Manual 1

General Description and Study Management

The National Heart, Lung, and Blood Institute
of the National Institutes of Health

ARIC Protocol

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General Description and Study Management

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FOREWORD

This manual entitled, General Description and Study Management, is one of a series of protocols and manuals of operation for the Atherosclerosis Risk in Communities (ARIC) Study. The complexity of the ARIC Study requires that a sizeable number of procedures be described, thus this rather extensive set 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 reading centers and central laboratories, make up Manuals 4 through 11. Manual 12 on Quality Assurance contains a general description of the study's approach to quality assurance as well as specific protocols for each of the study procedures.

ARIC Study Protocols and Manuals of Operation

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Manual 1: General Description and Study Management

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1. INTRODUCTION AND BACKGROUND

The Atherosclerosis Risk in Communities (ARIC) Study is a prospective study conducted in four U.S. communities to (1) investigate the etiology and natural history of atherosclerosis, (2) investigate the etiology of clinical atherosclerotic diseases, and (3) measure variation in cardiovascular risk factors, medical care and disease by race, sex, place, and time. It includes a Cohort Component and a Community Surveillance Component.

Community surveillance planning began as a consequence of recommendations of the 1978 National Heart, Lung and Blood Institute (NHLBI) Workshop on the Decline in Coronary Heart Disease (CHD) Mortality. A protocol for community surveillance was developed and pilot tested in the NHLBI Community Cardiovascular Surveillance Program (1980-1984).

The cohort component was subsequently created and added to the surveillance component to create the current ARIC Study for two reasons. First, cohorts can enhance the value of incidence rates derived from community surveillance by validating them using events ascertained by the standard methods of prospective studies and by providing information with which to interpret them, e.g. information on risk factors and out-of-hospital medical care. Secondly, community surveillance can enhance the generalizability of cohort findings by comparing incidence rates and the characteristics of clinical events in residents who do and who do not participate in cohort follow-up and by relating the study community CHD experience with that of other vital statistics reporting areas of the U.S.

Atherosclerosis is assessed in the ARIC Study by observing lesions through ultrasound imaging. This permits assessment of (1) the association of risk factors with the underlying arterial disease, (2) the association of the same factors with clinically recognized diseases and (3) the value of ultrasound diagnosis in predicting these diseases. The major atherogenic processes, lipid metabolism and thrombosis, are investigated by using laboratory procedures only recently made available. Storage of blood for future prospective case-control analysis increases the chance of discovering unsuspected precursors of cardiovascular disease.

In the Cohort Component, four random samples, totalling 16,000 persons, ages 45-64 years, are selected, one from each community. These persons receive two examinations and annual follow-up interviews. The four communities are Forsyth County, North Carolina; Jackson, Mississippi; Suburban Minneapolis, Minnesota; and Washington County, Maryland. The communities are clearly defined geographical entities, have well delineated medical care referral patterns, and provide an opportunity to study blacks and whites, males and females in urban and rural settings. The Jackson cohort is a sample of blacks, while the other field centers sample from their entire defined communities.

The study progresses in the following steps: definition of sampling frames, enumeration of households to determine study eligibility, interview in the household of all study eligibles, recruitment, clinical examination in each community, interview of participant annually to determine health status, contact of health care providers and family members and review of medical records of participants, and a second clinical examination three years after the first examination.

In Community Surveillance, these four communities are investigated to determine the occurrence of hospitalized myocardial infarction and coronary heart disease death in men and women age 35-74 years. Hospital records are reviewed for all age-eligible residents of each community with a discharge diagnosis of myocardial infarction or one of several related screening diagnoses. All age- and residence-eligible death certificates with various manifestations of coronary heart disease coded as the cause of death are reviewed. For deaths not occurring in a hospital, the decedent's physician and next-of-kin are queried about the circumstances around the time of death. The timetable for the ARIC Study is shown in Figure 1.

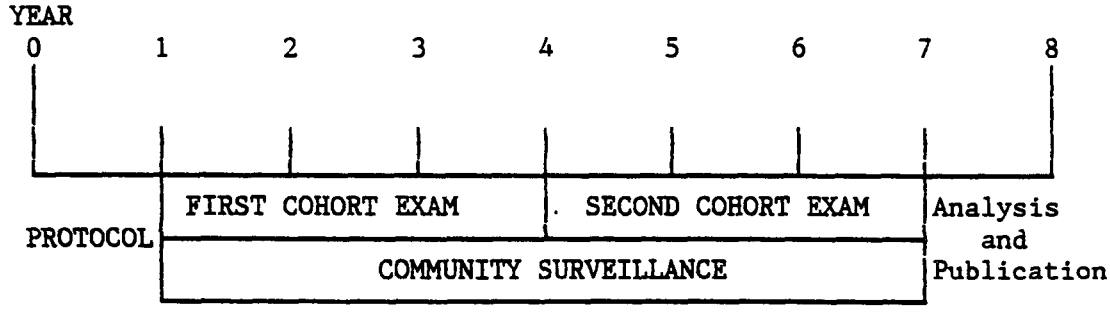

Figure 1. ARIC Study Timetable

2. STUDY DESIGN

2.1 Cohort Component Design

The Cohort component is divided into 8 operational sections: (1) sampling, (2) enumeration, (3) home interview, (4) recruitment, (5) first exam, (6) annual follow-up, (7) clinical review and diagnostic classification and (8) second exam. Sampling, enumeration and recruitment began in November, 1986. The first cohort baseline exam is scheduled for 1986-1989. The annual follow-up contact is done yearly in the interim between exams. The second exam is scheduled for 1990-92.

2.1.1 Sampling

Probability sampling, with high coverage rates, was used to select the cohorts in each of the four communities. Although the sampling methods differ among areas, randomized selection methods and current or updated frames were used in each design. The designs differ among the communities primarily by how the frames are constructed and in which units the sample is chosen.

2.1.2 Cohort Enumeration Procedures

Interviewers locate the designated sample housing units (Forsyth County) or sample individuals (Jackson, Minneapolis and Washington County) in each area to determine eligibility status. When contact is made with an occupant of a designated household, the interviewer introduces him/herself, shows the respondent his/her credentials, briefly describes the purpose of the visit, and proceeds with enumeration. Enumeration is the process of completing a household roster needed to select the sample member(s). All members of the designated households ages 45-64 are asked to participate in the cohort study.

The enumerator lists all the persons at least 18 years old who reside in the sample household. Persons who indicate that their permanent residence is outside the study area are excluded, as are individuals who would be physically or mentally incapable of full participation in the study.

2.1.3 Cohort Home Interview

After enumeration, the interviewer conducts a home interview with each eligible respondent. The home interview has 6 sections: Health Status and Risk Factors, Family Medical History, Smoking, Employment, Education, and Home Interviewer Debriefing. The purpose of each section is described in Table 1.

2.1.4 Cohort Recruitment and Scheduling for the Clinic Examination

During the home interview, eligible cohort members are given a written and verbal description of the study. They are asked to participate in the complete study, which includes two clinical examinations and the annual telephone follow-up.

Table 1. The Home Interview in the ARIC Study Cohort Component

Section	Purpose
Health Status and Risk Factors	Obtain general knowledge of the participant's health status; determine prior hospitalization(s) within the past year; determine selected risk factors for CVD.[1]
Family Medical History	Obtain general knowledge of the participant's family health status; determine past history or cause of death due to CVD, cancer or diabetes.
Smoking	Determine smoking status and amount.
Employment	Determine the participant's current employment status.
Education	Determine the participant's level of education.
Home Interview Debriefing	Assess the participant's cooperation during the interview; assess the quality of the interview; assess the participant's literacy/comprehension.

[1]Cardiovascular disease

The cohort member is scheduled for the clinical examination at the ARIC Field Center, which is located at or near a hospital in each study community. The participant is asked to come to the clinic after a 12 hour fast and to bring all medications (prescription and nonprescription) which he/she has used in the last two weeks.

2.1.5 Cohort Clinic Examination

The clinic examination takes approximately 3 1/2 hours. The sequence of the exam is flexible so one, two or three participants can be examined concurrently, in accordance with the available personnel and work station configuration. The following sequencing restraints are necessary. (1) Fasting and abstinence from smoking and alcohol are required prior to venipuncture and blood pressure measurements. (2) Sitting blood pressure must be measured before venipuncture. (3) Interviewing and Examination must precede the Medical Review. Participants must fast and abstain from alcohol and tobacco for not less than 12 hours. A snack, however, is provided during the exam. Table 2 identifies and describes the components of the baseline examination.

Table 2. Components of the Baseline Examination in the ARIC Cohort Study

Procedure	Description
Reception	Greet the participant; determine fasting status; obtain tracing data; collect medications.
Informed Consent	Obtain informed consent.
Sitting Blood Pressure	Obtain sitting blood pressure.
Anthropometry	Measure weight, height, skinfolds, girths, and wrist breadth.
Venipuncture	Obtain blood samples for lipid, hemostasis, hematology, and chemistry measurements.
Snack	Provide snack which contains no caffeine or stimulants.
ECG	Obtain a digitized 12 lead ECG and two minute rhythm strip.
Interview	Collect medical history (including Rose Questionnaire; stroke, transient ischemic attack and respiratory symptoms and reproductive history) and food frequency.
Physical Exam	Obtain a brief systems review including neck, neurological, chest and lungs, breast (optional), heart, extremities.
Pulmonary Function	Obtain digitized spirometric measurements of timed pulmonary function (FVC, FEV1).
Ultrasound, Postural Change	B-mode scan for wall measurements in carotids and a popliteal artery. Measure supine brachial and ankle blood pressure and heart rate and blood pressure changes as participant arises.
Medical Data Review	Ascertain the completeness of the exam and verify abnormal results. Review results of the medical history and exam with the participant. Refer participant for diagnosis on treatment elsewhere if appropriate.
Exit Interview	Return medication; thank participant.

2.1.6 Cohort Follow-Up

Annual follow-up of the cohort is used to maintain contact, to correct address information, and to ascertain medical events between examinations.

Follow-up contacts are made yearly within a month of the anniversary of the previous examination. Contact letters inform the participant that he/she will receive a telephone call soon asking about interim health problems.

The telephone interview asks about hospitalizations for illness or surgery, diagnoses and symptoms. The participant is asked a version of the Rose Questionnaire for angina, possible MI, and intermittent claudication. Address and phone number are verified and other contact information is updated. If the participant cannot be reached by telephone, a home interview is attempted. Similar procedures are used after the second exam. Every attempt is made to identify cohort participants who have died in advance of the annual contact, through regular review of obituaries and death certificates.

