Atherosclerosis Risk in Communities Study Protocol

Manual 12

Quality Assurance and Quality Control

Visit 4

Version 4.0

October, 1997

For Copies, Please Contact
ARIC Coordinating Center
Department of Biostatistics (CSCC)
University of North Carolina
CB# 8030, Suite 203, NationsBank Plaza
137 E. Franklin Street
Chapel Hill, NC 27514

FOREWORD

This manual, entitled Quality Assurance and Quality Control, is one of a series of protocols and manuals of operation for the Atherosclerosis Risk in Communities (ARIC) Study. The complexity of the ARIC Study requires that a sizeable number of procedures be described, thus this rather extensive list of materials has been organized into the set of manuals listed below. Manual 1 provides the background, organization, and general objectives of the ARIC Study. Manuals 2 and 3 describe the operation of the Cohort and Surveillance Components of the study. Detailed Manuals of Operation for specific procedures, including those of reading centers and central laboratories, make up Manuals 4 through 11 and 13 through 16. Manual 12 on Quality Assurance contains a general description of the study's approach to quality assurance as well as the details for quality control for the different study procedures.

ARIC Study Protocols and Manuals of Operation

MANUAL	TITLE
1	General Description and Study Management
2	Cohort Component Procedures
3	Cohort and Community Surveillance
4	Pulmonary Function Assessment - (Retired)
5	Electrocardiography
6	Ultrasound Assessment
7	Blood Collection and Processing
8	Lipid and Lipoprotein Determinations
9	Hemostasis Determinations
10	Clinical Chemistry Determinations - (Retired)
11	Sitting Blood Pressure
12	Quality Assurance and Quality Control
13	Magnetic Resonance Imaging
14	Retinal Photography
15	Echocardiography
16	DNA Repository

MANUAL 12. Quality Assurance and Quality Control

TABLE OF CONTENTS

1.0 INTRODUCTION

1.1 Brief Description of Quality Assurance and Control Procedures

The distinction between quality assurance and quality control is both arbitrary and philosophical. The former is considered here as relating to activities to assure quality of data which take place prior to collection of data, while the latter relates more to efforts during the study to monitor the quality of data at identified points in the collection and processing of data. It is quality control on which Manual 12 focuses, whereas quality assurance is the essence of the entire Manual of Operations, and includes the following activities:

1) Detailed protocol development. A clear description of the study design, training, certification, and the various data collection activities provides the blueprint for the study. Each protocol is a written reference for staff and researchers. Procedures for handling the routine, as well as the exceptional, are given. Those protocols constitute the ARIC Manuals of Operation.

2) Training and updating training. Training is the transfer of the study plans in the protocol to the research staff. The process has resulted in clarification and revision of the protocol. Special materials for this purpose have been developed for ARIC and are the basis for continuing education during the study. Continued investment in quality data during the study is made by periodic refresher training sessions which review the protocol and update personnel on any changes which have occurred.

3) Certification. Criteria to examine the adequacy of an individual's training have been established. Individuals meeting these criteria are qualified to execute a protocol or a segment of it. Certification and periodic re-certification indicate that an acceptable performance standard has been mastered or an adequate knowledge of material has been achieved. The Coordinating Center monitors the study to ensure that staff perform only those functions for which they are certified and that re-certification activities are implemented as planned and as scheduled.

For quality control purposes, ARIC data collection and transfer is monitored by observation (directly and by tape recording) and by quantitative assessment using both specific quality control procedures (e.g., repeat measurements) and statistical analysis of study data for quality control (QC) purposes. Monitoring is performed both by personnel within the field centers and by monitoring visits from the Coordinating Center and various central agencies. A summary of selected aspects of ARIC Cohort Study quality control follows.

1) Observation monitoring. Over-the-shoulder observations of staff by supervisors or those who wrote the protocols identify techniques that need improvement and points where the protocol is not understood. Also, periodic monitoring visits are made to each field center by Coordinating Center staff to observe actual clinic activities.

   Detailed checklists are used to assess strict adherence to protocol. Immediate feedback is given, and general recommendations for improvements are sent to the Steering Committee for action.

Another form of observation in the ARIC study takes place with the interview portion of the protocol. All interviews are tape recorded after permission is given by the participant. A supervisor reviews the tapes on a random basis, reviewing at least one of each type per month. The supervisor checks for adherence to protocol and for accuracy of recorded responses.

2) Quantitative monitoring. Random repeat measurement by the same and by different technicians are used as quality control tools. There are two important benefits from random repeat measurements. First, randomly re-doing a fraction of an individual's work is likely to stimulate a better overall quality of data. Second, the duplicate determinations provide measurements of data quality. At the time of reporting the results of the study, it is important to establish that the "error" in the data is not so large as to threaten the validity of conclusions.

   Actual study data are useful to monitor quality of performance. Mean and standard deviations of study variables, by technician, are monitored for differences among technicians or trends over time. Digit preference in anthropometry or blood pressure measurement is monitored with study data.

3) Reporting results. Two aspects of the reporting of quality control monitoring should be emphasized. First, the results must be timely. When remedial action is required, reporting must be prompt so that a return to an acceptable level of performance is not unnecessarily delayed. Second, the reporting format must be easily understood. Tabular presentations are accompanied by clear graphical displays.

4) Action on results. With conscientious and trained staff, quality control reports provide an opportunity to praise a job well done. On the other hand, a poor performance is the basis for some remedial action. Depending upon past performance, the amount of error, and, taking due account of personal circumstances, the appropriate action may be a simple discussion to encourage a better performance. Re-training may also be appropriate at times.

1.2 Monitoring of Data Quality and Implementing Corrective Action

The subsequent sections of Manual 12 describe the procedures and reports used to monitor quality control of the ARIC Study. These reports are designed to be clearly understandable, to be distributed to individuals responsible for reading them carefully, and to lead to corrective actions. A Quality Control Committee is designated by the ARIC Steering Committee to coordinate and direct the quality control activities.

The Quality Control Committee (QCC) is charged with establishing the content of the quality control reports and with the responsibility to review all reports with specific attention given to deviation from protocol, recurrent problems and trends or shifts in data over time. Working with the specialty subcommittees and the Coordinating Center, the QCC determines the content, areas of emphasis, and statistical treatment for each of the routine quality control reports. The QCC specifies quality control reports in response to priorities for quality assurance developed by the Steering Committee. The QCC prepares recommendations to the Steering Committee in matters of quality assurance, and contacts field centers, reading centers, or laboratories as needed, to advise them of a problem and to discuss the mechanism for

correction. Central logs of data and management quality problems are reviewed by the QCC. The QCC has representation from the Coordinating Center, Field Centers, Laboratories and Program Office.

The role of the Coordinating Center (CC) in quality assurance and control is described in general in ARIC Manual 1. More specifically, as the repository for ARIC Study data, the Coordinating Center is responsible for preparation and dissemination of QC reports. These reports consist of tabulated data and summary statistics, and identify specific QC problems. The Coordinating Center maintains contact with centers to confirm that a center has been notified of a problem and that corrective action has been implemented. The Coordinating Center maintains central logs of data quality problems and solutions. The Coordinating Center conducts periodic field center monitoring during which Coordinating Center staff participate in and observe a routine ARIC clinic visit. In response to requests from the QCC, the Coordinating Center replicates pertinent sections of quality control reports prepared by reading center/laboratories. Some external quality control programs for the reading center/laboratories are administered by the Coordinating Center, and reported to the QCC.

The distribution of the QC reports and the designation of persons or groups responsible for responding to the reports and implementing corrective action are described below. Each field center and/or reading center is given the responsibility of reading, implementing corrective action, and responding to the reports in their respective area. Monitoring reports for protocol deviations, recurrent problems, or temporal trends is the responsibility of the QCC. Immediate QC problems identified by reading centers, laboratories or the Coordinating Center (e.g., data entry problems, broken vials) are sent to the field centers directly for correction with a record kept by the reading center/laboratory/CC. Problems identified by periodic monitoring are sent to the field centers/reading centers/laboratories with concurrent monitoring by the QCC.

The distribution of periodic reports described in Chapter 4 is as follows:

1) QC reports on technician-specific performance are sent quickly to the respective field center principal investigators, study coordinators and the QCC.

2) QC reports on laboratories/reading centers' performance are sent quickly to the respective principal investigators, and to the QCC.

3) Summary QC reports without technician-specific data are sent to the Steering Committee through the QCC.

The following centers and committees have responsibility for responding to the reports as follows:

1) Field center PIs, study coordinators, local certifiers/trainers. Review each QC and monitoring report with technician-specific quality for their field center; identify a solution to each problem; implement corrective action; report corrective action to Coordinating Center monitor.

2) Laboratory and reading center directors. Review each QC and monitoring report for their laboratory/center; identify a solution to each problem; implement corrective action; report corrective action to QCC.

3) Quality Control Committee. Review each QC and monitoring report with attention to deviation from protocol, recurrent technician or field center problems, and temporal trends; direct field center/reading center/laboratory attention to problems and recommend additional corrective action if they persist; monitor the implementation of corrective action; contact and coordinate study agencies and investigators to review data quality problems and solutions; prepare summary reports and recommendations for the Steering Committee.

4) Specialty subcommittees. Review summary reports with attention to deviations from and deficiencies in the protocol; address recommendations to QCC.

5) Steering Committee. Review QC summary reports; monitor data quality trends; direct the QCC in areas needing special attention; responsible for changes in protocol.

1.3 Organization of the Quality Control Manual

For the cohort component of the ARIC Study, procedures are described (Sections 6-11) by source of data within the field center, i.e., by work station, e.g., anthropometry or electrocardiogram (ECG). For each area there appears a brief description of the data collected and a summary of the important quality control measures. There follows a detailed list of quality assurance or quality control measures addressing each data transfer point or possible source of error. The ARIC study's system of making (blinded) repeated measurements for quality control purposes is used in so many areas of the cohort study that a separate section, Section 2, is devoted to description of this topic. Section 3 discusses the analysis of study data for quality control purposes. Section 4 briefly discusses the types and schedules of quality control reports. Section 5 describes two types of quality control analyses that appear in many areas: replicate data analysis and monitoring for digit preference. Subsequent sections describe the quality control procedures for the various cohort study work stations, certification, and community surveillance.

2.0 DESCRIPTION OF THE QUALITY CONTROL SYSTEM FOR REPEATED MEASUREMENTS

In several areas, repeated measurements during a clinic examination are taken for quality control purposes and are recorded on study forms separate from the participant's original forms. These forms are designated as belonging to phantom participants. Approximately 7% of assigned study IDs are for phantom participants. The Data Coordinator in each field center (FC) generally creates phantom participant folders when needed, and initializes a phantom participant diskette. As a safeguard against gathering unnecessary data on the phantom participant forms, only a subset of the usual study forms are included for QC repeat studies. Currently, repeat studies are done for anthropometry, blood measurements, and urine collection. (Repeat scanning with ultrasound is handled differently and is described in Manual 6.) Repeat measurements are then entered, by the technician making the measurements, on the phantom forms/diskettes just as regular study data, as explained below, and the folders are processed as regular study data. There is one extra form in the QC phantom participant's folder, the ARIC QC Phantom Participant and Non-Participant ID Form (Appendix 1), which is used to match the phantom ID to the IDs of the ARIC participants contributing repeat measurements. This form is also used to record IDs used for data collected on persons who are not ARIC study participants (e.g., monitors from the Coordinating Center). This form is entered into the computer and the electronic copy is sent to the Coordinating Center with a copy kept in the phantom participant's folder. As a further backup, the QC phantom ID is entered on a form in the associated ARIC participant's folder, as explained below.

The procedures for using the QC phantom participant folders are:

1) The data coordinator creates phantom folders, putting the QC phantom participant labels on the Phantom Participant and Non-Participant ID Form, the anthropometry form and the laboratory form (for venipuncture and urine specimens), and places these in the folders. When QC phantom participant IDs are assigned, the person making the assignment does the following on the Quality Control Phantom Participant and Non-Participant ID Form:

   a) Places the label for the ID assigned to the QC phantom in the space provided at the top of the form;
   b) Circles "P" for "A QC Phantom Participant" on the form;
   c) Fills in their own ID and the date the QC phantom ID was assigned in the spaces provided.

2) As ARIC participants contribute replicate data, the matching ARIC participant labels are affixed to the QC Phantom Participant and Non-Participant ID form for the data that are contributed. Five replicate QC blood drawing tubes are assigned to a phantom participant. (The procedures for anthropometry repeats are discussed more thoroughly below in Section 6, Anthropometry. For venipuncture and urine repeats, see Manual 7 and Section 8 of the QC Manual.)

