Administration (GTAA) Form (Appendix 3.3.a).

3.6.2.6 Readiness for Emergencies

Field centers keep on hand orange juice or equivalent, sugar-containing beverages at all times.

Participants with known or undiagnosed diabetes may develop low blood sugar or an "insulin reaction". If recognized promptly by clinic staff, it should be mild and easily treated with orange juice or a similar sugar containing beverage.

**Hypoglycemia**, or an abnormally low blood glucose level, occurs when there is an imbalance between the dose of hypoglycemic medications (in the treated diabetic) or the blood sugar level (in any person) and the person's food intake and activity level. However, treated diabetics are excluded from the OGTT. Classic symptoms include anxiety, tremor, palpitations, sweating, faintness, and hunger. If untreated, a further decrease in blood glucose may lead to confusion followed by loss of consciousness. Prolonged hypoglycemia may precipitate angina pectoris or seizures.
It is important to remember that symptoms of hypoglycemia are variable and may be partially masked in older participants.

If a person displays any of these symptoms after ingesting the glucola and is able to take food orally, orange juice containing additional sugar should be given immediately and the clinic physician notified as soon as possible. When a hypoglycemic reaction occurs, the person is evaluated by medical staff prior to leaving the field center.

If an OGTT participant loses consciousness, hypoglycemia should be presumed until ruled out. Severe hypoglycemic reactions are a medical emergency and the person should be transported immediately to an emergency care facility.

3.6.3 Training

Training in the administration of the glucola, completion of the data entry form, blood drawing, processing, storage and shipping for laboratory technicians is provided centrally, or locally for new staff by a certified laboratory technician at each field center.

3.6.4 Certification

The lead technician is certified at central training by the central trainer; other technicians are certified either at central training or by the lead technician at the field center. Recertification is done bi-annually (January and July) by observation.

3.6.5 Quality Control

In addition to annual recertification authorized by the Hemostasis Laboratory, protocol adherence in the performance of each procedure is reviewed at least biannually by the lead technician and annually by Coordinating Center field center monitors. Deviations from protocol and possible remedial actions are discussed with study coordinators and staff at that time. Major deviations are brought to the attention of the Cohort Operations Committee.

3.6.6 Data Collection

Information on eligibility to participate in the OGTT is recorded on the Oral Glucose Tolerance Screening (GTSB) form, fasting status is recorded on the Fasting/Tracking (FTRD) form, the administration of the glucola is documented on the Oral Glucose Tolerance Administration (GTAA) form, and the collection and processing of the fasting and post-load blood samples is recorded on the Laboratory (LABB) form.

3.7 Sitting Blood Pressure

Sitting blood pressure is measured on all participants at each field center. It is measured in a resting state, and in contrast to the procedures in Visits 1-3, only two measurements are taken with a random zero sphygmomanometer. Data are recorded on the Sitting Blood Pressure (SBPD) form (Appendix 3.4.a).

3.7.1 Rationale

As one of the most powerful risk factors of cardiovascular disease, a measurement of sitting blood pressure is included in every clinic examination of the ARIC cohort. The procedures are the same used in previous examinations, except only two measurements are taken, as detailed in Manual 11 of the ARIC Protocol.
3.7.2 Procedures

Sitting blood pressure is a fixed component of the participant flow and is measured in conjunction with the anthropometric measurements and before the ECG and venipuncture (Table 2.3). Procedures for obtaining sitting blood pressure are found in Chapter 1 of Manual 11. Question by question instructions for completing the data collection form are in Appendix 3.4.c of this manual.

Guidelines for terminating the clinical exam and referring participants with abnormal blood pressures for clinical care or follow-up are listed in sections 4 (Medical Data Review) and 5 (Referrals and Review Guidelines) of this manual.

3.7.3 Training

Blood pressure technicians are trained centrally at the beginning of each examination. New technicians, hired after Visit 4 central training are trained locally by the designated local expert (Table 2.2). Refer to Manual 11 for further details.

3.7.4 Certification

Certification is required; criteria are listed in Manual 11. Recertification is performed biannually in January and July. Recertification criteria include:

1. Successful completion of double-stethoscope observation, semi-annually;
2. Semi-annual test with recertification tapes;
3. Absence of end digit preference for more than 6 months during one year;
4. Annual review by the central ARIC blood pressure trainer.

