REACT

Rapid Early Action for Coronary Treatment

STUDY PROTOCOL

TABLE OF CONTENTS

I. PURPOSE AND OVERVIEW OF REACT

A. Study Goal

The goal of REACT (Rapid Early Action for Coronary Treatment) is to reduce patient delay time from onset of acute myocardial infarction (AMI) symptoms to contact with hospital-based emergency medical care. To accomplish this goal, REACT will implement a community-wide intervention program and evaluate its effects on delay time. REACT will also evaluate the impact of the program on medical care, utilization of emergency medical services, and AMI associated outcomes.

REACT is a four-year multi-center randomized controlled community trial in which 10 communities will receive a community-wide intervention program and 10 matched communities will serve as a comparison group. The study is a collaborative effort between five Field Centers, a Coordinating Center, and the National Heart, Lung, and Blood Institute.

B. Study Specific Aims and Other Objectives

The primary aim of REACT is to evaluate the effect of an 18-month community-wide intervention program on patient delay time from onset of symptoms suggestive of AMI to arrival at the hospital in patients admitted for possible acute cardiac ischemia and receiving a cardiac-related discharge diagnosis.

The secondary aims of REACT are to:

1. develop, implement, and evaluate the implementation of an 18 month multi-component community intervention program based on sound behavior change theory and consisting of four components: community organization, community education, professional education, and patient education.

2. evaluate the impact of the intervention program on factors hypothesized to be important influences on patient delay, including knowledge, attitudes, and skills of adult citizens, health care professionals, and patients about the symptoms of AMI, appropriate actions to be taken, and specific skills necessary for taking action at the time of acute symptom onset.

3. evaluate the effect of the intervention program on delay time from onset of AMI symptoms to arrival at the hospital (ED) in patients with AMI symptoms, including patients presenting to the Emergency Department (ED) with chest pain/discomfort, patients admitted for possible acute cardiac ischemia (rule-out MI, unstable angina, chest discomfort (or synonym)) and patients receiving 410/411 discharge diagnoses.

4. evaluate the effect of the intervention program on other delay time intervals, including, symptom onset to contact with emergency medical personnel (either EMS or acute ED), symptom onset to receipt of reperfusion treatment in patients receiving such treatment, and symptom onset to time of taking action.

5. evaluate the effect of the intervention program on medical care and health outcomes in patients with diagnosed acute cardiac ischemia, including receipt of thrombolytic therapy and other reperfusion therapy, AMI severity, in-hospital case fatality rates, length of hospital stay, and community-wide CHD mortality rates.

6. evaluate the effect of the intervention program on utilization of medical services, including 911/EMS and E.D. and hospital admissions.

7. evaluate the impact of the intervention program on delay time in subgroups by gender, age, and race/ethnicity.

REACT will also:

1. estimate the current national average delay time and its trends from onset of AMI symptoms to ED arrival, and to describe the distribution of delay times by race/ethnicity, gender, age, socioeconomic status, geography, and symptom pattern.

2. study differences among communities and among subgroups identified by race/ethnicity, gender, and age, in symptom presentation and outcomes of acute ischemic cardiac disease.

3. study hospital practices for thrombolytic and other reperfusion therapy, and describe the distribution of such treatment by patient race/ethnicity, gender, age, and socioeconomic status.

4. evaluate, amongst patients receiving thrombolytic and other coronary reperfusion strategies, the time-to-treatment effect on in-hospital case fatality rates overall and by subgroups identified by race/ethnicity, gender, age, socioeconomic status, and geography, controlling for AMI severity.

5. contribute to methods for measuring and analyzing delay time and its components in diverse population groups with suspected acute cardiac ischemia.

6. study factors associated with various phases of the delay interval as well as overall delay time, including situational characteristics (e.g., location during symptoms, presence of others, day of week, etc.).

7. study patterns of behavior, including patient actions such as self-care, in response to AMI symptoms.

8. determine the impact of the various program components on knowledge, attitudes, skills, and behaviors of the general public and patients with acute CHD.

9. examine the cost-effectiveness of the intervention program and its components.

C. Study Timeline

The overall timeline for REACT is shown in Figure 1. The first year of the study consists of study planning and development, including: final selection of communities based on common inclusion/exclusion criteria; formative development of the intervention program, and development of the study protocol, manual of operations, data collection forms, training materials, and data entry and management

system. Measurement training will occur during the first four months of year 02. In year 02, formative development of intervention components (methods and materials) will continue and baseline data collection will be conducted for four months in all study communities. Random assignment of communities within pairs will occur during baseline data collection, with knowledge of randomization limited to those with a "need to know" for the purposes of hiring and training intervention staff in appropriate locations. The intervention will be implemented in phases, beginning with community organization and professional education late in year 02 and followed by all four education components, including community organization, community education, professional education, and patient education in year 03. The final 9 months of the four years will be utilized for data clean-up and analyses.

D. Study Framework

A conceptual study framework of the hypothesized causal pathway from community intervention program to health outcomes is shown in Figure 2. The framework illustrates a multi-component community-wide intervention program influencing intermediate behavioral factors which result in decreased delay time in patients with acute cardiac ischemic events which, in turn, results in decreased morbidity and mortality. REACT will study each of the components illustrated in the framework. (The study design, not shown in this framework, is described in Section IV.)

The community intervention program is comprised of four interrelated components: community organization, professional education, patient education, and community education. Evaluation of the implementation of each of these four components is termed process evaluation. Process evaluation also includes assessment of similar educational programs in the control communities. Each of the four education components has specific objectives to be met as a result of intervention. Measurement and evaluation of those objectives is termed impact evaluation.

The primary outcome is delay time, defined as the time interval from onset of symptoms to hospital arrival in patients with confirmed acute cardiac ischemia (validated AMI or unstable angina). It is hypothesized that the intervention program will decrease this patient delay time. Delay time in other groups also will be examined. If the intervention is successful, utilization of the medical care system (911/EMS use, ED visits, and hospital admissions) will increase in patients with AMI symptoms.

As a result of a decrease in delay time in patients with acute cardiac ischemia, use of thrombolytic and other artery-opening and coronary reperfusion treatments should increase, and the time from symptom onset to definitive treatment should decrease. This should result in decreases in AMI severity and AMI in-hospital case fatality rates.

Major potential confounders and effect modifiers are also shown in Figure 2. Confounders are factors that we want to assure are comparable between the intervention and control communities because of previously seen associations with patient delay time.

Pair-matching and randomization of communities will aid in the control of potential confounders and their measurement will allow for adjustment to control for residual confounding. Effect modifiers are factors that we hypothesize may influence the effect of the intervention program. Their measurement will enable assessment of intervention effects in subgroups defined by these factors.

REACT STUDY TIMELINE

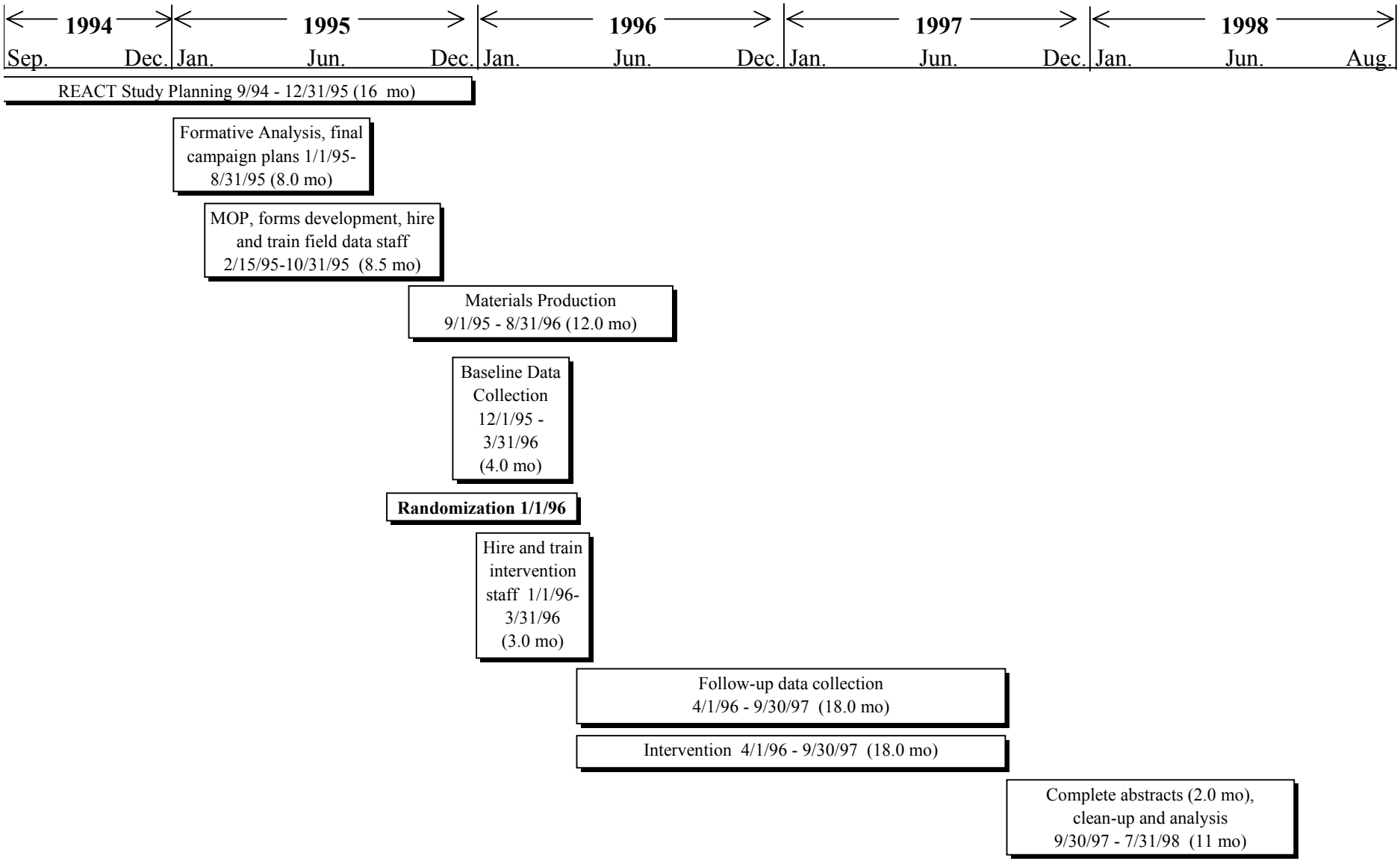
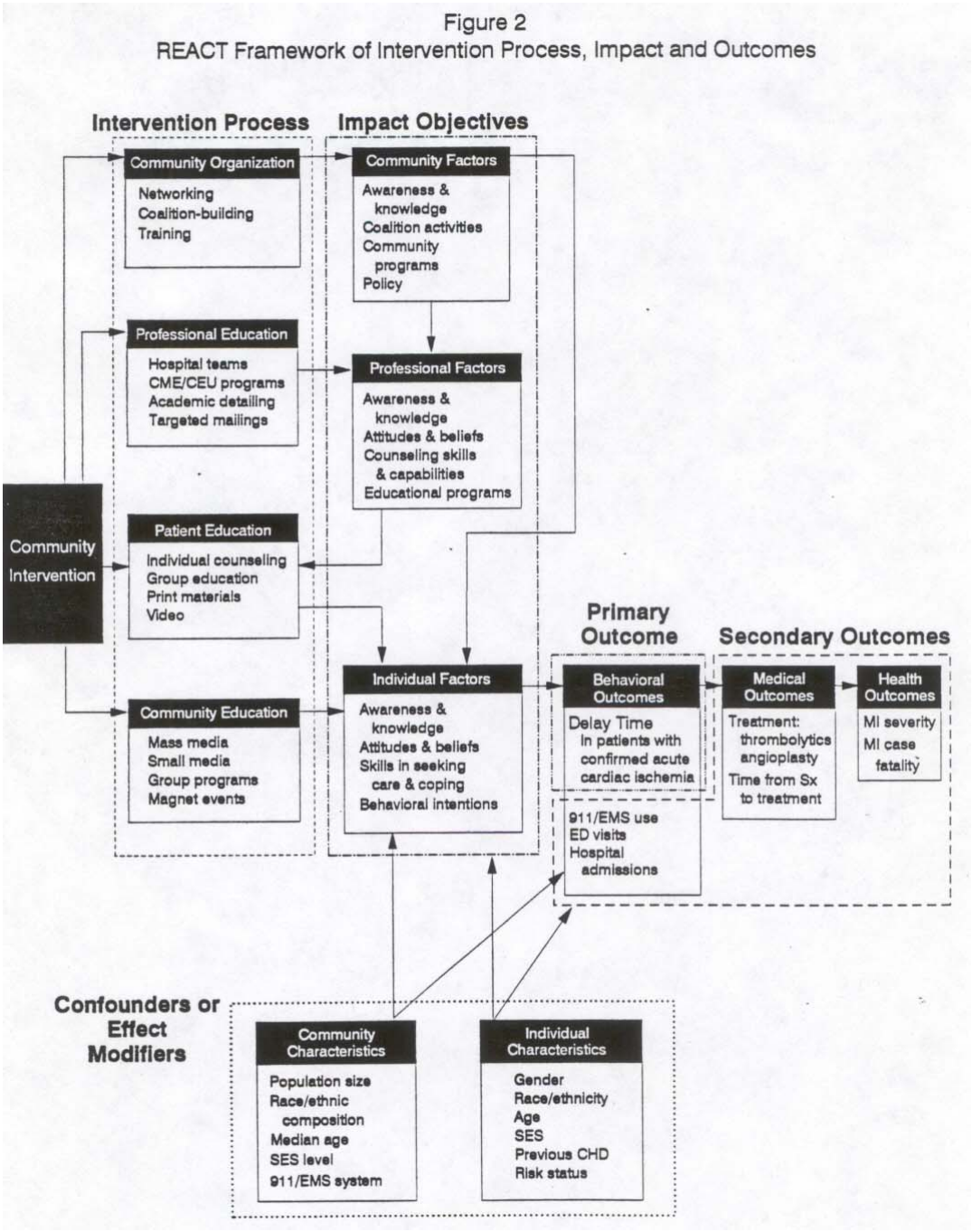


Figure 2

REACT Framework of Intervention Process, Impact and Outcomes



II. BACKGROUND AND RATIONALE FOR THE STUDY

A. Magnitude of Coronary Heart Disease Mortality and Morbidity

Despite declines in death rates from coronary heart disease (CHD) (1) and treatment and prevention advances (2), CHD remains the leading cause of death for all U.S. race/sex groups (3,4). An estimated 1.5 million Americans will have an acute myocardial infarction (AMI) in 1993, 500,000 will die, 300,000 of these deaths will occur out of hospital, and about one-half will occur suddenly within 1 hour of symptom onset (4-6). About 4 million persons in the United States have clinically manifest ischemic heart disease, half of whom are under age 65 (6).

High mortality and morbidity persist despite technological advances in treatment, including cardiopulmonary resuscitation and defibrillation for cardiac arrest; thrombolytic therapy, anticoagulation, aspirin, beta-blockade, and percutaneous transluminal coronary angioplasty (PTCA) for AMI; and anti-anginal medication, PTCA, and coronary artery bypass graft (CABG) for CHD (2). Considerable efforts have been expended to reduce major risk factors for primary prevention of atherosclerosis and prevention of CHD, and delivery and utilization of community-based emergency medical services and citizen CPR training have been used in the prevention of sudden coronary death.

B. Importance of Time to Treatment for Acute Myocardial Infarction

The minutes and hours from acute onset of AMI symptoms to receipt of medical care are critical for reducing morbidity and mortality. Early treatment by thrombolytic therapy holds particular promise. Thrombolytic treatment can decrease hospital mortality by 25-50% (7), with greatest benefit with earlier treatment (8-11). Pooled data from nine trials indicate that treatment from zero to 24 hours after symptom onset lowers short-term mortality rates, with the greatest reduction from treatment before six hours of acute CHD symptoms (12). In the first two hours following onset of symptoms, there is a steep decline in the curve of time to reperfusion versus benefit (13-15). Mortality reduction within the first two hours of symptom onset has been attributed to salvage of ischemic myocardium (14,16,17); mortality reduction seen with later treatment has been postulated to be due to improved healing of the infarcted area.

Evidence for the importance of time to treatment also comes from the MITI Trial, a multicenter study of pre-hospital vs. in-hospital thrombolytic therapy (13). Patients treated within 70 minutes from the onset of chest pain had a substantial reduction in left ventricle infarct size (4.9% vs. 11.4%) and in hospital mortality (1.2% vs. 8.7%) when compared with patients treated after more than 70 minutes.

C. Delay Time in Seeking Care

Despite the benefits of thrombolytic therapy, only 25-35% of AMI patients receive thrombolytics, (12,18-20), substantially lower than the estimated 51-62% of patients who are potentially eligible (21-22). A major contributing factor is substantial delay intervals from onset of symptoms to hospital arrival. Mean delay times range from 4.6 hours (23) to 21-24 hours (24) and medians range from two hours (25-27) to 6.4 hours (24). Because some individuals wait hours to days before seeking medical care, mean delay times are significantly longer than median delay times in all reported studies (24,26,28-31).

Delay has been considered as either a single overall period or segmented into phases. Six phases have been suggested by Alonzo (32): (a) the "prodromal" phase of initial health deviation to acute symptom onset, (b) the "definition" period of self-evaluation, from acute symptom onset to seeking lay consultation, (c) the "lay consultation" phase, from seeking lay advice to medical consultation or hospital transport, (d) the "medical consultation" phase, from the beginning of medical consultation to initiation of hospital travel, (e) the "travel" phase of transport to the hospital, and (f) the "hospital procedural" phase, from arrival at the hospital to treatment. The majority of the overall delay interval is attributed to the phases involving patient decision and action, with time of patient decision-making and action relatively long (27,29,33-37), and transit time relatively short (28,29,30,35,38-40).

A major objective of the NHLBI National Heart Attack Alert Program (NHAAP) is to educate health care professionals and institutions to reduce hospital-associated delays in delivery of thrombolytics and other appropriate therapies (41). At the same time, the delay time attributed to patient-associated factors outside of the hospital setting must be addressed to achieve reductions in the total delay interval.

D. Factors Associated with Patient Delay

1 Patient Characteristics

Older AMI patients delay longer than younger patients (25,26,35,37,42), although not always significantly (23,28,30,32,33,36,39,43,44). Sample size and methodological differences may account for inconsistencies, and when reconciled, data support longer delay among older patients (45).

Longer delays have been reported in women (25,37) for at least some phases of delay (32), although not consistently (16,35). In some studies, gender differences were not seen (23,28,29,30,33,36,42-44).