3) After all needed repeat measures are recorded on the phantom's venipuncture or anthropometry forms (or diskette), or when two weeks have passed since the first QC data were entered on the form, the data coordinator inserts the folder in the regular stream of participant folders as if the Exit Interview had just finished. It is processed as usual.

It is desirable to utilize each phantom participant ID for gathering both blood and anthropometry QC entries in order to use fewer ARIC IDs. However, there are times when this should not be maintained. For example, the study coordinator keeps a reserve of 2-3 phantom participant folders, so that if none is ready to leave the venipuncture station for anthropometry use, or vice versa, new folders from the study coordinator are used.

When monitors, volunteers or other persons who are not participants in the ARIC cohort go through at least some of the ARIC examination procedure, they are assigned an ARIC cohort ID, which are recorded on the Quality Control Phantom Participant and Non-Participant ID Form. The following procedure should be used:

1) The study coordinator assigns an ARIC cohort ID at the start of their visit.

2) As soon as the ID is assigned, a label for that ID is placed in the box marked "Phantom Participant ID Number" on the QC Phantom Participant and Non-Participant ID Form, and "N", for "An ID Used for a Non-Participant" is circled.

3) Also as soon as the ID is assigned, the person making the assignment records the date and their own ID number in the spaces provided.

4) The same week the non-participant is seen, an electronic copy (on disk) of the PNP (phantom non-participant) ID form is sent to the ARIC Coordinating Center.

Deadlines for sending Phantom Participant and Non-Participant ID forms to the Coordinating Center:

For quality control phantoms, the folder diskette for the phantom should go to the study coordinator for routine processing of any Venipuncture or Anthropometry forms filled out on the phantom, and entered into DES and sent via e-mail to the Coordinating Center.

3.0 ANALYSIS OF STUDY DATA FOR QUALITY CONTROL PURPOSES

The methods to monitor the quality of the ARIC data collection process include analyses of the study data itself. This section provides a summary and discussion of the analysis of the study data for quality control purposes.

To monitor the data entry process, most variables in the ARIC data base are analyzed periodically, by field center, in terms of:

1) status of the variables for each participant record (no problem, skipped due to skip rule, problem with the entry).

2) frequencies for categorical variables, or means, standard deviations and selected percentiles for continuous variables.

The first item, especially, allows a view of the prevalence of data entry problems.

Certain measurements which involve a degree of subjective judgment by technicians, such as blood pressure or anthropometry data, are commonly subject to digit preference. The Coordinating Center periodically analyzes such data for digit preference, by technician.

Some data sent to central reading centers (e.g. ECG, ultrasound) are assigned a quality grade by the respective reading centers. The Coordinating Center prepares periodic summaries of recorded quality grade, broken down by technicians or field center to monitor performance.

Certain items of data (e.g. fasting time before blood drawing) give information on protocol adherence and the validity of data obtained from each participant. The Coordinating Center periodically analyzes these data items by field center.

4.0 QUALITY CONTROL REPORTS FOR THE COHORT COMPONENT

A large number of reports are generated by quality control work. In order to spread out the workload and the distribution of the reports, a schedule for the Cohort Component reports has been developed (although it will undoubtedly be frequently modified).

Frequency of reports vary from quarterly to annually, although there are summary reports which are more of a historical nature, covering longer periods. For a report to be of use in correcting problems in data gathering, it must appear more frequently and be prepared as soon as possible after the end of the period covered. The frequency of reports is determined by balancing the study's need for prompt and frequent monitoring with the available resources to generate such reports and the need to accumulate enough data to have an adequate sample size. For example, analysis of adjusted means by technician and of repeat measures in anthropometry is not feasible on a monthly basis, but can usefully be done each quarter.

The standard QC reports generated for the categories within the Cohort Component are outlined below. (Frequency for analyses appearing less often than bimonthly appear in parentheses.)

1) *Certification*
   - a. *Number of studies performed in past quarter, by area, field center, and technician (quarterly)*
   - b. *As in (a.), for the whole period since Visit 4 started.*

   Note: In addition to the bimonthly reports, semi-annual reports are also produced to account for revisions generated by the bimonthly reports.

2) *Anthropometry*
   - a. *Digit preference (once for Visit 4)*
   - b. *Repeated measures (once for Visit 4)*

3) *Sitting Blood Pressure*
   - a. *Digit preference (annually)*

4) *Laboratory (lipids, hemostasis, clinical chemistries, hematology)*
   - a. *Repeated measures (annually)*
   - b. *Analysis of QC samples from frozen storage (when this is done to be determined)*
   - c. *Internal QC results (annually)*
   - d. *External QC results (annually)*

5) *ECG*
   - a. *Mean quality grade, by field center and by technician (annually)*
   - b. *Results on test pool submitted to EPICARE ECG center (annually)*
   - c. *Results on test pool of 12-lead ECGs submitted to Minneapolis ECG Reading Center (annually)*

6) *Ultrasound and Postural Change*
   - a. *Frequency of nonvisualized boundaries, by technician and site/angle (semi-annually)*
   - b. *Sonographer repeat studies (semi-annually)*

c. *Reader repeat studies (semi-annually)*
d. *Inter-sonographer repeat studies (once, unless problems detected)*

7) *Participant Protocol Compliance (annually)*
a. *Twelve-hour fast, abstinence from smoking, caffeine, and heavy exercise*

8) *Quarterly Observation with Checklists (semi-annually)*

9) *Venipuncture*
a. *Distribution of number of stick attempts, means and distribution of filling and processing time (annually)*

11) *New Procedures*
a. *Data evaluation: two hour blood draw, baldness assessment, and urine sampling (quarterly in the beginning of Visit 4)*

5.0 SPECIAL STATISTICAL ANALYSES IN QUALITY CONTROL REPORTS

5.1 Replicate Data Analysis

The collection of replicate data for anthropometry and blood chemistries is described above in Section 2 and in Manual 6a for Ultrasound. In this section, the statistical techniques used to analyze such data are described. Refer to Table 1 below for an example of a summary table of results from replicate data analysis. The following general model of variation in the study data underlies these techniques: suppose that the total variance of the study data, σ^2_T, is divided into two components, the measurement error component, σ^2_e, and the true variation between and within individuals in the study population, σ^2_b, so that $\sigma^2_T = \sigma^2_b + \sigma^2_e$. One quantity of interest in considering data quality is the reliability coefficient

$$R = \sigma^2_b/(\sigma^2_b + \sigma^2_e),$$

which is one minus the proportion of total variance due to lab variation. It can be shown that R is the correlation coefficient between two laboratory measurements made on the same (split) sample, in the blood chemistry case. In the anthropometry and ultrasound cases it is the correlation between two measures made a short time apart on a person. Let X_{i1} and X_{i2} be two repeated measures on the i-th subject in the QC replicate data, and X_i be the mean of these two measures. Then σ^2_e is estimated from that pair by

$$s_i^2 = \sum_{j=1}^{2}(X_{ij}-X_i)^2 = \frac{1}{2}D_i^2$$

where $D_i = (X_{i1} - X_{i2})$. Estimates of σ^2_e from all n pairs of replicates are combined by taking the average of the pair estimates (s^2_i). That is,

$$\sigma_e^2 = \frac{1}{n}\sum_{i=1}^{n}s_i^2 = \frac{1}{2n}\sum_{i=1}^{n}D_i^2$$

R may be estimated in two ways: (1) from the replicate data alone, using the technique of one-factor random effects ANOVA to divide the total variance in the replicate data into estimates of σ^2_b and σ^2_e (the estimator of σ^2_e is the same as the δ^2_e described above); (2) by combining the information from the replicates with information from the total ARIC study data set. This second method is the one which has been used in ARIC. From the sample variance of the study data, S^2_T, we may obtain a good estimate of σ^2_T. Then, σ^2_b is estimated by $S^2_T - \sigma^2_e$ so that the estimate of R is given by:

$$R = 1 - \frac{\sigma^2_e}{S^2_T}$$

R is useful for overall assessment of the reliability of the measurement method. For routine monitoring of the data collection process, the standard deviation σ_e (the square root of σ^2_e) is most closely watched. In monitoring laboratory data, σ_e for each assay is compared with the target standard deviation (S.D.) which the laboratory has set based on analyses of internal quality control pools. Blind replicate estimates of the laboratory S.D. which

are more than twice the target S.D. are considered cause for concern. Several additional statistics are calculated for each assay. For each QC replicate pair, the i-th pair coefficient of variation, $C.V._i$, may be calculated by

$$C.V. = \frac{s_i}{x_i}$$

s_i is defined as before, where s_i is the i-th pair standard deviation estimate. The mean sample pair C.V. is then calculated as the average of the n sample pair $C.V._i$'s. A mean sample pair C.V. greater than 10% is considered very large on most assays.

In order to monitor for systematic differences between original and replicate measurements, the proportion of non-zero differences which are positive is monitored. With no systematic trend, this proportion should be one-half. A sign test is done to test for significant differences, and significant differences which persist over several months are pointed out to the laboratory. (This test is done, but is less useful, for anthropometry and ultrasound data.) Means and percentiles of these differences are also presented. It should be noted that if the mean difference is non-zero, alternative estimates of σ_e and of the reliability coefficient, R, should be considered.

Frequencies of absolute percentage differences for the replicate pairs are also given, as are percentiles of the absolute differences. For ultrasound B-mode data, instead of frequencies of absolute percentage differences, frequencies of absolute differences are given.

Before any analysis is done on the QC replicate pairs, the data are screened for possible mismatches or "strange" observations. For each <u>laboratory</u> assay, the mean and standard deviation of the difference between repeat and original pairs from prior analysis are used to determine acceptable intervals. If the difference between the repeat and original is outside the interval (determined from previous data)

Mean Assay Difference $\pm$ (2 S.D. of Assay Difference)

on <u>three</u> or more assays, the pair is excluded from analysis. Likewise, if the difference between the repeat and original is outside the interval

Mean Assay Difference $\pm$ (1.5 S.D. of Assay Difference)

on <u>four</u> or more assays, the pair is excluded. These excluded pairs are also investigated by the Coordinating Center and the lab to find reasons for mismatching.

5.2 Monitoring for Digit Preference

Monitoring for digit preference is done by the Coordinating Center for blood pressure and for anthropometry, at frequencies determined by study needs. Summary reports are sent to the Quality Control Committee, and reports on individual technicians are sent to the Field Center. The actual technician-specific frequencies of final digits recorded are not revealed to the Field Center, to prevent technicians from overcompensating to avoid digits that they

had preferred in previous reports.

For blood pressure only final digits 0,2,4,6,8 are possible, while for anthropometry 0,1,2,... 9 are all possible. To discuss the analysis of both, let k be the number of possible final digits, so k = 5 or 10. For a technician with no digit preference, in a large number N of studies the expected frequency of each final digit is N/k. A Pearson chi-square goodness-of-fit test is done to test the null hypothesis that all possible final digits are observed with frequency N/k. The statistic is calculated as

$$X^2 = \frac{\sum_{i=1}^{k} (O_i - \frac{N}{k})^2}{\frac{N}{k}}$$

Where O_i is the observed frequency of the i^{th} possible digit and

$$N = \sum_{i=1}^{k} O_i$$

For large N, this statistic is distributed approximately as a chi-square distribution with k-1 degrees of freedom. Note that Chi-square = 0 when the observed number for each possible digit is N/k. For each calculated value of Chi-square, the p-value is calculated as the probability upon repeated sampling (N fixed) of getting a value as extreme as that actually observed. For the validity of this test, $N \geq 25$ for blood pressure and $N \geq 50$ for anthropometry are required. A cut point of $p < .05$ is used to determine if the divergence from a uniform distribution of digits is statistically significant. However, with large enough N, even small deviations from uniformity are declared statistically significant. Thus a "digit preference score" was developed:

$$DPS = 100\sqrt{\frac{X^2}{N(k-1)}}$$

This score can be shown to have values between 0 and 100. (It is 0 when all observed digit frequencies are N/k and is 100 when all observed counts are in one cell.) Arbitrarily, after consideration of the first few months of ARIC data, a cutpoint for marked digit preferences was selected: DPS $\geq$ 20. A technician is judged to show "strong evidence of digit preference" if all of the following are true: (1) N $\geq$ minimum N required (25 for blood pressure, 50 for anthropometry); (2) the p-value for the X^2 statistic is <.05; and (3) the digit preference score is greater than or equal to 20 (DPS $\geq$ 20). Technician specific data are reported in a table like the one below.