3.7.5 Quality Assurance

Detailed quality control procedures are provided in Manuals 11 and 12, and include periodic review by the Quality Control Committee of end digit preference, systematic differences between technicians in mean values, and completion of performance on checklists/logs. The observer checklist for observation of blood pressure techniques by (1) an observer, (2) by double stethoscoping, and (3) blood pressure training/certification tapes (Appendices in Manual 11) is completed biannually for each certified technician. Monitoring of certification status is conducted by the Coordinating Center.

3.7.6 Data Collection

The Sitting Blood Pressure Form is collected by direct data entry (Appendix 3.4.b) on screen unless the work station computer is disabled. A paper version of the form is available as backup.

3.8 Ultrasound

B-mode Ultrasound imaging of the carotid arteries is a core study measurement performed at each examination on all, or a sample of participants. It provides 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.
3.8.1 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 are also collected to test their ability to predict incident cardiovascular events in the ARIC cohort. During Visit 4, 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.

3.8.2 Procedures

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

3.8.3 Training

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

3.8.4 Certification

Certification of experienced sonographers is based on the ability to visualize arterial walls, consistent with the process average of all sonographers. Certification remains in effect as long as visualization is consistent with the overall sonographer process average, and protocol is adhered to.

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.

3.8.5 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, periodic scans of the same individual by different sonographers, 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.

3.8.6 Data Collection

Data are collected on a Biosound Phase II scanner. A microcomputer assists the sonographer during the standardized examination sequence and data collection. The B-Mode examination is recorded on 2 inch SVHS videotape and...
read at the URC. Participant ultrasound files and blood pressure files are sent to the URC.

3.9 Venipuncture

Blood collection and processing follow a standardized protocol and permits the standardized measurement of associations of atherosclerotic manifestations and new coronary heart disease with clinical chemistries, including glucose, and plasma lipid, lipoprotein cholesterol, and apolipoprotein levels and hemostatic factors which are known or suspected to be risk factors for CHD and stroke.

3.9.1 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.

3.9.2 Procedures

Venipuncture is performed in a fixed sequence in the participant flow (Table 2.3). The first venipuncture is performed after anthropometry, sitting blood pressure and ECG/HRV measurements, on all cohort members, regardless of their fasting status, and includes 3 plasma samples for the Lipid and Hemostasis laboratories; 2 serum samples for the Hemostasis and Dental laboratories; and an optional sample for a local Hematology laboratory (Figure 3.5). A second venipuncture is performed on OGTT participants, two hours after the administration of the glucose load. Detailed venipuncture, sample processing and shipping instructions are written in Manual 7.

3.9.2.1 Nonfasting Participants

Participants who have not met the ARIC fasting requirements (nothing by mouth except water, or one cup of black, unsweetened coffee or tea for the past 10 hours) are informed that because they have had something to eat or drink within the past 10 hours, it may not be possible to interpret some of their clinical chemistry values, but they are welcome to return to the field center at a later date fasting for a second venipuncture if there are no medical contraindications.

NOTE: persons who are non-fasting and indicate that they would like to be rescheduled for another blood draw are NEVER used as a QC blood phantom.

Persons who have not fasted for 10 hours, but who indicate that they would like to have an OGTT, have the regular ARIC panel drawn, and are also invited to return for a repeat blood draw in conjunction with the OGTT. See Manual 7 for instructions on completing a repeat blood draw on separate days.

3.9.3 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.

1 No Heart Rate data collected in U.S. for V4; no backup tape created for V3 or V4
3.9.4 Certification

Recertification is required annually and is performed by the chief ARIC technician at the Central Hemostasis Laboratory or by designated trainer/certifiers from the ARIC field centers. Criteria are described in Manuals 7 and 12.
Figure 3.5 Sample Processing Flow Sheet
3.9.5 Quality Assurance

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

3.9.6 Data Collection

Blood collection and processing data are collected on a hard copy of the Laboratory (LABB) Form for delayed data entry into the ARIC DES. Notes reflecting blood drawing or processing problems are recorded in the comment section of the Laboratory form (Item 16), and on at the bottom of the laboratory shipping forms which is forwarded as hard copy to the central laboratories and Coordinating Center. Sample Inventory (SMPD) Forms (Appendix 2.3.b) are also completed for each participant documenting the collection (yes/no and collection date) of the lipid, hemostasis and dental study blood samples.