2.1.7 Cohort Clinical Review and Diagnostic Classification

During the initial home interview, the examination or the follow-up contact, the cohort participant may indicate that he or she has been hospitalized. Records are obtained for all hospitalizations which occur after the baseline visit. ARIC abstractors record all discharge diagnoses and clinical information related to coronary or cerebrovascular diseases. The participant will have signed a medical release form allowing the study to access medical records.

Similarly, during the obituary review, a follow-up contact, or the community death certificate surveillance, it may be determined that the participant has died. In these cases, the death certificate is obtained and the place of death is determined. For in-hospital deaths, the hospital record is reviewed. For out-of-hospital deaths and decedents admitted without vital signs, the participant's family and physician are contacted to provide information on the circumstances surrounding the death. At entry to the study, the participant will have given consent to contact family members and physicians in the event of his or her death.

A special Morbidity and Mortality Classification Committee (MMCC) reviews the information on hospitalizations and provides the study diagnosis for coronary heart disease or cerebral vascular disease according to defined criteria. The MMCC also provides a classification of cause of death.

2.1.8 Second Cohort Clinic Examination

The second examination takes place three years after the first. The content is expected to be similar to that in the first exam, though modifications will be made based on the accrued experience. Items may be deleted if they are deemed nonproductive, or added if new techniques or hypotheses develop.

2.2 Community Surveillance

The community surveillance component provides measures of the geographical and temporal variation of the occurrence of clinical CHD in ARIC communities and will suggest reasons for the patterns observed. The distributions of demographic characteristics, as well as the changes in these measurements, will provide a set of possible explanatory factors for the atherosclerosis and CHD profiles of the communities under surveillance.

It is the aim of community surveillance to estimate the incidence and obtain a valid diagnostic classification of fatal CHD and non-fatal myocardial infarction (MI) in residents aged 35 to 74 years in the four communities for the period January 1, 1987 to December 31, 1992.

Community surveillance for hospitalized myocardial infarction involves a review of hospital records of age-eligible residents with either a diagnosis of MI or a related illness. All ICD-9 410 and 411 discharge diagnoses are included, and other diagnoses are sampled. Hospital records identified through this process are abstracted for information relating to history, symptoms, signs, times of onset and admission, enzymes, ECG and treatment. This information is used in a diagnostic algorithm which classifies each event as "Confirmed MI", "Possible MI", or "No MI". Selected events are reviewed by the MMCC for validation.

The surveillance of CHD deaths is accomplished by abstracting all age- and residence-eligible death certificates with various manifestations of CHD coded as the underlying cause of death. An additional subset of death certificates is sampled from a group with related ICD codes. Sources of validation for out-of-hospital deaths include interviews with the physician and next of kin, coroner or medical examiner reports, and hospital records. Deaths occurring in the hospital are classified by abstracting information from the medical record. CHD deaths identified undergo review by the MMCC. A diagnostic algorithm is also applied, providing a preliminary classification, as well as identifying events either with insufficient information or with unequivocally diagnostic information that do not require interpretation by the committee.

2.3 Study Communities

The ARIC Study collects data in four diverse communities. This design was chosen so that data could be obtained for groups which differ by geography, race, and socio-economic status. The ARIC Study was not designed to select a random or representative sample of the entire U.S. population. Each community provides information on the occurrence of coronary heart disease in a unique environmental setting. The cohorts representing each community are studied so that inferences about risk factors and disease relationships can be made from diverse population groups. This diversity permits the evaluation of the consistency of observed association.

The four communities studied are: Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis suburbs, Minnesota; and Washington County, Maryland. Each community contributes a cohort of 4,000 men and women between the ages of 45 and 64. The cohort in Jackson, Mississippi was sampled and recruited to have an all-black population. The population size

and socio-economic characteristics of the communities are summarized in Table 3.

Table 3. ARIC Study Communities: Demographic Characteristics, 1980

Study Community	Population		Percent		Percent Education 12+ years	Median Income
	Ages 35-74	Total	Black	Urban		
Forsyth County, North Carolina	95,863	243,683	24	75	63	$16,600
Jackson, Mississippi	68,303	202,895	48	100	71	$14,800
Minneapolis Suburbs, Minnesota	69,338	192,004	1	100	85	$24,165
Washington County, Maryland	45,539	113,068	4	57	60	$16,623
Total	279,043	751,668				

These communities were selected using criteria which included location, availability of census data, study population size, population stability, ischemic heart disease mortality rates, the cooperativeness of the population, the cooperativeness and accessibility of other agencies, and the medical facilities within the community. Table 4 provides age-adjusted all-cause and ischemic heart disease mortality rates for the four ARIC communities.

2.3.1 Forsyth County, North Carolina

Forsyth County is a single-county State Economic Area, located in the North Carolina Piedmont in the center of the state. Winston-Salem is the only large urban area in the county. The county constitutes a contiguous area with census-based boundaries and a relatively stable total population of about 250,000 persons.

The population of Forsyth County grew 13.3 percent between 1970 and 1980. In spite of this growth, 73.8 percent of the people surveyed in 1980 were born in North Carolina. The 1975-1980 migration patterns are similar to the patterns for the U.S., the southeast and North Carolina.

Medical care facilities are of high quality and highly concentrated for purposes of surveillance. The referral pattern is optimal with respect to outmigration of patients. In Forsyth County there are two major and one smaller general hospitals that serve this community. The complement of acute and general hospital care is thus highly concentrated. Of salient importance to the ARIC Study, residents of this community seek and obtain hospital care within Forsyth County. The place of hospitalization of 95 percent of Forsyth County residents is one of the three hospitals in

Table 4. Age-Adjusted Mortality Rates[1] for Men and Women, Ages 35-74, in the ARIC Study Communities, 1980

ARIC Study Communities	All-cause Mortality		Heart disease mortality[2]	
	Men	Women	Men	Women
Forsyth County, North Carolina	16.3	8.7	6.7	2.7
Jackson, Mississippi (Black only)	20.8	10.0	6.6	2.9
Minneapolis Suburbs, Minnesota	9.4	6.3	4.2	1.3
Washington County, Maryland	16.1	8.2	7.8	2.8
U.S. TOTAL	14.4	8.0	5.7	2.6

[1]Indirect age-adjustment; annual rate per 1,000
[2]ICD-9, International Classification of Diseases, Ninth Edition: 390-398, 402, 404-429

Winston-Salem. These establishments have general and intensive care medical surgical beds, and a high rate of autopsies. CAT scan procedures are available in the two main hospitals for the documentation of cerebrovascular endpoints. The two main hospitals in the study area have active cardiology medical staff, and the community has a favorable ratio of population to active providers of medical care.

2.3.2 Jackson, Mississippi

Jackson, Mississippi lies approximately midway between New Orleans to the south and Memphis, Tennessee to the north. Its location makes Jackson a major distribution center for the deep South. Jackson is a major retail and financial center for the state. In addition, Jackson is a major medical center offering a full range of educational, research, diagnostic and treatment facilities and services.

While the population of Jackson has grown 32 percent from 1970 to 1980, it is, nevertheless, a relatively stable population. In 1985, the Center for Population Studies at the University of Mississippi estimated that, for the period 1970 to 1980, of the total population in Hinds County for ages 45-64, 2,680 persons would migrate in and 2,360 would migrate out, for a net gain of 320 persons. This would represent an increase of 1.4 percent. Across the spectrum, from ages 25-69 among the total population of Hinds County, there was a net decrease of 1,960 persons representing less than one percent of the population. Most of the out migration occurred between the ages of 25-44 with either increases or stability beyond age 45. Among the black population, there was a net increase of 240 individuals between the ages of

25-70, an increase of less than one percent. These numbers reflect extrapolation to the population base, but the actual data used a 2.5 percent sample of the population. Thus the population is particularly stable between the ages of 45 and 64 and across all ages of interest. Of particular pertinence to the surveillance activities is the fact that of 3,687 deaths which occurred in Hinds County, 2,058 were residents of Hinds County. This reflects the referral into the Jackson area of patients rather than the referral of Jackson area residents to other areas.

Jackson is the largest city in Mississippi and the major medical area. Hinds County, in which Jackson is located, has 8 general and 3 speciality hospitals, a total of 2,932 hospital beds. There is little need for patients from the Jackson area to seek medical attention elsewhere for reasons of available facilities, manpower, or services.

There are five emergency rooms within the Jackson area which have approximately 130,000 visits a year. There are three coronary care units within the Jackson area and one coronary care unit in Vicksburg, 45 miles distant. Of the cardiac catheterizations performed in the state in 1983, 57 percent were performed in Jackson hospitals, while of 1,058 open heart surgery procedures on adults, 83 percent were carried out in Jackson hospitals. One of the four special stroke care units established in the state is located in Jackson. In previous population studies, the proportion of patients seeking medical care outside the Jackson area has been less than 3 percent.

2.3.3 Minneapolis Suburbs, Minnesota

The study community is a collection of seven geographically contiguous Minneapolis suburbs: Golden Valley, Robbinsdale, Crystal, New Hope, Plymouth, Brooklyn Center, and Brooklyn Park. The community constitutes the first tier of suburbs lying to the northwest of the city of Minneapolis. All of the individual suburbs lie within Hennepin County and are U.S. Census-defined cities of greater than 10,000 population. The community is located about 10 miles northwest of the University of Minnesota. At the eastern border of the community lies the Mississippi River or the city of Minneapolis; the north is bounded by Anoka County; at the west and south borders lie other suburban areas in Hennepin County.

While the population in the Twin Cities (Minneapolis-St.Paul) has grown 5.9 percent from 1970 to 1980, the percentage change in the ARIC Study communities for the same period was 21.9 percent. In spite of this growth, for the period 1975 to 1980, 53.1 percent of the persons surveyed were in the same house, 81.6 percent were in the same county and 89.8 percent were in the same state. This compares favorably with census data for the U.S. as a whole.

An example of successful follow-up of Twin Cities populations involves the Hypertension Detection Follow-Up Program (HDFP) screenees (ages 30-69) who were not selected for the HDFP Trial. This population was from the suburb of St. Louis Park, which is adjacent to the south of the ARIC Study community. Three-and-one-half years after the screening visit, 92% of 770 screenees were found and re-examined. Only five subjects (less than 1%) could not be located even though there had been no contact with them for 3-1/2 years. Only 4% had moved from the Twin Cities area, suggesting the stability of this population.

There are 32 hospitals in the seven county Twin Cities area. Only two hospitals lie within the ARIC Study community: one is a psychiatric hospital exclusively and the other is North Memorial Medical Center, a 500-bed facility where cohort examinations are held. Seventeen area hospitals admit patients from the ARIC Study community.

The Twin Cities metropolitan area has a wide range of primary, secondary, and tertiary care hospitals and physicians. There is a uniform emergency medical system which responds to 911 dispatching. A full range of cardiovascular diagnostic and treatment procedures, including cardiac transplants and artificial heart implantation are available in the area.