TABLE 1

Clinic Visit - Blood Pressure
Digit Preference on Three BP Readings
Data received at Coordinating Center for July 1987

Field Center: **Technician ID:**_____

Total Frequencies of Even Final Digits

Measurement	N	Most Freq.	2nd	3rd	4th	Least Freq.	Probability*	Digit Preference Score
Systolic BP	57	19	13	10	8	7	0.065	19
Diastolic BP	57	21	13	11	7	5	0.009	24
Random Zero	57	15	13	12	10	7	0.515	12

*Probability of at least this much variation if no digit preference.

As noted above, a sample size $N \geq 25$ for blood pressure and $N \geq 50$ for anthropometry are needed for the validity of the chi-square test for digit preference. For this reason, the smallest period examined for digit preference is one month for blood pressure and two months for anthropometry. All reports are broken down into these periods for the two types of measures, although they usually summarize the data over a longer time interval.

Although all occurrences of a month with marked digit preferences are recorded, only repeated occurrences are especially noted and the Field Center asked to initiate re-training and increased observation. If digit preferences persist over a number of months, it is requested that the technician be moved to another station. Digit preference monitoring is also used in determination of re-certification.

6.0 ANTHROPOMETRY

6.1 Brief Description of Anthropometry Procedures in the ARIC Cohort Study and Related Quality Assurance and Quality Control Measures

Anthropometry is performed with the participants wearing underwear under a scrub suit or examination gown. Weight and height are measured without shoes. Values are rounded down to the nearest unit indicated and entered into the PC on the participant's disk or on a paper form. The measurements include standing height, body weight, abdominal girth, hip girth, arm circumference, and male pattern baldness (in males). Male pattern baldness in male participants is assessed for the first time in Visit 4. The technician assessment of hair loss is also recorded on the anthropometry form. Important quality assurance/control measures include clear and detailed protocols for each measure, training and certification, instrument checks (logged in daily or weekly), random repeatability studies, biannual observation of technicians by other technicians, and a periodic quality review of study data by the Quality Control Committee.

6.2 Maintenance of Measuring Tools

6.2.1 Log of equipment checks

A log shall be kept of the equipment checks listed below (see sample log in Appendix 3.1.d of ARIC Manual 2). These equipment checks may be done by any certified anthropometry technician. At the end of each January and July, the FC needs to summarize these logs on a Report on Use of Observation and Equipment Checklists form (see Appendix 3.1.j, Manual 2), which is then sent to the Coordinating Center.

6.2.2 Standing height

The ruler used for standing height measurement is checked weekly to confirm that it touches the floor and is mounted perpendicular to the floor. Every six months, or whenever the ruler is moved, a check is made to confirm that the floor where the ruler is placed is firm and level and that the wall is perpendicular to the floor.

6.2.3 Wooden angle

Field Centers are urged to use a wide balsa wood right angle to measure height rather than a narrow carpenter's rule, in order to guarantee that the right angle is actually balanced at the top of the head. The FC confirms every six months that the wooden angle remains at 90°, and repeats this check whenever the wooden angle is dropped.

6.2.4 Scales

a) Daily: Check daily that the scales read zero when there is no weight on them.

b) Weekly: Calibrate the scales using the 50-pound known weight. This calibration is performed again whenever the scales are moved. If the scales are outside the 49.5 to 50.5 range, an independent service

technician is called in to recalibrate the scales. Calibration with the 50-pound weight is performed for both balance arms (light and heavy) on the scale.

c) Annually: The scales are certified annually by an independent scale technician.

6.2.5 Measuring tapes

The condition of each measuring tape is checked monthly, and any that have become worn or stretched are replaced. The tapes are checked for regular stretching by comparing them with the standing height ruler. If the measure falls outside the 119.5 - 120.5 cm the tape should be replaced. Note: This check also applies to tapes used in the sitting blood pressure station, if arm circumference is measured there.

6.3 Biannual Observation

Each January and July quality control observations of technicians by an observer are performed by field center staff. A checklist is filled out (see Manual 2, Appendix 3.1) noting whether correct procedures were followed for each item on the lists, including participant clothing. The IDs of observer and observed are recorded in the Use of the Observation and Equipment Checklists and mailed to the CC at the end of each January and July. Major deviations from the protocol are brought to the attention of the Cohort Operations Committee.

6.4 Preparation of Participant

The anthropometry examination comes before the clinic snack. The participants wear underwear under a scrub suit or gown, without shoes.

6.5 Making Measurements

The FC has mirrors at the anthropometry station which are positioned to allow the technicians to ensure that the measuring tapes stay level all around when taking measurements of hip and waist girth.

6.6 Recording of Measurements

Use of mirrors: The anthropometry technician should verify that the participant's ID matches that on the data screen when entering data directly onto the PC. This verification is repeated when the forms are transcribed onto the PC at the FC. When paper forms are used, the technician uses the ID labels in the participant's folder.

6.7 Blinded Random Replicate Measurements

At a fixed time after the anthropometry exam, a sample of participants is called back to the anthropometry station to all measurements repeated by the same or a different technician. Which participant within a day is repeated and which measurements are repeated are determined by a random scheduling

process (see below). The participant is matched with a QC Phantom Participant ID and the repeat measurement is keyed in directly onto the Phantom non-Participant form (PNP) in the computer. (See Section 3 describing the QC phantom IDs.) This process is described in more detail as follows:

1) An indicator in the DES (Data Entry System) screen for anthropometry will signal whether a participant has been selected for the Participant Repeatability Studies.

2) A fraction (5%)of the participants are randomly selected for repeat measurements (four measurements each time for females, and five -- including baldness -- for males), with half of the repeat studies being done by the same technician who performed the measurements earlier and half by a second technician. If repeat measurements are to be made, the receptionist notifies the technician who is to make the measurements. These measurements are to be done as soon after the snack as they can be fitted in to the participant's and technician's schedules.

3) The technician who is to repeat the measurements takes the folder of a Quality Control Phantom Participant, and enters the date, the participant's ID label, and the ID of the technician performing the repeat measurements on the Quality Control Phantom Participant and Non-Participant Form for that phantom. Quality control phantom IDs are used to record measurements. As noted above, the data for these measurements are recorded directly onto the PNP form (in the computer). In filling out the form, the item "Date of Data Collection" should be filled out with the date the first measurements are made for the phantom participant. The term "ID of person recording data" should be filled out by the last technician entering data onto the form. As soon as all measurements have been made for a particular QC Phantom ID, the QC phantom participant's folder goes through any additional data-processing steps at the FC along with the regular participant folders. (See Section 2 on closing out the phantom.)

   The ARIC Quality Control PNP form (in the computer), which matches the IDs of real and phantom participants, is sent to the CC. The phantom participant's folder is filed with regular ARIC participant folders in the Field Center or all phantom folders can be filed together. Note that in doing the repeat measurements the technician should have the phantom's folder but not the participant's folder.

4) The FC should attempt to spread the repeat measurements by other technicians among the staff certified for anthropometry.

5) Each week the FC sends the CC any Quality Control PNP forms (in the computer) which are completely filled out for blood and/or urine QC samples, and/or for anthropometry measurements. If groups of anthropometry measurements are not sampled at the same rate it is necessary to send the CC some QC PNP forms in the computer that are only partially complete with respect to anthropometry. All QC PNP forms should be sent in no later than two weeks after the first data is entered on them. The data for the PNP forms are sent with the regular shipment of data from the FC to the CC.

6.8 Baldness Quality Control

Baldness assessment requires the technician to match the participant's hair loss to one of the 12 figures on the male pattern baldness scale (Appendix II); a value of "13" is used to indicate total baldness. Differences between figures are both quantitative (degree of baldness), and qualitative (area of baldness).

Repeat assessment (QC) for baldness is performed on participants selected for anthropometry QC through the Data Entry System (DES). use of the same (intra) or different (inter) technician is stipulated by the DES. The rate of repeat measures for anthropometry is 5% so the rate for baldness is approximately half that or 2.5%. In so far as possible, the same technician should not always do the first (or repeat) reading. As many different pairs of technicians as possible should be used.

In order to increase the number of baldness QC records, an additional sampling scheme was designed where the first male participant each day was selected for baldness QC for a 20-day period that began April 1, 1996 and ended April 26, 1996. If this participant was also selected by the DES, then the technicians were to do all anthropometry QC; otherwise, they were to just repeat the baldness measure. A total of 20 participants were selected for baldness QC using this additional process. All of these additional repeat baldness measures were inter-technician. In other words, the technician doing the repeat measure was always different from the technician who did the original measure. Even if the participant was selected by the DES and intra (same) technician repeat measures was indicated, the repeat baldness was done by a different technician.

6.9 Coordinating Center Analysis for Quality Control

6.9.1 Digit preference: The CC periodically analyzes the study data from each technician for digit preference.

6.9.2 Replicate measurements: The CC periodically analyzes quality control data on repeated measures.

6.9.3 Original/Repeat pairs: The CC periodically analyzes study data and quality control data for comparison of systematic differences for original/repeat pairs.

6.9.4 QC review: The CC review anthropometry QC data with the Quality Control Committee based on results from the aforementioned analyses.

7.0 SITTING BLOOD PRESSURE

7.1 Brief Description of Sitting Blood Pressure Procedures and Related Quality Assurance and Quality Control Measures

The following equipment is used for measuring sitting blood pressure: a standard Littman stethoscope with bell; standardized Hawksley random-zero instrument; standard Baum manometer for determining peak inflation level; four standardized cuffs (from Baum). After the technician explains the procedure to the participant, measures the arm circumference and wraps the arm with the correct cuff, the participant sits quietly for 5 minutes, and then the technician makes two readings, with at least 30 seconds between reading one measure and beginning the next. The average of the two readings is reported to the participant.

From the detailed protocol for sitting blood pressure in ARIC Manual 11, the various data transfer points and other possible sources of error have been considered, and needed quality assurance and control measures have been derived. Important elements in quality assurance are training and certification programs, observation of data collection by supervisors, biannually simultaneous blood pressure measurements using Y-tubes by two technicians, and standard equipment maintenance procedures performed and entered into logs.

7.2 Maintenance of Equipment

1) Availability of all sizes of cuffs: The field center blood pressure supervisor makes certain that the field center always has the full range of blood pressure cuffs available at each blood pressure station. Field center staff report immediately to the blood pressure supervisor if they cannot find all cuff sizes at the station.

2) Sphygmomanometers: Regular inspections of random-zero and standard sphygmomanometers are described in ARIC Manual 11, Section 1.13.1 and Appendices I, II, and V. A log sheet is kept by the field center blood pressure supervisor, who records the performance of these checks and comments on any problems found (see copy of log sheet in Manual 11, Appendix IV). By the end of each January and July, the summary form for the checklists should be filled and mailed to the Coordinating Center.

3) Measuring tape: Each week the blood pressure supervisor checks the condition of the measuring tape used to measure arm circumference at the blood pressure station(s), and replaces any that have become worn. The results of this check are recorded on the anthropometry weekly log. (See the anthropometry section for details.)

7.3 Field Center Monitoring of Technician Performance

1) Double stethoscoping: To help assess the accuracy and precision of blood pressure measurements, once each January and July each blood pressure technician takes part in measuring blood pressure simultaneously with another technician, using a Y-tube. This procedure should be carried out using volunteers or other field center staff members, not ARIC study

participants. The two technicians also perform independent measurements of arm circumference, which they record on the forms. If the two technician measurements lead to a disagreement on which blood pressure cuff to use, then both re-measure the arm together and use the cuff size determined by that measurement. Each records this disagreement on the Sitting Blood Pressure form. Each technician separately records all blood pressure measurements on paper on a standard Sitting Blood Pressure form. The two paper forms are given to the field center blood pressure supervisor, who compares the results.

The field center blood pressure supervisor reviews the results of these duplicate examinations, calculating the disagreement between technicians on the blood pressure measurements and recording it on the form. The two technicians should agree on each of the two measurements of diastolic and systolic blood pressure within 4 mmHg, and their average should agree within 3 mmHg, as is required by the standards for certification. If they do not, further duplicate readings are taken to determine if either or both technicians require recertification. These further measurements should again be recorded as described in the previous paragraph.

The IDs of each set of technicians paired for simultaneous measurement of blood pressure are recorded in the Report on Use of Observation and Equipment Checklist, which is mailed to the Coordinating Center at the end of each January and July.

2) Biannual observation: Once every January and July, the field center blood pressure supervisor observes each blood pressure technician performing the entire measurement procedure with a study participant. The field center supervisor notes any problems with technique and discusses them with the technician after the examination has been completed. Also, another technician observes the field center blood pressure supervisor perform the entire measurement process. After the examination, the two of them discuss any questions that come up in the course of this observation. In performing these observations, the supervisor and technicians use the checklist given in Appendix III of ARIC Manual 11. For each technician, the date that the technician was observed and the observer's ID number are recorded in the Report on Use of Observation and Equipment Checklist.