3.10 Snack

A light snack is scheduled as soon as possible after venipuncture for non-OGTT eligible participants, and after the second venipuncture for OGTT participants. Caffeine-free refreshments are provided, including decaffeinated coffee and tea. Menus are locally determined.

4.0 MEDICAL DATA REVIEW

Although it is made clear to all cohort participants in the informed consent and their providers of medical care in the cover letters for the final results report that the interviews and clinical exams which participants 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 trained staff to provide the participant with a summary of study results for height, weight, sitting blood pressure and a preliminary report of the ECG (Appendix 4). Participants are reminded that their clinically relevant study data which are processed at the study's central reading centers and laboratories are not available for several weeks.

4.1 Rationale

From the perspective of the investigators, the primary objective of the medical data review is to safeguard participant safety. Clinical and interview data are reviewed with participants to confirm selected positive symptoms reported during the interviews/exams and to determine if these appear to warrant immediate (same day), urgent (same week) or routine medical follow-up. Conditions requiring emergency referral are dealt with as soon as observed and in general have been dealt with before the Medical Data Review takes place. For example, cardiac events, blood pressure readings > 210/120 mm Hg and acute pattern abnormalities detected on the ECG are attended to as soon as observed. The ARIC physician is consulted, the clinic visit terminated, the person referred for immediate medical care, and a return visit to complete missed procedures and interviews is scheduled as appropriate. Persons with elevated blood pressures less than 210/120 mm Hg are referred to their source of medical care at the Medical Data Review following the guidelines shown in Table 4.2. Likewise, observations of an ECG abnormality identified as major in Table 5.1 are reviewed by an ARIC physician on call before the participant leaves the field center.

When clinically relevant laboratory data processed at the study's central agencies (laboratories and reading centers) have been received at the field centers, the 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, participants' clinically relevant Visit 4 data are reviewed at three levels. The first review takes place during the Medical Data Review (see below, section 4.3), which is conducted after all interviews and physical exams have been completed and data have been assembled as part of the Data Inventory step (section 3.11). The second and third levels of medical data review take place after data processed at the study's central agencies (Dental Study Laboratory, ECG Reading Center, Hemostasis Laboratory, Lipid Laboratory, and Ultrasound Reading Center) are returned to the field centers and are reviewed by the study clinicians (Chapter 6, Physician Review) and summarized for inclusion in the final results reports (Chapter 7, Results Reporting) that are mailed to participants and their providers of medical care.

4.2 Data Inventory

The data inventory step initiates the last fixed component of the field center examination sequence (Table 2.3), 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 4 and require summarization and placement in the participant's folder for nurse/clinician review.
4.2.1 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 immediate (same day), urgent (within one week) or routine (within one to two months or first convenient appointment) referral for medical care (Table 5.1) are put together into one document, the Medical Data Review Printout (Appendix 4.a), and reviewed with the participant prior to the completion of the examination. (Note: data required for emergent referrals are compiled as soon as the condition is observed, e.g., blood pressures in the range of very severe hypertension as listed in Table 4.1 and 4.2). Data inventory is the data management process by which the Medical Data Review Printout is produced.

4.2.2 Procedures

A staff person reviews the participant itinerary sheets to determine that all interviews and procedures have been completed, participants' folders to verify they contain the paper versions of the forms to be completed by ARIC staff, and participants' self-administered forms to determine completeness and whether assistance is required/requested. 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.

4.2.3 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.

4.2.4 Certification

Certification for data inventory is the responsibility of the field center Data Coordinator at the beginning of Visit 4. No recertification is required, but staff performance is monitored by the study coordinator.

4.2.5 Quality Assurance

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

4.2.6 Data Collection

Please refer to the Manual of Operations for Data Coordinators.

4.3 Procedures

Trained staff conducts the medical data review to

1. summarize the results of selected measurements obtained during the exams/interviews,
2. determine whether a reported stroke/TIA symptom(s) constitutes a possible cerebrovascular event(s),
3. identify potential medical problems,
4. answer participant questions.