African Americans delay longer than whites in seeking care generally for AMI symptoms (16,24,39). A few reports have not found delay differences between races (25,44), but sample sizes were small. Longer delays among patients of color may stem from cultural factors (46) or lack of usual care provider, which has been associated with delay (47).

In countries with socialized health care, neither sociodemographic (43) nor urban/rural (30) characteristics have been associated with delay. Although limited by insufficient inclusion of low income patients, some U.S. studies have similarly reported no relationship between SES and delay (28,33,39,42). With more representative samples, delay has been associated with income (37), SES and insurance (47). Treatment cost is often cited as a reason for delay (37,47). Delay appears unaffected by occupational level (39) and education (23,25,30,33,35,48). In only one report did less well educated patients have shorter delays (44).

2. Medical History, Clinical Status, and Symptom Characteristics

History of prior CHD does not reduce delay and may actually increase delay (16,23,25-31,35,36,39,40,42,49-52). History of CHD risk factors also is associated with longer delay (25,35,37). Patients with Q-wave infarctions, and unstable hemodynamics have been reported to have shorter delay (25,31,42), although no relationship between MI size and delay has been reported (27). Patients with

confirmed AMI (25) and ST-segment elevations and/or Q-wave infarction (23,25) also have been reported to have shorter delays.

The influence of symptom severity is controversial, with two studies reporting no association (31,42) and several studies reporting shorter delays with more severe symptoms (43,50,53). Although an early report suggested no association of symptom characteristics and delay (36), a more recent report suggests shorter delays for "typical" AMI symptoms, such as chest pain (37). Other studies have found similar, but nonsignificant, shorter delays with typical AMI symptoms (35,50). Slowly developing symptoms are associated with increased delays (30,32,48), perhaps from self-treatment (32) and/or the attribution of symptoms to non-cardiac origins (37,47). Having previously experienced the same symptoms as cardiac-related has been associated with decreased delay (30).

Patients' beliefs that symptoms are cardiac in nature have been associated with shorter delays (28,34,35,43,49,50). Beliefs that symptoms would subside or were not serious have been related to increased delays (37,47). Believing that CHD is preventable is associated with reduced delays (34,49).

3. Behavioral and Environmental Factors

Being at home during symptom onset, traveling home after symptom onset, and having a spouse at home have been associated with increased delays (25,32,36). Being alone (32) and attempting to cope by oneself increase delay (30,33,54). Delay appears shortest when the decision to seek treatment is made by the patient (28,35). Family members are especially likely to increase delays (28,32,37,47) and may be more willing to support patients in self-treatment (32), which increases delay (25,30-32,39). Assistance by authoritative strangers produces the shortest delays (28).

Patients transported by EMS have shorter delays than those traveling by car (16,30,33,35,39). Patients who contact their physicians have increased delays (27,29,32,50). Patients' report of not wanting to disturb their physician is associated with increased delay, even among those believing that they were having fatal episodes (43).

E. Intervention Studies to Reduce Delay

1. Non-U.S. Intervention Studies

The earliest intervention study (55), conducted in Nottingham, England, consisted of an educational program to encourage early symptom reporting in over 13,000 men and women over age 40 registered with three general medical practices. Patients were instructed to telephone a special hospital number for chest pain lasting more than 10 minutes. Patients from three intervention practices reported chest pain earlier than patients in 10 comparison practices. There was a lower percentage of definite and probable AMIs among the calls received by the special phone line than calls received by the patients' own doctors, implying that patients did call earlier but were more likely to call their own physician than the special number. The study included a comparison group which was selected by convenience rather than through a randomized design.

A study in Canada employed an eight-week television and radio campaign ("Signals and Actions") to emphasize two concepts: symptoms of a heart attack can be recognized, and it is important to seek immediate professional help (56). A higher

percentage of patients presented to the ED within two hours after symptom onset, increasing from 16% to 29% pre-to-post-campaign. Delay time decreased in men during and after the campaign, but increased in women.

A public education media campaign was conducted in Australia three times for one week each, in 1975, 1985, and 1989 (57,58). The percentage of patients admitted to a coronary care unit within four hours of symptom onset increased from 40-50 percent to about 55 percent after the first two media weeks. The effects dwindled after the campaign was discontinued. The third week resulted in no decreases in patient delay.

A six-month community-wide media campaign was conducted in Heidelberg, Germany, which employed mass media, including posters, newspapers, and radio- and TV-spots (59). From pre-to-post intervention, hospital admissions within four hours of symptom onset rose from 48 to 81 percent, and median delay time decreased from four hours to 3.2 hours.

A one-year media campaign was conducted in Geneva, Switzerland, using television, radio, newspapers, posters, and leaflets (60). During the first week, hospital visits for chest pain due to cardiac disease increased by 145%, and chest pain due to non-cardiac causes increased by 210% (both significant). At six months, the increases from baseline were 27% for cardiac ($p<0.02$), and 17% for non-cardiac (NS). Thrombolysis rates increased, but not significantly.

The largest and most well-reported study was conducted in Göteborg, Sweden (61,62). Mass media was used to educate the general population and patients to dial an emergency number to call for an ambulance for chest pain lasting longer than 15 minutes. A three-week intensive media campaign was followed by a maintenance phase of one year, primarily using print materials. A catchy and rhythmic slogan, "Hjarta-Smarta-90000", was used, the primary intent of which was to enable individuals to remember the message and the emergency number. Institution of a special telephone number for dispatch of ambulances for chest pain was combined with the media campaign. For patients with confirmed AMI, median delay time was reduced from three hours to 2 hours-20 minutes, and the distribution of delay times shifted significantly downward. The percentage of AMI patients who received thrombolysis increased, and the estimated infarct size was reduced significantly (63). Although hospital mortality was not affected, the study met other criteria for success, including 66% of the community aware of the campaign, a 6% increase in patients presenting within six hours of symptom onset, and a 9% increase in use of thrombolysis. Infarct size and number of patients developing ventricular fibrillation also were reduced. During the first week of the campaign, there was a marked increase in the number of patients with chest pain arriving at the ED, with the greatest increase observed in those in whom AMI was not suspected; the number of these patients decreased after the first week (62).

2. U.S. Intervention Studies

A two-month public education campaign in Seattle, WA, was carried out in collaboration with the local American Heart Association affiliate (64). The primary messages of the campaign, which used print media and radio and television public service announcements, emphasized the symptoms of AMI, the importance of acting quickly in response to symptoms, and the need to call 911 to activate the EMS

system. Median time from symptom onset to ED arrival decreased from 2.6 hours to 2.3 hours, with no change in the number of patients who arrived within two hours. There was a significant increase in the proportion of patients who heard new information on AMI, but no change in EMS use.

One study was carried out in a rural setting in Jacksonville, Illinois (65). The intervention used patient education brochures, television and newspaper advertisements, posters, radio spots, and talks to the general public, extensively utilized during the first two months of the two year program, followed by the intermittent delivery throughout the remainder of the study. There was a statistically nonsignificant increase in the number of ED visits during the three-year study and no change in time from onset of symptoms to ED arrival.

Currently, Eisenberg et al. in King County, Washington are investigating the effects of mass media and household mailings to residents over 50 years of age and targeted interventions to high-risk patients in an educational campaign called "Call Fast, Call 911." The attempt is to reduce the time between symptom onset and presentation to the ED and to increase the percentage of individuals calling 911. The campaign consisted of television and radio advertisements broadcast over a six-week period during programs aimed at the target group, and included both information and emotional barriers. The interventions began in December, 1991 and continued for 12 months. The proportion of patients experiencing AMI symptoms who called 911, visited EDs, and were admitted to coronary care units increased significantly (66).

A direct mail campaign to households with people age 50 and over followed the television and radio campaign. Households received six brochures over 12 months emphasizing benefits of quick and appropriate action for heart-related symptoms. Preliminary results of a post-intervention telephone survey of 432 subjects indicated that individuals receiving the informational or emotional brochures had greater intentions to call 911 for chest pain than individuals who received the social brochures or did not receive any brochures. Individuals who remembered one or more of the brochures were more likely to report coping strategies for chest pain compared with people who did not recall receiving a brochure (67). Additional analyses are underway.

3. Assessment of State of Intervention Research

Although the interventions used in the community-based studies conducted to date have been promising, the studies must be considered preliminary. Most had limited internal validity because the effects were measured pre-to-post intervention, without a control or comparison group, which makes it difficult to distinguish the magnitude of the effect from confounding factors or secular trends. The studies had few communities and small numbers of individuals with AMI symptoms. Few examined the effect of the interventions on the receipt of thrombolytic therapy or the impact on AMI associated case fatality, and few reported the effects on EMS or ED utilization. Most of the interventions were limited in duration and scope and relied on public education using mass media, and most were not tailored to those more likely to have an AMI nor had strong underpinnings in behavior change theory. In addition, most of the studies were conducted in countries other than the U.S. where there are quite different healthcare systems.

The studies do, however, indicate the promise of community educational interventions to reduce delay time, and they provide insights into approaches that might be utilized in an effective population-based educational program. Reductions in delay times have been variable, but 40- to 48-minute reductions in median delay times have been achieved (59,63).

F. Rationale for REACT

The importance of early treatment of evolving AMIs to reduce morbidity and mortality has been shown. There is strong evidence that many people experiencing AMI symptoms delay seeking treatment and that patient delay is the major contributor to pre-hospital delay. A variety of factors have been examined in association with delay time with no clear-cut profile of those most likely to delay delineated. Community interventions to reduce delay have shown promise. Thus, the research base is now present to justify a large-scale controlled study of community-based educational approaches to reduce MI delay. REACT will address this research need by assessing the effects of a multi-component, community-based, educational intervention to reduce pre-hospital delay with a sufficiently large and geographically representative sample of U.S. communities.

III. STUDY ORGANIZATION

REACT is a collaborative study supported by cooperative agreements from the National Heart, Lung and Blood Institute (NHLBI). The participating institutions and governance structure of the study are described below.

A. Participating Institutions

The REACT study is being carried out by five participating study centers, a Coordinating Center, and the NHLBI project office. The Study Centers are as follows:

1. University of Alabama at Birmingham, Birmingham, AL
2. University of Massachusetts Medical School, Worcester, MA
3. University of Minnesota, Minneapolis, MN
4. University of Texas Health Science Center at Houston, Houston, TX
5. University of Washington, Seattle, WA and Oregon Health Sciences University, Portland, OR

The Coordinating Center is New England Research Institutes (NERI) located in Watertown, MA.

The Project Office is located in the Division of Epidemiology and Clinical Applications (DECA), National Heart, Lung and Blood Institute, Bethesda, Maryland. Biostatisticians are part of the Project Office and a Grants Management Specialist works closely with the Project Scientist regarding policies and procedures related to fiscal matters. The NHLBI Project Scientist serves as a direct link between REACT investigators and the Director of NHLBI. The NHLBI Office of Prevention, Education, and Control (OPEC) is also involved in the development of this project.

B. Governance Structure

1. Steering Committee

The REACT study is governed by the Steering Committee, consisting of the Principal Investigator (P.I.) from each of the five Study Centers, the Principal Investigator of the Coordinating Center, and the NHLBI Project Officer. The chair of the Steering Committee is elected by the Steering Committee. The chair serves as spokesperson for the study, develops agendas for and chairs Steering Committee meetings and conference calls, works closely with the Coordinating Center P.I. and the Project Officer on day-to-day matters, and attends DSMB meetings as the study representative. Each member of the committee has one vote. If a member of the Steering Committee is not present at a meeting, that center's vote may be delegated to another investigator from that center. All study protocol decisions are made through Steering Committee consensus or, if necessary, a Steering Committee vote. A motion or proposal can be passed by simple majority; in case of a tie, the motion will be tabled for repeat consideration at the next meeting or conference call.

The Steering Committee will meet regularly, as needed for the first year, to direct the development of the study protocol and manual of operations, and to review and approve all major design, intervention, and measurement aspects of the study. The

Steering Committee is the decision-making body for all scientific aspects of the study, including the study design, interventions, and measurements. It can seek advice from the DSMB or NHLBI regarding a Study Center or the Coordinating Center if they do not appear to be carrying out REACT activities satisfactorily.

2. Subcommittees

There are four major subcommittees for the REACT study as follows: Design and Analysis Subcommittee, Measurement and Quality Control Subcommittee, Intervention Subcommittee, and Publications and Ancillary Studies Subcommittee. The chair of each subcommittee is a Principal Investigator from a study center and is elected by the Steering Committee. For all subcommittees, at least one representative from each study center, one representative from the Coordinating Center and one representative from NHLBI is a member. The responsibilities of each subcommittee are outlined briefly below:

a. *Design and Analysis Subcommittee*

(1) Develop the study design

(2) Determine the primary and secondary outcomes for the study

(3) Estimate Sample Size and Power for the specified effects and determine a sampling scheme, if needed

(4) Develop the analytical methods for evaluating the specified study hypotheses.

(5) Review and advise on all proposed ancillary studies and substudies

b. *Intervention Subcommittee*

(1) Determine a behavioral theory model for the intervention

(2) Define the intervention components and strategies

(3) Develop standardized intervention materials

(4) Develop a standard intervention approach for all communities

(5) Define and develop process and impact evaluation

c. *Measurement and Quality Control Subcommittee*

(1) Define the primary endpoint of delay time

(2) Determine subject eligibility criteria and methods for identifying subjects

(3) Develop and standardize the data collection instruments designed to measure primary and secondary trial outcomes, as well as impact measures.

(4) Determine the training required for all data collectors

(5) Develop quality control protocols for all data collection methods

d. *Publications, Presentations, and Ancillary Studies Subcommittee*

(1) Develop the study publication policy

(2) Review and approve all publications, presentations and ancillary studies proposed by investigators that relate to data collected through REACT

(3) Assure accurate and timely presentation of pertinent information from REACT to the scientific community

(4) Assure that all REACT investigators have the opportunity to participate in the presentation and publication of study wide data.

3. Working Groups

Specific tasks are assigned by the subcommittees to working groups, as the need for such are ascertained. Three working groups were created by the Intervention Subcommittee to develop the major components of the intervention. The Process Evaluation and Impact Working Group combined members from the Intervention and Measurement Subcommittees.

a. Community Organization Working Group

b. Community Education Working Group

c. Patient and Provider Education Working Group

d. Process and Impact Evaluation Working Group

4. Protocol Review Committee/Data and Safety Monitoring Board

The Protocol Review Committee (PRC) and Data and Safety Monitoring Board (DSMB) are advisory to NHLBI and are convened by NHLBI, independently of the REACT investigators. The PRC has six members with expertise in the areas of Clinical Cardiology, Emergency Medicine, Behavioral Sciences, Epidemiology, Biostatistics and Clinical Trials. It is the responsibility of this committee to review the study protocol developed by the REACT investigators, suggest revisions, if necessary, and recommend approval to NHLBI. After review and approval of the REACT study protocol, the DSMB for the study will be formed consisting of former PRC members. The DSMB will oversee the study in terms of safety, ethics, data quality and science. The DSMB will be convened at least once each year. Presentations to the DSMB will be made by the Chair of the Steering Committee, the NHLBI Project Officer, and other individuals proposed by the Project Office or requested by the DSMB. The NHLBI Project Officer, Steering Committee Chairman, and Coordinating Center Principal Investigator are ex-officio members of the DSMB. An NHLBI staff member, generally the Project Officer, will serve as Executive Secretary.

IV. STUDY DESIGN

A. Experimental Design

An experimental design will be used consisting of 10 matched pairs of communities selected and recruited by field-site investigators. This has proved to be an efficient, workable design in other multi-center investigations such as the COMMIT study of smoking cessation. Each Field Site will study four communities, organized into two pairs and matched according to relevant criteria. The inclusion of ten pairs provides adequate statistical precision and power given the size of the expected effect and the expected number of events to be observed in each community.

In each community, the emergency department logs of study hospital(s) will be retrospectively monitored by the measurement staff throughout the trial for patients presenting to the Emergency Department with symptoms of acute CHD, specifically chest pain, pressure, tightness and/ or discomfort. An initial four-month period will serve as the baseline. The random assignment to intervention of one community from each pair will be made at the beginning of the second month of baseline data collection to allow for the hiring and initial training of intervention personnel. Knowledge of the randomization status will be limited to those who have a "need to know" for the purposes of hiring and training personnel. Randomization status will be made public at the end of the baseline period.

The principal endpoint is delay time. Covariates and ancillary endpoints to be measured will include sociodemographics, medications, procedures, IHD severity and mortality, and health care utilization. Additional process and impact measures will be collected to document the implementation and penetration of the intervention and the achievement of intervention objectives.

The primary hypothesis to be tested is that the median delay time will decrease in the intervention communities relative to their respective comparison communities. This hypothesis will be tested in such a way as to control for the influence of secular trends, which might affect the delay times in comparison cities as well as intervention cities.

B. Randomization

Community pairs were selected such that either community would be appropriate to receive the intervention. Responsible persons in each community, including hospital administrators, ED staff, EMS Directors, and cardiologists understand that they may or may not receive the intervention. The randomization will be carried out by the Coordinating Center in a two-stage process similar to that of COMMIT. A computer-based pseudo-random number generator will be used to make the random assignment within each pair, with one community labeled "red" and the other "black." A second random assignment will determine whether "red" or "black" communities are to receive the intervention. This two-stage randomization serves to negate the effect of any flaws or tampering that may occur at either stage and adds credibility to the process. The nature of the intervention makes blinding impossible; all members of the study staff and concerned individuals in the communities will know whether or not the intervention is being implemented. It is therefore critical that intervention staff be separated from measurement staff in order to minimize bias.

C. Community Selection and Matching Criteria

1. Community Selection Criteria

Communities were selected so as to have sufficient population to provide an adequate number of patients hospitalized for acute ischemic heart disease required to achieve 80% statistical power for detecting a 30-40 minute net reduction in median delay time. All communities have hospitals whose catchment areas, when considered together, include the boundaries of the community. All communities have local media channels available for use in the intervention and have either basic or enhanced 911 service and Emergency Medical Services.

Within and across pairs, communities were selected to minimize media overlap and therefore, contamination. Whereas, it is impossible to completely insure that media coverage of local intervention events will not spread to comparison sites (e.g., via the Associated Press wire service), the process of community selection has attempted to minimize the potential for such contamination. Contamination of the comparison communities will be monitored through process and impact evaluation measures.

In addition, the following factors were considered:

a. *variability among Field Sites* - greater variability will provide for better generalizability for the primary and secondary trial outcomes; and

b. *homogeneity within pairs of communities on key characteristics* - homogeneity will provide a more efficient design by reducing within-pair community variability.