7.4 Recording of Participant ID Data

In filling out the Sitting Blood Pressure screen, the technician verifies that the name and ID number on the DES screen which accompanies the participant match the participant's to avoid ID errors. If the PC is down and a paper form is used, the technician verifies the name on the folder accompanying the participant before using the ID labels in the folder on the forms.

7.5 Measurement of Arm Circumference and Choice of Blood Pressure Cuff

As described above, once every six months duplicate measurements of blood pressure are performed on a volunteer or field center staff member (not an ARIC participant). During the course of this procedure, both technicians measure arm circumference and record their results. The field center blood pressure supervisor compares these results, and if they differ by more than 1 cm, the measurement technique is reviewed with both technicians.

Both the arm measurement and the cuff size chosen are recorded on the SBP form. The data entry system checks for the consistency of cuff size and arm circumference.

7.6 Participant Posture and Rest Before Blood Pressure Measurement

The field center blood pressure supervisor monitors that the station(s) used for blood pressure measurement continue to meet the conditions specified in the protocol, e.g., that blood pressure measurements are done in a quiet room away from other field center activities. Coordinating Center staff on monitoring visits also take note whether this condition is being maintained.

The field center blood pressure supervisor is responsible for seeing that the protocol is followed by timing blood pressure measurements early in the visit, before blood drawing or other stressful activities. Each month the field center supervisor reviews a sample of participant Itinerary forms for the previous month to confirm that this is done.

To assist in judging that a full five-minute rest is allowed before taking the first blood pressure measurement, the blood pressure technician uses a hand held timer or other means of accurately timing the rest period. Biannually, the field center blood pressure supervisor observes each technician performing the full blood pressure procedure and notes whether the correct rest period is being allowed.

7.7 Coordinating Center Quality Control Analyses

The Coordinating Center analyzes data from each technician for digit preference in reading systolic or diastolic blood pressure. This check is performed annually, unless problems detected call for more or less intensive monitoring. The Coordinating Center reports these results to the field center, and the field center blood pressure supervisor reviews these results with each technician.

The Coordinating Center checks that correct data entry procedures are used for recording missing data. The Coordinating Center communicates with the field centers when problems are identified.

8.0 BLOOD AND URINE COLLECTION AND PROCESSING

8.1 Brief Description of Blood Collection and Processing and Related Quality Assurance and Quality Control Measures

At the time of the telephone contact participants are requested to fast for 12 hours before field center visit, unless they are diabetics taking insulin or have other medical reasons that make fasting inadvisable. A detailed protocol, set out in ARIC Manual 7 (Blood Collection and Processing) has been developed, which describes the preparation of blood tubes, the anticoagulants to be used for samples for each laboratory, and the specific steps to be taken in blood drawing and processing. After the blood is drawn, the sample tubes go through further processing at the field center. Blood samples used for lipid and hemostasis analyses are frozen at -70°C for weekly shipment to the ARIC central laboratories. Samples for hematology analyses are sent to local laboratories. All shipments to Central Laboratories are by overnight delivery services. All of these steps are performed by technicians trained in the ARIC protocol and certified to have adequately mastered its details.

The first step in quality assurance for blood drawing consists in this training and certification process. Other steps include maintaining logs of equipment checks, observation of technicians (by other technicians and by monitors on visits) as they go through the sequence of steps in blood drawing and processing; review of the condition of samples received at central laboratories for problems in shipment; and periodic analysis of the study data for participant compliance with fasting and for signs of problems in drawing or processing, such as hemolysis or delays in completing processing.

8.2 Maintenance of Equipment

Each field center performs daily temperature checks on refrigerators, freezers, the refrigerated centrifuge, and the heating block (see ARIC Manual 7). The actual speed of the centrifuge is checked and recorded monthly with a tachometer. The results of these checks are recorded on a log sheet kept at the blood processing station, and are summarized onto the Report on the Use of Observation and Equipment checklist at the end of each January and July. A copy of the report is sent to the Coordinating Center at that time.

8.3 Participant Compliance with Protocol

In contrast to previous visits, venipuncture is performed on all cohort members, regardless of their fasting status (Manual 2, Section 3.9.2), and includes 3 plasma samples for the Lipid and Hemostasis labs; 2 serum samples for the Hemostasis and Dental labs; and an optional sample for a local Hematology lab. In addition, a second venipuncture is performed on OGTT eligible participants. The post glucola blood draw must occur within 2 hrs. (plus or minus 10 min.) of administration of the glucola drink. Failure to meet criteria can affect the values of various measurements (e.g. lipids, glucose) and compromise their value to the study. ARIC participants should also abstain from smoking and vigorous physical effort before the visit to the field center, since smoking may affect electrocardiograms or blood pressure and vigorous activity may activate fibrinolysis and alter blood levels of tPA and FPBβ. Interviewers are trained to explain the importance of compliance

with these restrictions. When Field Centers contact participants before their appointment to remind them about the scheduled visit, they repeat these instructions.

The Coordinating Center analyzes study data for information on length of time fasting and time since smoking and hard exercise, broken down by field center, to obtain the number and percent of participants at each field center each month who do not comply with these restrictions.

8.4 Maintaining Proficiency

To maintain their proficiency, technicians are urged to perform blood drawing and processing at least once each week (or 8 times each 2 months). The Coordinating Center analyzes the study data to report on the number of times that technicians collect and process blood in the Field Centers.

8.5 Periodic Observation

Periodically (each month in the beginning) each field center technician performing blood drawing and processing is observed performing the entire procedure by either another trained technician or a supervisor, using a detailed checklist to verify that the technician is continuing to follow all parts of the ARIC protocol. Carrying out this observation also provides a review of the protocol for the person doing the observation. (See ARIC Manual 7 for further details and for a copy of the checklist, "ARIC Venipuncture and Processing Procedure Certification Checklist"). This checklist is also used for observations by monitors from the Coordinating Center performing monitoring. The IDs of observer and observed are recorded in the "ARIC Venipuncture and Processing Procedure Certification Checklist". They are also recorded on the Report on the Use of Observation and Equipment Checklist which is mailed to the Coordinating Center by the end of each January and July.

8.6 The Laboratory Form

To avoid ID errors in which information regarding a given participant's samples is written down on the wrong form, the technician should begin filling out each Laboratory form (LABB) as the blood is drawn, verifying the ID from the folder which accompanies the participant.

8.7 Quality Control Replicate Data

The system of drawing extra tubes of blood for QC replicate analysis is fully explained in ARIC Manual 7. In this system specified extra tubes of blood are drawn from a number of participants and matched to one "phantom participant" per week. The post-glucola blood sample is designated as Tube #6 on the Phantom Participant and Non-Participant ID form. See also Chapter 2 of Manual 12 for an explanation of the QC phantom system.

Persons who are non-fasting and indicate that they would like to be rescheduled for another blood draw should never used as a QC blood phantom.

The field center blood drawing station maintains a schedule of which tubes should be drawn for phantoms each day (see ARIC Manual 7) to help fit the QC

phantom sets into the work flow and make it easy to keep track of what is required.

The Coordinating Center reviews each month, broken down by field center, the number of QC phantom forms for which blood drawing is indicated. If Field Centers fail to provide sufficient sets of QC phantom blood, the Coordinating Center contacts the Field Centers to discuss the problem.

To reduce the risk of labeling a QC phantom blood tube with the wrong ID or of recording the wrong match between phantom and participant IDs on the QC Phantom Participant Forms, QC blood is drawn from no more than one member of each pair of participants whose blood is processed together.

To help make certain that the correct match is recorded between real participant ID and QC phantom ID, as soon as blood-drawing has been completed an ID label for the real participant ID is added to the appropriate space on the QC Phantom Participant and Non-Participant ID Form in the QC phantom folder.

8.8 Analysis of Venipuncture and Processing Data for Quality Control

The Coordinating Center analyzes the study data annually to determine the frequencies of filling time, number of stick attempts and reported presence of hemolysis, and for selected markers of lack of adherence to protocol during phlebotomy and/or processing of specimens at the field center laboratory. These analyses include field center tabulations by the ID of the technician performing the blood drawing or processing. (Standards for time needed for various processing steps are given in ARIC Manual 7.) Adherence to the 2-hr. post glucola blood draw window is assessed quarterly and reported to field centers.

8.9 Packing Samples for Shipment to Laboratories

All vials of blood samples as well as the plastic bags in which the samples for a given participant are packed for shipment to the several laboratories are labeled with the participant's ID. A shipping list is enclosed with each shipment to the Central Laboratories giving the IDs for all sets of samples that are enclosed. The person unpacking these samples at the Central Laboratories verifies that the IDs on the vials match the ID on the plastic bag and checks both against the shipping list. If any discrepancies are detected, the Central Laboratory contacts the field center to resolve the problem.

Blood vials shipped to the Central Laboratories must be packed securely to avoid both breakage and warming. Full instructions for packing samples are specified in ARIC Manual 7, Sections 5.1-5.3. The laboratories monitor the arrival condition of the samples sent from each field center. If problems are encountered, the laboratories notify the Field Centers involved. If a pattern of sample damage becomes apparent that suggests a need to modify the materials used to ship samples (e.g. excessive leakage of a certain type of vial) or how samples are packed, the Laboratory Subcommittee takes appropriate action.

ARIC blood samples are mailed promptly to the Central Laboratories at the start of the week after they are drawn. The laboratories monitor the dates of blood drawing on samples which they receive and notify the field center and

the Coordinating Center if they receive samples that were shipped at a later date than that called for under this schedule. (Note: quality control phantom blood tubes are held over one week before shipping, but the date of drawing on these samples that is reported to the laboratory is altered to conceal their identity as QC.) The field centers should phone the central laboratories to notify them if they are shipping on a day other than Monday.

To avoid delays in transit to the laboratories which might cause samples to be warmed or thawed in shipping, all samples are shipped by an overnight delivery service. To avoid delays over weekends or holidays in delivering samples or in moving them to the Central Laboratory freezer once they are delivered to the receiving area, all samples are shipped out at the beginning of the working week, on Monday or Tuesday. The laboratories notify the Coordinating Center and the field center if a shipment is received that was shipped out on a later day in the week, and the field center reports to the Coordinating Center on the reasons for this deviation from protocol. The laboratories notify the Field Centers if sets of samples are received late. If a pattern of delays is encountered with the delivery service a field center is using, the field center will change to an alternate delivery service.

8.10 Description of Urine Collection and Processing and Related Measures for Quality Assurance and Quality Control

After a participant is greeted at the clinic, he/she is asked to provide a urine specimen at the participant's convenience (e.g., when the participant expresses the need to void). When the participant is ready to void, a specimen cup (labeled with the participant's Id and TIME VOIDED) is provided, and the participant is instructed to fill the cup if possible. If the sample is insufficient for processing, the participant is requested to void again in a clean container prior to leaving the field center. Prior to processing, the technician records on the participant's Laboratory form whether a urine sample was obtained, the collection time of the initial (if more than one) urine sample), and adequacy of volume.

8.11 QC Sample Preparation

The following instructions describe specific additions to urine collection and processing protocols in order to meet QC requirements. These instructions assume that the normal procedures for collecting, processing, and shipping creatinine and albumin samples (see Manual 7, Section 6.0-6.3) are being followed.

8.12 Urine QC Schedule

The Visit 4 schedule for urine QC sampling parallels the blood QC sampling protocol: a minimum of one sample is required each week. QC specimens should be taken from the first participant either Tuesday or Thursday who provides sufficient urine. If no participant on Tuesday (or Thursday) provides a sufficient amount, the first participant to do so on Wednesday (or Friday) should be selected.

Urine QC sample collection should be added to the weekly checklist maintained by the Field Center venipuncture technicians. As with blood QC samples, each urine sample should be checked off as it is prepared. On Wednesday or Friday

mornings, the checklist is consulted to see if a additional urine sample is still needed.

8.13 QC Sample Requirements

Each participant's urine specimen is divided into three separate sample tubes and frozen at the field centers until shipping. Aliquots for creatinine and albumin on each participant 3.5 ml each) are shipped to the Minneapolis ARIC Field Center. The 50 ml conical tube (one per participant) for the hemostatic metabolites is shipped to the ARIC Hemostasis Laboratory; this tube must contain a minimum of 40 ml. When the schedule calls for collection of a QC sample (phantom) for creatinine and albumin, the participant's specimen cup must contain at least 54 ml (14 ml for a total of four 3.5 ml vials, and one 40 ml hemostasis sample). For a hemostasis laboratory phantom, 87 ml (7 ml for two 3.5 ml vials and two 40 ml hemostasis samples) are needed.