Prior to the Visit 4 Medical Data Review, the participant's data are reviewed for positive findings during Visit 3 (i.e., alert values and referral letters), positive findings during any of the Annual Follow-up interviews.
between Visit 3 and Visit 4 (such as positive Rose Angina, cardiac procedures or hospitalizations), or comments on the participant's current itinerary form made by interviewers or technicians. Visit 4 data from the following sources are then reviewed from the participant folder and the Medical Data printout (Appendix 4.a) with the participant:

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.

3. Physician Diagnosed Medical Problems Reported by Participant
   a. Physician diagnosis of diabetes;
   b. Physician diagnosis of high cholesterol;
   c. Physician diagnosis of cancer.

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. Physician diagnosed Stroke/TIA or symptoms consistent with TIA or stroke reported on TIA/Stroke form;
   d. 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 re-vascularization 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/height
   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 to item 4 (uterine bleeding) of the Female Reproductive History form are followed-up as part of the Medical Data Review. If the response to Item 4 is either I, O, or D, the participant is asked if she 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.

Access to data from previous examinations (Visits 1-3) by field center staff during Visit 4 is limited to two purposes: (1) to prepare the Visit 4 folder, and (2) to conduct the medical data review. Data from previous exams should not be accessed for other purposes during the course of the Visit 4 exam to avoid the possibility of biasing the collection of new data.

The data coordinator, or staff member designated by the study coordinator to prepare participant folders, should be the only person accessing Visit 1-3 information prior to Visit 4. 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 information from previous exams to be brought to the attention of the entire staff and is noted on the Visit 4 Participant Itinerary Sheet. The person performing the medical data review, however, has access to all previous ARIC findings relevant to the medical review, immediately prior to discussing the participant's clinic visit report (Appendix 4).

If during the course of the Visit 4 examination a participant asks about changes in his/her laboratory values/clinical procedures since any of the previous exams, 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 exams, 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.

The following guidelines are used for explaining study results from Visit 4 or for recommending medical follow-up on the results reported in the clinic visit report during Medical Data review.

1. Changes in height and weight from previous exams should be focused on weight gained or lost, e.g., more than 10% since Visit 3; decrease in height of greater than 2 cm.

2. The blood pressure readings, based on the average of the first and second measurements, are recorded on the Report on Blood Pressure and Recommendations graph (Figure 4.1) and medical follow-up recommendations (Tables 4.1 and 4.2) are discussed with the participant. As these recommendations apply specifically to newly diagnosed hypertension, the following statement has been added to the graph: "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 of individuals with a previous history of high blood pressure, other CVD risk factors, or target-organ disease, the ARIC referral guidelines (Figure 4.1), adapted from the
fifth Joint National Committee recommendations, are followed for all participants, unless the participant's physician has recommended 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 4 in an asymptomatic participant does not warrant repeat referral. This decision is made by the ARIC physician who reviews the ECG tracings on a weekly basis.

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.

Table 4.1 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 4.2. Medical Care Referral Guidelines for Blood Pressure, Based on Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC-V, 1993) 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>Emergency Referral</td>
<td>SBP ≥ 260 or DBP ≥ 130</td>
<td>Transportation to emergency care facility. Stop exam and reschedule clinic visit.</td>
<td>Your BP is very high.</td>
</tr>
<tr>
<td>Immediate Referral</td>
<td>SBP 210-259 or DBP 120-129</td>
<td>Consult with ARIC MD. Refer to source of care immediately (today). Stop exam and reschedule clinic visit.</td>
<td>Your BP is very high.</td>
</tr>
<tr>
<td>Urgent Referral</td>
<td>SBP 180-209 or DBP 110-119</td>
<td>Consult with ARIC MD and proceed unless otherwise indicated. Refer to source of care within 1 week.</td>
<td>Your BP is high.</td>
</tr>
<tr>
<td>Routine Referral</td>
<td>SBP 160-179 or DBP 100-109</td>
<td>Refer to source of care within 1 month.</td>
<td>Your BP is elevated.</td>
</tr>
<tr>
<td></td>
<td>SBP 140-159 or DBP 90-99</td>
<td>Refer to source of care within 2 month.</td>
<td>Your BP is elevated.</td>
</tr>
<tr>
<td>No Referral</td>
<td>SBP 130-139 or DBP 85-89</td>
<td>Recheck in 1 year (no ARIC referral)</td>
<td>Your BP is high normal.</td>
</tr>
<tr>
<td></td>
<td>SBP &lt; 130 or DBP &lt; 85</td>
<td>Recheck in 2 years (no ARIC referral)</td>
<td>Your BP is normal.</td>
</tr>
</tbody>
</table>

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

2. Unusually low readings should be evaluated for clinical significance.
Figure 4.1 Report on Your Blood Pressure and Follow-up Recommendations
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. As part of the data inventory process, participant's responses to selected items with potential medical care impact or participant safety implications are printed by the networked DES on the Medical Data printout for ease of review before the Medical Data Review. The back-up procedure in case of computer failure or incomplete data collection is to identify such items on the paper forms. Relevant alert values and referral guidelines are listed in Chapter 5.1.