The variability of populations across community pairs is demonstrated by the geographic distribution of the Field Sites and the race/ethnicity diversity of the populations. A major goal of community selection was to approximate the sex and race/ethnicity distributions in the U.S. population and to provide geographic distribution across the U.S. See Section VI. for a description of community characteristics.

2. Community Matching Criteria

The use of a pair-matched design in this trial has the potential to considerably reduce between community variation - especially as the total number of communities will not be large. However, the problems of over-matching as well as ineffective matching have been well-documented (68,69). Moreover, as shown from recent estimates (71), the between community component of total variation is remarkably small - even among seemingly very different communities. Therefore, the pair-matching criteria were kept as relevant and as few as possible as follows.

a. *Size of community:* This will largely determine the number of hospital facilities, the organization of emergency medical services, and the media channels available for intervention.

b. *Sociodemographic variables*: age, race/ethnicity, sex, median income, and educational attainment are important in estimating the baseline rate of acute IHD as well as the probable response to intervention. The inclusion of matched pairs with substantial minority populations will improve the generalizability of the results.

As shown in Table 1: Community Characteristics, paired communities are very similar with respect to population, age, race/ethnicity, sex, and socioeconomic status.

D. Hospital Inclusion Criteria

The goal of our hospital inclusion criteria is to maximize the catchment of patients from the study communities with acute ischemic heart disease while enabling us to maintain quality assurance and manage study resources efficiently. *Specifically, all hospitals that provide care to patients from the study community with acute IHD will be included, as is practical. Pediatric, psychiatric, rehabilitation, convalescence hospitals, and hospitals without emergency departments will be excluded.*

Two special situations deserve specific comment.

1. Hospitals within the study communities with small market shares for the treatment of MI patients. If a Field Site P.I. requests to exclude a small market share hospital, the PI must show conclusively that minority representation will not be adversely affected and, furthermore, that the expected number of events at that hospital is so low (no more than 10% of community MI patients) as to make data collection quality assurance difficult. Hospitals that traditionally provide care to minority populations will not be excluded. Investigators proposing to exclude a hospital will provide data regarding MI patient market share and the race/ethnicity and sex composition of the hospital population to the Design and Analysis Subcommittee for consideration.

2. Other hospitals near, but not in the study community, which provide care to MI patients who experience their events while away from their home community. In these hospitals, many MI patients from outside the study community would need to be enrolled in order to capture a few MI patients from the study community. This issue is more challenging for those investigators who are studying a suburban community near a larger metropolitan area. Nevertheless, the study benefits from the inclusion of urban and suburban communities as this leads to greater generalizability of study results. Therefore, Field Centers proposing the exclusion of such hospitals will provide information to the Design and Analysis Subcommittee regarding the extent of this challenge. Specifically, this information shall include, the percentage catchment of MI patients by individual hospitals within and outside, but near, the study community.

In any case as described above, exclusion or inclusion of a hospital that falls under one of these special situations will be considered on a case-by-case basis. The Design and Analysis Subcommittee will first make a recommendation to the Steering Committee. The Steering Committee will then make the final decision as to the inclusion or exclusion of hospitals.

All of the study investigators have extensive experience recruiting and maintaining hospital participation in large-scale studies and will take all possible measures to prevent attrition from occurring (including periodic hospital visits for updates and feedback). We will work with the individual hospitals to anticipate and respond promptly to any unforeseen challenges that might arise. Hospital administrators are typically "good citizens" and support this type of altruistic endeavor as consistent with and supportive of the hospital's mission. The visible support of

other community leaders and organizations will serve to reinforce continued hospital participation.

E. Case Inclusion Criteria

Patients will be eligible for inclusion in this study who meet the following criteria:

1. Age ≥ 30 years (acute cardiac ischemia is uncommon at younger ages),
2. Residence within one of the study communities as defined by zip code of residence,
3. Not institutionalized (i.e. nursing homes, prisons, or chronic care facilities)
4. Not a transfer from a non-participating hospital, and
5. Presenting complaint of chest discomfort, with no obvious source of trauma, during initial evaluation in the ED of a participating hospital.

In addition to the above criteria, the primary population for the study will be those patients who are admitted to the hospital for possible acute ischemia and receive an ICD discharge code indicating a cardiac-related diagnosis. We will include all such patients irrespective of a previous history of MI. Since previous findings are consistent with the idea that patients with a history of CHD delay longer than those without such a history, we will examine this issue as an a priori subgroup hypothesis.

F. Primary Outcome

The primary specific aim of the study is to evaluate the effect of an 18 month community-wide intervention program on patient delay time from the onset of symptoms of acute IHD to arrival at the hospital in patients admitted for possible acute ischemic cardiac events who receive a cardiac-related diagnosis. This group is most readily identified as patients who are seen in the ED for chest pain, admitted with rule-out MI, unstable angina, or chest discomfort (or a synonym), and receive a cardiac-related discharge diagnosis (ICD 410-414, 427, 428, 429, 440, 786.5) .

This group of patients was chosen as the population for the primary analysis for several reasons. First, this group includes those patients who will benefit most from a reduction in delay time by virtue of faster receipt of medical services. Hence, the presence of a reduction in delay should be established in this group, rather than in the larger group of patients that also includes those who have non-cardiac causes of their symptoms. Second, patients with cardiac diagnoses will be more stable across communities and over time than the larger group of patients who present to the ED or who are admitted with symptoms suggestive of acute IHD. Third, patients with cardiac diagnoses will be identified more uniformly and consistently across Field Sites and over the study period. Fourth, sufficient numbers are expected for the purposes of statistical precision and power to adequately examine differences in the primary trial outcomes between intervention as compared to control communities.

A 30-40 minute net reduction in median delay time is considered to be a clinically meaningful intervention effect; thus, in the primary analysis, we will examine delay time as a continuous variable. However, it is also important to increase the percentage of patients who arrive at the hospital within six hours of onset of acute

symptoms, early enough to be treated within the optimal window for receipt of thrombolytic therapy or immediate PTCA. Thus, we will also examine delay time classified as a dichotomous variable (i.e. the proportion of cases delaying < six hours vs ≥ six hours).

G. Secondary Outcomes

The following secondary outcomes will be measured and analyzed. The definition and measurement of each outcome is described in Section VII.

1. Secondary Populations and Subgroups

a. The primary intervention effect will be examined among *patients with diagnosed MI.* Since this subgroup includes the vast majority of patients eligible for thrombolytic therapy and/or immediate PTCA, we will examine the intervention effect on their prehospital time delays.

b. The primary intervention effect will be examined in patients seen in the ED for chest pain and admitted for possible acute ischemia. These patients have been identified by physicians as warranting further diagnosis and/or treatment, and they are targets of the intervention.

c. The primary intervention effect will be examined in patients seen in the ED for chest pain/discomfort and sent home. Since the intervention messages focus on chest pain, these patients are also targets of the intervention.

d. The primary intervention effect will also be examined in subgroups defined by factors associated with delay that might affect the effectiveness of the intervention. These are sex, race/ethnicity, age, history of previous CHD, health insurance coverage, and current event (AMI vs. unstable angina vs. other cardiac diagnoses).

2. Secondary Definitions of Delay Time

Since the different components of the delay interval may be affected differentially by the intervention, alternative definitions of delay time will be examined. We hypothesize that all delay times will be reduced by the intervention. The following definitions will be offered:

a. Time from onset of acute symptoms to taking action to seek care (e.g., time of calling 911) because this reflects patient recognition and action.

b. Time from onset of acute symptoms to in-person contact with the medical care system (either the ED or the EMS) because this reflects time to contact with any available treatment.

c. Time from onset of symptoms to receipt of reperfusion therapy (thrombolytic therapy or immediate PTCA) among those who receive such therapy.

3. Secondary Outcomes

We will examine the effect of the intervention on the following outcomes:

a. Receipt of early revascularization in patients with IHD diagnosis (ICD 410/411): thrombolytic therapy or immediate PTCA.

   Receipt of myocardial revascularization procedures, reperfusia or artery opening therapy is hypothesized to increase because earlier arrival will increase the proportion of patients who are eligible for treatment.

b. Severity of infarction (e.g., peak CPK, peak LDH) in patients with AMI diagnosis (ICD 410)

   Severity of infarction is hypothesized to decrease because earlier treatment will reduce infarct size.

c. In-hospital case-fatality rates in patients with cardiac diagnoses.

   Case fatality is hypothesized to decrease because earlier treatment will reduce infarct size and improve survival.

d. Duration of hospitalization in patients with cardiac diagnoses.

   Duration of hospitalization will be reduced.

e. Total community CHD mortality.

   Total community CHD mortality is hypothesized to decrease because earlier arrival will reduce pre-hospital mortality and earlier treatment will reduce in-hospital mortality.

f. Number of EMS calls (911 calls) for chest pain/discomfort.

g. Number of ED visits for chest pain/discomfort.

h. Number of patients dismissed to home from the ED with presenting complaint of chest pain/discomfort ("false positives").

i. Number of patients admitted to the hospital for evaluation of chest pain/discomfort.

j. Number of patients discharged with diagnosed acute IHD ("true positives").

   Utilization of health care services (f.-j.) is hypothesized to increase because the public will be made aware of chest discomfort as a symptom of AMI and sensitized to using the ED for rapid early evaluation. This increased utilization will result in increased numbers of false and true positives. The magnitude and time course of any increases will be estimated from baseline data.

Table 1. Community Characteristics

Project Site	Study Community	Population Total (1990)	Area (sq. miles)	Median Hshld Income	Per Cap. Income	Gender (% Male)	Median Age (Years)
AL	Anniston, AL	115,432	611.0	$28,340	$13,776	51.4	33.6
	Opelika, AL	89,714	609.0	$32,596	$13,470	47.6	26.8
	Huntsville, AL	238,912	806.0	$39,264	$18,990	49.2	31.5
	Tuscaloosa, AL	154,131	1336.0	$30,135	$13,886	48.1	31.5
MA	Worcester, MA	169,759	38.6	$28,955	$13,393	47.6	31.8
	Lowell, MA	103,439	14.5	$29,351	$12,701	48.7	29.4
	Pittsfield, MA	48,622	40.7	$29,987	$15,426	47.5	35.7
	Dalton, MA	7,155	21.9	$36,518	$17,061	48.1	35.7
	Westfield, MA	38,372	46.6	$33,489	$14,225	47.5	32.7
	West Springfield, MA	27,537	16.8	$32,194	$15,905	48.2	35.8
TX	Brownsville, TX	98,962	28.0	$15,890	$6,284	47.2	25.9
	Laredo, TX	122,899	33.0	$18,395	$6,981	47.8	25.9
	Tyler, TX	75,450	41.0	$23,661	$13,400	47.0	32.5
	Lake Charles, LA	70,580	32.0	$21,225	$11,475	47.2	32.1
MN	Sioux Falls, SD	123,809	809.0	$29,764	$13,345	48.1	31.5
	Fargo, ND & Moorhead, MN	153,296	2811.0	$26,551	$12,449	49.2	29.9
	La Crosse, WI	97,904	453.0	$26,857	$12,141	48.0	31.1
	Eau Claire, WI	137,543	1648.0	$25,876	$11,560	48.4	31.5
WA	Eugene, OR	112,669	39.1	$25,369	$13,886	48.1	32.2
	W. Portland, OR	87,594	35.5	$36,253	$15,645	48.6	31.2
	Olympia, WA	69,156	37.5	$28,686	$14,700	47.4	34.2
	Shoreline, WA	126,647	32.6	$36,258	$18,279	48.1	36.2
Mean value for all communities				$28,844	$13,116	48.1	31.8
Mean value for U.S. based on 1990 census				$29,943	$15,898	48.8	32.8

* 2 Matched pairs for each site are separated by shaded lines.
** Dotted lines indicate 2 towns which represent one study community.

Table 1 cont.

		Ethnicity (%)						Age Categ. (%)			
Project Site	**Study Community**	White	Black	Hispanic *	Am. Indian	Asian/ Pacific Isl.	Other	0-19	20-29	30-54	55+
AL	Anniston, AL	79.2	18.4	1.0	0.3	0.7	0.4	29.0	16.0	33.0	22.0
	Opelika, AL	74.1	23.3	0.6	0.1	1.8	0.1	29.0	27.0	29.0	15.0
	Huntsville, AL	77.1	20.1	1.3	0.7	1.2	0.3	25.0	15.9	34.0	16.3
	Tuscaloosa, AL	72.2	26.0	0.6	0.2	0.8	0.2	29.0	20.0	31.0	20.0
MA	Worcester, MA	87.1	4.5	9.6	0.3	2.8	5.3	26.8	19.9	29.2	24.0
	Lowell, MA	81.1	2.4	10.1	0.2	11.1	5.3	28.0	23.7	28.9	19.4
	Pittsfield, MA	96.5	3.1	1.1	0.2	0.8	0.4	25.2	15.6	32.0	27.2
	Dalton, MA	99.0	0.4	0.6	0.1	0.4	0.1	28.5	12.3	35.2	23.9
	Westfield, MA	96.0	1.0	4.0	0.1	0.6	1.2	28.2	17.5	32.6	21.7
	West Springfield, MA	98.2	1.3	2.7	0.1	1.1	1.3	23.6	15.8	34.5	26.1
TX	Brownsville, TX	9.2	0.2	90.1	0.1	0.3	0.1	40.7	15.5	28.2	15.6
	Laredo, TX	5.4	0.1	93.9	0.2	0.4	0.0	40.0	16.8	28.4	14.8
	Tyler, TX	62.1	28.2	8.9	0.3	0.5	0.0	29.3	16.7	30.8	23.2
	Lake Charles, LA	56.6	41.6	1.1	0.3	0.4	0.0	30.7	15.8	30.9	22.6
MN	Sioux Falls, SD	97.3	0.6	0.5	1.2	0.7	-	30.0	17.2	33.5	19.3
	Fargo, ND & Moorhead, MN	97.4	0.3	1.1	1.0	0.8	-	28.6	21.0	33.8	16.6
	La Crosse, WI	96.1	0.5	0.7	0.5	2.8	-	29.2	20.0	31.4	20.4
	Eau Claire, WI	97.3	0.3	0.4	0.5	1.8	-	30.4	17.2	31.4	21.0
WA	Eugene, OR	93.4	1.3	2.7	0.9	3.5	0.9	26.5	22.9	31.4	19.2
	W. Portland, OR	90.0	0.9	3.5	0.6	7.2	1.4	30.4	16.8	39.6	13.2
	Olympia, WA	90.5	2.1	3.1	1.20	5.2	1.0	26.5	15.9	35.2	22.5
	Shoreline, WA	86.0	2.2	2.7	1.0	9.8	.9	23.7	14.4	37.9	24.1
	Community Mean	79.1	8.1	10.9	0.5	2.3	1.1	29.0	17.2	32.2	21.7
	U.S. Population Mean	80.3	12.0	8.9	0.7	2.9	1.0	28.8	16.3	33.9	20.9

***Persons of Hispanic origin may be of any race**

Table 1 cont.

Project Site	Study Community	Education (25+ yrs old) % HS Grad.	Education (25+ yrs old) % Col. Grad.	# of Eligible Hospitals	Total # of Hospital Beds	Expected # of Eligible Cases (22 months) ICD 410**	Expected # of Eligible Cases (22 months) ICD 411**	Expected # of Eligible Cases (22 months) ED (Chest Pain)***
AL	Anniston, AL	67.4	14.2	1	283	472	472	3934
	Opelika, AL	73.2	25.3	1	324	501	501	4217
	Huntsville, AL	80.2	30.1	1	578			
	Tuscaloosa, AL	69.6	20.0	1	538	367	367	3447
MA	Worcester, MA	74.7	18.9	3	1206	818	975	N.A.
	Lowell, MA	67.9	14.0	2	558	398	307	N.A.
	Pittsfield, MA/	78.1	19.2	2	445	202	231	N.A.
	Dalton, MA	85.8	22.0	0	-	32	39	N.A.
	Westfield, MA	78.7	19.3	1	111	143	129	N.A.
	West Springfield, MA	81.0	19.2	3	1148	110	200	N.A.
TX	Brownsville, TX	45.5	12.2	2	339	293	440	2420
	Laredo, TX	48.8	11.6	2	380	293	440	2420
	Tyler, TX	77.1	24.7	3	910	220	330	1833
	Lake Charles, LA	69.4	18.4	4	747	220	330	1833
MN	Sioux Falls, SD	83.2	29.2	2	883	414	414	2270
	Fargo, ND & Moorhead, MN	85.1	35.9	3	727	517	517	2810
	La Crosse, WI	82.5	30.4	2	750	328	328	1795
	Eau Claire, WI	79.5	25.1	3	804	461	461	2522
WA	Eugene, OR	88.6	34.9	2	470	443	527	2235
	W. Portland, OR	90.6	29.1	2	551	346	294	2064
	Olympia, WA	88.3	28.9	2	490	202	186	1485
	Shoreline, WA	89.3	33.1	2	468	231	213	1697
	Community Mean	67.6	22.9					
	U.S. Population Mean	77.6	21.3					

**ICD Discharge Code.

***** Patients Presenting at EDs with Chest Discomfort.**

N.A. equals not available

V. INTERVENTION

A. Introduction

The study framework described in Section I. shows an overview of the components of the proposed intervention, as well as the factors upon which we hypothesize that we will impact and outcomes that we hypothesize will occur. The intervention components include: community organization to mobilize the community and enlist support of key individuals and agencies; community education to develop changes in attention/awareness, knowledge, beliefs, skills, and behavioral intentions of high-risk individuals, spouses of high-risk individuals, and community residents at large; education of professionals to increase their knowledge, behavioral capacity and self-efficacy, and their behaviors for educating patients about methods to reduce delay in seeking treatment for AMI; and patient education to alter knowledge, beliefs, skills, behavioral capacity and self-efficacy, and behaviors of high risk patient groups for increasing quick action in seeking treatment for AMI. These components comprise a multi-faceted intervention designed to be comprehensive coordinated and reinforcing and to target the several audiences hypothesized to be necessary to reduce overall delay in seeking treatment for AMI.

Two, somewhat different, types of messages will be used: 1) a simple message, emphasizing chest pain as the primary symptom and shortness of breath as a commonly occurring symptom, but ensuring that this message is framed to convey that chest pain and shortness of breath may not be the only symptoms which occur, for use with the large media portions of the community education component; and 2) a more complex message, emphasizing the variety of symptoms that may occur, for use with the interpersonal methods proposed for the patient component of the intervention and the group education sessions of the community education component. The action component of the message will to be to get to the ED quickly, preferably by calling 911.