8.14 Laboratory and Phantom Forms

To ensure that the correct match is recorded between the real participant ID and the QC phantom ID, as soon as it can be ascertained that sufficient urine for a QC sample has been provided, an ID label for the real participant ID is added to the appropriate space on the QC Phantom Participant and Non-Participant ID Form.

To avoid ID errors in which information regarding a given participant's urine sample is entered on the wrong form, the technician should begin filling out a URINE SAMPLE section of the Laboratory form for the a phantom ID at the same time the participant's URINE SAMPLE section of this form is completed.

8.15 Sample Preparation

When creatinine and albumin phantom urine specimens are to be prepared, a total of four 3.5 ml aliquoting vials are required. Two vials are labeled with the participant ID and the remaining two with the phantom ID.

The two CREATININE and two ALBUMIN specimen vials are distinguished by cap inserts: YELLOW for CREATININE, and BLUE for ALBUMIN. The creatinine participant and phantom cryovials are filled first by the lab technician. Then the procedure for pH balancing of the Albumin sample is executed (Manual 7, Section 6.1.2), and the pH balanced specimen is pipetted into the participant and phantom cryovials.

The phantom hemostasis urine specimen is prepared at the same time and manner as the participant hemostasis urine sample.

8.16 Procedure for Small Samples

For QC purposes, the pairs of participant and phantom creatinine, albumin, and hemostasis urine samples must come from the same batch. If a single batch is inadequate for both the participant and phantom samples, then the specimens should be combined prior to drawing the samples.

8.17 Storage Instructions

Storage instructions (Manual 7, Section 6.2) stipulate that samples be packed in the order of the date drawn, putting a single participant's two specimens (CREATINE and ALBUMIN) side by side in the row. Since the phantom and participant specimens are drawn on the same date, they will likely be on the same row, possibly next to each other.

Record the Box and Position numbers on the participant's LABORATORY Form, and be sure to do the same for the Phantom.

Finally, record the IDs of all participants and phantoms in each box on a Box Log Form.

8.18 Quality Assurance and 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. Deviation 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 Operation Committee.

The CC will produce reports based on replicate data from the labs. Results of these reports will be examined by the QC Committee, and recommended corrective actions will be implemented.

The Coordinating Center will provide to the QC Committee and field centers a report based on the procedural data recorded on the Laboratory form. This report will evaluate data for consistency, and for missing or out of range values.

9.0 ELECTROCARDIOGRAPHY

9.1 Brief Description of Electrocardiography, and Related Quality Assurance Measures

A resting 12-lead ECG is performed on each participant in Visit 4 using procedures and equipment identical to those employed in the 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.

Electrocardiography for the ARIC cohort is done with the MAC PC Personal Cardiograph. During the Visit 4 examination a standard supine 12-lead resting ECG is recorded after a 12-hour fast, prior to the light snack, smoking tobacco or ingestion of caffeine. For each participant a 12-lead ECG, consisting of 10 seconds of each of the leads simultaneously, is stored in the MAC PC, and the accumulated records are transmitted daily by telephone to the EPICARE ECG Reading Center, where the ECGs are computer-coded.

All ECGs with Minnesota Codes related to myocardial infarction and major ischemic abnormalities and a random sample of normal 12-lead ECGs are transmitted from EPICARE and visually coded at the Minnesota center. Results from EPICARE and Minnesota are independently reported to the Coordinating Center. Differences in coding found by the Coordinating Center are then adjudicated in Minnesota.

Important elements in the Quality Assurance and Control for the field centers are training and certification programs, biannual observation checklists, quality requirements built into the ECG recorder for accepting data, and evaluation by EPICARE of quality of ECGs received. There are transmissions every other week of test sets of data from Minnesota to EPICARE to check phone transmission and reproducibility of coding at EPICARE. Repeat visual coding of 12-lead tracings from a test library provides a quality check for the Minnesota ECG Reading Center, and also repeats visual coding of abnormals in the set sent from Minnesota to EPICARE.

9.2 Recording of the ECG at the Field Centers

The EPICARE ECG Reading Center evaluates the technical quality of ECGs received from each field center. See ARIC Manual 5 for criteria for assigning quality grades for noise, overall drift, and beat-to-beat drift. The EPICARE Computer ECG Center computes the quality grade of each ECG. Periodic summaries of ECG quality grade are prepared by the Coordinating Center.

Twice a year the field center ECG supervisor observes other ECG technicians, using the ECG Technician Procedure Review Checklist (Manual 5, Appendix Q). Also, the supervisor is observed by another technician. The IDs of the technicians observing and the technicians that are being observed are recorded in the Report on Use of Observation and Equipment Checklist, which is mailed to the Coordinating Center at the end of each January and July. ECG technicians are also observed by visiting monitors from the Coordinating Center on periodic visits.

9.3 Transmission of the ECGs to EPICARE

IDS on the ECG PC directory are verified before transmission of the data to EPICARE.

Before transmission of the ECGs to EPICARE, the field center technician verifies that the best quality recording for each participant is sent.

To avoid loss of data, the field center awaits verification from EPICARE of which records were received before deleting any records from memory. The field center normally only keeps data 1-2 days before EPICARE confirms arrival by electronic mail. In the event of loss of one of these records, the field center paper ECG strip is the backup.

9.4 Coding of ECGs at EPICARE

The repeatability of the EPICARE coding is tested with the test sets sent from Minnesota. Periodically the Coordinating Center sends to the Minnesota ECG Reading Center a list of IDS from the test library, together with the match between the QC ID and the original ID of the test recording. Every two weeks five ECGs from one field center are sent to EPICARE with Visit number, and with the QC IDS and dates replacing the original IDS and dates, so that EPICARE is blinded to the test status of the ECGs. The Minnesota ECG Reading Center notifies the respective field center of the transmission.

Paper copies of the abnormal ECGs in the test set sent bi-weekly and retransmitted to Minnesota are compared regularly with the original paper ECG strips for this set to monitor any changes in the quality of reproduction of paper ECGs at Minnesota. A log is kept of this comparison, and EPICARE and the Coordinating Center are notified immediately if any problems are detected. The accuracy of coding by the EPICARE computer algorithm is confirmed by visual coding (in Minnesota) of all ECGs with abnormal Minnesota codes and a 10% random sample of the normals. Paper tracings for these ECGs are regenerated at Minnesota from ECGs sent by diskette along with the hard copy from EPICARE.

9.5 Transmission by EPICARE of Abnormal and a Random Sample of Normals to Minnesota for Visual Coding

In each transmission of ECGs by the EPICARE Computer ECG Center to the Minnesota ECG Reading Center, a transmission list is included. The Minnesota ECG Center notifies EPICARE when each transmission is received and verifies that the transmission list matches the records received.

Some of the records transmitted to Minnesota come from the test set sent electronically from Minnesota to EPICARE. Comparisons between old and new copies of this set are made to check accuracy of transmission.

9.6 Visual Coding at Minnesota of ECGs Transmitted by EPICARE

Abnormal tests in the weekly test sets of ECGs transmitted from Minnesota to EPICARE are regularly returned to Minnesota for visual coding. If results on these repeat codings do not agree with the original coding, it may be due to problems in the visual coding process at Minnesota. By itself, repeated

visual coding of these few tracings is not a sufficient check on the accuracy of visual coding at Minnesota, since it is highly likely that the coders soon become familiar with this small group of abnormal tracings, and that results on this set are not reflective of how reproducible the visual coding is overall.

Repeat visual coding of actual ARIC ECGs is done in a blinded fashion to test the reproducibility of visual coding. To carry this out, in the first year of the study the Coordinating Center selected a sample of ECGs that had already been visually coded at Minnesota. Periodically the Coordinating Center sends EPICARE a list of IDS selected from this test set together with matched QC IDS. EPICARE replaces the original IDS on the test set with QC IDS. EPICARE then transmits groups of these QC ECGs along with the regular transmission of ECGs to Minnesota. These QC ECGs are transmitted to Minnesota at the rate of 5 QC ECGs per 50 study ECGs. The 5 test ECGs should not be at the beginning of the transmission so as to not reveal their QC nature. Dates and other identifying information on the tracing are altered to conceal the repetition.

Analysis of EPICARE-Minnesota disagreements which go through the adjudication process also provides a check on the accuracy of visual coding at Minnesota. The analysis looks for trends in the proportion of disagreements on particular codes, trends in proportion of disagreements on which the adjudication sustained the visual or computer coding, and patterns in the codes on which computer and visual coding disagree. Such an analysis is prepared periodically by the Coordinating Center, and is supplemented by review of actual tracings by an experienced specialist in electrocardiography to help detect causes for underlying patterns in the visual-computer disagreements.

The Minnesota codes for ECG abnormalities set up rules for suppressing certain codes when other codes are present (e.g. T-wave abnormality codes 5-1 to 5-3 are not assigned in the presence of the code 7-1-1 for complete left bundle branch block). See Appendix E of ARIC Manual 5 for details of these coding and consistency rules. The Coordinating Center analyzes all visual coding results received and flags any records on which incompatible Minnesota codes are reported. The Minnesota ECG Reading Center reviews and reports the corrected codes for these records.

Coders should carefully guard against errors in recording the participant ID listed on the paper strip on the coding form. Instructions include a step in which, at the completion of coding, a computer based logging and tracking system double-checks the ID entered in the computer against the original paper strip to verify its accuracy. At later stages of the process of analyzing the data, ID errors may be detected when records are sent to adjudication due to disagreements with EPICARE, or when a record fails to appear for one ID, or appears for an ID that has not been assigned to any participant. At those stages, discovering the correct ID and tracing to match to an erroneous record may be extremely difficult. When ID errors are detected, the visual coders responsible are made aware of them so that they will be encouraged to take more care in the future.

9.7 Shipment of Results to Coordinating Center

To avoid loss of data in shipment to the Coordinating Center, shipping lists accompany each shipment indicating which records have been sent. The Coordinating Center sends the respective ECG Reading Center an electronic response (e.g. cc-mail or e-mail) confirming that each shipment has arrived.

9.8 Coordinating Center Identification of Tracings on Which EPICARE and Minnesota Disagree and Notification of Minnesota

Any disagreements between the Minnesota ECG Reading Center and the EPICARE Computer ECG Center on Q-wave codes are identified by the Coordinating Center and referred back to Minnesota for adjudication. Certain records may be identified as disagreements in the Minnesota codes assigned by the computer in EPICARE and the visual coders at Minnesota due to errors in recording the ID during the coding process. A check by the Minnesota Coding Center to see whether such an error may have occurred is part of the adjudication process.

The Coordinating Center carefully monitors its computer algorithm to identify disagreements between Minnesota and EPICARE to guarantee that all disagreements which should go to adjudication are flagged.

The Coordinating Center analyzes all ECG data received for disagreements between EPICARE and Minnesota that require adjudication. Once records have been received from both reading centers, the Coordinating Center sets and monitors the frequency for comparing the EPICARE and Minnesota ECG codings so as to prevent the time lag from becoming excessive.

9.9 Use of Adjudication for Feedback on the Accuracy of Coding at Minnesota

ECG coders are notified when adjudication identifies records for which inaccurate visual codes were assigned.

9.10 Reporting Results from Adjudication to Coordinating Center

The Coordinating Center checks that the IDS on adjudication results received match those on records identified for adjudication.

The Coordinating Center monitors the time lag between referral of records to Minnesota for adjudication and receipt of the result at the Coordinating Center.

9.11 Storage of ECG Computer Records at Minnesota

To prevent loss of original ECG data in computer files, back-up files are kept, including some stored off site to avoid catastrophic destruction of all back-ups.

9.12 CC Analysis for QC

9.12.1 Adjudication

The CC periodically identify disagreements between Minnesota and EPICARE.

9.12.2 Replicate measurements at EPICARE

The CC periodically identify disagreements of repeated reading done by the EPICARE reading center.

9.12.3 Replicate Measurements at Minnesota

The CC periodically identify disagreements of repeated reading done by the Minnesota reading center.

9.12.4 Quality grades

The CC periodically analyzes the quality grades assigned to each ECG records.

10.0 HEMOSTASIS AND LIPIDS

10.1 Brief Description of Procedures for Hemostasis and Lipids and Quality Assurance and Quality Control Measures

In the ARIC study blood samples are collected and processed at the field centers for shipment to two central laboratories for analysis of hemostatic factors, and lipids and lipoproteins, respectively. At the lipids laboratories, certain assays are performed on all blood samples soon after they are received. Assays at the Hemostasis Lab and other assays at the Lipids Lab are only performed on samples in case-control studies. Aliquots of blood for each participant are kept in frozen storage at -70°C at each laboratory for the latter purpose.