Symptoms of TIA or stroke which are reported to have occurred within the six months prior to the interview which appear to be cerebrovascular in nature are discussed with the field center medical director for recommendations on referral for medical care. A TIA/Stroke Worksheet is available to document (1) the presence of a noncerebrovascular cause which explains the symptom, (2) the impression as to whether the symptoms are indicative of a TIA or stroke since Visit 3, and (3) the most recent date of the putative event.

In summary, factual information (ARIC Clinic Visit 4 Report, Appendix 4.b) is given to participants about their results during the Medical Data Review, identifying abnormalities and recommending referral as needed, but avoiding medical advice about prognosis, prevention or therapy. Physician back-up is available at all times.

4.4 Training

Staff are trained for the Medical Data Review tasks by the ARIC medical director and/or field center principal investigator.

4.5 Certification

The local trainer is responsible for certification of the physician assistants, and nurse practitioners/clinicians responsible for medical data review.

4.6 Quality Assurance

The medical director of each ARIC field center is responsible for ensuring that the medical data review, referrals and reporting of results are done according to procedures in the ARIC protocol.

4.7 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/Referral Form (Appendix 5.c).
5.0 REFERRALS AND REVIEW GUIDELINES

5.1 Rationale

Participants are referred based on the guidelines for referral listed below. Prior to the Medical Data Review, a DES utility retrieves 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 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, Section 5.1.2, and are summarized in Tables 4.2 and 5.1. 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 5.c and 5.d, respectively.

5.2 Procedures

Referrals are made during the Medical Data Review or upon receipt of the study's clinically relevant data which 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 also sent a letter of explanation (Appendix 6.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. This usually occurs during the Medical Data Review, but can occur when alert values are returned to the field center from a central agency. The ARIC physician calls the participant's provider of care, and sends a referral letter. (Appendix 6.a and 6.b). Follow-up letters are also sent to the participant (Appendix 6.c,6.d).

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 (Appendix 7.e-h) and his/her physician (Appendix 7.b or 7.c) as a cover letter for the final results report.

5. No Referral. The study results are summarized for the participant and held for a routine results letter which are sent as cover letters for the final results report (Appendix 7.d).

Procedure/symptom specific guidelines are summarized in Table 5.1. Certain interview items or measurements (identified with an asterisk) require confirmation from additional questions during the Medical Data Review.
Referral guidelines for blood pressure differ based on a prior history of an elevated blood pressure during previous examinations. 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 7.2; examples of the texts of these letters are provided in Appendices 6 and 7.
Table 5.1  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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP &gt; 210 mm Hg or DBP ≥ 120 mm Hg</td>
<td>See M.D. today.</td>
<td>BP very high.</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td></td>
<td>&quot;</td>
<td>Your symptoms may be important</td>
</tr>
<tr>
<td>Neurologic symptoms in past week</td>
<td>&quot;</td>
<td>Your symptoms may be important.</td>
<td></td>
</tr>
<tr>
<td>Other severe symp-toms or findings</td>
<td>&quot;</td>
<td>Your symptoms may be important.</td>
<td></td>
</tr>
<tr>
<td>URGENT REFERRAL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
<tr>
<td>Neurologic symptoms, untreated, one week to six months ago</td>
<td>&quot;</td>
<td>Your symptoms may be important.</td>
<td></td>
</tr>
<tr>
<td>Acute congestive heart failure</td>
<td>&quot;</td>
<td>Your symptoms may be important.</td>
<td></td>
</tr>
<tr>
<td>Other acute, but less severe symptoms</td>
<td>&quot;</td>
<td>Your symptoms may be important.</td>
<td></td>
</tr>
<tr>
<td>SBP &gt; 180-209 mm Hg or DBP ≥ 110-119 mm Hg</td>
<td>&quot;</td>
<td>BP high.</td>
<td></td>
</tr>
<tr>
<td>ROUTINE REFERRAL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
<tr>
<td>Neurologic problem (stroke, TIA exam findings) &gt;6 months ago, unrecognized</td>
<td>&quot;</td>
<td>Your symptoms may be important.</td>
<td></td>
</tr>
<tr>
<td>Claudication, previously unrecognized</td>
<td>&quot;</td>
<td>Your leg pain may be important.</td>
<td></td>
</tr>
<tr>
<td>Other symptoms or findings needing evaluation/not being followed</td>
<td>&quot;</td>
<td>Your symptoms may be important.</td>
<td></td>
</tr>
<tr>
<td>Uterine bleeding; response I,O,D on Reproductive Hx form.</td>
<td>&quot;</td>
<td>Your symptoms may be important.</td>
<td></td>
</tr>
</tbody>
</table>