The Minnesota State Health Department is within one block of the University of Minnesota. The Department of Epidemiology has an excellent working relationship with the Department of Health and has ready access to death certificates. Each county in the Twin Cities has a coroner whose records are available for research purposes.

2.3.4 Washington County, Maryland

Washington County is located in western Maryland, 75 miles northwest of Baltimore and Washington, DC. Most of the county is located in the broad valley between the Blue Ridge on the east and the Allegheny Mountains on the west. These mountains and the Potomac River on the county's southern edge tend to decrease inter-county travel.

Industry is light and diversified. The largest employer is the Mack Truck engine and transmission plant with approximately 3,500 employees. London Fog, the second largest, employs 1,000 persons to make clothing. Because of the intersection of major east-west and north-south interstate highways and rail lines, transportation is another large source of jobs. Agriculture is also important, especially dairying in the valley and orchards on the mountain slopes.

The adult population of Washington County is very stable. Census data for 1980 showed that 60 percent of non-institutionalized persons 5 years of age or older had lived in the same house, and 89 percent in the same county for five years or more. Follow-up of 4,328 persons enumerated in a private census in 1963 showed that 93 percent of persons initially aged 45 to 65 years who were still alive were residing in Washington County eight years later, the proportion being nearly the same for males and females. Among 130 persons aged 50 to 70 years in 1973, 85 percent were living in the same house they had occupied in the 1963 private census.

In 1983-84, 148 persons were selected from the 1975 private census listings as age-matched controls for a study of colon cancer. Of these, 5 were known to have died in the county, and 133 were known to be living in the county. Comparable information from 229 controls selected at the same time for a study of lung cancer indicated that 8 had died and 212 were still living in the county. Among controls in the two studies combined, there was a 5.0 percent loss from emigration over an 8 1/2 year period, a rate of only 0.6 percent per year for these middle-aged and older residents.

There are 165 practicing physicians in the county with virtually every speciality represented. An efficient medical examiner service for investigating sudden and unattended deaths is part of a state-wide system. Washington County Hospital, the only general hospital in the county, has 415 beds. It serves as the medical center for the surrounding area so that few local residents go elsewhere for treatment. Most of the residents who are hospitalized elsewhere go to one of six hospitals in adjacent counties. Western Maryland Center, a state rehabilitation hospital, and a private psychiatric hospital, Brook Lane Center, are the other two hospitals in the county. It is estimated that 95 percent of non-fatal MIs are hospitalized in Washington County Hospital.

Washington County Health Department provides clinic and home nursing services to the community. The Department also houses the Training Center for Public Health Research which acts as the custodian of death certificates for the county. The Training Center also keeps a current file of obituaries.

2.4 Central Agencies

In addition to the four field centers described above, the ARIC study includes seven central agencies. The protocols for the procedures performed by each of these agencies are contained in separate manuals: clinical chemistry (Manual 10), hemostasis (Manual 9), lipids, (Manual 8), electrocardiograms (Manual 5), pulmonary function (Manual 4), ultrasound (Manual 6), and quality control (Manual 12). The role of these agencies is summarized in this section.

2.4.1 Central Clinical Chemistry Laboratory

The clinical chemistry measurements performed by the Central Clinical Chemistry Laboratory are: glucose, creatinine, urea, calcium, magnesium, sodium, potassium, phosphorus, total protein, albumin, uric acid, and insulin (Table 5). The determinations are made on frozen sera for all cohort participants which are shipped from the Field Centers. The analytical methods and quality control programs (both internal and external) follow those of the University of Minnesota Hospital Laboratories. In addition, blind replicate samples are submitted by the Field Centers as an additional means of monitoring laboratory performance.

2.4.2 Central Hemostasis Laboratory

Atherosclerosis, long recognized as a disease of lipid deposition into arterial walls, is increasingly believed to involve the hemostasis system. Hemostasis may be critical both for the onset of clinical disease (thrombotic occlusion leading to cerebral or myocardial infarction) and for initiation and progression of the underlying atherosclerotic lesions. Since the hemostasis system is highly reactive, prospective studies, rather than studies of clinical cases, are necessary to test this hypothesis. The Central Hemostasis Laboratory evaluates each component of the hemostasis system in ARIC cohort participants: coagulation proteins and platelets (which promote arterial clot formation) and coagulation inhibitors and the fibrinolytic system (which prevent or lyse clots). The specific measurements to be made (Table 5) are classified as follows:

1. Platelets - plasma levels of Beta-thromboglobulin (β-TG) and Platelet Factor 4 (PF-4), serum levels of TXB_2.
2. Coagulation
   a. Pro-enzymes - plasma levels of fibrinogen and von Willebrand factor antigen; activity of factors VII and VIII.
   b. Coagulation activation - plasma levels of Fibrinopeptide A (FPA).
6. Coagulation inhibitors - plasma levels of Antithrombin III (AT-III) and protein C.
4. Fibrinolysis - plasma levels of Tissue plasminogen activator (tPA) and Fibrinopeptides Bβ (FPB-β) (1-42).
5. General screen - Activated PTT (aPTT).

Table 5. Measurements Performed at the ARIC Central Laboratories

Central Clinical Chemistry Laboratory	Central Hemostasis Laboratory	Central Lipid Laboratory
Glucose	Activated PTT (aPTT)	Total cholesterol
Creatinine	Fibrinogen	Total triglycerides
Insulin	Factor VII	HDL cholesterol
Total protein	Factor VIII C	HDL_2 cholesterol
Albumin	von Willebrand factor antigen	HDL_3 cholesterol
Uric acid	Protein C	LDL cholesterol
Urea nitrogen	Antithrombin III (AT-III)	LDL subfractions*
Calcium	Fibrinopeptide A* (FPA)	Lipoprotein Lp (a)
Phosphorus	Fibrinopeptides Bβ (FPB-β) (1-42) and (15-42)*	Apolipoprotein AI
Magnesium	Beta-thromboglobulin* (β-TG)	Apolipoprotein B
Sodium	Platelet factor 4* (PF-4)	ApoB epitopes*
Potassium	Thromboxane B_2* (TXB_2)	ApoE phenotypes*
	Tissue plasminogen activator* (tPA)	Apolipoprotein polymorphs*

*Performed only for case control studies.

Seven of these measurements (fibrinogen, factors VII and VIII, von Willebrand factor antigen, aPTT, protein C and AT-III) are made on blood from every cohort participant; the remainder, on blood from selected cases and controls only.

Methods used at the field centers for blood collection and processing, designed to minimize activation of the hemostasis system, were pretested at the Central Hemostasis Laboratory. Serum is prepared for Thromboxane B_2 (TXB_2) measurement. The remaining tests use plasma. Aliquots are processed differently (different anticoagulants and methods of centrifugation and filtration) for the three sets of plasma tests. Aliquots are shipped frozen to the Central Hemostasis Laboratory.

The assay procedures are summarized as follows:

1. Fibrinogen, Factors VII and VIII and aPTT by automated clotting time bioassays.
2. Von Willebrand factor antigen, tPA, protein C and FPB-β(1-42) by enzyme-linked immunosorbent assay.
3. TXB_2, β-TG, PF-4 and FPA by radioimmunoassay.
4. AT-III by a chromogenic substrate technique.

Field center laboratory technicians were trained in proper venipuncture and processing methods and are certified and periodically recertified by the chief technologist from the Central Hemostasis Laboratory.

Sample collection, processing, storage and analysis are monitored using an internal and external quality control program and through the analysis of blind duplicates. An added check on drift or shifts in laboratory performance is provided by analysis of blood from monthly random subsamples of the cohort in each community.

2.4.3 Central Lipid Laboratory

Central Lipid Laboratory measurement of lipids, cholesterol in lipoprotein fractions, and apoproteins with key roles in lipid metabolism permits ARIC to discriminate among important hypotheses which relate lipid factors to atherosclerosis. Total cholesterol and triglycerides, HDL and HDL_3 cholesterols, lipoprotein Lp(a), and the apoproteins A-I and B are measured directly; VLDL, LDL, and HDL_2 cholesterols are derived quantities.

Each of these determinations is made for all cohort participants on frozen plasma. Additional, newer lipid measurements are made on selected cases and controls, using stored plasma. The Central Lipid Laboratory recommends measurements for case-control studies and develops or refines the methods to be used.

Methods of collection, processing and storage were developed and tested, and limits for accuracy and precision were established, prior to analysis of specimens from ARIC participants. Assay methods are as follows:

1. Cholesterol and triglycerides by enzymatic methods.
2. HDL and HDL_3 cholesterols by enzymatic methods following sequential precipitation of VLDL + LDL and HDL_2 by magnesium and dextran sulfate.

3. Apoproteins A-I and B by radioimmunoassay.
4. Lp(a) by enzyme-linked immunosorbent assay.

Sample collection, processing, storage and analysis are monitored by means of internal and external quality control and the analysis of blind duplicates.

2.4.4 ECG Reading Center

Electrocardiograms (ECGs) are collected in the ARIC Study both for the cohort and in community surveillance. There are two ECG reading centers: the ECG Computer Center at Dalhousie University in Halifax, Nova Scotia, and the ECG Reading Center at the University of Minnesota Division of Epidemiology.

2.4.4.1 ECG Data Collection and Coding in the Cohort Component

A standard supine ECG and a two-minute rhythm strip are obtained on each subject at baseline and all subsequent clinic visits. The purpose of the initial test is to determine ECG status of each participant at baseline. Subsequent tests determine changing ECG status with regard to myocardial ischemias, left ventricular hypertrophy, and arrhythmias. The examination ECGs are recorded electronically and transmitted to the Dalhousie ECG center where continuous computer measurements are made on the ECG wave forms (including the Minnesota Code and additional indices of electrocardiographic findings). All abnormal ECGs and a sample of normal ECGs are also read manually in Minneapolis, using the method described below. All rhythm strips are read in the Minnesota ECG Reading Center.

ECGs of hospitalized cohort members are photocopied locally and coded manually by the Minnesota ECG Reading Center. Each ECG is read independently by three technician readers, and unresolved disagreements are adjudicated by the ECG supervisor and/or an electrocardiographer at the reading center. Serial change rules are used for suspected MI. All readings are made without knowledge of clinical or laboratory findings for the subject. At periodic intervals, a subsample of hospital and clinic examination ECGs are re-submitted for masked reading to monitor the ECG Center performance.

2.4.4.2 ECG Data Collection and Coding in the Community Surveillance Component

The Minnesota ECG Reading Center trains field center abstractors to perform Minnesota coding of Q-waves for surveillance in hospitals in each community. At periodic intervals, a subsample of ECGs is also coded by the Minnesota ECG Reading Center in order to monitor abstractor performance and to determine the proportion of Q-wave to non-Q-wave infarctions.