In Section 8 quality assurance has been discussed for blood collection and processing in the field centers. In the present section, the emphasis is on quality assurance in the central laboratories, beginning with the receipt of samples. This section differs somewhat from other chapters of this manual in being more of a general overview and summary of quality assurance measures. These matters receive careful and detailed discussion in each of the central laboratory manuals, which cover procedures for: receiving samples and storing them at a proper temperature until analysis; schedules of equipment maintenance; storage and handling of reagents, calibration standards, and quality control materials; internal and external quality control programs; long-term storage of case-control samples; and transcription and reporting of measurement results. This section of the manual supplements the laboratory manuals by its discussion of reporting on the effectiveness of laboratory quality assurance procedures and of the utilization for quality control of (1) analyses of ARIC study data and (2) blind replicate samples from ARIC participants sent to the laboratories.

10.2 Shipment of Samples to Laboratories

To reduce the possibility of damage to samples due to excessive delays at the Field Centers while awaiting shipping, the ARIC protocol calls for shipping samples to the central laboratories once each week, regardless of the size of the shipment. These shipments are done using an overnight delivery service. To avoid the possibility that samples might arrive at a central laboratory on a weekend and wait several days to be unpacked and moved to the freezer, the protocol prescribes that shipments should only be sent on Mondays or Tuesdays. (See ARIC Manual 7, Section 5.3.) If a field center does not send specimens on Monday, it should notify the respective central laboratories. In the event that a laboratory receives a shipment that is sent out other than on Monday or Tuesday, the laboratory notifies the ARIC Coordinating Center and contacts the field center involved to remind them of protocol. If a shipment is received that has been delayed in transit, the laboratory notifies the field center. If a pattern of delays becomes apparent, the field center should look for a more reliable means of overnight shipping.

The Coordinating Center analyzes the study data to identify the time lag between date of visit to the field center and when a report of the laboratory results is received by the Coordinating Center. If prolonged reporting delays are noted, the Coordinating Center works with the lab to determine if these result from delays in shipping samples at the field center, delays in

analyzing samples at the lab, or delays in reporting results.

A shipping list accompanies all shipments to the central laboratories. Upon receipt of the samples, the laboratory verifies the contents of the shipment and notifies the field center of the arrival of the samples. The verification includes comparison of the IDS on each vial against the ID numbers on the plastic bags holding them, and on the shipping list. In the event of any discrepancies, the laboratory contacts the field center and works to resolve any ID errors or other problems that caused the discrepancy. (See ARIC Manual 8, Section 2.1.2 and ARIC Manual 9, Section 1.4)

The laboratories note the status of the samples on arrival on their local data bases (e.g., frozen, vial unbroken; frozen, vial broken; thawed, vial intact; thawed, vial broken). The laboratories contact the Field Centers if problems are encountered with sample condition. If patterns of frequent problems with sample condition appear, the laboratories will work with the field center to decide what appropriate steps (changing packing materials, changing source of vials, changing shipping service, etc.) will correct these problems.

10.3 Receiving Samples at Laboratory

Procedures for creating and identifying a record for each specimen upon arrival differ among the central laboratories. At the Central Lipid Laboratory, a record in the local data base is created for each specimen when it arrives. This record includes a local specimen identification number, as well as the ARIC ID number. The local specimen ID number is the linking variable used to update the record for each specimen (either by direct data transfer from the analytic instrument or by entry of results from worksheets) after the specimen is analyzed. It is therefore crucial that care be taken when labeling specimens with local IDS that the local ID recorded for each ARIC specimen on the data base matches that by which the specimen is actually identified as it is processed in the lab. Laboratory supervisors periodically review how this process is carried out and instruct laboratory technicians in techniques to use to avoid ID errors. The Central Hemostasis Laboratory uses only the ARIC ID rather than adding a local ID number.

It is important in handling ARIC frozen blood samples to avoid any unnecessary exposure to room temperature. Clear procedures for unpacking specimens upon arrival are set out in each central laboratory's protocol to minimize such exposure. (See ARIC Manual 8, Section 2.1.3; ARIC Manual 9, Section 1.5). While awaiting analysis, specimens are to be kept in storage at -70°C. Each laboratory has provisions for (1) prompt detection of power failure or of failure of freezer to maintain the proper temperature, including both local alarms and alarm signals to a central security office that will notify appropriate laboratory personnel if a problem develops after hours; (2) back-up power supplies in the event of power failure; (3) plans for the use of dry ice to maintain the sample temperature until any problems with the freezer can be repaired. In addition, the Central Hemostasis Laboratory has one back-up freezer available. (See ARIC Manual 9, Section 1.5.)

The probable stability of different analytes in frozen storage has been assessed and standards set for how soon analyses (other than for case-control studies) will be performed after the arrival of specimens at the laboratory.

10.4 Maintenance Procedures at the Central Laboratories

Maintenance procedures for laboratory equipment are fully specified in the laboratory protocols or in manufacturers' manuals referenced in the protocols. Technicians are fully instructed in these procedures. (See ARIC Manual 8, Section 2.2.2 and ARIC Manual 9, Section 5.0)

A regular schedule is set up for routine maintenance procedures, with logbooks kept on their performance. The laboratory supervisors review these logs on a regular basis to verify that proper maintenance procedures are being carried out according to the schedule set and that any special maintenance procedures needed are carried out.

The laboratory protocols fully specify the reagents used, the sources from which they are procured, and the procedures used to prepare and store reagents to guarantee the stability of the reagent and the accuracy of the assay. The laboratory protocols also fully specify the sources of calibration standards and quality control materials, the procedures used to prepare and store calibration standards and quality control materials, to guarantee the stability of the material and the accuracy of the assay. (See ARIC Manual 8, descriptions of each assay and Appendix A and B)

To guarantee accuracy of measurements which are calibrated with standard pools which may decay with time, it is necessary to replace these pools when their "shelf-life" is over. (Replacement of standards may also be necessary for other reasons, such as exhaustion of the stock on hand, or a decision to switch to a new supplier of a commercially prepared standard.) To maintain the comparability of measurements using the new and old standards, an overlap period is carried out, during which concentration values for the new standard are determined using the standard which is being replaced. At the Central Hemostasis Laboratory, an overlap of 20 runs is provided when a new standard is brought into use. Similar considerations occur when new internal quality control pools are brought into use to replace old pools. If results on QC pools are to be used to estimate measurement trends (see below, Section 11.5, 11.8), it is necessary to establish an overlap between measurements on different pools. (For discussions of overlap of quality control pools, see ARIC Manual 8, Chapter 4.)

10.5 Internal Quality Control Pools

Each laboratory in the ARIC study maintains an internal quality control program involving the analysis of multiple samples from quality control pools in each analysis run in which ARIC study samples are analyzed. Results on these samples are used to decide whether the measurement process is in control and whether the results on the study samples will be accepted or whether the measurements should be repeated after taking corrective action. Every three months the Central Laboratories prepare for the Coordinating Center a quarterly summary of the internal quality control results, including the following information for each assay: (1) monthly summary statistics (n, mean, and standard deviation) on all quality control pools, including new pools being overlapped to replace established QC pools; (2) summaries of any unusual problems or conditions noted. The Coordinating Center reviews these reports for evidence of trends with time in results on these pools. A summary of internal quality control at each laboratory is shown in Tables 3 A-B. (For details of internal quality programs at each laboratory see ARIC Manual 8, Chapter 4; ARIC Manual 9, Chapter 4.)

Results on analyses of quality control pools are analyzed by the Coordinating Center for trends over time that may represent either (1) shifts in measurement or (2) changes over time in the concentration of the analyte in a given pool. To determine which of these is the case, trends in a given pool can be compared with (1) trends in other pools (if any) used to control analyses of a given analyte; (2) trends in differences on measurements of samples from quality control phantom participant duplicates which are repeated several months apart (see Section 10.9, below); (3) trends in the study data. If there is evidence of changes in the concentration of a control pool over time, it should be replaced.

Table 3A.

Summary of Internal Quality Control Measures in the ARIC Central Hemostasis Laboratory

Analyze Assayed	Assay Procedure	Internal Quality Control		Replicate Analysis of Indiv. Samples	Maximum # of Unknowns Per Run or Row	Ratio of QC to Max. Unknowns
		Control Pools	Pool Specimens Used			
APCR	Coag-a-Mate	UCRP	2 sets per tray	Yes	10	20
Fibrinogen	Coag-a-Mate	UCRP	3 sets per tray	Yes	16	19
Factor VIIa	Coag-a-Mate	UCRP	2 sets per tray	Yes	18	11
Factor VIIc	Coag-a-Mate	UCRP	2 sets per tray	Yes	16	13
Factor VI:Ag	ELISA	UCRP	7 sets per tray	Yes	35	20
Factor XIIa	ELISA	UCRP S1 & S2	5 sets per tray 2 sets per tray	Yes	35	20
D-dimer	ELISA	UCRP	7 sets per tray	Yes	35	20
β-thromboglobulin	ELISA	CACP	7 sets per tray	Yes	35	20
FL2	ELISA	CACP	7 sets per tray	Yes	35	20
Thrombomodulin	ELISA	UCRP	7 sets per tray	Yes	35	20
Plasminogen	ELISA	UCRP	7 sets per tray	Yes	35	20
tPA	ELISA	UCRP	7 sets per tray	Yes	35	20
PAI-1	ELISA	UCRP	7 sets per tray	Yes	35	20
CRP	ELISA	TdxFLx	7 sets per tray	Yes	35	20
FV Leiden	PCR	P&N	2 sets per run	No	*	*
FVII genotype	PCR	P&N	2 sets per run	No	*	*

Analyze Assayed	Assay Procedure	Internal Quality Control		Replicate Analysis of Indiv. Samples	Maximum # of Unknowns Per Run or Row	Ratio of QC to Max. Unknowns
		Control Pools	Pool Specimens Used			
FXIII polymorphism	PCR	P&N	2 sets per run	No	*	*
Fiblinngen genotype	PCR	P&N	2 sets per run	No	*	*
GP Ib polymorphism	PCR	P&N	2 sets per run	No	*	*
GP IIIa polymorphism	PCR	P&N	2 sets per run	No	24	08
PAI-1 genotype	PCR	P&N	2 sets per run	No	*	*
Platelet α2β1 polymorphism	PCR	P&N	2 sets per run	No	*	*

* Information not furnished by lab as of 9/30/97

UCRP: Universal Coagulation Reference Plasma
CACP: Normal Combined-Anticoagulant Reference Plasma
S1&S2: Shield Control Plasma level 1&2
P&N: DNA positive and negative control
TdxFLx: Abbo Control plasma

Table 3B.

Summary of Internal Quality Control Measures in the ARIC Central Lipid Laboratory

Factor Assayed	Assay Procedure	Internal Quality Control		Replicate Analysis of Individual Samples	Maximum # of Unknowns Per Run or Row	Ratio of QC to Max. Unknowns
		Control Pools	Pool Specimens Used			
I. Assays Performed on All Participant Samples						
Total Cholesterol	BMD Enzymic	A,B,C PN95, PA166	2 each from either 2 or 3 pools	No	50	*
Triglyceride	BMD Enzymic	A,B,C PN95, PA166	2 each from either 2 or 3 pools	No	50	*
II. Assays Performed for Case-Control Studies						
Glycerol	BMD enzymic	CDC MQ?	one per run?	No	ND	ND
LDL-Cholesterol	ultracentrifuge & precipitate LDL	NA	NA	No	ND	ND
LDL-apoB	ultracentrifuge & precipitate LDL	NA	NA	Δ	Δ	Δ
epitopes of apoB	monoclonal antibodies	NA	NA	No	ND	ND
phenotypes of apoB	?	NA	NA	No	ND	ND
RFLP of apo genes	electrophoresis of gene fragments	NA	NA	No	ND	ND

* Number of pool specimens used counts the total number of measurements obtained on a pool, whether from replicate measurements of one aliquot or measurements from several aliquots.

** Samples are re-analyzed when CV of sample analyzed in triplicate exceeds 18%.

*** Individual samples re-analyzed when CV of replicates exceeds 15%.

CLL PP: Central Lipid Lab Plasma Pool

CLL IP: Samples from individuals (not pooled) prepared by Central Lipid Lab for Lp(a) QC--3 separate levels in each run

CDC: Pool prepared by Pacific Biometrics & Bohringer Mannheim

NA: Not applicable

ND: Not decided as of June 10, 1987

* The ratio was 0.21 New instruments allow more unknowns on run.