* Interview items/measurements require confirmation during Medical Data Review
Table 5.1  Medical Care Referral Guidelines, continued

<table>
<thead>
<tr>
<th>Classification</th>
<th>Findings</th>
<th>Referral Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ROUTINE REFERRAL</strong></td>
<td><em>SBP 160-179 mm Hg or DBP 100-109 mm Hg</em></td>
<td>See MD within one month.</td>
</tr>
<tr>
<td></td>
<td><em>SBP 140-159 mm Hg or DBP 90-99 mm Hg</em></td>
<td>See MD within two months.</td>
</tr>
</tbody>
</table>

| NO REFERRAL          | *Angina, stable on None. treatment/being followed* | Confirm only. |
|                      | *MI, previously documented* | Confirm only. |
|                      | *SBP 130-139 mm Hg or DBP 85-89 mm Hg* | Recheck in 1 year Your reading is high normal. |
|                      | *SBP ≤ 140 mm Hg and DBP ≤ 90 mm Hg* | Recheck in 2 years Your reading was normal. |
|                      | Height, weight | None. Report only. |

<table>
<thead>
<tr>
<th>ECG Findings</th>
<th>Acute pattern abnormalities</th>
<th>Per review by MD.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review by M.D.</td>
<td>MI, ischemia...)*</td>
<td>Would like to review with M.D.</td>
</tr>
<tr>
<td>Before Participant leaves Field Center.</td>
<td>Any other ECG finding, alone or in conjunction with symptoms, causing concern.*</td>
<td></td>
</tr>
<tr>
<td>Other ECG Findings or Normal ECG</td>
<td>A copy of the ECG will be sent to your physician with the other results.</td>
<td></td>
</tr>
</tbody>
</table>

1. Interview items/measurements require confirmation during Medical Data Review

2. 2nd or 3rd degree block, ventricular tachycardia, R on T, atrial fib/flutter with ventricular rate < 60 or > 110, sinus bradycardia < 50, sinus tachycardia > 110, PR interval > 0.26 sec.
6.0 PHYSICIAN REVIEWS

6.1 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 during 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 confirmed 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.

6.2 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 at this time.
7.0 RESULTS REPORTING

This activity concludes a process which extends over 4 to 8 weeks after the participant completes Visit 4. 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 5.1.2, and mailed to participants and physicians.

As alert values are returned from the central laboratories and reading centers, the medical staff reviews them and assumes responsibility for referrals (see Table 5.1). 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.

With participant approval, normal and abnormal results of the clinically relevant medical tests are reported to the participant's physician. Clinically relevant 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 the field center.

Reporting of Visit 4 values is made in the context of Visit 3 results. The alert values listed in Table 7.1 are reported with recommendations for medical follow-up. When a value is outside of the reference-range listed in Table 7.1, but falls in a "gray zone" (marginally outside of the reference range, but probably not clinically relevant) or is similar or identical to one that resulted in a referral at Visit 3 (an ECG for example), a referral in Visit 4 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.