2.4.5 Pulmonary Function Center

The Pulmonary Function Center provides centralized processing of all pulmonary function studies performed in the cohort component and the standardization of pulmonary testing in the four field centers through (1) a protocol for testing procedures; (2) the training and certification of field center pulmonary function technicians; and (3) ongoing quality control.

The Pulmonary Function Center reviews every 10th spirogram. The paper graphic volume-time tracing of every 10th participant is sent to the Pulmonary Function Center (including previous tracings for this participant for comparison). It electronically reviews each participant's results. A floppy disk copy of the digitized records of the three best spirograms of each participant is also sent to the Pulmonary Function Center. These digitized spirograms are electronically reviewed for quality and reproducibility. Appropriate indices of volume and flow are derived. An electronic consistency check of each participant's result is made against his previous spirometry.

The Pulmonary Function Center also reviews the data distributions of each field center. A routine comparison of sex and race specific regressions on age and height is programmed into the electronic review. This permits comparison of results between field centers, with the same center on previous occasions and with predicted values.

2.4.6 Ultrasound Reading Center

The Ultrasound Reading Center performs a centralized reading of the cohort ultrasound videotapes produced at the four Field Centers. The videotapes, which are created following procedures in the protocol, are copied to an optical disk and read as follows.

Each reader uses a reader station to evaluate the images. The reader station consists of an optical disk reader, a 15" monitor, a personal computer, and a graphics tablet for cursor control. The personal computer is also the input device for participant data, date, frame number, reader identification, artery identification, site, angle, cursor location, etc. The reader station is designed so that no electronic error in the reader station is more than one-half the axial resolution of the instrument. This requires electronic position accuracy of greater than 0.1 mm in biological tissue. After the personal computer generates the data file on the study, the file is transmitted to the central computer for storage on hard disk with backup copy on a floppy disk.

Measurements are made in the popliteal artery at the level of the knee joint and in the common carotid, the carotid bulb and the internal carotid arteries. The measurements at each site include mean and maximal far wall thickness, mean and maximal near wall thickness, and mean and maximal lumen.

The Ultrasound Center also provides estimates of arterial distensibility in the carotid artery.

2.4.7 Coordinating Center

The Coordinating Center provides centralized administration, planning, and management for all components of the ARIC Study. Its administrative functions include supporting the Project Office and the chairman of the Steering Committee in convening meetings, documenting decision and action items, preparing and distributing meeting minutes and coordinating the work of the Steering Committee's various subcommittees. The central computer for electronic mail is housed at the Coordinating Center and technical support for the installation, use, and maintenance of local equipment and software

is provided by in-house staff. The Coordinating Center serves as the official repository for all ARIC Steering Committee records, manuals of operations, data collection instruments, research data and publications.

During the initial phases of the study, Coordinating Center staff participate in the activities of the Steering Committee and all subcommittees providing technical assistance in study design; data collection, processing and analysis; training and certification; quality assurance; pilot testing and evaluation; and study implementation. Once the study collects data, the Coordinating Center supports the Morbidity and Mortality Classification Committee in monitoring the status of each study endpoint, preparing documentation of events to be verified and creating a final diagnosis file.

The Coordinating Center's responsibility for the centralized management of the study includes the provision and tracking of training and certification; monitoring protocol adherence in the field centers and central agencies; the design, implementation and monitoring of quality assurance programs in the field centers, laboratories and reading centers; and data management, including the development of a computerized data collection system, on-site and centralized data processing and data analysis. Training and certification, protocol adherence and quality control programs are discussed in detail in Manual 12, Quality Assurance. The specific procedures for the distributed data management systems and data analysis are described in the following section of this manual.

The Coordinating Center also supports the design, management, and analysis of case control studies, and the publication of results of the collaborative study.

3. DATA MANAGEMENT

This section describes the distributed data management systems used for the collection, processing and distribution of data and materials among the various ARIC study components. The data management system has three major components: a Computer Assisted Data Collection (CADC) system, a local data base management system (DBMS) and the collaborative DBMS. The CADC system uses PC/XTs and compatible lap top microcomputer workstations for data collection, editing and correction during the cohort examination, for record abstraction, and for entering data collected on paper forms. Each field center has a PC/AT for local data base management, ad hoc retrieval and reporting, scheduling and other study management functions, and communication with the Coordinating Center. The collaborative DBMS is maintained at the Coordinating Center and is used to store, update, and access the data from the four field centers, central laboratories, and reading centers. Section 3.1 briefly outlines the flow of data and materials such as blood samples, ultrasound tapes and ECG tracings through the various study agencies and centers. Subsequent sections provide a more detailed description of each field center's and central agency's data management system. Additional information on specific operational procedures is documented in each agency's separate Manual of Operations.

3.1 Overview of ARIC Data Flow

The data and materials flow for the ARIC Study can be grouped into three main categories: 1) the study data and materials collected and processed by the various study components; 2) inventory and study management information used to monitor the study data and materials and to schedule various study activities; and 3) various types of reports on performance and quality control. A large portion of the study data is collected and processed using the microcomputers described elsewhere in this document. These data, as well as some of the inventory information and reports, are transferred between centers by mailing floppy diskettes or by telecommunications. Study materials, including blood samples, tapes and tracings from the various examination procedures are transferred to the appropriate centers by mail or other carrier as described in specific sections of the protocol.

3.1.1 Cohort Component

As shown in Figure 2, the flow of study data for the cohort component begins with the enumeration of the study communities and the selection of the study sample. Next, participants are recruited and scheduled for the base line interview and examination. At this visit interview and examination data are recorded for each subject, either directly into the microcomputer using the CADC system or by completing paper forms that are entered into the CADC system at some later time. These data are then transferred to the Coordinating Center by mail on a regular schedule.

Note: Throughout this manual a personal computer is identified as PC.

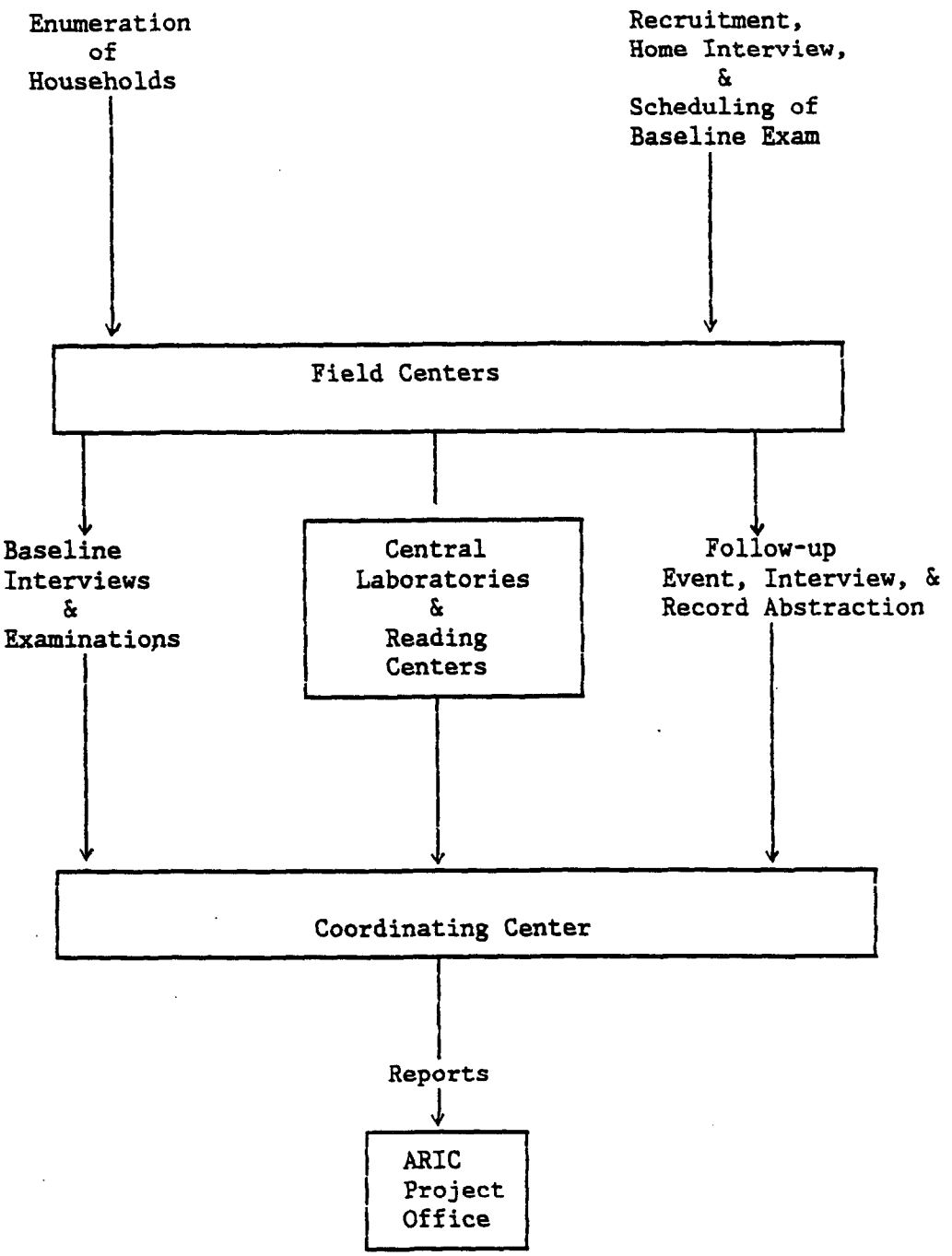

Figure 2. ARIC Cohort and Materials Flow

Blood samples are shipped to the Lipids, Hemostasis, Chemistry and local hematology laboratories, ultrasound tapes to the Ultrasound Reading Center, ECG data to the ECG Reading Centers and pulmonary function data to the Pulmonary Function Center. After the laboratories and reading centers have made their respective determinations, the results are sent to the Coordinating Center where they are added to the collaborative database.

The data collected during the interview and examination are used to identify existing cardiovascular disease and other diagnoses of interest. In addition, the participant is contacted annually to ascertain his or her health status. Data collected during the annual follow-up precipitate the collection of additional data from medical records, abstractions and interviews with doctors or next-of-kin. These data are sent to the Coordinating Center and added to the collaborative database. Potential events are classified with the appropriate diagnostic criteria by applying diagnostic algorithms.

A sample of pulmonary function tracings and results is sent to the Pulmonary Function Center for quality control purposes. Similarly, ECG data are sent for interpretation to the ECG Reading Center. The results of these readings and quality control samples are sent to the field centers and the Coordinating Center.