We conceptualize two major groups of strategies of intervention delivery: interpersonal strategies and impersonal strategies. *Interpersonal strategies* are those which involve interaction between at least two people, such as individual counseling, group education or counseling, or telephone contact and education. *Impersonal strategies* are those which do not involve interpersonal interaction, such as various media approaches, using both large (TV, radio, newspapers) and small (pamphlets, posters, or videotapes) media. Within each intervention strategy, a variety of techniques or methods could be used, such as role modeling with or without role play, and contracting. Objectives for each intervention component have been designed to affect: 1) awareness and knowledge; 2) attitudes and beliefs; and 3) skills or capabilities.

B. Theoretical Model

In considering the theoretical model for the proposed intervention, we addressed two different forms of theory: behavior change theory and implementation theory. While elements of other theories were considered, two theories served as the primary behavior change theoretical basis upon which the four components of our proposed intervention have been developed: Social Cognitive Theory and Self-Regulatory Theory. These behavior change theoretical approaches are described below along with the overall, combined study approach. We also considered the theoretical

methods that would be used for implementing the interventions. Three primary theoretical approaches emerged: Diffusion Theory, Social Marketing Theory, and Community Organization Theory.

1. Behavior Change Theories

A number of theories were considered, including those that were adopted but also the Theory of Reasoned Action, the Health Belief Model, and Attribution Theories. Social Cognitive Theory emerged as providing an important overall behavior change theoretical framework for the proposed intervention. Aspects of the Self-Regulatory Theory also emerged as important.

a. *Social Cognitive Theory*

Social Cognitive Theory suggests that individuals' behavior is explained by a dynamic, reciprocal interaction among behavior, personal factors, and environmental influences (72). Crucial personal factors include individuals' capabilities to foresee the outcomes of given behavior patterns, to learn by observing others, to self-determine or self-regulate behavior, and to reflect and analyze experience. In terms of the social environment, verbal persuasion, feedback, support and reinforcement from credible people in the environment are important in establishing long-term behavior change. Social Cognitive Theory emphasizes the importance of individuals' beliefs of efficacy, or the self-appraisal of one's capabilities. People's efficacy perceptions influence the types of anticipatory scenarios they construct. The importance of self-efficacy for motivating people to respond more quickly to chest pain lies in the fact that people's beliefs about their coping efficacy affects not only their behavior (or willingness to engage in certain behaviors), it also affects their emotional reactions in taxing situations.

Perry and colleagues (73) have outlined the major concepts of Social Cognitive Theory and implications for interventions. Table 2 summarizes key constructs of Social Cognitive Theory along with the definition of these key constructs and their implications for professional/patient/community interventions (see page 42).

b. *Self-Regulatory Theory*

Leventhal and colleagues (74-76) argue that illness behavior and help seeking can best be conceptualized as a self-regulating process in which people's perceptions of physical states produce illness representations with concomitant emotional responses that then provide the basis for coping plans and actions that people evaluate and reformulate if necessary (Figure 3). This model posits three main stages that are activated at the onset of an illness threat. The first stage, problem representation, comprises individuals' use of a set of attributes to identify or specify the features of the problem and goals for action. In the second stage, action plan, individuals generate a set of coping responses, for both the illness and affective responses, perceived as relevant to the problem representation. The third stage is the appraisal process, during which individuals employ their own set of rules for comparing the pre- and post-action relationships between current discomfort and the goal of symptom elimination. The stages may cycle repeatedly as individuals generate new hypotheses,

initiate coping actions, and evaluate their consequences. Self-Regulatory Theory also posits that this cognitive process is paralleled by an emotional process (e.g., fear, anger, distress) that unfolds in response to symptoms, the labels and perceived health consequences, coping failures, and reinterpretation of the illness conditions.

c. *Combined Study Theory*

Social Cognitive Theory provides the basic model for the proposed intervention; however, the utility of aspects of Self-Regulatory Theory argued for a combined intervention model. This combined model is represented in Figure 4 in which aspects of both theories are represented as providing the overall behavior change theoretical approach for the proposed interventions.

2. Implementation Theories

The implementation theories identified as key for the proposed interventions are discussed below.

a. *Diffusion Theory*

Diffusion theory describes and explains how people adapt "innovations". An innovation pertains to anything (i.e., idea, behavior) that is perceived as "new" by some target audience. Diffusion theory suggests that, in general, individuals adopt innovations by a process of: 1) knowledge (awareness), 2) persuasion, 3) decision, 4) implementation, and 5) confirmation (77). This implies that health care professionals and health care organizations in the REACT intervention communities need to be: 1) made aware of the REACT trial and its objectives, 2) persuaded to implement patient and professional education interventions, 3) assisted in implementing these activities, and 4) encouraged to continue these interventions.

b. *Social Marketing Theory*

A variety of programs suggest the benefits of social marketing principles in formulating and implementing broad-based behavior change programs (78,79). The principles and basic methods of social marketing emphasize the use of a consumer orientation to develop and market intervention messages (78). The emphasis on consumer orientation suggests that a social marketing approach in minority communities may be particularly relevant since community representatives are actively involved in the development of the messages and the marketing approach and the likelihood of cultural sensitivity is thus increased (79). Key stages in the marketing process have been identified and include: market analysis in which the marketplace, the consumers, and the organizational structures are analyzed; planning in which marketing-mix strategies are formulated into a marketing plan; development, testing and refinement of plan elements in which communication concepts and messages are pre-tested and refined; implementation in which the marketing plan is put into effect, monitored, and refined as necessary; evaluation of in-market effectiveness; and use of feedback is used to re-shape market analysis and further refine the process (80). This social marketing theory provides the basis for our proposed community education component.

c. *Community Organization Theory*

Community organization is a planned process of assisting communities to use their structures and resources to accomplish goals endorsed by community leaders and representatives (81). Five typical phases of the community organization process include: 1) community analysis; 2) design initiation; 3) implementation; 4) maintenance; and 5) dissemination/reassessment. There are at least four models of community organization, including: 1) a coalition model in which existing organizations are used to address community issues through a process in which linkages between existing organizations are constructed; 2) a leadership model in which community leaders identified as necessary for achieving project goals are brought together, generally from diverse segments of the community, to work toward a common goal; 3) a lead agency model, in which a community agency is identified as the primary liaison for activities in the community; and 4) a networks/grassroots model in which community mobilization occurs through direct involvement with residents on a broader scale with grassroots support. Community organization theory and principles are envisioned as providing the means to generate support from professional groups for the professional and patient education components of the intervention and the service of volunteers to support activities of the community and patient education components of the proposed intervention.

C. Intervention Messages

While we propose conducting additional, ethnically-diverse focus groups to refine the message of our intervention, much deliberation has already gone into the basic REACT message. Reviews of available quantitative data as well as qualitative information from focus groups conducted by the Office of Prevention, Education and Control (OPEC) as well as several of the project sites suggest two, somewhat contradictory findings: 1) quantitative data suggest that the majority of all AMI patients, regardless of gender or ethnic group, experience chest pain, with shortness of breath being the next most common symptom; and 2) qualitative data suggest that patients and their spouses report that actual symptoms commonly appear diffuse with chest pain and shortness of breath appearing among a constellation of symptoms. Thus, even though chest pain and shortness of breath may be the most common symptoms, they may not be the most prominent symptoms in some cases and may be mixed in with a variety of symptoms. Focus group information suggests that patients and spouses report a common pattern of symptoms that differed from a classic, "movie-version" picture of crushing chest pain.

Despite this diversity of symptom pattern, there was a strong desire to keep the essential REACT message simple. It was decided that the multiple components involved in the proposed intervention could accommodate two, somewhat different types of messages which would also allow appropriate tailoring of the message to cultures and gender: 1) a simple message, emphasizing chest pain as the primary symptom and shortness of breath as a commonly occurring symptom, but ensuring that this message is framed to convey that chest pain and shortness of breath may not be the only symptoms which occur, for use with the large media portions of the community education component; and 2) a more complex message, emphasizing the variety of symptoms that may occur, for use with the interpersonal methods proposed

for the patient component of the intervention and the group education sessions of the community education component.

Consideration was given to having "call 911" be the primary action message, particularly in areas in which Advanced Life Support (ALS) is available. However, in areas in which 911 may generate a response from a volunteer with little training, this message might delay the individual further in receiving proper medical care. To add to the complexity, there was a great deal of concern about generating a message that would promote patients driving themselves to the ED, threatening not only their life but that of others as well. After considerable debate, the decision was made to focus the basic REACT message on getting to the ED quickly, preferably by calling 911.

D. Intervention Schedule

REACT will begin different components of the intervention at different times, as well as stage different aspects of the intervention within each component. The community organization component will begin first to ensure adequate initial community support. Professional education will also begin early to serve as the basis for later patient education activities. Starting with community organization and professional education will allow additional time for materials development for the community education component. The community education activities will also be varied over time to ensure adequate marketing salience of the message. Key components in developing and implementing the intervention are summarized in Table 3.

E. Intervention Components

The community organization component of REACT will be a planned process in which organizations and individuals within each intervention community are engaged in a collaborative effort to reach the study goals. The individual behaviors we seek to change occur within the environmental context of the community. Thus, the interventions used must accurately reflect the values and realities faced by community members. Community organization techniques and strategies will be used to gather support from communities and institutional structures for the purpose of reducing MI delay. The organizational model chosen for each community will depend on that community's culture, competence and readiness for change. The lead agency model is the primary model to be used in study communities which contain a suitable lead agency. In other communities an advisory board, coalition or network model will be used.

The REACT community education program will target groups at risk for MI, their spouses and families, and the general public through programs and messages designed to reduce delay in seeking care for MI symptoms. At-risk target groups include those who have experienced a previous MI; those with diagnosed CVD/CHD conditions but who have not experienced an MI; and those who have not experienced an MI but with known MI risk factors (hypertension, hyperlipidemia; smoking; diabetes); and bystanders who may witness an acute ischemic event. Education methods include programs and messages aimed at each group delivered through a common core of social group settings; through social group settings unique to some communities; and through mass and small media. Intervention objectives include building attention, awareness, and knowledge about AMI and the problem of delay;

modifying beliefs that may act as barriers to seeking treatment; and building specific skills in responding to MI symptoms to improve behavioral intentions and actions. Finally, the intervention will be implemented in partnership with community organizations that will provide resources for, and access to, important community education programs.

The various health care professionals who have contact with persons at risk for heart attack have a pivotal role in the reduction of delay time and have opportunities to provide education to patients. The professional education component of the intervention is thus critical to the success of REACT. Professional education intervention components will be designed to change clinicians' behavior in the following areas: 1) to alter their motivation to learn skills and to intervene with patients and to support the REACT project by changing their knowledge, attitudes, and beliefs; 2) to enhance their patient-centered counseling skills and skills about recognition of high risk patients; and 3) to impact their clinical practice environment. The professional education component will consist of multiple personal and impersonal strategies designed to change behaviors in each of these three areas. Professionals who will be targeted for inclusion in the professional education component are those through whom patients with risk factors for MI can be reached, such as those who work in hospitals, doctors' offices, pharmacies and even patients' homes, as well as in community settings.

The patient education program includes interpersonal (individual and group counseling) as well as impersonal (flyers/brochures, posters, magnets and other "tokens" and video) strategies to reach high-risk patients and their families with information regarding the importance of prompt and appropriate actions in response to MI symptoms. The interventions are designed to affect patients' knowledge, beliefs, attitudes and behaviors regarding prompt action for MI symptoms. Enhancing skills and self-efficacy is particularly important to the patient groups within these strategies, principles of patient-centered counseling, role-modeling and behavioral rehearsal are employed.

1. Community Organization

a. *Objectives*

(1) assist in creating a supportive community context in which the goals of REACT can best be realized.

(2) obtain the endorsement of community leaders and organizations to legitimize the project.

(3) motivate existing community organizations to commit resources in support of the intervention effort.

(4) motivate individuals and/or organizations within the community to provide volunteer service in support of the intervention effort.

(5) form productive partnerships with community organizations, particularly health care organizations, to further the goals of REACT

(6) seek input from minority groups to elicit culturally sensitive intervention messages for the project.

(7) influence community norms to be more supportive of actions desired by REACT.

(8) sustain levels of community participation and enthusiasm throughout the intervention period.

b. *Formative Research and Development*

Community analyses will be conducted in all study communities before randomization and in all intervention communities after randomization. The purpose of these analyses are to provide a clear picture of community needs, resources, social structures and values. This information will lay the groundwork for an informed community mobilization effort. These community analyses will examine socio-demographic information, sector analysis, emergency medical system resource analysis, health services analysis, identification of possible key informants (special attention will be paid to differing cultural and ethnic groups), and assessment of potential obstacles and competing community and health service programs or issues.

c. *Community Mobilization*

Efforts will begin shortly before the start of the intervention phase. The mobilization process will activate communities to recognize the problem of MI delay and become involved in addressing the issue. Key community leaders, including healthcare organization leadership, and institutions identified during the community analyses will be involved early on in the planning process. Decision-making will be shared to the extent possible and roles and responsibilities of the partners will be clarified and agreed upon. Specific objectives of the implementation process in each community will include: a) hiring a field intervention coordinator; b) developing a hospital team, where feasible, consisting of members of the disciplines and departments involved in the care of heart attack patients and those at risk for heart attack, to serve as the catalyst for a comprehensive hospital component; c) identifying or developing a broad-based community board/group to advise the project; d) creating and staffing subgroups, as needed, to provide input in specific intervention areas, such as community education, professional education and patient education; e) soliciting volunteer support as appropriate; and f) conducting training sessions for local leaders to improve knowledge and skills related to the achievement of REACT goals.

2. Community Education

a. *Objectives*

(1) increase exposure to the REACT message

(2) raise attention/awareness of the REACT message

(3) increase knowledge regarding the REACT message

(4) change beliefs about the benefits and efficacy of rapid response to heart attack, increase self-efficacy expectations to perform recommended actions and reduce perceptions of barriers to action

(5) increase skills to identify critical MI symptoms and take appropriate action

(6) increase behavioral intentions to respond rapidly and effectively to heart attack symptoms in themselves and others

b. *Target Groups*

High-risk target groups for the community education component have been segmented based on a combination of AMI risk level and characteristics known to increase risk for delay in seeking care. Research suggests the need to reduce delay especially in the following AMI risk groups: a) persons who have previously experienced MIs; b) persons with diagnosed CVD/CHD conditions but with no previous MI (e.g., angina; ischemic disease); and c) persons with known risk factors (hypertension, hyperlipidemia; diabetes; smoking) but with no previous MI. Characteristics known to increase risk for delay include age, ethnicity, gender, and socioeconomic status (SES) as discussed in the review of research. In addition, research demonstrates the need to focus on the following groups: d) spouses and family members of those at high MI risk; and e) the general public.

c. *Message Elements and Educational Techniques*

(1) Key elements to emphasize for each target group

The study framework proposes a number of key factors that influence delay. From the study of these in the research literature, our own preliminary studies, and focus groups of high-risk target groups and their spouses and family members, we will derive messages for use in the educational and media intervention. Intervention messages will be culturally sensitive, community appropriate, and target-group specific. Key elements to be refined and utilized include:

(a) MI symptoms -- In addition to the primary symptom of chest discomfort, the intervention will modify groups' beliefs about expected AMI symptoms. These beliefs include expectations of severe, crushing chest pain and unconsciousness (the so-called "movie" heart attack). In fact, far less severe symptoms occur in the majority of cases. The intervention will address confusion in labeling symptoms frequently experienced by some high-risk groups. In addition, the intervention will employ language and terminology used by target groups and subgroups that have previous personal experience with MIs.

(b) Knowledge -- Our previous research and other studies reveal that individuals know relatively little about newer reperfusion strategies such as thrombolytic drugs and their benefits in stopping an AMI and in reducing the risk of myocardial damage. Few recognize that the efficacy of these therapies depends upon their initiation soon after symptom onset. There are also indications that knowledge of risk among women is not well understood.

(c) Beliefs and Motivations -- The intervention will emphasize messages designed to increase target groups' belief in the efficacy of recommended actions to reduce delay, and their self-efficacy in

performing recommended actions; and in reducing perceptions of barriers to taking action.

(d) Other Barriers to Seeking Care -- Only a minority of MI patients use 911 EMS. Many fail to engage EMS due to fear of embarrassment, a desire not to inconvenience health care staff, or concerns about costs. Few recognize that EMS personnel are trained to bring a high level of medical care to the individual experiencing an AMI -- medical care that can stabilize a patient and reduce the risk of sudden death as part of a larger "chain of survival" concept uniting all levels of the health care system.

(e) Relevant Skills -- Those experiencing MI symptoms and those interacting with them find themselves sorting out complex cognitive and emotional matters in a crisis setting. Clear thinking often fails to materialize. To address this, the intervention will emphasize coping and planning skills -- encouraging individuals at risk and their spouses and family members to consider the possibility of an event and to develop a plan for mutual rapid and effective action.

(f) Behavioral Intentions -- The intervention will emphasize attitudinal and normative perceptions of the need to act rapidly and effectively in the event of AMI symptoms.

(2) Message techniques

Although intervention messages will be refined through focus group analyses, REACT will use several techniques for their presentation in group educational and media settings. These include especially: role modeling; behavioral rehearsal; and expert testimony.

(a) Role Modeling -- Self-Regulatory and Social Cognitive Theory emphasize the use of role models and role model stories in health behavior change. The primary purpose of role model stories is demonstration of risk-reducing behaviors. Community role models will be used to provide an opportunity for observational learning and vicarious reinforcement by showing selected positive behaviors and their consequences. Attractive packaging serves to contribute to the perceived attractiveness of the role model and raises the perceived status of the sponsoring project. Role models are most effective when viewed as attractive and similar to the audience. They will describe their experiences in their own language. Actual quotes about the perceived outcomes, especially the reactions and perceptions of significant others, are particularly powerful.

(b) Behavioral Rehearsal -- Self-Regulatory and Social Cognitive Theory suggest that rehearsing behaviors in advance of a real event is a key technique. Behavioral rehearsal is also key to planned decision-making, a central need in the case of individuals experiencing AMI symptoms and the accompanying anxiety and fear. In this context, the intervention will emphasize rehearsing behaviors that will reduce delay in the event of MI symptoms.

Partners may agree, for example, on what they will do in case either experiences an MI. Partners in educational settings may act out a discussion as if one were experiencing an MI and out of this rehearsal further reinforce intentions to act rapidly, assertively, and effectively.

(c) Expert Testimony -- Many individuals view physicians and other health care personnel as highly credible sources of information about actions to take to protect and preserve their health. Individuals in lower SES circumstances and often older persons view prevention information provided in this context as important. The intervention will use the framework of the physician or other health care personnel to communicate important information about reducing MI delay both in group and media educational settings. This approach may be particularly effective by engaging physicians and other health care personnel in legitimating for high-risk individuals the use of 911 EMS for transport to hospital.