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.
Table 7.1  Laboratory Alert, and Normal Reference Values

<table>
<thead>
<tr>
<th>Chemistries</th>
<th>Reference Ranges for ARIC Labs**</th>
<th>Gray Zone</th>
<th>Significant Range</th>
<th>Alert Values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>total cholesterol</td>
<td>&lt;200 Desirable 200-239 mildly elevated &gt; 240 markedly elevated</td>
<td>200-204</td>
<td>205-244 &gt; 245</td>
<td>none</td>
</tr>
<tr>
<td>LDL</td>
<td>&lt; 130</td>
<td>130-133</td>
<td>&gt; 134</td>
<td>none</td>
</tr>
<tr>
<td>HDL</td>
<td>&gt; 35</td>
<td>34-35</td>
<td>&lt; 33</td>
<td>none</td>
</tr>
<tr>
<td>TG</td>
<td>&lt; 220</td>
<td>220-223</td>
<td>224-1000 &gt; 1000</td>
<td></td>
</tr>
<tr>
<td>creatinine</td>
<td>&lt; 1.5 men</td>
<td>none</td>
<td>1.5-2.5 &gt; 2.5</td>
<td></td>
</tr>
<tr>
<td>fasting glucose</td>
<td>70-130</td>
<td>none</td>
<td>60-69 131-200 &lt; 60</td>
<td></td>
</tr>
<tr>
<td>2 hour glucose</td>
<td>70-139</td>
<td>none</td>
<td>60-69 140-300 &lt; 60</td>
<td></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.
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.

7.1 Overview of Results Reporting

Figure 7.1 (ARIC Referral/Notification Procedures) provides an overview of this process and illustrates the interface between the review of medical data, the referral process, and the notification of study results. The figure also illustrates 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 7.2 and Appendices 6 and 7) 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.

The following is a review of results reporting procedures.

1. At reception, the Schedule of ARIC Results Reporting (Appendix 5.b) is reviewed with (and at local option, given to) the participant to describe 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 4.1. A pre-printed Summary of Visit 4 Report (Appendix 4.b) is filled in during the Medical Data Review and given to the participant to summarize the exam results which do not require processing by a central laboratory or reading center.

3. At the Medical Data Review, a referral may be necessary. Three levels of referral are designated: Immediate (same day), Urgent (within one week), Routine (within one to two months, depending on study guidelines), and the corresponding referral letters are sent to the participant's physician (Appendix 6). (Emergent referrals are made as soon as the condition is observed and are generally not held until the Medical Data Review). For immediate or urgent referrals, a phone call to the participant's provider of medical care may be made to facilitate the referral recommendation given to the participant.

4. Once a week, a physician review occurs during which the ARIC physician reviews participant data and interprets ECG tracings, as described in section 6.1.2. If an abnormality is detected at this time, a report or referral letter is sent to the participant and his/her physician (Appendix 7).

5. The central laboratories and reading centers send the field centers the clinically relevant study results 4-12 weeks after each participant's Visit 4 exam. If there are "alert values", the participant is notified using an Alert Value Referral Letter (Appendix 7.e and f) and the medical care provider is notified (Appendix 7.b and c). If there are no "alert values", normal results reports and cover letters indicating no
abnormal findings are sent to participants and their physicians if requested.

6. 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 7.2 and prototype letters are found in Appendix 7.

7. 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.

8. A record is kept of all alert values and referrals on the Report and Referral (REFB) form (Appendix 5.c) and on the Alert/Referral Log (Appendix 5.d) Copies of all referral letters and results reports are filed in participant folders.
Figure 7.1  ARIC Referral/Notification Procedures
<table>
<thead>
<tr>
<th>RECIPIENT</th>
<th>TYPE OF COVER LETTER FOR RESULTS REPORTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>REFERRAL LETTERS FOR ALERT VALUES</strong></td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>a) referral post clinic visit</td>
</tr>
<tr>
<td>Participant</td>
<td>a) referral at clinic visit (N/A)</td>
</tr>
<tr>
<td></td>
<td>b) referral post clinic visit (w/ MD)</td>
</tr>
<tr>
<td></td>
<td>c) referral post clinic visit (no MD)</td>
</tr>
<tr>
<td><strong>COVER LETTERS FOR SUMMARY Visit 4 RESULTS REPORT</strong></td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>a) Normal results</td>
</tr>
<tr>
<td></td>
<td>b) Abnormal results, no previous referral made</td>
</tr>
<tr>
<td></td>
<td>c) Abnormal results, previous referral made</td>
</tr>
<tr>
<td>Participant</td>
<td>a) Normal results</td>
</tr>
<tr>
<td></td>
<td>b) Abnormal results, no previous referral made</td>
</tr>
<tr>
<td></td>
<td>c) Abnormal results, previous referral made</td>
</tr>
<tr>
<td></td>
<td>d) Normal results, no MD designated</td>
</tr>
<tr>
<td></td>
<td>e) Abnormal results, no MD designated</td>
</tr>
<tr>
<td>INSURANC.LTR</td>
<td>Study results sent to third party</td>
</tr>
</tbody>
</table>
7.2 Report of Ultrasound B-Mode Scan Measurements