In addition to the data and materials transferred among the study components, inventory, identification and study management information is also required. This information, in general, follows the same direction as the flow of data shown in Figure 2. Once the sampling units are enumerated, samples are drawn and eligible residents are recruited. The results of recruitment and the scheduling of visits are stored in the field center database. Identification information accompanies the materials sent to the laboratories and reading centers in order to verify that all materials shipped are received. This information may be a paper shipping list or a floppy diskette, depending on the requirements of the specific laboratory or reading center. Inventory information pertaining to these materials is also sent to the Coordinating Center. After a suitable time delay, this inventory information is compared with the laboratory/reading center results received at the Coordinating Center and any discrepancies explored.

A similar system ensures that laboratory/reading center results are returned to the field centers. Schedules for data transfer and a system of acknowledgements is used to monitor all transfers and shipments. When a shipment is received by a study component, an appropriate acknowledgement is returned to the sending component. These acknowledgements flow in the opposite direction of the arrows in Figure 2. If either the expected shipment or the acknowledgement is not received, action is taken to trace the problem.

Routine performance and quality control reports are generated by the Coordinating Center and distributed to the other study components. Exception reports are generated when problems are identified and immediate action is required. Laboratory or reading center alert values constitute another important group of exception reports. These results are communicated to the field centers and relayed to the participant as expeditiously as possible.

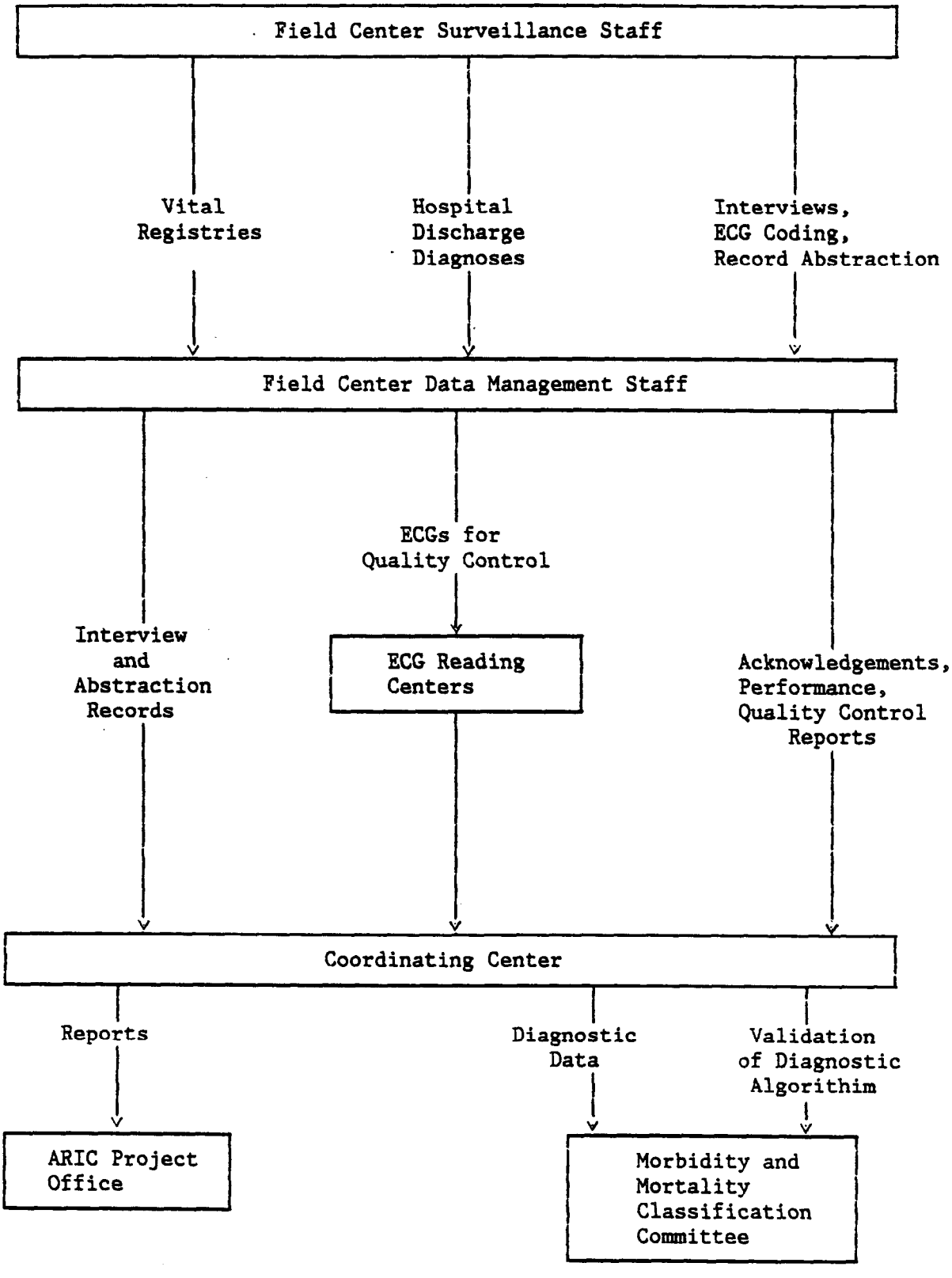

Figure 3. ARIC Study Community Surveillance Data and Report Flow

3.1.2 Community Surveillance

Data flow for community surveillance begins with the identification of potential cases from vital statistics registries, hospital discharge diagnoses and other sources as shown in Figure 3. These cases are added to the local database at each field center. Cases meeting the eligibility criteria are investigated and additional data are collected from hospital records and interviews. The CADC system is used to collect the study data. The data are keyed directly into microcomputers when feasible. Paper forms are used when direct entry is not possible or desirable. These data are then transferred to the Coordinating Center in the same manner as the cohort data. Once at the Coordinating Center, the diagnostic criteria are applied to the data using the appropriate diagnostic algorithm. In addition, the data are summarized and presented to the Mortality and Morbidity Classification Committee for validation.

Various inventory control systems ensure that all potential cases are classified and all appropriate data are collected. Random samples of ECG tracings and their coding by the hospital record abstractors are reviewed by the ECG Reading Center for quality control purposes. Quality control results are sent to the field centers and to the Coordinating Center. Performance and quality control reports are generated and distributed in a manner similar to that described for the cohort component of the study.

3.2 Field Center Data Management

In the distributed data management system, each ARIC Field Center is responsible for managing the data collected during the cohort examinations and event abstractions in its community. This includes the initial recording, keying, editing, correction, and transmission of data to the ARIC Coordinating Center. It also includes maintaining an inventory of data forms and other materials collected (e.g., blood, ultrasonography tapes) and sent to the ARIC Central Agencies and Coordinating Center. Each center maintains a cumulative database for clinic management.

The CADC workstation allows field center personnel to enter, edit and correct data values directly eliminating the need for paper forms, except as a back-up. During the cohort examination, the CADC system is used to collect, interview and enumerate data in this manner. The portable lap top computers use the same system to abstract, cohort and surveillance data from medical records library in the study hospitals. In those situations where use of CADC is not desirable or possible, the same system can be used to enter data from completed paper forms.

3.3 Ultrasound Reading Center Data Management

B scan ultrasonography is performed on each subject with results sent weekly to the Ultrasound Reading Center on 3/4 inch video tape and floppy disks. The video tape images are transferred at the Reading Center to optical disks and digitized; wall and lumen area calculations are then made. Changes in lumen diameter are measured with an arterial wall tracker which uses the radio frequency output from the ultrasound scanner and transfers the results

to a floppy disk and to a paper strip chart for backup. Supine and postural blood pressures are recorded using an automated recorder and the measurements are transferred to a floppy disk. Pulse rate response to postural change is measured and the signal recorded on the floppy disk. All results from spectral analysis, arterial distensibility and postural challenge measurements are sent weekly on floppy disks to the Ultrasound Reading Center for appropriate calculations and for quality control. Completed test results for all three types of ultrasound measurements are sent weekly from the Ultrasound Reading Center to the Coordinating Center on floppy disks for transfer into the main study database.

Inventory records lisitng ID numbers of subjects tested are sent weekly from the field centers to the Coordinating Center. Data backup at the field centers includes 1/2 inch video tapes and electronic copies of raw data. The Coordinating Center stores all data received from the Ultrasound Reading Center in the collaborative database and sends weekly to each field center a floppy disk containing study results of its participants in order to update the local databases.

3.4 Central Hemostasis Laboratory Data Management

Thirteen aliquots of plasma and serum per subject are sent in weekly batches from each field center to the Hemostasis Laboratory. Donor Information Forms and an inventory record on paper and on a floppy disk accompanies each batch of specimens. Specimen analyses are performed on a gamma counter, a Coag-A-Mate analyzer and an ELISA reader; software written for each machine permits transmittal of results directly onto a PC-XT. Results (approximately 20 variables per subject) are sent weekly from the Hemostasis Laboratory to the Coordinating Center on floppy disks for transfer into the main study database.

Inventory records listing participant ID numbers for blood specimens are sent weekly from the field centers to the Coordinating Center. Data backup at the field centers includes electronic copies of the inventory records of specimens sent. The study has elected not to draw extra blood specimens as backup in case of loss or damage during processing or shipping. The Coordinating Center stores all data received from the Hemostasis Laboratory in the collaborative database and sends weekly to each field center a floppy disk containing study results of its participants in order to update the local databases.

In addition to the blood samples processed by the central laboratories, one sample of whole blood is analyzed in local laboratories in each field center for routine hematology determinations. Results are returned to the field centers on paper, entered into the DMBS and sent to the Coordinating Center on floppy disks containing other baseline interview and examination data.

3.5 Central Lipid Laboratory Data Management

Ten aliquots of plasma and two tubes of buffy coat per subject are sent in weekly batches from each field center to the Lipid Laboratory. An inventory record on paper and on a floppy disk accompanies each batch of specimens.

Specimen analyses are performed on a Cobas-Bio autoanalyzer, an automatic gamma counter and an ELISA reader; software written for each machine permits transmittal of results directly onto a PC compatible floppy disk. Results (approximately 12 variables per subject) are sent weekly from the Lipid Laboratory to the Coordinating Center on floppy disks for transfer into the main study database. Additional tests are run on selected cases and controls. These results are entered from the laboratory's Compupro 816 computer onto a PC compatible floppy disk for transmittal to the Coordinating Center.

Inventory records listing participant ID numbers for blood specimens are sent weekly from the field centers to the Coordinating Center. Data backup at the field centers includes electronic copies of the inventory records of specimens sent. The study has elected not to draw extra blood specimens as backup in case of loss or damage during processing or shipping. The Coordinating Center stores all data received from the Lipid Laboratory in the collaborative database and sends weekly to each field center a floppy disk containing study results of its participants in order to update the local databases.