(3) Educational Strategies

Educational strategies of the Community Education Component of the intervention will utilize the following channels for intervention:

(a) Mass Media -- Utilizing the message elements and frameworks described above, mass media (e.g., television, radio, newspapers, magazines, display advertising) will be used to generate community and target group exposure to the MI delay message and to assist in placing the issue of MI delay on the agenda of the public at large, community organizations, and policy makers. Mass media will be used specifically to generate news stories and publicity about MI delay issues; and to place public service and paid advertising about MI delay in local mass media channels. In generating news and publicity, community intervention staff will work with local media outlets to educate them about the issue and to assist them in developing news and feature stories. In placing public service and paid advertisements, messages will contain elements described earlier. These will be created for television, radio, newspapers, magazines, display media, and direct mail.

(b) Small Media -- Studies have indicated that "small media" (e.g., educational videos, books, pamphlets, direct mail, other printed materials) can be effective, particularly when combined with group or individual interpersonal communication. These media are also intended to provide a point of reference from personal contacts and face-to-face communications about symptom recognition and care-seeking. Small media will be prepared for distribution through group settings (described below) and will use the message elements and frameworks described above.

(c) Social Group Settings -- While media strategies are useful in achieving intervention objectives, community group settings will serve as a set of more intensive opportunities for education about MI

delay. Each community will implement programs within an identified common core of group settings, but some may use settings unique/ important to their community. The common core of group settings includes: worksites, community organizations, and magnet events such as health fairs and public displays. Settings relevant only to some study communities, particularly ethnic and minority communities, include churches and schools.

(d) Worksites -- Worksites have generally been effective channels in providing health information to the general public. In each intervention community, major employers have been identified during the community analysis. Age and residence summaries of employees will determine whether an appropriate portion of employees falls within the study target population. Such worksites will be recruited to assist in planning an implementation of an MI delay reduction program. Popular formats for worksite-based programs include breakfast or lunch seminars, cafeteria displays, participation in employee health events, and distribution of print materials. Existing health programs, including on-site CPR training, will also be assessed for possible collaboration with the study.

(e) Community Organizations -- Group education sessions will be arranged with other community groups such as senior centers and clubs, elder housing or nutrition programs, neighborhood, ethnic or social clubs, unions, fraternal organizations, service clubs such as Rotary Club, League of Women Voters, community service agencies and YMCA/YWCA. Educational sessions will be planned specifically for women as well.

(f) Magnet Events -- Large scale magnet events are designed to attract large groups of the target audience from the general public. They will be co-sponsored with one or more agencies with links to heart health, such as the American Heart Association, hospital, local fire department or ambulance service and/or groups with strong ties to the community. Such events will be held to maximize public visibility. Local celebrities will be recruited to speak or to participate as appropriate. Other activities will include speakers or panels, information booths, and CPR instruction. Such events will be promoted through media and sponsoring agencies. Examples of small scale events include health fair displays, displays at local malls, etc. For these smaller events, collaboration with other community groups may or may not be used.

(g) Churches and Schools -- Churches are an important community resource, especially for the older members of the community and some ethnic groups, and are effective avenues for health promotion. They are particularly useful in scheduling programs in conjunction with other activities, such as women's, mens' or senior groups, or around worship services. Churches may be particularly helpful in emphasizing norms for bystander action because of the value placed on community and mutual care. Schools are also effective avenues

for providing information to parents and grandparents, especially in communities with a high proportion of extended families living in the same home or in close proximity. The approach will seek to engage children and adolescents in providing information useful to older adults.

d. *Intervention Program Development*

(1) Planning

Intervention development will be carried out in accordance with the study framework and appropriate steps in the social marketing planning framework. Specifically, the Intervention Committee will: 1) oversee analysis of target audience formative data (focus groups and other sources of information); 2) conduct a channel influence analysis for the development of effective group educational settings and placement of media messages to gain the most exposure and impact; 3) develop operational plans for the implementation of the intervention; 4) arrange for the production of materials; and 5) arrange for process and impact evaluation.

(2) Pre-testing Group Materials

REACT investigators and staff will develop group session protocols that will include outlines of the content, methods and materials. This will be reviewed by other members of the Intervention Committee. Supporting audio-visual materials will be developed as needed. Following professional review, the program will be piloted with a small group of persons from the target population. At the end of the session, they will be asked to critique it, to ensure that it is relevant, interesting, understandable, sensitive and acceptable to specific needs of that community. Feedback from these various sources will be used to modify the program as needed.

(3) Recruitment to Group Education Settings

A strategy to recruit participants in group education sessions will be planned in conjunction with members of each relevant community association. This strategy will incorporate flyers, posters, sign-up sheets and other announcements. It will also incorporate participation of volunteers from each community association to assure the identification and inclusion of high risk participants and their families and friends.

(4) Pre-testing Media Materials

While target audience focus groups are planned in part to evaluate the appeal of message concepts, media materials will be further pre-tested as they proceed through the production process. Specifically, we will empanel groups of 7-10 appropriate target audience members to review materials in progress for their reaction and response; and second, we will also empanel local intervention community advisory groups or lead agency members to review and to respond to media materials.

3. Professional Education

a. *Objectives*

(1) increase awareness and knowledge of and support for the REACT initiative

(2) increase appropriate professionals' knowledge about CHD, MI, treatment and delay, and needed education of patients;

(3) increase appropriate professionals' behavioral capacity and self- efficacy to perform patient-centered counseling skills related to MI;

(4) increase appropriate professionals' patient education behaviors using REACT programs and materials, referrals to other educational sources, and support for REACT project activities.

b. *Formative Research and Development*

Two strategies will be used to gather information from various professional groups as part of the formative research and development for use in refining the professional and patient intervention plans and intervention messages. These strategies will include:

(1) Key Informant Interviews

Key informant interviews of 30 to 60 minutes in length will be conducted with cardiologists and emergency department physicians during the prerandomization phase. These face-to-face interviews, by experienced interviewers familiar with the goals of the study, will take place in out-of-study communities to avoid contamination of control communities, given the small numbers of relevant physicians in some study communities.

(2) Focus Group Interviews

Focus group interviews will be conducted with primary care physicians, inpatient nurses and outpatient nurses. These focus group interviews will be conducted. These will be 60 to 90 minutes in length and conducted according to a common, theory-based question route by an experienced focus group facilitator.

Following community randomization, known members of the various professional groups in the intervention communities will be contacted, via key informant interviews or group meetings, to continue the process of needs assessment. Among other questions, these professionals will be asked to identify colleagues in the community who could assist with the project. These contacts will create a body of information and a network of professionals to use in planning and delivery of the professional education component. Interdisciplinary teams will also be initiated and developed in intervention hospitals where feasible. These REACT teams will foster interdepartmental cooperation (i.e., CCU, ED) and refine the protocol for education, where phased messages will be delivered at teachable moments by several staff members. Depending on the community health services profile, the team building approach will be encouraged in other provider organizations, such as health maintenance organizations and community health centers.

c. *Professional Target Audiences*

Professional target audiences include those who come into contact with patients and families in ambulatory settings, at the time of presentation at the hospital, during hospitalization, at the time of discharge, and during follow-up. These professionals include: cardiologists; emergency department physicians and nurses; primary care professionals, including physicians and nurses; hospital staff and EMS support personnel; and other potential key providers, such as cardiac rehab staff and case managers. Certain professional groups will receive more frequent or intensive educational programs than others in view ot their potential for delivering intervention strategies and messages.

d. *Intervention Strategies, Techniques, Messages*

(1) Strategies for Professional Intervention

These strategies include: a) hospital-based, interdisciplinary REACT teams, which will provide advice and coordinate activities and refine and implement REACT protocol activities; b) continuing medical education programs for physicians sponsored in cooperation with hospitals and medical associations; c) academic detailing for individual specialist physicians; d) continuing education programs for nurses; and e) mailings about the study, tailored to specific professional groups. In addition, individual sites are considering other strategies including training for pharmacists, EMTs, medical office staff, and visitng nurses (VNAs).

(2) Techniques and Methods

Techniques and methods to be used during the professional education component include interactive lectures, role modeling by respected physicians, and building of professional norms using videos and providing specific action steps in written materials, slides and lectures.

(3) Key Messages

Key messages to be used in the strategies will include: a) information about prompt action is essential; b) professional messages do have key impact on patients' behavior; c) clinician patient-centered counseling is feasible; d) meaningful intervention can happen in a few minutes; e) messages can be tailored to patients' individual characteristics; f) practices can be organized to identify high-risk patients for education and g) education efforts are an essential component of quality care.

(4) Message Technques

Several complimentary techniques for delivering message to providers will be used. These include role modeling by influential clinicians in both the provider and community interventions, which help promote "professional norms" of behavior. CME and targeting in-services will stress behavioral rehearsal and skill building. Materials and presentations will also stress the empirical evidence available which support REACT objectives.

e. *Program Implementation Objectives and Intervention Management*

Specific program implementation objectives will be defined during the development of plans of operation. Minimum standards for provider interventions will be articulated in order to promote appropriate site flexibility and tailoring, while simultaneously fostering scientifically-based choices and assuring accountability. Objectives concerning amount and periodicity of each activity will be formulated. In addition to amount and periodicity, objectives related to penetration and exposure will be delineated. Specific common professional activity outlines, guidelines, and curricula will be developed for use in intervention communities in cooperation with OPEC. Recruitment and marketing plans will be defined. Professional interventions will begin during the earliest phase of the intervention because of the key role of professionals in delivery of patient education, as well as building of community commitment to REACT activities.

4. Patient Education

a. *Objectives*

(1) increase exposure, attention and awareness of REACT messages;

(2) increase in patients' knowledge about MI symptoms and appropriate actions including awareness of MI signs and symptoms; personal risk profile; understanding of MI treatment and the need for rapid response; and steps to take to respond rapidly;

(3) increase in patients' behavioral capacity and self-efficacy to perform skills related to MI including change in perceived barriers to fast action; confidence in personal ability to respond rapidly; reduced tendency to deny symptoms; ability to communicate about the subject and to plan a course of action; and behavioral rehearsal;

(4) increase in patients' behaviors related to REACT including participation in program activities.

b. *Patient Target Groups*

Educational and counseling strategies will be directed primarily towards patients that have been identified as being at high risk for AMI. As delineated in the Community Education section above, these include persons with previous MIs; persons with known CVD/CHD diagnoses (e.g., angina, IHD), but who have not previously experienced an MI; and persons with established risk factors for CHD such as hyperlipidemia, hypertension, smoking and diabetes. Because spouses and families frequently figure prominently in an individual's decision to seek care for MI symptoms, they too will be included in educational and counseling strategies, and reached through the community education component.

c. *Research and Development*

Contacts with high-risk patients in the formative planning phase will be established through focus groups. These will be conducted to help inform development of patient education message strategies for reducing delay. Patient groups will be recruited from local MI registries, heart study participant lists,

and hospital and clinic patient populations. Previous reports by OPEC, as well as individual sites, will also inform study decisions. Development of materials and curricula will be a collaborative process between the Patient/Provider working group and the NHAAP's Office of Prevention, Education and Control.

d. *Intervention Strategies and Messages*

(1) Key Messages

Key messages in the strategies (for both patient and patient's family) will include: 1) be informed (about MI symptoms and appropriate actions); 2) be ready (develop a plan of action; discuss with MD and spouse what to do in response to possible MI event); 3) stay calm (learn how to cope with emotions that accompany such an event); and 4) act fast (don't delay; get to hospital at once, call 911).

(2) Patient Education Intervention Strategies

Patient education intervention strategies include both interpersonal and impersonal strategies. Interpersonal strategies involve individual counseling and education, as well as group strategies. Strategies will be used in hospitals, clinics, rehab centers, pharmacies, or patients' homes and be delivered by community providers.

(a) Individual Counseling -- Individual education counseling will be done by a variety of health care professionals trained through REACT's professional education. Individual counseling can result in high levels of understanding of the message and participation in decision making due to the advantage of immediate feedback and tailored discussion of barriers and problem solving.

(b) Group Education or Counseling -- Group education/counseling sessions will be conducted by a variety of health care professionals in settings including hospitals, clinics, and senior centers. Patients will receive relevant medical information as well as share their feelings with people having similar medical concerns. The advantage of this approach is that more than one patient at the same time can be educated and that the dynamics of a group encounter can be reassuring and motivating for the patient. Group counseling sessions may be "new" programs developed in collaboration with a sponsoring agency, or may be an "add on" to an existing discussion group (e.g., a diabetes session sponsored by a community "health center").

(c) Print Materials -- Print materials including brochures, flyers, and posters will be distributed in many ways (in clinics, pharmacies, mailed to patient's home, etc.). These materials can be useful in communicating fairly detailed information since they can be read, reread and saved for reference at a later time. Such materials could include a Heart Action Plan. This is a pre-printed plan on which a patient can write down his or her strategy for action in response to certain symptoms and can facilitate mental rehearsal regarding a possible MI event. A patient should be encouraged to discuss his/her

plan with a spouse or his/her health care professional. Other materials will include human interest stories which focus on "patient stories" in local print and radio media, small media in doctors' offices, and target group-specific articles in organization-specific publications, such as an HMO newsletter.

(3) Techniques

Three techniques will be used in the design of these patient education interventions in REACT. These include:

(a) Principles of Patient-Centered Counseling -- Patient-centered counseling is a structured method of enhancing the interactions between the professional and patient for the purpose of helping the patient change key health-related behaviors. It "emphasizes the importance of the patient's input in developing an effective plan for change and strategies for altering behaviors." Advice-giving and the provision of information can be integrated into the counseling approach. The use of counseling, as well as support materials such as booklets, appears to augment the effectiveness of advice alone. This technique can be used in at least two of the strategies: individual and group counseling.

(b) Role-Modeling Testimonials -- Role-modeling can be used in almost any strategy since people can model behavior after many different vicarious observations (print, broadcast or interpersonal observations).

(c) Behavioral Rehearsal -- This technique is useful in teaching patients how to solve problems and how to prepare themselves for action. Patients learn to be prepared for acting during an MI event by rehearsing (mentally and behaviorally) the behaviors that will be required at such a time. This can take many forms: role-play, discussion, writing up a plan, etc. The technique can be used in all strategies since patients can learn how to solve problems and how to be prepared through interpersonal as well as impersonal strategies.

d. *Intervention Management*

Process documentation activities will be defined and monitored to insure timely implementation and facilitate attention to needed mid-course corrections. Specific program implementation objectives will be defined during the development of the plans of operations. Objectives concerning the amount and periodicity of each activity will be formulated. Specific common patient education activities outlines will be developed for use in intervention communities. Recruitment and marketing plans will be developed. An overall timeline, in concert with the professionals and community activities, will be delineated.

Table 2. Major Concepts in Social Cognitive Theory and Implications for Intervention

Concept	*Definition*	*General Implications*	*Implications for Provider Interventions*	*Implications for Patient/Family and Community Interventions*
Environment	Factors that are physically external to the person	Provide EMS, hospital, provider and social support.	Encourage organized approaches within hospitals; form hospital teams; provide materials. Promote as a CQI project. Increase (perceived) support from colleagues and administrators for the providers role in encouraging patients to seek prompt action for symptoms of AMI.	Assure provider systems are in place. Increase (perceived) social support from health care providers for prompt care seeking for symptoms of AMI (i.e., "Legitimize prompt care seeking"; all players reinforce messages). Involve families in interventions, reinforcing community interventions.
Situation	Person's perception of the environment.	Correct misperceptions and promote norms.	Activities which promote interdisciplinary provider communication. Promote systems which facilitate action (e.g. medical record check lists). Correct provider misconceptions about prompt care seeking for symptoms of AMI (i.e., patients overreact to symptoms; emergencies burden the system; prompt care seeking is bothersome for patient and hospital staff, etc.)	Improve knowledge about how system works (including costs). Collaborate with insurers on education strategies. Correct misconceptions about prompt care seeking for symptoms of AMI, (i.e., Ambulance is only a method of transportation; MI can't be treated, etc.) If a false alarm, emphasize legitimacy and explicit steps for future. Consider all situational needs, such as feeling need to call son/daughter/spouse.
Behavioral Capabilities:	Knowledge and skill building.	Promote mastery learning through skills (cognitive/behavioral) training.	State of the art CME; on-site technical assistance.	Patient Centered Counseling. Behavioral Rehearsal; Have spouses verbalize concerns. Work through barriers. Encourage patients to initiate discussion with providers.
* Cognitive	Knowledge and skill to perform certain cognitive tasks.		Educate care givers on how to teach their patients to evaluate symptoms in view of patients' medical histories and general knowledge of illness and disease which may vary by gender, age and/or other factors.	Educate individuals on how to evaluate AMI symptoms in view of their medical histories and general knowledge of illness and disease (particularly heart disease). Emphasis on discouraging patients to associate AMI symptoms with other medical conditions. Increase knowledge on the varied and individualized nature of MI presentation. (Interactive computer game; testimonials of people presenting with "ambiguous" symptoms; counseling; etc. Discussion groups and role models can educate via scenarios.

Table 2 cont.

Behavioral capabilities (cont'd) * Behavior	Knowledge and skill to perform given behaviors.		Educate care givers on how to teach their patients how to cope and to take appropriate action in response to symptoms; how to reinforce/educate the "false alarm" patients about next time. Encourage provider's "risk-based" targeted action by giving epi and efficacy data.	Educate individuals about the appropriate actions in response to (particularly ambiguous) symptoms. (Contracting with health provider or spouse; "Action plan" brochure; Patient Counseling; Interactive computer game, discussion groups, peer modeling.)
Expectations	Anticipatory outcomes of a behavior	Model positive outcomes of behavior desired.	Include "scripts" which emphasize patient/ provider behavioral rehearsal. Emphasize the positive outcomes of teaching patients about prompt care seeking for AMI (i.e., save a life, increase quality of life after MI, grateful patient/family, etc.) Emphasize how important it is for provider to acknowledge support even if it turns out not to be an MI.	First assess patient/family perceived benefits/barriers, then address and problem solve one by one via patient centered counseling. Highlight unanticipated benefits/barriers. Use scenarios which portray "positive outcome" (even if false alarm).
Expectancies	The values that the person places on a given outcome, incentives	Present outcomes of change that have functional meaning.	Understand their priorities/problems; design strategies to address them (hospitals teams, office coordinator). Emphasize the value of outcomes; e.g., patient outcome, hospital image.	Emphasize the positive outcomes (i.e., survival, greater quality of life after MI) of prompt care seeking for symptoms. Counsel through expected negative outcomes.
Self-control	Personal regulation of goal-directed behavior or performance	Provide opportunities for self-monitoring and contracting.	Provide standardized checklists; staff teams agree on a monitoring system.	Prepare for action to a heart emergency. Behavioral rehearsal; cues to action—phone sticker, keychain.
Observational learning	Behavioral acquisition that occurs by watching the actions and outcomes of others' behavior.	Include credible role models of desired behavior.	Use credible provider role models to communicate behavior and the positive outcomes of this behavior. Find key provider leadership to endorse participation; role plays in CMEs; role model in newspaper human interest stories.	Use credible role models to communicate the targeted behavior and the positive outcomes contingent on this behavior, via magnet events, print and broadcast media. Community discussion groups can include "testimonials," use of peer influentials.
Reinforcements	Responses to a person's behavior that increase or decrease the likelihood of reoccurrence.	Promote self-initiated social and affirmation incentives.	Visible hospital leadership support; MD support and affirm staff involvement. Give concrete suggestions on how to support - tokens from study staff, thank-you notes.	Reinforcement for quick action (even if it wasn't an MI)—ER, EMT staff, skills critical. Primary care, cardiologist sponsored education (one on one) patient centered counseling, targeted mailing or phone call) as well as MD endorsed and/or hospital team sponsored community sessions.