Δ Information not furnished by lab as of 9/30/97

10.6 External Quality Control

For many of the assays performed in the ARIC study, the Central Laboratories participate in various standardization or certification programs run by outside agencies, such as the College of American Pathologists or the Minnesota State Board of Health. The ARIC laboratories should continue to maintain acceptable results in these programs and promptly provide the Coordinating Center with copies of any reports on their performance generated by these programs. Should any of the results achieved in these programs appear problematic, they are reviewed by the Coordinating Center and the Laboratory Committee together with other quality control information on the assay in question to determine what action is appropriate. See Table 4 for a summary of external standardization programs in which the ARIC central laboratories participate.

10.7 Quality Control Replicate Blood Sample Program

Each week, each ARIC field center draws duplicate blood tubes from ARIC participants sufficient to make up one-full sets of the blood tubes sent to the Central Laboratories, with each ARIC participant contributing no more than two extra tubes. The vials prepared from these duplicate tubes are sent to the Central Laboratories under the QC Phantom IDs and are sent one week later than the matching participant tubes. The field center records the match between original donor ID and QC phantom ID for each tube on a QC Phantom Participant and Non-Participant ID Form and sends this information to the Coordinating Center. For a more complete description of this procedure, see ARIC Manual 7, Section 7.2. After the laboratory has reported to the Coordinating Center results on both the tube sent in under the original donor ID and the tube sent in under the QC phantom ID, the Coordinating Center matches these two results and compares them to estimate measurement precision. The Coordinating Center prepares a summary report on these QC repeated measures annually. Copies of the reports are sent to the Quality Control Committee, Central Laboratories, and the Steering Committee.

10.8 Long-Term Consistency of Methods

The laboratory protocols fully describe the measurement methods and procedures to be used in the ARIC study. To maintain the long-term comparability of measurement results throughout the ARIC study, the same measurement methods will be maintained throughout the study. If measurement methods are to be changed, comparison studies must demonstrate to the satisfaction of the ARIC Steering Committee that the method to be used has been shown in the ARIC Central Laboratory to give results fully comparable to the method initially used. It is important to demonstrate that comparable results can successfully be achieved in the implementation of the method in the ARIC laboratory, rather than to rely merely on descriptions of comparisons in the literature, as there are often significant differences in the results achieved by the same analytic method at different laboratories. Use of a back-up method in the event of the temporary failure of the usual ARIC method to achieve in-control results should only be done with the permission of the ARIC Steering Committee after the back-up has already been implemented in the laboratory and shown to maintain comparable results. In both cases, the experiments to demonstrate method comparability will be designed jointly by the laboratory in question and the Coordinating Center.

Table 4.

Participation in External Standardization or Certification Programs by the ARIC Central Lipid Laboratory

Factor Assayed	Agency Running Program	Frequency with Which Samples Sent For Analysis	Frequency of Reports on Lab Performance
I. Assays Performed on All Participant Samples			
Total Cholesterol	CAP	Quarterly	Quarterly
Triglyceride	CAP	Quarterly	Quarterly
HDL-Cholesterol	CAP	Quarterly	Quarterly
Lp(a)	none	N.A.	N.A.
Creatinine			
Glucose & 2-hr. Glucose, Insulin			
II. Assays Performed for Case-Control Studies			
Glycerol	none	N.A.	N.A.
LDL-Cholesterol	none	N.A.	N.A.
LDL-apoB	none	N.A.	N.A.
epitopes of apoB	none	N.A.	N.A.
phenotypes of apoE	none	N.A.	N.A.
RFLP of apo genes	none	N.A.	N.A.

CAP: College of American Pathologists
N.A.: Not Applicable

10.9 Use of Quality Control Replicates to Monitor Measurement Drift

Use of duplicate sets of samples which are sent in under phantom IDs means that some of these duplicate tubes are sent to frozen storage for future case-control studies. These duplicate tubes can be used for another purpose without giving up the ability of the study to use the blood tubes sent in under the real participant ID for future case-control studies or to monitor measurement drift in the analyses that are routinely performed.

While not all blood tubes set aside for case-control analyses are suitable for repeating the analyses routinely performed, in each laboratory there will be stored blood from QC phantoms which can be used for this purpose. Periodically, the Coordinating Center designates to the laboratories IDs of tubes from QC phantoms to be taken from long-term storage and thawed. These tubes are analyzed for the routine tests in the same batches as the samples currently being analyzed at the laboratories. The results on these samples are processed and reported to the Coordinating Center in the same fashion as are the results from current samples.

The Coordinating Center compares these results with those obtained when the QC phantoms were originally analyzed. The result of this program is a series of overlapping sets of difference scores (original analysis--delayed repeat) which may be used to estimate measurement trends. The analyses are repeated frequently enough that the analytes in question are believed to be stable in storage at -70°C for that length of time. These results may be compared with trends observed on the internal QC pools and standards and may give evidence to judge whether a pool is decaying and should be replaced. Note that this program will not use all of the case-control phantom samples set aside, in order to preserve some from each period of the ARIC study for QC of case-control analyses.

The phantom tube stored for case-control and then thawed to repeat the usual assays has the same ID as the phantom tube on which we performed the assays when the blood was first sent to the lab. Because having repeat measurements coming in under the same ID is not possible under the data management systems in use in some of the ARIC Central Laboratories, these results must be reported separately. Care must be taken that these later results for the same ID are not entered into the local database, since this would result in "updating" the original data value for the phantom ID and the possible loss of the original measurement result.

10.10 Analysis of Study Data

The Coordinating Center analyzes the study data periodically for trends in age- and sex-adjusted means for each field center which may indicate measurement shifts or problems with blood collection at the Field Centers. The Coordinating Center also monitors the variability of the study data, to see if there are changes in overall variability, or increases in the number of outlying values which may indicate problems in the measurement process.

10.11 Storage of Materials for Case-Control Studies

Each central laboratory has a clear protocol for how materials for case-control studies are to be handled on arrival at the laboratory and their separation for long-term storage. (See ARIC Manual 8, Section 2.1.3 and ARIC Manual 9, Section 1.5). Separate freezers are used for blood vials stored for case-control studies and those blood vials used for routine analyses.

Over the projected twelve-year course of the ARIC study, some 32,000 sets of samples for case-control studies will accumulate in each laboratory. This makes it essential that each laboratory develop an inventory control system for recording the arrival of samples that fully and accurately describes the physical location of each sample in the freezer. Current back-ups for these inventory records exist both on the local computer data base and in a hard copy form. It is not unknown for studies to accumulate serum banks which they later have great difficulty in using because the specific samples needed can no longer be located years after they were first placed in the freezer. (See ARIC Manual 8, Section 2.1.3; ARIC Manual 9, Section 1.5)

The periodic removal of QC phantom samples from long-term storage for repeat analyses (see Section 10.9, above) tests the frozen storage inventory system maintained at the laboratories. The Coordinating Center follows up on failures by the laboratories to locate QC samples requested for this purpose to determine if there are problems with the storage and record-keeping systems in use at the Central Laboratories.

As noted above, precautions must be taken to prevent loss of samples due to freezer failure. This need is even more crucial for the case-control samples than for the samples awaiting routine analyses, since there is a much greater volume of case-control samples which are vulnerable at any one time in the event of failure, and the impact of freezer failure upon the study data would be correspondingly greater. Each laboratory has provisions for prompt detection of power failure or failure of the freezer to maintain the proper temperature. (See ARIC Manual 9, Section 1.5.)

Back-up power for freezers and provisions to use dry ice to cool samples temporarily until a broken freezer can be repaired are ready at all Central Laboratories. In addition, the Central Hemostasis Laboratory has one back-up freezer in the event of failure and a liquid nitrogen system which could be used for up to 72 hours to maintain temperatures.

10.12 "Running-in Time" for Case-Control Analyses

The assays performed on case-control samples will not necessarily be in routine use in the laboratories. A certain amount of "learning time" is needed to set up a new assay in any laboratory and be certain that analyses are "in control" before reliable results can be obtained. This process must be implemented and quality control procedures put into operation for any assay used in an ARIC case-control study before any samples are thawed. The laboratory in question will have established quality control pools to be used for each assay used for case control studies and will have repeated that assay enough times to have established QC limits and demonstrated that the assay is in control. Normal QC procedures will be used during the analysis of samples from case-control studies.

10.13 Transcription of Measurement Results onto the Local Data Base

The Central Laboratories differ in the extent to which the linkage between analytic instruments and the local computer data base is automated. In cases where hand entry of data is required, a variety of steps are taken to reduce data entry errors. These include (1) minimizing the number of transcription steps that take place between printing out the instrument result and entering the data; (2) use of double-entry techniques in which the data must be initially entered and then verified by repeating entry before they are added to the data base; (3) range checks in the data entry programs which flag improbable values for confirmation. (Such checks should also be used to flag

alert values which require notification to the Field Centers.) Range checks should also be used with automated data entry systems so that the laboratory may confirm that some error has not been made (e.g. failure to enter a dilution factor correctly) that invalidates the measurement result. For details of data entry at each laboratory, see ARIC Manual 8, Section 3 and ARIC Manual 9, Section 3.

10.14 Additional Quality Assurance Measures

The Coordinating Center monitors the delay between visit to field center and receipt of laboratory measurements at the Coordinating Center and follows up on instances where individual records are delayed or where the average lag in reporting has become prolonged.

Periodic monitoring visits to the laboratories may be conducted by Coordinating Center staff at the request of the Quality Control Committee or study investigators. In addition to reviewing laboratory and data management procedures, the monitor will verify the retrievability of frozen specimens. The laboratories are expected to locate all the blood samples for a random list of IDs provided by the monitor. In a report prepared by the monitor and provided to the Quality Control Committee and laboratory director, the results of the blood sample retrievability will be included.

11.0 ULTRASOUND

11.1 Introduction

The examination of participants in the ultrasound area in this cohort consists of the following components:

(1) ultrasonic imaging of the carotid arteries in the neck and
(2) monitoring of arterial blood pressure throughout the ultrasound examination.

Procedures for assuring high quality of the ultrasound data are in place at each field center where the ultrasound scanning is done, at the ARIC ultrasound reading center, and at the ARIC statistical coordinating center. Sonographer performance is addressed at all three sites. Reader performance is addressed both at the reading center and at the statistical coordinating center. In addition, the maintenance and performance of all sonography equipment are addressed at each field center.

This section is divided into two main subsections. The first deals with specific quality control procedures related to visualization and scanning, and the second deals with specific procedures related to reading.

The ultrasound system selected for use in the ARIC Visit 1 and Visit 2 exams was the Biosound 2000 II. The ultrasound system selected for ARIC Visit 3 and Visit 4 is the Biosound Phase 2.

11.2 Quality Control Procedures at the Field Center

11.2.1 Sonographer training, certification, and monitoring

Manual 6a describes sonographer training and certification in detail.

The training program includes training sessions held at the respective field centers and the Ultrasound Reading Center, followed by practice scans at the respective field centers and certification steps at the field centers.

A sonographer attains certification to scan based upon ability, while following the ARIC/FHS scanning protocol, to visualize arterial walls consistent with the average of all sonographers certified in Visits one and two of ARIC, as measured by the number of paired points marked by certified readers at the Ultrasound Reading Center. The process average for visualization will be monitored using statistical process control techniques at the Ultrasound Reading Center. As long as a sonographer maintains visualization consistent with the process average of his/her peers, certification is retained.

Sonographer performance is monitored throughout the Atherosclerosis Risk in Communities Study at the respective field centers. The chief sonographer at each field center reviews one scan per sonographer each month for his/her field center.

11.2.2 Ultrasound area equipment maintenance

The ultrasound area instrumentation consists of a Biosound Phase 2 ultrasound imaging system, an NEC PC ½" Video Cassette Recorder, an RMI 414B Tissue Mimicking Ultrasound Phantom, a 486-SX computer, an IBM-XT computer, a Dinamap

automated blood pressure machine and a computer software study flow program. Each field center is required to have Biosound representatives perform a preventive maintenance check on the ultrasound imaging system four times a year, and to send copies of all Biosound reports to the Ultrasound Reading Center. The NEC PC-VCR is cleaned every six months by a Biosound technician during one of their preventive maintenance visits to the field center. The RMI 414B phantom is checked weekly.

URC quality control procedures also include the calibration of image pixel size at the beginning of each participant study, and the reading of an RMI tissue mimicking phantom twice a month. The quality control evaluation, performed on this phantom scan by a certified reader consists of the following:

a. Evaluation of image quality;
b. measurement of axial resolution and axial and lateral diameter of a simulated vessel in the phantom;
c. measurements of pulse length and focal accuracy on a set of filaments within the phantom;

This program has been established to insure that arterial images obtained from the Biosound equipment at each field center conform to uniform standards of quality, accuracy and repeatability. With a scan of identical phantoms, consistency is maintained throughout the project.