3.6 Central Clinical Chemistry Laboratory Data Management

Three tubes of frozen serum per subject are sent in weekly batches from each field center to the Central Chemistry Laboratory. An inventory record on paper and on a floppy disk accompanies each batch of specimens. Specimen analyses are performed on a DACOS analyzer and a gamma counter. Test results which are initially printed on paper are keypunched by Central Chemistry Laboratory personnel onto a PC. Results (approximately 15 variables per subject) are sent weekly from the Central Chemistry Laboratory to the Coordinating Center on floppy disks for transfer into the main study database.

Inventory records listing participant ID numbers for blood specimens are sent weekly from the field centers to the Coordinating Center. Data backup at the field centers includes electronic copies of the inventory records of specimens sent. The study has elected not to draw extra blood specimens as backup in case of loss or damage during processing or shipping. The Coordinating Center stores all data received from the Clinical Chemistry Laboratory in the collaborative database and sends weekly to each field center a floppy disk containing study results of its participants in order to update the local databases.

3.7 ECG Reading Center Data Management

Twelve lead ECG tracings recorded in field center clinics are transmitted by phone daily from the PC ECG machine at each field center to the MAC/12 ECG machine at the Halifax ECG Computer Center (approximately 6 ECGs per field center per day). Confirmation of receipt is received at the field centers via electronic mail from Halifax early the next morning prior to erasing a day's tracings from the PC memory. The 12 lead ECGs are coded by computer in Halifax. Tracings of all records with abnormal Minnesota Codes and a sample of records with normal codes are sent weekly as paper tracings

tracings to the Minnesota ECG Reading Center for Minnesota Coding and for quality control. In addition, two minute paper ECG rhythm strips recorded in the clinics are sent weekly from the Field Centers to Minnesota for coding. Results of 12 lead ECGs (approximately 300 variables per subject) are sent weekly from Halifax to the Coordinating Center on floppy disks for transfer into the main study database.

ECGs recorded in study community hospitals are also coded by Field Center staff for community surveillance and by the Minnesota ECG Reading Center for cohort members. The Reading Center also codes a sample of community surveillance ECGs for quality control. Hospital ECG interpretation by the Reading Center is implemented by means of a combination of photocopied ECGs mailed to the Reading Center and visits by Reading Center staff to the hospitals. ECG codes are recorded on paper forms and mailed to the Coordinating Center for data entry.

Inventory records listing ID numbers of subjects tested are sent weekly from the field centers to the Coordinating Center. Data backup at the Field Centers includes paper ECG tracings which can be read by the Minnesota ECG Reading Center if necessary, but does not include an electronic backup initially. The Coordinating Center stores all data received from the ECG Reading Center in the collaborative database and sends weekly to each field center a floppy disk containing study results of its participants in order to update the local databases.

3.8 Pulmonary Function Center Data Management

After spirometry is done on each cohort participant, initial calculations are performed on the PC-XT locally at each field center. Results are sent weekly on floppy disks to the Pulmonary Function Center for further calculations and for quality control. A sample of paper tracings is sent weekly to the Pulmonary Function Center for quality control. Completed pulmonary function test results (approximately 50 variables per subject) are sent weekly from the Pulmonary Function Center to the Coordinating Center on floppy disks for transfer into the main study database.

Inventory records listing ID numbers of subjects tested are sent weekly from the field centers to the Coordinating Center. Data backup at the field centers includes paper spirometry tracings and electronic copies of raw data. The Coordinating Center stores all data received from the Pulmonary Function Center in the collaborative database and sends weekly to each field center a floppy disk containing study results of its participants in order to update the local databases.

3.9 Collaborative Database

The collaborative portion of the database management system is used to store, update, and access the data from the four field centers, the central laboratories, and the central reading centers. Since each data item is edited, corrected, and verified at the data collection site, editing by the collaborative system largely consists of record level "data base closure" checks, such as ensuring the receipt of all expected records from each exam,

contact, hospitalization, and death. The focus of the collaborative DBMS is retrieval for analyses. The DBMS directly generates analysis files in SAS data set, BMD save file, and SPSS save file formats. It includes a relational query language, a programming language, and a full-screen forms-oriented retrieval facility. It includes comprehensive security and confidentiality facilities including passwords, encryption, and audit trails. Given the size of the collaborative data base, it is maintained on the University's mainframe computer.

4. STUDY MANAGEMENT

4.1 Introduction

The ARIC Study is funded by the National Heart, Lung, and Blood Institute, and directed by the Epidemiology and Biometry Program of the Division of Epidemiology and Clinical Applications. Principal investigators, directors, and their affiliations are listed in Appendix I. The operations of the study are directed by the ARIC Study Steering Committee whose members are the Principal Investigators of the field centers, coordinating center, the ultrasound reading center, the lipid and hemostasis laboratories, and the NHLBI Project Officer as shown in the organizational chart in Appendix II.

The Steering Committee is supported by subcommittees responsible for the details of study design and implementation, and a Morbidity and Mortality Classification Committee (MMCC). These committees report and make recommendations to the Steering Committee. The subcommittees and their charges are listed in the section below. The composition of each committee is given in Appendix III.

4.2 ARIC Study Subcommittees and Charges

The Criteria and Diagnoses subcommittee (DX) decided which events were to be ascertained in the cohort and what specific information was to be collected for each type of diagnosis. It established criteria for diagnosing these events as well as the procedures by which the Morbidity and Mortality Classification Committee makes these diagnoses. Other functions included the review of criteria provided by the Surveillance and Medical Care Subcommittee for surveillance events (acute hospitalized MI, CHD death) and the establishment of guidelines for safety, ethics, medical referrals, confidentiality, and quality control in the study.

The Laboratory and Sample Processing subcommittee (LAB) was responsible for developing the procedures for laboratory measurements and ensuring the quality control of all procedures associated with the laboratories. The subcommittee makes recommendations for lipid and hemostasis measurements, insulin, and routine chemistries. It directs the field center hematology laboratories, the measurement of stored blood, quality control, technician training, interpretation, monitoring, and the collection, processing, and transport of samples.

The Risk Factors and Clinic Operations subcommittee (EXM) developed protocols for clinic operations and risk factor measurement for the cohort component: blood pressure and postural effects, anthropometry, ECG, pulmonary function, questionnaires, interviews, and the physical exam. In matters pertaining to the examination, the committee was also responsible for equipment, exam flow, training (nurses, technicians, physicians,

interviewers), quality control, pretests, pilot study, interpretation, monitoring, and the second examination.

The Sampling, Recruitment, and Follow-Up subcommittee (SRF) established guidelines for sampling and recruitment, and for the characterization of non-respondents. It developed the protocol for follow-up. The subcommittee is responsible for training, quality control, interpretation, the pilot study, and monitoring in matters pertaining to sampling, recruitment, and follow-up.

The Surveillance and Medical Care subcommittee (SMC) reviewed the surveillance pilot study and developed diagnostic criteria for community surveillance. The subcommittee refined the protocol for the areas of hospital surveillance, death investigations, and medical care in hospital, and developed the protocol for recording care received from physicians and hospitals by the cohort participants. In matters pertaining to surveillance, the subcommittee is responsible for training for interviewers, abstractors, and ECG coders; pretesting direct data entry; quality control; data interpretation; and monitoring and protocol adherence.

The Ultrasound subcommittee (US) was responsible for preparing the Ultrasound Manual of Operations. Areas covered include the scanning protocol, instrumentation, sonographer training, quality control, the pretest, pilot study, interpretation, monitoring, and protocol for the second examination. It also provides a forum for discussing new concepts in ultrasonography, equipment, software, and workstation design.

4.3 Morbidity and Mortality Classification Committee

The Morbidity and Mortality Classification Committee (MMCC), comprised of physicians from the Coordinating Center and each field center, is responsible for the process of assigning all medical events of interest in the ARIC Study into diagnostic classes defined by the study. Hospitalized events are classified into MI categories by computer algorithm. The MMCC reviews this process by independent diagnoses of all cohort events and a sample of surveillance events. For fatal events, computer assignment is limited to events with insufficient information to merit physician review and events whose information is unequivocal and sufficient to produce a certain diagnosis. MMCC classifies the cause of death wherever classification cannot be done by computer and independently reviews the computer classification for most cohort deaths and a sample of the surveillance deaths.

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

4.4 Communications

4.4.1 Periodic Reports

The field centers and central agencies prepare routine periodic reports to the ARIC Study Project Office which document the progress to date in each major activity, administrative matters, staffing changes, and current or anticipated problems. The Coordinating Center also provides reports on the data collection at the field and laboratory centers, quality control findings on examinations, reabstracted records, recertification, laboratory determinations, and protocol adherence. Status reports on recruitment and data collection prepared for the Project Officer are also sent to the field centers. Quality control reports are likewise sent to the central laboratories and reading centers.

4.4.2 Newsletter

The Coordinating Center prepares and distributes a quarterly newsletter to facilitate communication among ARIC Study staff. In general, each edition includes (1) reports from the Project Office, the Coordinating Center, at least one of the central laboratories or reading centers, and the Steering Committee, (2) a description of the facilities and staff of one field center or central agency, (3) general information on data management and (4) a calendar of events. The newsletter also provides reports on issues such as recruitment and participant follow-up rates, the development and the use of new ECG, laboratory, pulmonary function, or ultrasound methods and equipment, and preliminary study results and abstracts.

4.4.3 Electronic Mail

All field centers, central agencies, the Coordinating Center and the Project Office are linked by electronic mail using microcomputers at each center. The electronic mail network is used to facilitate rapid and efficient communication among centers for messages such as announcements, meeting agendas, abstracts for clearance and acknowledgements of receipt of data.

4.4.4 Field Center Visits

Project Office and Coordinating Center staff conduct periodic monitoring visits to field centers as needed to (1) maintain channels of communication with field center investigators and staff, (2) solve participant recruitment or follow-up problems, (3) monitor adherence to the protocol and (4) provide technical support for activities such as data management and quality control.

4.5 Publication Policy

Overall responsibility for manuscript and abstract generation and approval for the ARIC Study lies with the Steering Committee, which also serves as the Publication Committee. This committee has developed procedures for generating manuscripts and abstracts as well as the formal requirements for manuscript approval prior to submission for publication or abstract submission before presentations.

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

This section discusses the procedures for both the generation phase and the approval phase. It reviews the different types of possible publications and presentations, authorship, the general strategy for preparation of manuscripts and abstracts, and describes in more detail the requirements for each type of publication or presentation.