Table 2 cont.

Self-efficacy	The person's confidence in performing a particular behavior	Approach behavior change in small steps; provide specificity about the change sought.	Provide specific guidelines and scripts for teaching patients about MI symptoms and actions; opportunity to observe, "make it easy" - checklist, aides, have nifty patient education materials. Provide multiple intervention strategies that a provider may choose from to educate their patients.	Provide very specific guidelines for evaluation and action in response to heart-related symptoms (verbal and written). Encourage mental and verbal rehearsal of behavior with patient and, if possible, with families. Provide multiple behavioral strategies that can be employed in response to heart-related symptoms (verbal and written).
Emotional coping responses	Strategies or tactics that are used by a person to deal with emotional stimuli.	Provide training in problem solving and stress management; include opportunities to practice skills in emotionally arousing situations.	Provide concrete ideas on how to deal with needs to reassure/comfort, yet help patients/family understand it can "happen to them," or "happen again."	Provide specific guidelines for behavior in order to reduce emotional anxiety (or panic) during a symptom episode. Talk frankly and openly about fear reactions; mental and verbal rehearsal of coping responses; emphasize behavioral capability to minimize negative emotional states and heighten self efficacy (controllability).
Reciprocal determinism	The dynamic inter-action of the person, behavior, and the environment in which the behavior is performed.	Consider multiple avenues to behavioral change including environmental, skill, and personal change.	Multi-level, multi-organizational, multi-strategy, multi-provider, multi-message - all reinforcing the other.	Multi-strategy, multi-provider, multi-message—all reinforcing the other.

* Adapted from Perry et al in Glanz et al. (1990).

Table 3. Timing of Key Intervention Activities

Component	Duration	Begin Date	End Date
focus groups of identified target audiences and analysis	6 months	3/95	8/95
materials production	12 months	9/95	9/96
hire/train intervention staff	3 months	12/95	2/96
community organization	18 months	3/1/96	9/1/97
professional education	15 months	3/1/96	6/1/97
patient education	12 months	9/1/96	9/1/97
community education intervention	16 months	4/96	9/1/97

Figure 3. The self-regulatory model of health and illness behavior as adapted from Cameron, Leventhal, and Leventhal (1993). "Symptoms are perceived and elaborated on to generate both a cognitive representation of the symptom episode and emotional responses, typically stress. Both the representation and the emotional responses lead to the selection and initiation of coping procedures. The effectiveness of the coping attempts are appraised, and appraisals of coping failure lead to modifications of the representation or coping strategies and to decisions that one is well, stressed, or sick. Failure to cope either with the symptom episode itself or with the distress induced by the episode can motivate health-care use" (p. 172).

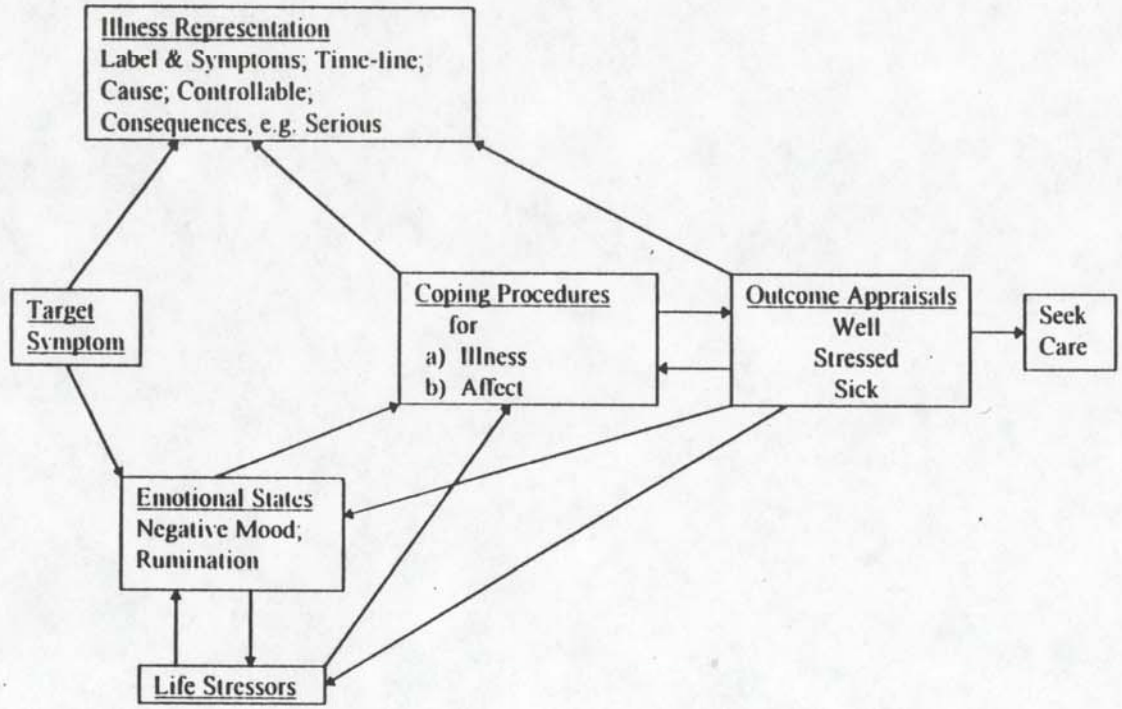
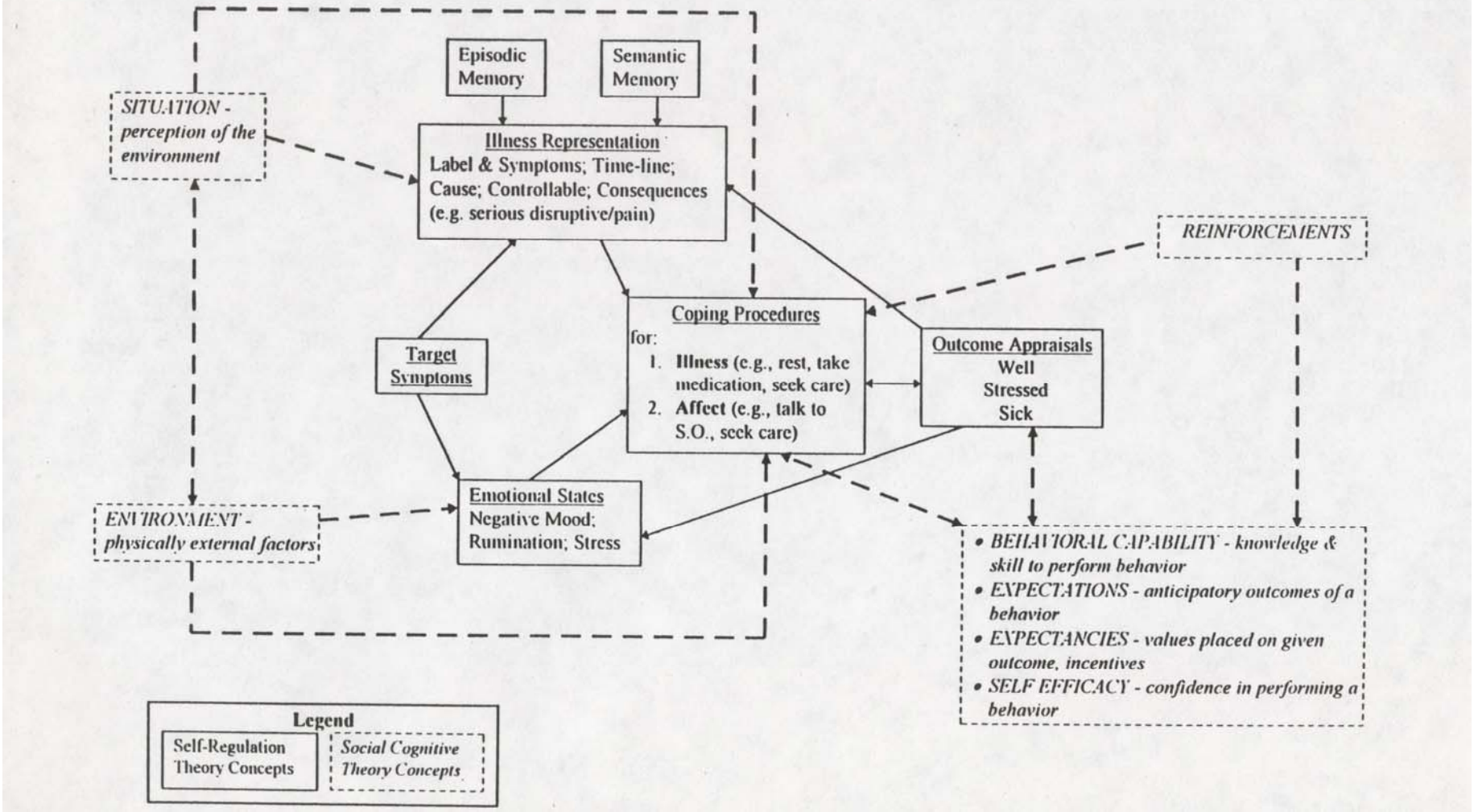


Figure 4. The relationship of concepts of social cognitive theory on the self-regulatory model of health and illness behavior as adapted from Cameron, Leventhal, and Leventhal (1993). "Symptoms are perceived and elaborated on to generate both a cognitive representation of the symptom episode and emotional responses, typically stress. Both the representation and the emotional responses lead to the selection and initiation of coping procedures. The effectiveness of the coping attempts are appraised, and appraisals of coping failure lead to modifications of the representation or coping strategies and to decisions that one is well, stressed, or sick. Failure to cope either with the symptom episode itself or with the distress induced by the episode can motivate health-care use" (p. 172). The concepts of social cognitive theory in this diagram and their related implications for intervention at the patient level are diagrammed below.



VI. STUDY COMMUNITIES

A. Recruitment of Communities

Each field site has initiated relationships with key community leaders in each study community to secure the support of public, private and volunteer organizations. Contact has been made with hospital and EMS administrators, practicing physicians, nursing groups, media executives and health-related volunteer groups. Commitments have been obtained from participating hospitals to allow access to patients and hospital records in order to collect study measurements. At some field sites, investigators have strong connections in study communities resulting from other independent community research.

Community contacts also serve as qualitative assessments designed to evaluate the resources and capacity of each organization to implement the proposed interventions. Discussions with key informants have yielded information regarding vested interest groups, informal networks, advocacy movements, potential community-specific barriers to intervention implementation and existing community organizations that may facilitate initiation of community activites. After baseline data are collected, contact with community leaders will be intensified in the intervention communities.

B. Characteristics of Study Communities

A number of community-specific variables were collected to assess variability across and comparability within pairs of communities. These variables include factors used to compare community sample distributions with the U.S. population and variables designated as matching criteria. In Section III., Table 1 provides variable categories and values applicable to each study community at a specific field site. The bottom of the table includes selected aggregate study percentages and comparable values based on 1990 U.S. Census statistics for comparison.

A few comments regarding figures tabulated in Table 1 simplify the interpretation of the data. Some field sites plan to combine two smaller communities to represent one study site. In this case, values shown in the table represent a weighted average of the two communities or individualized data is provided for each community. Finally, the numbers of expected emergency department visits for chest pain and discharges for myocardial infarction (ICD 410) and unstable angina (ICD 411) were estimated in some cases using data from the participating hospitals and, in other cases, using previously collected data from similar nearby communities.

VII. MEASUREMENT OF OUTCOME, PROCESS, AND IMPACT

A. Clinical Outcome Measurements

1. Primary outcome: primary definition of delay time

The primary outcome of delay time will be defined as the interval from symptom onset to arrival at the emergency department (ED) for patients admitted for possible acute cardiac ischemia and receiving a cardiac-related discharge diagnosis (ICD 410-414, 427, 428, 429, 440, 786.5). (The primary population)

Data defining this interval (from acute symptom onset to ED arrival) will be obtained from the patient medical record. For all patients presenting at the ED with "chest discomfort", a related clinical descriptor, the E.D. staff at participating hospitals will be trained by all REACT study staff to document symptom onset time using two standard questions: "What are the symptoms that brought you here today?" and "What was the time of onset of these acute symptoms?" "Chest discomfort" refers to any descriptor used by the patient in reference to thoracic discomfort (e.g., pain, ache, pressure, tightness, squeezing, bloating, burning, indigestion, etc.)

The same measurements as made for the primary clinical outcome will be made in a sample (200 per community) of eligible patients evaluated in the ED for chest discomfort and sent home without admission to a chest pain unit or other diagnostic unit.

Nursing and physician personnel also will be instructed to record ED arrival time. When arrival time is not documented, the earliest ED time will be used. If time of symptom onset is not documented in the ED nursing record, the following sources will be reviewed in sequential order until documentation of acute symptom onset is obtained: emergency department physician note; admitting physician note; ward/unit nursing note; and hospital discharge note.

2. Secondary definitions of delay time

a. Interval from symptom onset to time of taking action measured by interview on a sample post discharge.

In a random sample of patients who have a confirmed discharge diagnosis of 410 or 411, a telephone interview will be conducted 7-9 weeks after discharge to obtain information on the time patients took action. The time to taking action will be defined as the time the patient calls 911 or an ambulance or leaves for the hospital if emergency services are not used.

b. Interval from acute symptom onset until in-person contact with emergency medical services (EMS) personnel.

For those patients transported by EMS personnel, the interval defined as the time from symptom onset until EMS personnel arrival at patient location will also be measured (note: if arrival time to patient is not available, arrival at geographic location will be used). EMS records (appended to the patient medical record or obtained from EMS agencies) will be reviewed to determine the time of EMS arrival. Because EMS unit staffing and equipment may vary, as may availability of a tiered EMS response, the times of first arrival will be collected separately for the first basic emergency medical technician (EMT), the first defibrillator equipped and trained person (e.g., EMT-D or paramedic), and the first paramedic. These additional time endpoints will be used in subgroup analyses (see below).

c. Interval from symptom onset until initiation of reperfusion therapy

In the eligible population of patients with AMI, the time reperfusion therapy (i.e., coronary angioplasty, thrombolytic agents, or coronary artery bypass surgery) is initiated will be determined by chart review. Subgroup analyses will individually address each specific type of reperfusion therapy.

3. Secondary Outcomes

a. Receipt of early revascularization or reperfusion therapy: thrombolytic therapy, immediate PTCA, or either.

Hospital records will be reviewed to determine the receipt and timing of such therapy. Based on NHAAP guidelines, therapy within one hour of ED arrival will be considered "early."

b. Size of MI and severity of infarction

The size of MI will be estimated by use of peak cardiac enzyme levels. While standardized assays will not be available at all trial hospitals, it is expected that each institution will demonstrate satisfactory consistency of test use and standards. Data will be obtained regarding the type of test, time of peak level draw, and peak value for each enzyme ordered. The upper limit of normal will be obtained from the hospital lab on a regular basis.

Severity of infarction will be assessed by hemodynamic instability and the occurrence of ventricular arrhythmias. Hemodynamic instability will be measured by vital signs at presentation, i.e. initial heart rate and initial blood pressure upon hospital presentation.

c. In-hospital case fatality

Hospital discharge status (dead or alive) will be obtained from medical records for the primary population.

d. Length of stay (LOS)

Hospital records will be reviewed for determination of critical care unit and total hospital LOS in the primary population. Stays will be rounded to closest hour using first recorded times for CCU admission/discharge and hospital admission/discharge, respectively.

e. Community and out-of-hospital mortality due to coronary heart disease

Statewide mortality tapes will be used to determine the number of adults 30+ years old from the respective community catchment areas with a death certificate diagnosis of coronary heart disease (CHD). The absolute number of adults 30+ years living in the catchment area (based upon most recent census data) will be utilized for the calculation of community CHD mortality rates. Incidence rates for out-of-hospital CHD-related deaths will also be determined.

f. Use of EMS system

EMS records will be reviewed to monitor total EMS calls throughout the study.

g. Use of ED by patients with chest discomfort

The total number of ED visits by patients with chest discomfort, the number of chest pain patients dismissed to home from the ED and the number of patients admitted through the ED to the hospital for evaluation of chest pain/discomfort will be obtained from ED logs and documented patient disposition.

h. Number of patients discharged with acute IHD ("true positives").

The total number of these patients will be estimated based on the sampling fraction and proportion of 410/411 cases in the chart reviewed sample.

4. Other Measurements

The following other measurements will be obtained:

a. associated symptoms with chest discomfort will be obtained from chart review

b. EMS personnel skill level (basic life support only or defibrillation capability or paramedic skills) will be determined from review of EMS ambulance reports.

B. Measurement of Potential Confounders and Effect Modifiers

1. Community based variables - Characteristics of the 20 study communities are described in Section VI.

Sources of information for community characteristics include U.S. census reports, hospital discharge abstract databases, phone book listings, etc. Information about EMS systems will be obtained from EMS agencies. This information will include 911 response level (e.g., standard vs. enhanced), ambulance response interval profiles, advanced cardiac life support (ACLS)

transport capability, EMT-Defibrillator program, out-of-hospital ECG program, and existence of billing for EMS transport.