11.2.3 Ultrasound equipment performance check

An ongoing quality assurance check of Biosound instruments is performed on the second and fourth Wednesdays of each month at each field center. This is accomplished by a scan of identical RMI Tissue Mimicking Phantoms. A log is maintained to insure these tests are performed per the above schedule.

The scan of identical phantoms at each field center provides data for an ongoing quality assurance program to monitor the performance of each Biosound instrument. Through this program, uniform standards are maintained throughout the project. For details, see ARIC VISIT 3, Manual 6a.

The Dinamap Model 1846 SX should be calibrated every six months using calibration procedures in the Dinamap instruction manual and copies of calibration reports are to be forwarded to the Ultrasound Reading Center.

The supplies to be used for each day are checked.

11.2.4 Repeat carotid scans for quality control

Right Carotid Scan: Scans are performed on the right common carotid, right internal carotid, and right bifurcation. Additional scans are done on the far and near walls of the right bifurcation. Following the final scan on the bifurcation, the sonographer removes the transducer from the neck and presses the NEXT SITE footswitch.

The sonographer looks at the computer monitor to see if a site will be repeated on the right side for quality assurance purposes (QC site). If no QC site scan is required on the right side, the sonographer will exit the right side.

If a QC site scan is required, the monitor displays, in red, the QC site (common carotid, internal carotid, or bifurcation) and the flow screen highlights the code. The sonographer obtains an image of the QC site and angle; moves the cursor to the appropriate landmark and optimizes the arterial

interfaces. When the best possible image has been obtained, he/she presses the SELECT footswitch and holds the image for at least five cardiac cycles, marking the site on video tape.

Left Carotid Scan: The sonographer looks at the PC to see if a site will be repeated on the left side for quality assurance purposes (QC site). If no QC site scan is required on the left side, the program will advance to the blood pressure screens. If a QC site scan is required, the monitor displays, in red, the QC site and the flow screen highlights the code. The sonographer obtains an image of the QC site and angle, moves the cursor to the appropriate landmark and optimizes the arterial interfaces. When the best possible image has been obtained, he/she presses the SELECT footswitch and holds the image for at least five cardiac cycles, marking the site on video tape.

11.3 Reading Center Monitoring of Sonographer Performance

Sonographer performance is monitored at the Ultrasound Reading Center using a number of quality assurance procedures. The quality assurance procedures include but are not limited to:

(1) comparing results of repeat studies on a randomly selected identical site and angle of individual participants;
(2) periodic reports containing statistics of boundary visualization by individual sonographer and study wide;
(3) visual review of randomly selected participant scans;
(4) on-site monitoring of sonographer performance by designated URC personnel.

Reports are generated and distributed quarterly by the Ultrasound Reading Center. Results of these evaluations are reported periodically to the ARIC Coordinating Center and the field centers.

11.4 Coordinating Center Monitoring of Sonographer Performance

11.4.1 Visualization

The term "paired points" refers to two visualization points one on each side of an interface, that form an imaginary line perpendicular to the artery wall. The greater the number of paired points, the better the ability to estimate degree of stenosis. Twice a year a statistical report is generated by CSCC summarizing and graphically depicting the percentage of readings with three or more paired points over time. This is done separately for the near and far walls of the carotid arteries.

11.4.2 Repeat scans

Repeat scans are described in 11.2.4 above. Twice a year, an in-depth statistical report is done summarizing the reliability of scanning over time. There are five sites and four variables examined for each of the five sites. The five sites are: Common carotid, Bifurcation, Bifurcation near wall, Bifurcation far wall, and Internal carotid. The four variables are Average arterial diameter, average far wall width, average near wall width, and minimum lumen diameter.

a. Total number of paired scans by each sonographer.

b. Number and percent of non-missing values, relative to the number of repeat scans requested. For each sonographer, the percent of non-

missing pairs is compared to other sonographers combined by use of a Fisher's exact test.

c. Mean, standard deviation, and p-value based on the paired student's t-statistic, of the differences (QC minus original). In future analyses, the 90% confidence interval on the differences may be presented instead, along with Pearson's correlation coefficient on the pairs. It is desirable that all confidence intervals should be contained within a reasonable range, say +/- 3% of the original measurement, and all correlation coefficients should be greater .95.

d. Number of unequal pairs and percent of pairs for which QC scan is greater than the original.

e. The reliability coefficient, which is the proportion of total variability explained by the between subject variability. The total variability is equal to the sum of the between subject variability plus the within measurement variability, since the actual within-subject variability is presumed to be zero. It is desirable that all reliability coefficients be greater than .95. Other related statistics that are displayed, include the Intra-sonographer S.D., and coefficient of variation. (For each sonographer, the within sonographer variance is compared to the within-sonographer variance of the other sonographers combined by use of an F-test.)

f. Listing of outlying differences (QC-original).

This report includes a summary of the performance of each sonographer.

11.5 Quality Control Procedures at the Reading Center

11.5.1 Reader training, certification and monitoring

The reader training program includes training sessions held at the Ultrasound Reading Center, followed by practice readings and certification steps at the Ultrasound Reading Center. There are three stages of such training. These are described in detail in Manual 6B.

In addition Manual 6B gives details for monitoring readers, for recertification procedures and for continuing education.

11.5.2 Quality control process for readers

A computer-controlled assignment program is run weekly at the Ultrasound Reading Center which assigns three quality control studies in addition to assigning routine reading assignments.

a. Inter QC: one study assigned to two readers. This checks for variability between readers.

b. Intra QC: one study assigned to one reader at different times. This checks for variability of results.

c. All Reader QC: one study chosen by the chief reader and assigned to all readers. This checks variability between all readers on one study.

Statistics are reviewed quarterly to monitor the performance of individual readers as well as the entire reader group. Trends suggesting a deterioration in performance levels are promptly discussed with the individuals concerned in

order to correct deficiencies as soon as possible. Sustained high performance levels during the studies are recognized and commendation and incentives provided to the individuals involved.

11.5.3 Reading center reports

Each quarter, a report is generated by the reading center that provides visualization statistics by reader. Summary quality assurance reports are produced on a monthly basis for benefit of readers. Inter- and intra-reader studies will be performed on a routine basis, in order to evaluate the degree of consistency in measurements among readers. These procedures are describe in Manual 6B, Section 8.

11.6 Coordinating Center Monitoring of Reader Performance

Twice a year, a statistical report is generated by CSCC to examine the reliability of repeat readings described in section 12.5.2, above. Results of the weekly repeat readings are summarized and graphically displayed over time. Summary statistics for intra-reader reliability and inter-reader reliability include all of the following.

a. Total number of pairs read by each reader.

b. Number and percent of non-missing pairs. (Additionally for intra-reader data pairs, the percent of non-missing pairs is compared to other readers combined by use of a Fisher's exact test.)

c. Mean, standard deviation, and p-value based on the paired student's t-statistic, of the differences (QC minus original). In future analyses, the 90% confidence interval on the differences may be presented instead, along with Pearson's correlation coefficient on the pairs. It is desirable that all confidence intervals should be contained within a reasonable range, say +/- 3% of the original measurement, and all correlation coefficients should be greater .95.

d. Number of unequal pairs and the percent of pairs for which QC reading is greater than the original.

e. The reliability coefficient, which is the proportion of total variability explained by the between subject variability. The total variability is equal to the sum of the between subject variability plus the between reader variability plus the within reader variability, since the actual within-subject variability is presumed to be zero. It is desirable that all reliability coefficients be greater than .95. Other related statistics that are displayed, include the Intra-reader and inter-reader S.D., and coefficient of variation. (For pairs read by the same person, the within reader variance is compared to the within-reader variance of the other readers combined by use of an F-test.)

f. Listing of outlying differences (QC-original).

The report includes a summary of the performance of each reader.

ARIC
Atherosclerosis Risk in Communities

QUALITY CONTROL PHANTOM PARTICIPANT AND NON-PARTICIPANT ID FORM

Form Code: PNPD (12/21/95)

Note: This form should be collected on paper and entered into the Data Entry System (DES) within two weeks of the first assignment for a QC phantom. The paper form should be stored in the Field Center.

Phantom Participant ID Number: _____ Contact Year: 10

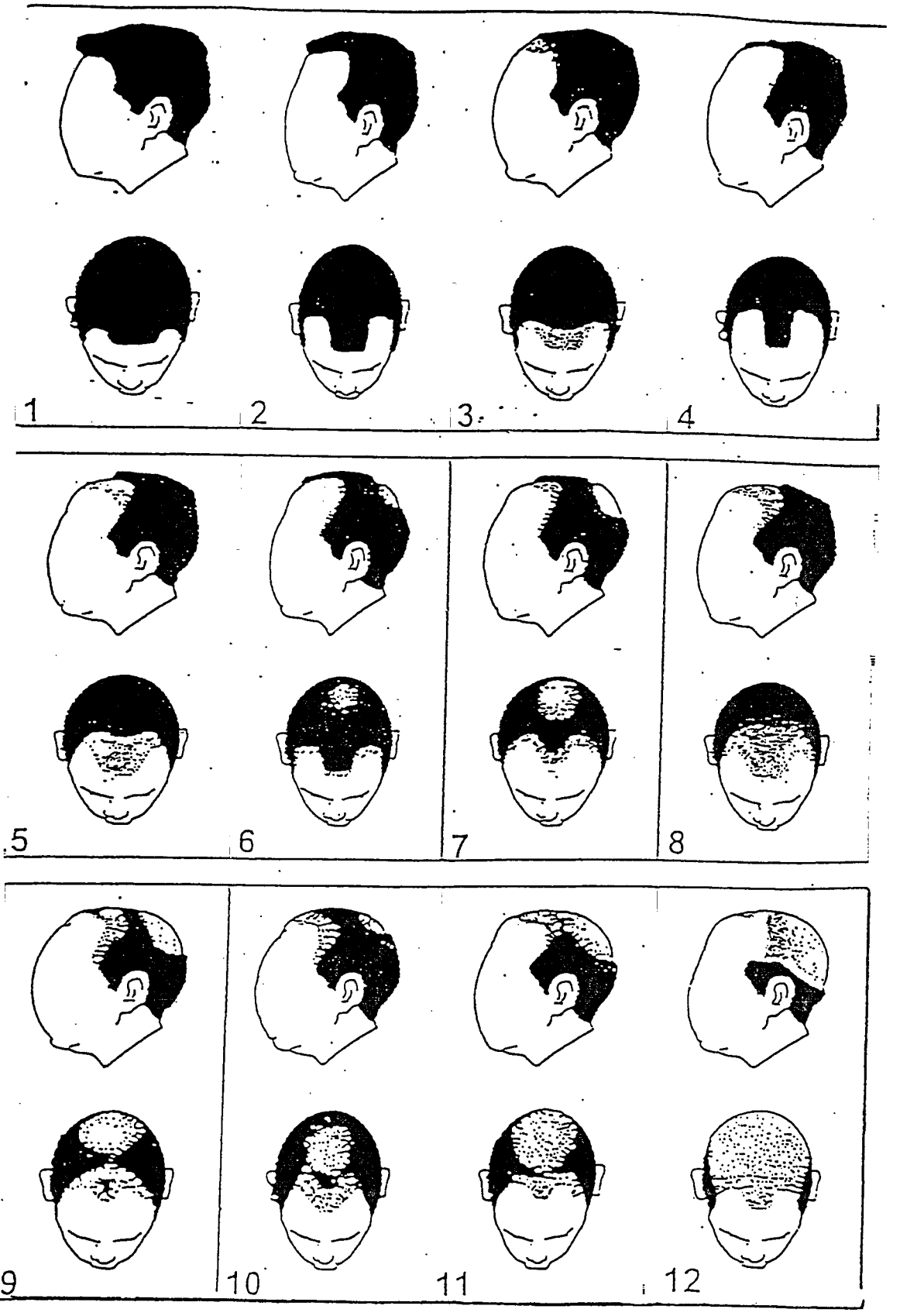
1. This ID is for: (circle one)
   - P A QC Phantom Participant
   - M An ID used for Monitoring Visit
   - N An ID used for a Non-Participant

2. Date ID assigned: ___/___/___ (mm dd yy)

3. Code number of person assigning phantom ID: _____

Procedure	Matching ARIC Participant ID a.	Date Drawn (Mo/Day/Yr) b.	Technician ID c.
Venipuncture			
4. Tube 1		___/___/___	
5. Tube 2		___/___/___	
6. Tubes 3 & 4		___/___/___	
7. Tube 6		___/___/___	
8. Anthropometry		___/___/___	
9. Urine Specimen		___/___/___	

The Modified Hamilton Male Pattern Baldness Scale



*Norwood OT. Male pattern baldness: classification and incidence. *South Med J.* 1975;68:1359-1865.