4.5.1 Types of Publications and Presentations

There are several types of publications and presentations for which approval procedures are established. These include:

1. Major descriptions of the design and conduct of the ARIC Study.
2. Major descriptions of results, based on data from all field centers, addressing the main objectives of the ARIC Study.
3. Descriptions of results, based on data from all field centers, addressing issues other than the main objectives of the ARIC Study.
4. Descriptions of results based on data collected from a single field center.
5. Descriptions of methodological developments required to meet the needs of the ARIC Study.
6. Articles to appear in proceedings of meetings for which no abstract was required.
7. Invited presentations for which no abstract is submitted and for which there are to be no published proceedings.
8. Press releases or discussions with the media.
9. Lectures or other informal presentations.

The Steering Committee is responsible for resolving any uncertainties as to which category a specific presentation or publication belongs.

4.5.2 Outline of the Preparation and Approval Process

The basic steps for the generation and approval of publications and presentations are listed below:

1. The Steering Committee designates a topic.
2. The Steering Committee selects a writing group and its chairperson.
3. The writing group prepares specifications for the manuscript and obtains Steering Committee approval.
4. The writing group prepares and communicates computational specifications to the Coordinating Center.
5. The Coordinating Center prepares statistical computations according to priorities specified by the Steering Committee.
6. The working group prepares, reviews internally, and submits the completed document to the Steering Committee for review and approval.
7. The Steering Committee reviews and approves the document.
8. NHLBI review occurs concurrently with Steering Committee review.
9. The manuscript is sent to the Coordinating Center for final data verification.

10. The manuscript is formally submitted to a journal or abstract selection process.

The overall responsibility for managing the entire process lies with the Steering Committee; however, for some steps a subgroup may be given responsibility. Further, the nature of the approval process varies according to the type of document. These issues are discussed below.

4.5.3 Authorship

The authorship policy varies according to the type of publication or presentation being considered. For some publications, the author is listed as the "The ARIC Study Investigators," with the preparers clearly indicated. In other cases, the persons preparing the manuscript are listed as authors. Similarly, for some presentations, the paper is listed as presented by someone for the ARIC Study. In other cases the individual is listed as the author. In all cases, however, the person who assumed the lead responsibility for a particular publication or presentation is to be listed as the first author or preparer. In addition, the phrase "ARIC Study" is to be included in the title and listed as a "key word" whenever possible.

The Steering Committee is responsible for resolving any conflicts or confusion that occur with respect to appropriate recognition of authorship.

4.5.4 Manuscript and Abstract Generation

The general procedure for generating manuscripts or abstracts is for the Steering Committee to designate a writing group with the charge to develop the manuscript for publication or presentation. The impetus for this designation may come directly from the Steering Committee or may be in response to a request or suggestion from outside the committee. Once it is decided that a specific manuscript will be developed, the writing group and its chairperson will be specified.

Under normal circumstances the chairperson, who has the lead responsibility for this task, will also be listed as the first author for those documents where individual recognition is appropriate or as the first preparer for those where the ARIC Study is listed as the author. The chairperson also has the responsibility for listing the co-authors in the appropriate order. As indicated above, the Steering Committee serves as final arbitrator of any conflicts.

Individuals interested in preparing a manuscript or abstract on a specific topic must submit their proposal, which should include suggestions for writing group members, to the Steering Committee for approval. The proposal must include a clear statement of the nature of the publication, and should, if appropriate, also include the hypotheses to be addressed and the types of statistical computations or data summarizations likely to be required.

The Steering Committee has the responsibility for reviewing these proposals, both for appropriateness and for a priority designation. The Steering Committee also ensures that the different participating centers and groups are appropriately represented and that appropriate recognition is provided.

Once the specifications for the manuscript have been approved, the requirements for statistical computing can be formally communicated to the Coordinating Center. Requests will be processed according to the priorities specified by the Steering Committee. The Coordinating Center has representation on the writing group whenever possible and this person serves as the liaison to the writing group, both for communications about computing issues and for providing or obtaining appropriate statistical input.

The Steering Committee reviews the progress that each writing group is making toward the completion of its task and makes those changes required for the timely completion of each manuscript or abstract.

4.5.5 Approval Procedures

A manuscript stemming from the ARIC study is submitted to the chairman of the Steering Committee, who sends copies of the manuscript to two primary reviewers and Steering Committee members for their critique. A detailed critique is expected from the primary reviewers. Upon receiving the critiques, two courses of action are possible: (1) If the chairman deems the reviewers' suggestions to be mainly editorial in nature, he may approve the manuscript and request that the authors incorporate suggested changes to the final version, or submit in writing reasons for not doing so. No further action is needed from the Steering Committee; or (2) If, in the chairman's judgement, critiques entail substantive changes, the revised manuscript must be further reviewed by the primary reviewers and the Steering Committee before approval is granted.

The approval procedures are presented separately for each type of publication or presentation listed in section 4.5.1.

4.5.5.1 Publication Types 1,2, and 6

The procedures described here are to be followed prior to submitting for publication any document describing the design and conduct of the ARIC Study or including results, based on data from all field centers and addressing the main objectives of the study. All such documents are to be processed through each of the preparation and approval steps listed above. This includes the data verification step. Abstracts are a special case of this procedure and are discussed separately later.

All papers meeting the conditions of this section (publication types 1, 2, and 6) are to be published under the by-line "The ARIC Study Investigators." In addition, a statement that the article was "prepared by (Writing Group Chairperson, then other members, listed in order specified by the chairperson)" is also to be included.

The above specifications for authorship apply also to abstracts submitted for presentations, whether or not they are to be published. They also apply to articles to be published in the proceedings of meetings (type 6). In this case the presenter can also be identified.

4.5.5.2 Presentation Types 1 and 2

The same conditions apply to abstracts for presentations of type 1 or 2 as apply for manuscripts for these publication types with the exception that a Steering Committee subcommittee of two persons is responsible for the initial review of the abstract. If this subcommittee is uncomfortable with the proposed abstract, it may be referred to the full committee.

Authorship is to be listed as described for publications above with the exception that the designation "presented by ..." may be added. The text for the presentation itself is to be treated as a publication and is to receive the same checks and approval actions as for publications, with reasonable adaptations for the different format.

4.5.5.3 Publication or Presentation Type 3

The preparation and approval procedures for publications and presentations of results based on data from all field centers which do not address one of the main objectives of the ARIC Study are identical to those which do address one of these objectives. However, the listing of the authors can be different. For these publications, it is permissible, subject to the approval of the Steering Committee, for individual investigators to be listed as authors. The order of this listing follows guidelines consistent with those for other papers. Namely, the working group chairperson is listed as the lead author and this person recommends to the Steering Committee the order of the listing of the other authors.

4.5.5.4 Publication or Presentation Type 4

The ARIC Study discourages the publication or presentation of results based on data from a single field center or from a collection of field centers that is less than the full dataset. Should this appear desirable for some reason, the nature of what is to be prepared and presented or published is to be reviewed and approved by the Steering Committee prior to its full development or submission.

4.5.5.5 Publication or Presentation Type 5

Publications or presentations describing methodology developed to meet the needs of the ARIC Study are to be prepared and approved by the same procedures as those based on data collected by the study. For papers generated by one of the subcommittees responsible for developing a specific method, the subcommittee could also function as a writing group. As such, its activities would fall under the purview of the Steering Committee and the same procedures that exist for the writing groups applies.

4.5.5.6 Presentation Type 7

For those presentations for which the formal submission of an abstract is not required and for which no proceedings are to be published, the invited or otherwise designated presenter is to submit a letter containing information equivalent to that of a typical abstract to the Steering Committee for review and approval. The Steering Committee will treat the letter in the same way that it treats an abstract.

If an abstract is subsequently required, it should be submitted for review as other abstracts are. In a similar fashion, if it should be decided later to publish the proceedings, then the document detailing the presentation is to be submitted for review as are other publications.

4.5.5.7 Press Releases and Media Discussions Type 8

In general, scientific findings from ARIC made available to the media will involve those findings being presented at scientific meetings and being published in the scientific literature. Such presentations and publications require prior clearance as noted above. In some circumstances, media discussions and press releases may be appropriate to clarify scientific findings for the lay public, but they should not be used as forums to release new information. Investigators are requested to keep the Project Office informed of contacts with representatives of the major national media and of major national media coverage of information which they have supplied. If a situation arises in which it appears desirable to release to the media new information not otherwise cleared for presentation or publication, prior clearance from both the Steering Committee and the Project Office is required.

Release of general descriptive information about the ARIC Study for local use (such as a local newspaper, university newsletter or state medical society journal) does not require prior approval. Use of centrally prepared materials for such purposes is encouraged. A copy of any resultant article should be sent to the Project Office.

4.5.5.8 Lectures and Other Informal Presentations Type 9

No formal approval is required for lectures and informal presentations so long as they do not constitute the initial release of ARIC results. Otherwise, the rules for presentation type 7 apply.

4.6 Ancillary Studies Policy

4.6.1 General Policy

To enhance the value of ARIC and to ensure the continued interest of the investigators, the Steering Committee welcomes proposals from individual investigators to carry out ancillary studies. Nevertheless, to protect the integrity of ARIC, such ancillary studies must be reviewed and approved by the Steering Committee before their inception. In general, ancillary studies require outside (non-ARIC) funding.

4.6.2 Definition of an Ancillary Study

An ancillary study is one based on information from ARIC participants in an investigation which is not described in the ARIC protocol and involves data which are not collected as part of the routine ARIC data set. The core ARIC study includes the use of blood stored for case-control studies selected by the Steering Committee; these are not considered ancillary studies.

4.6.3 Requirements for Approval of an Ancillary Study

Before an ancillary study can be approved, it must be shown that the ancillary study will have scientific merit but will not do any of the following:

1. Interfere with the completion of the main objectives of ARIC.
2. Adversely affect participant cooperation in compliance in ARIC.
3. Create a serious diversion of study resources (personnel, equipment or study samples), either locally or centrally.
4. Jeopardize the public image of ARIC.

4.6.4 Preparation of request for approval of an Ancillary Study

A written request for approval of an ancillary study should be submitted to the Steering Committee and should contain the following information:

1. Description of objectives.
2. Scientific merit of study.
3. Methodology for data collection.
4. Proposed statistical analyses.
5. Names of definite or possible collaborators.
6. Proposed funding sources.
7. Discussion of impact on main ARIC study.

4.6.5 Review of Ancillary Study Proposals

The Steering Committee will review and will approve, reject or request modification of ancillary study proposals in a timely manner. At least one ARIC investigator must be included as a co-investigator in each proposal. ARIC investigators other than those submitting the proposal may request to become collaborators on a proposal if they have a specific interest in the topic. The key criteria for approval of proposals are scientific merit and impact on the main ARIC study.