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 and 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. If a referral is recommended, field centers are notified to contact the study participant and their provider of medical care a letter signed by the medical director (Appendix 7.a-c). 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.

7.3 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 7 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.

7.3.1 Results routinely reported to the participant

Results reported to the participant during the clinic visit (ARIC CLINIC Visit 4 REPORT, Appendix 4.b) include current weight and weight at the previous examinations, current height and height at Visit 1 and 3, current blood pressure and blood pressure measurements from the previous 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 three months after Visit 4, the SUMMARY OF ARIC Visit 4 RESULTS FOR PARTICIPANTS AND THEIR PHYSICIANS (Appendix 5.a) is mailed to the participant. This report includes the following confirmed study results from Visit 4: weight and height; blood pressure; summary report of electrocardiogram; summary report of echocardiogram (Jackson participants); summary report of the retinal photograph of one eye for participants in the repeatability study at the beginning of Visit 4; B-scan ultrasound exam of the carotid arteries, and
blood tests (total, LDL and HDL-cholesterol values, triglycerides, creatinine, fasting glucose, and a 2 hour glucose for OGTT participants).

7.3.2 Results routinely reported to the physician

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

7.3.3 Results Reported Only by Request

All other study measurements, i.e., those not routinely reported to 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 from the participant authorizing the release of ARIC study data to anyone other than the participant or his/her identified provider of medical care is required prior to the release of study data by the ARIC study. A copy of the request and the authorization for release of study data 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.

3. This information is sent with a cover letter (Appendix 7.i) 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.

7.3.4 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 7.1. 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, 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 7.2.
8.0 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 participants' 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 2.11).

8.1 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 4. 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 major and minor emergencies are described in sections 8.3.1. and 8.3.2, respectively.

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 6.A (Ultrasound Scanning). 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 person 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 light-headedness when standing (postural effects). When the postural changes are measured, the sonographer is positioned closely behind the person as a protective measure should he or she become faint. A sturdy chair is positioned 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 below in Section 8.3.2 and in Manual 11 are followed.

8.2 Stopping Rules for Interviews and Procedures

Participant safety and comfort during the clinical examination are monitored throughout the clinic visit. Interviewers and technicians observe participants for signs of fatigue or physical and/or emotional discomfort. When any one of these conditions are observed, participants are offered the opportunity to discontinue the interview or procedure, and are given an opportunity to rest before being taken to the next work station. Persons incapable of completing all of the clinical exam are invited to change back into their street clothes and participate in the medical data review and reschedule the clinic exam on another day.

For persons with conditions which require emergency and immediate referrals, such as cardiac events, unstable angina, ECGs with acute pattern abnormalities or blood pressures > 210/120 mm Hg (See Tables 4.2 and 5.1), the ARIC physician is consulted immediately, the clinical exam is terminated as soon as the condition is observed, and another appointment for Visit 4 is rescheduled as appropriate. For blood pressures requiring referral within one week (SBP 180-209 mm Hg or DBP 110-119 mm Hg; the urgent referral category in Table 4.2), the ARIC physician is also consulted, and the clinical exam is either continued and the participant advised to seek medical care within one week or the clinical exam is terminated and rescheduled, based on the physician's recommendation. The termination of any interview or procedure is documented on the participant itinerary sheet.

8.3 Methods for Handling Emergencies
While all life threatening emergencies (e.g., 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.

8.3.1 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. A staff person with certification in basic life support is on duty and physically present at every clinic session. 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 and the home and work telephone numbers of one or more contact persons are available on the UPD form. 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.

ARIC staff are trained to carry out their specific responsibility during an emergency. Retraining is the responsibility of each field center, following institutional guidelines.

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.
8.3.2 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., after 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 8.2.1 are followed.

8.4 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.
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