2. Individual based variables

Data on individual based variables will be obtained from patients' medical records. Analyses of delay time intervals and other outcomes described above will address differences in outcomes for, or impact of, the following factors:

a. patients with UA/AMI (ICD 410/411)
b. patients with MI (ICD 410)
c. gender
d. ethnicity/race
e. age
f. previous history of coronary artery disease (CAD) e.g., prior MI or history of angina, bypass surgery, or PTCA)
g. insurance status

C. Process and Impact Measurement

1. Process Evaluation of Intervention Components

Specific program activities and objectives for each of the four components of intervention are linked to three elements of process evaluation: measuring program effort (e.g. REACT staff time to implement activities); dose of the intervention delivered or the amount of the activity carried out (e.g. the number of sessions conducted or the number of professionals or patients attending training programs) and secular trends (or competing activities) in the intervention and comparison sites. The following outlines the process evaluation activities for each of the four intervention components.

a. Community Organization

The process evaluation of the community organization activities includes assessment of both community factors and intervention objectives. To track achievement of objectives for these community factors, a series of standardized activity logs will be established by all sites. Such activity logs will document community contacts, the reasons for the contacts, and the resulting activity.

b. Community Education

A series of standardized logs will be developed to track community education activities at each of the intervention sites. These logs will record public service announcements released and appearing in various media channels. Educational programs and magnet events offered and held in various organizational settings will be documented including the dates, topics of the program and attendance. Flyer and pamphlet distribution will be recorded to track population exposure to the print media by distribution channel. The documentation of the number and types of community education activities (i.e., target segments reached), and the community organization field notes can inform us of special groups in need of education.

Measuring the extent to which various segments of the community have been reached by REACT program messages (or similar activities) is an issue of central concern in process evaluation. The extent of coverage (or exposure) by target segment will be assessed directly through three surveys: 1) a follow-up telephone survey of hospitalized patients with acute cardiac ischemia, 2) a follow-up survey of a sample of patients with chest discomfort sent home from the ED, and 3) a series of random-digit-dial surveys of community residents. Analysis of exposure for various target segments can inform the study about the extent to which the population was reached, by demographics, location of residence, age, and other variables important to the community education process. Furthermore, the process data can help us to differentiate exposure and awareness due to community education vs. patient education sources.

Tracking exposure, awareness, and specific media and community events in the REACT comparison communities is also an essential focus for process data in community education. This information will inform the project of the extent of the anticipated secular trend, so that subsequent analysis can differentiate the effects of REACT from similar activities that would be occurring in any case.

c. Professional Education

Tracking of professional education includes documenting activities offered and conducted to educate physicians, nurses, emergency medical technicians and other professionals at each site. This documentation will include logs of training sessions offered and held over the course of the intervention at each site. These logs would include information about the date and location of a program, the topics covered during the training session, attendance by the target audience, and key characteristics of the attendance (e.g. physician specialty). A count of the number of programs offered or a count of attendance can serve as a measure of program dose or exposure. Staff assessments of target group reactions or response to the training session can be recorded to provide qualitative information for feedback to the project staff. Similar logs would be maintained for academic detailing visits to physician's offices or educational sessions offered to the professionals, and use and frequency of mailed strategies.

d. Patient Education

Process evaluation of the patient education component will include documentation of patient education activities carried out at each site. Logs of individual counseling sessions will be maintained to record the date of an encounter, the topics covered and educational materials provided. Logs will also be kept to document use and frequency of mailed strategies. Patient satisfaction will be assessed during the development of interventions, and periodically from a sample of patients in order to control quality.

2. Impact Evaluation of the REACT Intervention

Impact evaluation is defined as the assessment of program intervention effects on intermediate objectives including changes in knowledge, attitudes, and skills of the public, patients and professionals, and in environmental and organizational factors.

Community organization objectives include participation in teams and advisory groups, resulting programs or activities initiated by the community groups, and relevant community or institutional policy changes. Changes in community norms, one of the objectives of community organization and other components of the intervention, can be partially assessed through the various surveys (hospital and ED follow-up telephone surveys; community survey) described below. In addition, qualitative assessments recorded through semi-structured project staff field notes can further describe and document changes in community relations and norms. Analysis of community structures created or facilitated by REACT (advisory boards, hospital teams, etc.) will include group composition, meeting attendance, participation in activities, and productivity.

The impact of community education on knowledge, attitudes, relevant skills and behaviors will be assessed directly through a series of random-digit-dial surveys of the community, and indirectly through post-discharge telephone interviews of AMI/UA patients and those patients sent home from the ED. Patient education objectives will be assessed from the interviews of AMI/UA patients and patients discharged from the ED.

The development of both community and patient education impact measures will proceed as follows. Existing instruments will be assessed for their relevance to constructs of importance in the present study. Preliminary studies, focus groups and key informant interviews will inform the project of the most appropriate terms to use in eliciting patients' relevant knowledge, attitudes, and skills.

3. Collection of Process and Impact Data

a. Follow-up interview of hospitalized patients.

At seven to nine weeks following hospital discharge (but no more than 90 days after hospital discharge), a telephone interview will be conducted by the coordinating center with a subsample of 200 patients per community who have a discharge diagnoses of 410 or 411. The purpose of the telephone interview is fivefold: (1) to characterize these individuals, their symptom experiences, and their reasons for seeking treatment; (2) to identify specific intervention components that prompted these patients to seek treatment; (3) to collect self-reported information on decision time; (4) to assess the impact of the patient and professional education interventions on the knowledge, beliefs and attitudes, and behaviors of these individuals; and (5) to assess the intentions and preparations to take action if another event occurs. This survey will provide an assessment of the impact of intervention messages delivered in the hospital and

during the rehabilitation period. Process data will also be collected on the specific content and sources of educational messages received.

b. Community survey

The study will monitor intervention impact in the communities in part through use of a series of random-digit-dial cross-sectional surveys conducted at four time points during the study: a baseline survey (n=60/community) , two interim surveys (n=60/community and n=30/community) , and a final survey at the end of the intervention (n=30/community). The surveys will be conducted by phone in both intervention and comparison communities. This will permit both estimation of intervention impact and the impact of non-intervention messages from other sources on MI delay with ability to pinpoint messages and their effects over time (i.e., the secular trend in information). For most communities in the study, an average of two to five percent of households lack telephones. However, a few communities indicate a lack of household phones at somewhat higher rates (10-15%). Because this survey method is designed to summarize impact across all intervention and comparison communities as a group, the higher lack of phones in a few communities is not regarded as a serious disability.

c. Survey of patients sent home from the ED

At seven to nine weeks following a visit to the emergency department, the study will also conduct a follow-up telephone interview on a sample of 100 patients per community who present to the ED with chest pain, but who are subsequently released without an acute cardiac diagnosis. The purpose of the telephone interview is fourfold: (1) to characterize these individuals, their symptom experiences, and their reasons for seeking treatment; (2) to identify specific intervention components that prompted these patients to seek treatment; (3) to collect self-reported information on decision time; and (4) to assess the impact of the patient and professional education interventions on the knowledge, beliefs and attitudes, and behaviors of these individuals. The impact and process evaluation questions included in the phone survey will be similar to those in the random digit dial survey of community residents.

D. Informed Consent

Initial data collection will be conducted by emergency department nurses at participating study hospitals, who will be instructed on the use of a common protocol asking patients with acute chest pain or related descriptors about the time of onset of acute symptoms. These questions are part of routine medical care and do not require informed consent from patients.

The chart abstractions and telephone follow-up interviews will be conducted by specifically trained REACT staff and will involve the collection of demographic characteristics, diagnoses, symptom attribution, and clinical course. In the review of the medical records, patient identifiers will be separated and kept in a locked file, with access limited to REACT staff. Informed consent from the patient will not be obtained for review of medical records, as no patients will be individually identified. Telephone interviews of ED patients sent home and hospitalized patients with a diagnosis of CHD telephoned after discharge will require the patient's informed consent. The method of obtaining this consent may vary according to local hospital IRB requirements. The current plan is to obtain passive consent from patients selected to be called. A letter, on hospital letterhead, will be mailed to patients by study center staff explaining the study and requesting their participation in a telephone survey. If patients do not want to participate they may return the enclosed postcard indicating refusal. It is assumed that for those who do not return the postcard that passive consent has been obtained. Verbal consent to participate will also be obtained at the time the patient is called to conduct the telephone survey by specially trained REACT staff. Patients will be allowed to refuse answering any questions during the telephone interview **(see model consent letter at end of this section).**

E. Summary of Data Collection Sources

The data described above will be obtained through the following data collection sources:

1. EMS records
2. ED logs
3. ED chart review of ED patients with chest pain/discomfort sent home (200 patients per community).
4. Medical and ED chart reviews of patients admitted for MI, rule-out MI, UA, chest pain or related descriptors.
5. Follow-up telephone interview of ED patients sent home (100 patients per community)
6. Follow-up telephone interview of a sample of hospitalized AMI/UA patients discharged alive (200 patients per community)
7. Community survey (60 surveys per community at T1 and T2 and 30 surveys per community at T3 and T4.)
8. Records of intervention implementation
9. Vital statistics datatapes

F. Measurement Training, Certification, and Performance Review

1. Research Telephone Interviews

The Coordinating Center will hold a local training for those coordinating center staff that will be responsible for the telephone administration of REACT interviews. The training will be led by the Director of Survey Research. The didactic component of the training will review the following areas 1) an introduction to the telephone interviewing process, 2) the role of the research interviewer, 3) telephone interviewing techniques - principles of probing, non-biased or non-directive interviewing, and 4) an in depth review of the REACT interview data collection instrument(s), the rationale for the questions as well as instructions on coding responses. The REACT telephone interviews will first be demonstrated by the CC trainers. The trainees will then participate in role playing practice sessions and feedback on performance will be provided.

Certification will be required of all coordinating center interviewers. For this initial evaluation, each interviewer will be paired with a CC staff person who assumes the role of the subject. Each pair is then observed by a CC certified trainer and evaluated using standard performance criteria. A 90% score or better will be required for certification. During the first two weeks of data collection, interviewers will then be monitored during two actual patient interviews (with permission from the subject) by the CC supervisor. A 90% score or better will be required to complete certification at baseline. Interviewers will also be monitored every four months thereafter and evaluated by the CC supervisor using a standard quality control check list. The supervisor will then meet with the interviewers to review their performance and items on the interview form which are not complete, missing or unclear. Suggested areas for improvement will be discussed. The results will permit an on-going evaluation of adherence to protocol, consistency of interpretation and recording of standardized responses.

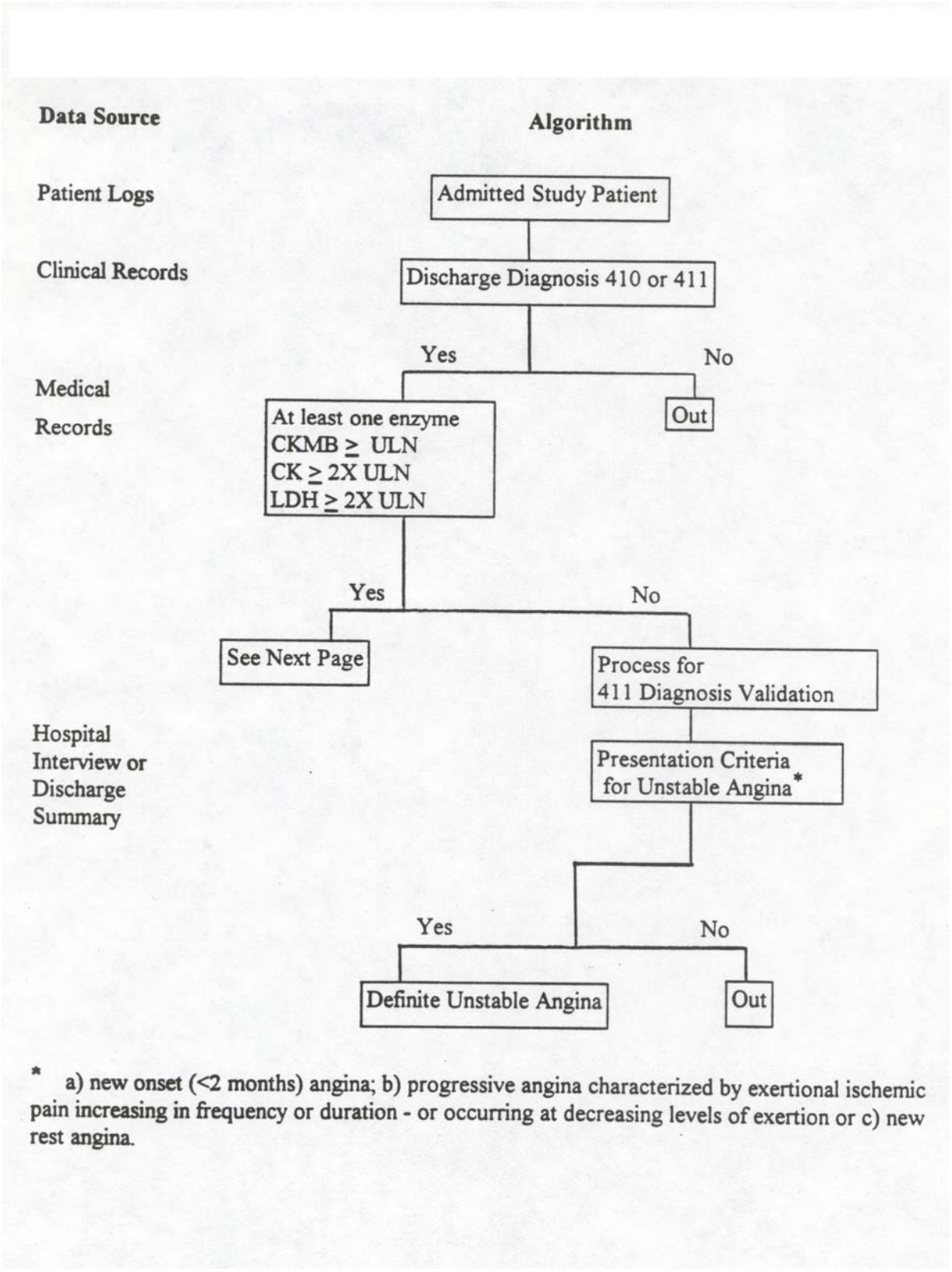
2. Record Abstraction

The Coordinating Center will hold a central two day training for those study center staff that will be responsible for training field staff to abstract hospital records. The didactic component of the training will review the following areas: 1) an introduction to abstraction and issues concerning reliability and validity, 2) the role of the abstractor and interpretation of the record, 3) procedures for accessing the medical record, 4) the content of the medical record(s) and 5) an in-depth review of the REACT abstract data collection instrument(s), the rationale for the questions, as well as instructions on how to record and edit responses. Trainees will then practice by abstracting two sample medical records. Questions and problems with interpretation will then be reviewed.

Certification will be required of all study center abstractors. Five actual medical records will be selected on patients hospitalized with acute coronary heart disease which also represent a range of severity of illness. These records will be abstracted by three study physicians and agreement on the gold standard for each record will be reached by consensus. Trainees will then be tested by abstracting these five cases using the REACT data collection forms. Abstracts will be compared to the gold standard and a score of 90% agreement or better will be required for certification.

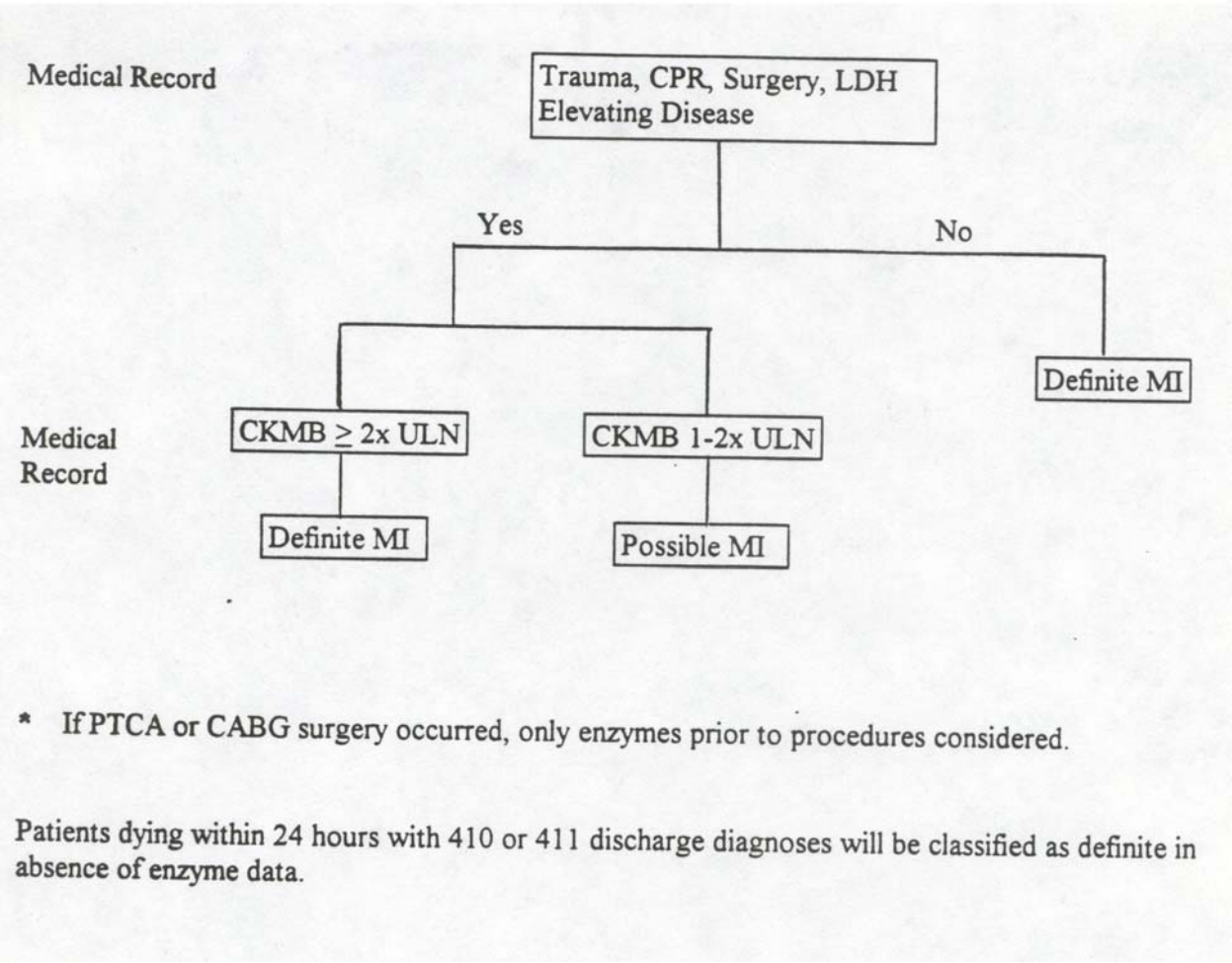
A similar process will be repeated semiannually for re-certification of all abstractors, as well as to assess inter rater reliability or agreement among abstractors across the sites. A written report and feedback will be provided to each abstractor.