4.6.6 Analysis and Publication of Results of Ancillary Studies

The investigator of the ancillary study, and if necessary the Steering Committee, will consult with the Coordinating Center during data analysis to ensure that all study data used in analysis of ancillary study results are consistent with data in the main study database. Manuscripts resulting from ancillary studies shall be submitted for review and require approval by the Steering Committee and by NHLBI prior to submission for publication or presentation. The investigator who assumes lead responsibility for the ancillary study shall be listed as senior author. The phrase "ARIC Study" should be included in the title and listed as a key word whenever possible. Manuscripts will also contain an appendix listing all ARIC principal investigators as well as other individuals deemed appropriate.

4.6.7 Feedback of Results of Ancillary Studies to Participants

Results of ancillary studies shall be reported to participants and/or their physicians if medically useful. Such reporting should follow standard ARIC protocol for notification of participants.

Appendix I. ARIC Principal Investigators and Directors

Ralph Barnes, Ph.D. Director
ARIC Ultrasound Reading Center
4310-78 Enterprise Drive
Winston-Salem, NC 27106

George Comstock, M.D., Dr.P.H., Co-principal Investigator
ARIC Washington County Field Center
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Hagerstown, MD 21740

Richard Crow, M.D., Director
ARIC ECG Reading Center
Division of Epidemiology
School of Public Health
University of Minnesota
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Minneapolis MN 55455

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ARIC Central Clinical Chemistry Laboratory
Department of Laboratory Medicine
University of Minnesota
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Wolfgang Patsch, M.D., Principal Investigator
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Baltimore, MD 21205

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Center for Occupational and Environmental Health
Department of Environmental Health Sciences
The Johns Hopkins School of Hygiene and Public Health
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O. Dale Williams, Ph.D., Principal Investigator
ARIC Coordinating Center
Collaborative Studies Coordinating Center
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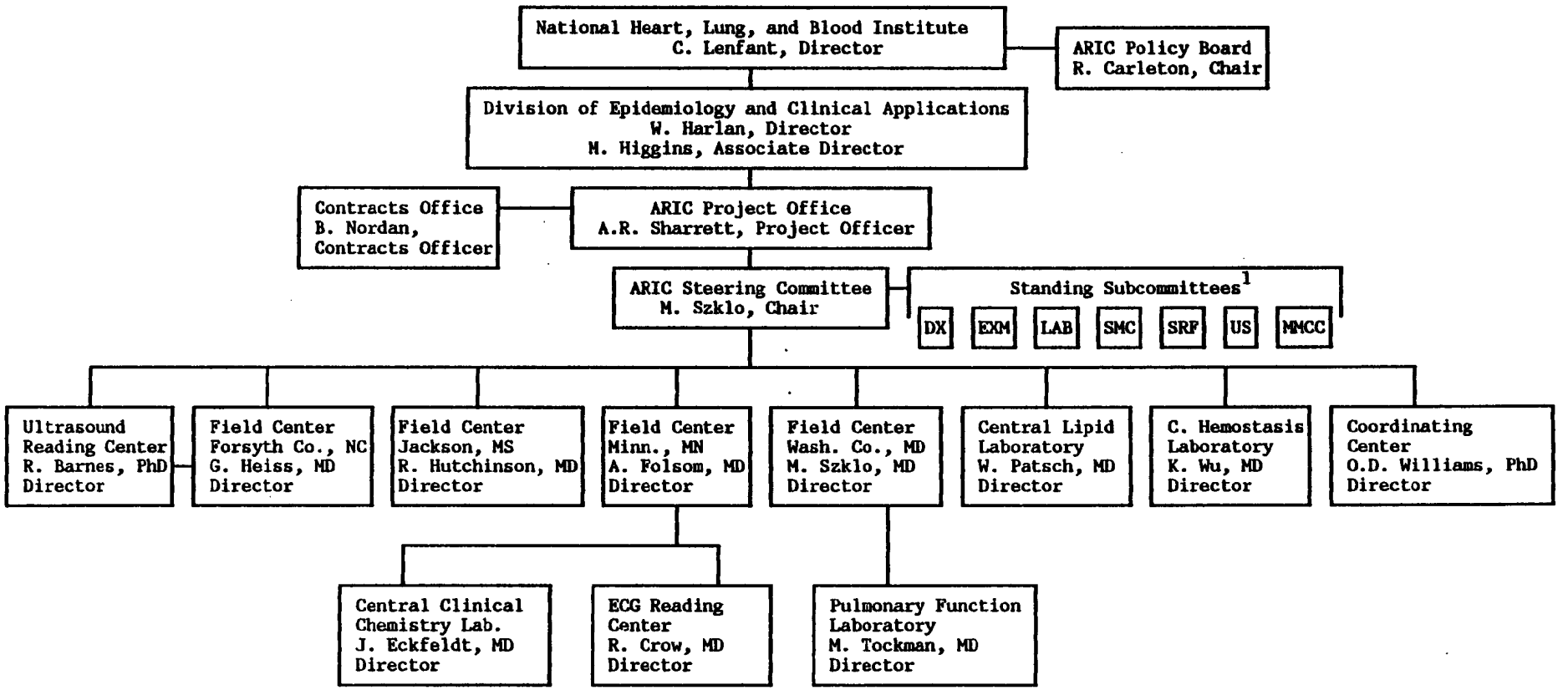
Chapel Hill, NC 27514

Kenneth Wu, M.D., Principal Investigator
ARIC Central Hemostasis Laboratory
Division of Hematology-Oncology
University of Texas Medical School
6431 Fannin
Houston, TX 77030

Appendix II. Organizational Chart of the Atherosclerosis Risk in Communities (ARIC) Study



[1] DX - Criteria and Diagnoses, EXM - Risk Factors and Clinic Operations; LAB - Laboratory and Sample Processing; SMC - Surveillance and Medical Care; SRF - Sampling, Recruitment and Follow-up; US - Ultrasound; MMCC - Morbidity and Mortality Classification Committee

Appendix III. ARIC Committee and Subcommittee Members

1. ARIC Study Steering Committee

Moyses Szklo, M.D., Washington County Field Center, Principal Investigator, Chairperson
Ralph Barnes, Ph.D, Ultrasound Reading Center, Director
Aaron Folsom, M.D., Minneapolis Field Center, Principal Investigator
Gerardo Heiss, M.D., Forsyth County Field Center, Principal Investigator
Richard Hutchinson, M.D., Jackson Field Center, Principal Investigator
Wolfgang Patsch, M.D., Central Lipid Lab, Principal Investigator
A. Richey Sharrett, M.D., ARIC Project Office, NHLBI
O. Dale Williams, Ph.D, Coordinating Center, Principal Investigator
Kenneth Wu, M.D., Central Hemostasis Lab, Principal Investigator

2. ARIC Study Policy Board

Richard Carleton, M.D., The Memorial Hospital in Pawtucket, RI, Chairperson
Stephen Fortmann, M.D., Stanford University School of Medicine
C. Morton Hawkins, Ph.D., University of Texas School of Public Health
William B. Kannel, M.D., Boston University School of Medicine
Karen Kaplan, M.D., Columbia University, Health Sciences Division
Ernst J. Schaefer, M.D., Tufts University, Human Nutrition Research Center on Aging
Jeremiah Stamler, M.D., Northwestern University Medical School
Marvin C. Ziskin, M.D., Temple University Medical School
Millicent Higgins, M.D., National Heart, Lung, and Blood Institute, Executive Secretary

3. Morbidity and Mortality Classification Committee

(The Morbidity and Mortality Classification Committee has not yet been appointed.)

4. Criteria and Diagnoses Subcommittee

Richard Hutchinson, M.D., University of Mississippi, Chairperson
Andrew Dannenberg, M.D., National Heart, Lung, and Blood Institute
Lars-Goran Ekelund, M.D., University of North Carolina
Linda Fried, M.D., Johns Hopkins University
Linda Goldman, M.D., University of Minnesota
James Toole, M.D., Bowman Gray School of Medicine

5. Laboratory and Sample Processing Subcommittee

Kenneth Wu, Ph.D., University of Texas, Chairperson
John Eckfeldt, M.D., Ph.D., University of Minnesota
Kenneth Lippel, Ph.D., National Heart, Lung, and Blood Institute
Wolfgang Patsch, M.D., Baylor College of Medicine
Robert Rock, M.D., Johns Hopkins University
Fredric Romm, M.D., Bowman Gray School of Medicine
A. Richey Sharrett, M.D., National Heart, Lung, and Blood Institute
Lloyd E. Chambless, Ph.D., University of North Carolina

6. Risk Factors and Clinic Operations Subcommittee

Gerardo Heiss, M.D., University of North Carolina, Chairperson
Aaron Folsom, M.D., University of Minnesota
Millicent Higgins, M.D., National Heart, Lung, and Blood Institute
Richard Hutchinson, M.D., University of Mississippi
Fredric Romm, M.D., Bowman Gray School of Medicine
Moyses Szklo, M.D., Johns Hopkins University
Melvyn Tockman, M.D., Johns Hopkins University
O. Dale Williams, Ph.D., University of North Carolina

7. Sampling, Recruitment, and Follow-Up Subcommittee

Aaron Folsom, M.D., University of Minnesota, Chairperson
Jane Bergsten, Ph.D., Research Triangle Institute
George Comstock, M.D., Johns Hopkins University
William Kalsbeek, Ph.D., University of North Carolina
Paul Sorlie, Ph.D., National Heart, Lung, and Blood Institute
Ann Toledo, Research Triangle Institute
Robert Watson, Ph.D., University of Mississippi

8. Surveillance and Medical Care Subcommittee

Aaron Folsom, M.D., University of Minnesota, Chairperson
David Conwill, M.D., University of Mississippi
Stanley Edlavitch, Ph.D, University of Minnesota
A. Richey Sharrett, M.D., National Heart, Lung, and Blood Institute
Moyses Szklo, M.D., Johns Hopkins University
H. A. Tyroler, M.D., University of North Carolina
O. Dale Williams, Ph.D., University of North Carolian
Janet Wittes, Ph.D, National Heart, Lung, and Blood Institute

9. Ultrasound Subcommittee

Ralph Barnes, Ph.D., Bowman Gray School of Medicine, Chairperson
Alan Berson, Ph.D., National Heart, Lung, and Blood Institute
Gene Bond, Ph.D., Bowman Gray School of Medicine
David Christiansen, Dr.P.H., University of North Carolina
Kenneth Cram, M.D., University of Minnesota
Gerardo Heiss, M.D., University of North Carolina
Seshadri Raju, M.D., University of Mississippi
Roger Saunders, M.D., Johns Hopkins School of Medicine
A. Richey Sharrett, M.D., National Heart, Lung, and Blood Institute