Figure 5. REACT 410/411 Discharge Validation



* a) new onset (<2 months) angina; b) progressive angina characterized by exertional ischemic pain increasing in frequency or duration - or occurring at decreasing levels of exertion or c) new rest angina.

Figure 5 cont. REACT 410/411 Discharge Validation



* If PTCA or CABG surgery occurred, only enzymes prior to procedures considered.

Patients dying within 24 hours with 410 or 411 discharge diagnoses will be classified as definite in absence of enzyme data.

(ON HOSPITAL LETTERHEAD)

REACT Model ED Patient Consent Letter

Dear (NAME OF PATIENT),

Recently you were treated at (NAME OF HOSPITAL) on (DATE). The purpose of this letter is to invite you to take part in a research study whose goal is to better understand patients with symptoms of chest discomfort who present to the emergency department. This study is being done by the (NAME OF UNIVERSITY) and is funded by the NATIONAL HEART, LUNG and BLOOD INSTITUTE.

If you agree to participate, an interview from the New England Research Institutes in Massachusetts will be calling you on the telephone to conduct an interview. You will be asked about your medical history, the signs and symptoms that led you to seek care at the Emergency Department, use of emergency medical services, your opinions about seeking care for these symptoms and your experiences at the Emergency Department. The telephone interview will take approximately 15 minutes.

All information will be strictly confidential. You will have an identification number assigned to you and your name will not be used in any reports.

If you do not wish to participate in this interview, your refusal will have no effect upon your medical treatment. If you do not wish to participate, please sign and return the enclosed postcard and you will not be contacted again. If we do not receive the enclosed postcard, we assume that you have agreed to allow us to call you. Regardless, you may decline the interview at the time you are called.

If you have any questions or concerns about this research project or the telephone interview, please feel free to call (NAME OF SITE PROJECT DIRECTOR OR COORDINATOR) at the (NAME OF UNIVERSITY). The telephone number is (SITE TELEPHONE NUMBER).

Thank you for participating in this important research project. It is important that people like yourself share their experiences and opinion. Your hospitals also know and support the study.

REACT Sample Patient Refusal Postcard

PRINT NAME _____

_____ I do not wish to participate in the REACT study. I understand that my refusal to participate in the REACT study will in no way affect my medical care.

_____

SIGNITURE

(ON HOSPITAL LETTERHEAD)

REACT Model In-Patient Consent Letter

Dear (NAME OF PATIENT),

Recently you were treated at (NAME OF HOSPITAL) on (DATE). The purpose of this letter is to invite you to take part in a research study whose goal is to find better ways to help people recognize the signs and symptoms of possible heart disease as rapidly as possible so patients can receive the best available treatment. This study done by the (NAME OF UNIVERSITY) and is funded by the NATIONAL HEART, LUNG and BLOOD INSTITUTE.

If you agree to participate, an interview from the New England Research Institutes in Massachusetts will be calling you on the telephone to conduct an interview. You will be asked about your medical history, the signs and symptoms that led you to seek care at the (NAME OF HOSPITAL), use of emergency medical services, your opinion about seeking care for these symptoms and your experiences during your hospitalization. The telephone interview will take approximately 15 minutes.

All information will be strictly confidential. You will have an identification number assigned to you and your name will not be used in any reports.

If you do not wish to participate in this interview, your refusal will have no effect upon your medical treatment. If you do not wish to participate, please sign and return the enclosed postcard and you will not be contacted again. If we do not receive the enclosed postcard, we assume that you have agreed to allow us to call you. Regardless, you may decline the interview at the time you are called.

If you have any questions or concerns about this research project or the telephone interview, please feel free to call (NAME OF SITE PROJECT DIRECTOR OR COORDINATOR) at the (NAME OF UNIVERSITY). The telephone number is (SITE TELEPHONE NUMBER).

Thank you for participating in this important research project. It is important that people like yourself share their experiences and opinion. Your hospitals also know about and support this research.

VIII. DATA MANAGEMENT SYSTEM

To successfully maintain and analyze the data collected in this multi-site study a consistent, reliable, and secure system for entering and managing data must be implemented. A central data management system with some distributed direct laptop entry will be established for REACT which ensures: a) efficient data entry at each Study Center, b) secure and reliable data transfer from the Study Centers to the Coordinating Center, and c) system maintenance at the Coordinating Center. The querying, sorting, relating, merging, and final analysis of the complete data base will be done centrally by the Coordinating Center with statistical analysis software (SAS). This section outlines the Distributed Data Management for the REACT study.

A. Data Forms and Forms Handling

REACT data collection hard copy forms (or the computerized versions for direct entry) will be the primary medium for recording data related to the study and will be prepared and supplied by the REACT Coordinating Center. Separate sets of data collection instruments and procedures for their administration will be prepared for each type of measurement. Data collected from the emergency department and hospital medical records will utilize direct laptop data entry. The telephone surveys will be conducted on a CATI system (computer assisted telephone interviewing) with direct entry. Hard copy forms will be available as back-up for all direct entry.

Each data form will be labeled with a form version date and subject ID number and contain specific instructions for completing each entry. Data forms will be initialed by the person responsible for the information on the form. All forms completed by REACT staff will be filled out in ink. Photocopies of the original paper forms will be maintained at the REACT Study Center where the data was collected. The original forms will be mailed to the Coordinating Center for data entry. A filing system will be developed for the five REACT Study Centers to permit rapid retrieval of data forms for the resolution of any data discrepancies.

Prior to mailing to the coordinating center, all REACT forms will be reviewed by Study Center staff for accuracy and completeness. Any data changes will be recorded in ink and initialed by the person making the changes.

Data from laptop direct entry will be stored on diskettes and mailed to the Coordinating Center on weekly basis.

B. Data Entry and Editing Procedures

A menu driven data management system will be developed by the REACT Coordinating Center. The REACT Coordinating Center will design data entry modules for each REACT data form and provide periodic updates of the software. The hospital medical record abstract and emergency department record abstract will utilize direct laptop data entry programs as described above. All other data entry, such as process evaluation forms, will be done by trained personnel at the Coordinating Center under the direction of the REACT Coordinating Center data manager.

During data entry, each subject is initially identified in the data management system by a unique REACT ID number which will then allow the system to accurately track the status of all forms and information related to each subject. The study identifier is a unique ten digit code comprised of the one digit study center

code, one digit community code, two digit hospital code, five-digit sequentially assigned patient ID and a final check digit which is generated by the computer as a mathematical function of the previous nine digits in the ID. The check digit serves to validate ID's in the data entry process, making incorrect entry of an ID unlikely.

This identifying information is entered into the REACT data entry system under an enrollment menu. The REACT data entry system also includes software for keeping track of which forms have been entered for each patient. This system ensures that all REACT data records are unique, identifiable, and capable of being related later.

The REACT DMS will provide for complete on-line editing of data as they are entered into the microcomputer or the laptop. Under program control, this editing capability includes range checking, table look-up for value accuracy, intra and inter-form logical consistency checks and context specific help messages for data coding errors and edit reports. Whenever an error occurs, the system automatically notifies the user and explains the nature of the error. If the error cannot be corrected immediately, the error can be overridden for temporary bypass. This override function during direct keyboard entry merely permits the operator to continue to enter data for that form. Upon completion of data entry, all errors are automatically printed out in hard copy edit reports for resolution by the coordinating center and study center data collection staff.

During edit resolution, the study center data manager will document the corrections on the edit reports and on their photocopies of the data forms along with the date of change and initials of the person providing the correction. The coordinating center data manager corrects the database and attaches the edit correction form to the original study data form. All database corrections generate audit trails that document the old and new data values, when the change was made and who made it. This audit trail permits recovery from operator change errors and provides the potential for roll-back of the database in case of major data change errors.

C. Maintenance of the Data Base

The REACT data base is maintained on a Novell Network at the REACT Coordinating Center. Data will be transmitted to the CC from the Study Centers by mail on a weekly basis during data collection. A combined database is made storing all data from all sites. This allows the Coordinating Center to produce study wide summary and status reports. A number of data management reports will be generated by each REACT Coordinating Center to assist in the local maintenance of the data. These reports include frequency tables and status reports on all forms, indicating missing forms and unresolved edit reports. Problems requiring edits to data will be referred back to study center data managers for resolution.

D. Communication Among Centers

Electronic mail transmission via computers facilitates rapid communication between the Coordinating Center and the Study Centers and the Program Office at NHLBI. Other means of communication among centers include facsimile machines, overnight carrier, and telephone.

The Coordinating Center will utilize a custom communications system that integrates Electronic mail, Fax, Fedex and U.S. mail. REACT staff around the country can express their preferences for receiving documents. Staff E-mail, Fax numbers, Fedex and U.S. mail addresses are stored at the Coordinating Center in a database. Documents produced by the Coordinating Center are routed by each person's preferred method. This system will automatically reduce expenses, depending on the time sensitivity of the material, by faxing after hours, and using two-day delivery Fedex.

REACT staff can communicate back to the Coordinating Center using E-mail, Fax, Fedex, U.S. mail or phone.

IX. QUALITY ASSESSMENT

A primary concern of REACT will be to assure the quality and consistency of the data being collected and analyzed. The validity of the reports and results produced and published by the study will depend upon the integrity of the data submitted by the Study Centers, and upon the appropriateness, thoroughness, and correctness of the data processing and data analysis procedures carried out at the Coordinating Center. Routine data management system quality control reports will be developed for periodic review by the Measurement and Quality Control Subcommittee of the Steering Committee. These reports will provide site comparisons and include at a minimum: data entry error rates, missing data rates, missing participant form rates, and refusal/ participation rates for study interviews. Additional quality control review occurs at the level of the Data Safety and Monitoring Board, which periodically reviews the progress of the REACT study.

A. Quality Assessment of Study Procedures

Quality control of study center procedures begins with the planning and preparation for data collection and continues throughout the course of the study. The collection of high-quality, consistent, complete data and their efficient processing into data sets for analysis therefore depends on at least the following:

- clear, unambiguous manuals of operations both at the Study centers and at the CC
- regular collaborative communications between the Study Center Coordinators and the CC
- training and certification of data collection interventions and data management personnel
- automated procedures for data checking/editing
- regular review of all site data collection procedures, including re-abstraction of at least 5% of all records
- regularly scheduled site visits

Each of these activities as well as specific procedures for monitoring the performance of the Study Centers and Coordinating Center are given in the following sections.

1. Manuals of Operations

The operations manuals (MOO) will specifically define how to carry out all aspects of the study protocol including approaches to recruitment, sampling schemes, measurement procedures, intervention implementation and data management. The CC will be responsible for developing the Study Manual of Operations in collaboration with the Study Center Investigators and NHLBI staff for REACT. The manuals are maintained in three ring binders with each page dated such that updated instructions , with revision date can be generated by the CC and sent to the study center as replacement pages for the manual. Each staff member will be required to refer to one of these manuals and will have his/her own copy, to ensure constant, ready access. Updates to these manuals will be distributed by the CC .

2. Field Coordination and Communication

Each Study Center will have a Project Coordinator who is responsible for ensuring all aspects of the implementation of the study protocol. This persons' responsibilities include communication with the CC on all protocol issues, supervision of all interventions and measurement activities, and review of data forms and edit resolution activities. The work of these coordinators will be monitored through the completeness and timeliness of data transmissions to the CC as well as through periodic site visits. The CC will schedule regular conference calls among the Study Center coordinators and the CC. The conference calls will be used to discuss and resolve questions or problems with implementation of the protocol early in the process of data collection.

3. Training, Certification and Performance Review

A major contributor to data quality and consistency across sites is through training and certification as well as regular performance monitoring with re-training as required. Centralized trainings at the CC will take place prior to the start of baseline data collection. Designated Study Center staff will be trained on all aspects of the study including design of the study, abstraction of records, data form completion and editing, implementation of intervention components, and data management procedures such as data transfer and edit resolution. These trainings will be organized by the CC with expertise drawn from the Study center staff and outside consultants as needed. Standard evaluation checklists will be used to assess the adequacy of training and to ensure a minimum competency for all Study Center staff. This evaluation must be passed before Study Center staff are certified as competent to implement protocols. Once the initial training and certification is completed, interviewer and abstracter technique will continue to be monitored in the field. Details of the training, certification and on-going performance review of data collectors is described in Section VII. Details of Quality Assessment of the Intervention are described in Part B.

Finally, the central trainings will be videotaped to assist in staff training in two important ways:

a. This device facilitates standardization by clearly demonstrating correct and incorrect, acceptable and unacceptable procedures; and

b. In conjunction with a written manual, this device provides standard on-site training of new staff, between site visits as well as "refresher" re-training of other staff as needed.

4. Regular Review of Data Collection Procedures

One of the components of Coordinating Center's DMS is a mechanism for randomly selecting a percentage of entered data forms for re-entry. The Coordinating Center data managers will begin with 100% reducing to a random sample of forms for re-entry depending on the observed error rate. A report is then prepared on the frequency of errors by data item and resolved with the Study Center. Finally, a 5 % random sample of original medical records at each Study Center will be selected and re-abstracted on-site by the CC staff. A report will be prepared on the frequency of discrepancies by data item and reviewed with the Study Center for resolution.

5. Data Checking and Editing

The basic procedures to ensure the highest quality data and prevent file degeneration include screen data entry with built-in logic and range checks, duplicate form detection, re-entry of sampled forms, restricted access to data editing routines, and the use of transaction files to provide audit trails of data edits. The transaction (edit) file structure which includes information on the staff person making the change, the date executed, the original datum and the new value provides a basis for monitoring all data entry and data quality. These procedures are described in Section VIII.

6. Regular Site Visits

Site visits will occur annually to ensure standard implementation of protocols. These visits also serve as an opportunity to observe and certify any new staff. Site visits will be conducted each year of data collection to review study center procedures, observe form completion, and measurement implementation as well as to check for correct filing of forms, data corrections and maintenance of subject confidentiality. A single team of site visitors will observe staff from each study center to evaluate adherence to protocol and to suggest modifications where necessary. An evaluation checklist will be completed at these site visits for inclusion in a Site Visit Report to the Principal Investigator. Immediate feedback will be provided to Study Center investigators and a written report will be available for review by the Steering Committee and the DSMB.

B. Quality Assessment and Monitoring of the Intervention

Several monitoring methods will be employed to ensure that the intervention is being implemented as planned. Deviations from the manner in which the intervention is planned will be captured within the process evaluation, but these deviations will also be monitored by the Intervention Subcommittee and Working Groups (Community Organization Working Group, Community Education Working Group, and Patient and Provider Education Working Group) as well as the Measurement and Quality Control Subcommittee. Substantial deviations from the intervention protocol and MOO will be reported by these subcommittees to the Steering Committee, and proposals for ensuring conformance to the protocol will be developed and implemented.

An essential component of REACT quality control procedures will involve the clear delineation of intervention activities within the MOO and careful training and semi-annual re-training of key REACT intervention staff. In addition, monthly conference calls will be held by the Intervention Subcommittee and Working Groups (Community Organization Working Group, Community Education Working Group, and Patient and Provider Education Working Group) during which intervention implementation issues can be discussed and community-specific progress in meeting the intervention objectives can be reviewed. These training sessions and conference calls will ensure that: 1) everyone is familiar with the intervention protocol; 2) differences in interpretation of the protocol are resolved; 3) problems in implementation are noted early and corrective action taken; and 4) accountability for implementing the intervention within each community is ensured. In addition to these general methods, specific methods discussed below will be used to monitor the implementation quality of each of the four components of the intervention.

For the community organization component, logs will be developed and maintained to ensure that specific implementation objectives are being met. These logs will characterize for each community: the hospital teams and their activities; members of the community board/group and their activities; task forces within boards and their activities; numbers of volunteers and their activities; and training sessions for local trainers and leaders. Summary quality control data will include whether the groups have been established, their meeting frequency, and numbers of activities.

For the community education component, records will be kept of the placements of community education information. Also, periodic content analysis will be conducted of the themes in media messages developed by community organization or journalists. If certain media have not incorporated REACT messages, then ongoing contacts will attempt to correct this. Group community education sessions will undergo rigorous development and quality control. Training of group leaders will emphasize close adherence to the outline of topics developed by REACT staff. Observation and feedback to community group educators will be a key feature of their initial training, and "refresher" sessions will be offered subsequently. The same principles will be used at those sites that develop speakers' bureaus for community group education. Group leaders and speakers will be asked to submit tape recordings of their presentations from time to time so that adherence to the outlines can be assessed. Summary quality control data will include the numbers of media messages used by type and channel of message for media, and numbers of group leaders and presentations.

For the professional education component, recruitment of REACT staff will ensure that they have appropriate training and experience to implement the professional education strategies. Throughout the development and implementation of strategies, a variety of techniques will be employed to monitor the quality of the delivery of the activities. The protocol for teaching patient-oriented counseling will be developed according to an explicit outline that reflects the overall goals and objectives. Training for physicians, nurses, EMTs and other target professionals will be pilot tested with opportunity for feedback from participants and observation by the trainers. A CME protocol will be developed by the REACT working group to insure that minimal standards for content and methods are addressed. A participant feedback (satisfaction) sheet will be required of attendees to give feedback on CME facilitators' skills. Summary quality control data for the professional education component will be developed to reflect the numbers of professionals involved in education activities and their satisfaction with the content and methods of the sessions.

For the patient education component, patient interviews (follow-up of hospitalized patients and those sent home from the ED) and the rolling cross-sectional survey will provide periodic monitoring and quality control information regarding coverage. The interviews and surveys will reveal the audiences receiving the messages and reflect potential weaknesses in people's understanding of the educational material. For patient group education, a session protocol will be developed by the REACT working group to help insure that minimum standards for content and methods are being addressed. A participant feedback (satisfaction) sheet will be asked of attendees to give feedback on session facilitators' skills. Educators will also be asked to tape record a sample session from time to time in order to receive feedback from other

REACT staff. Other patient education activities will be carried out by existing providers in the community. The quality of the educational effort is, in part, related to the quality of the training. Initially, these professional "patient educators" will undergo training by REACT staff, in the context of continuing education or through videotape and written materials that permit a more flexible schedule for learning the patient education techniques. Staff will observe educators' practice and provide feedback to them about adherence to the protocols and effective presentation. Periodic "refreshers" will be offered by sites in order to assess whether educators are adhering to counseling protocols. Summary quality control data will reflect the content provided by the patient interviews, participant feedback, staff ratings of professionals' counselling performance, and numbers of professionals involved in refresher programs.

C. Quality Assessment of the Study Centers

Performance of the Study Centers will be assessed by periodic consideration of the following:

1. Subject Recruitment and Participation Rates

2. Number of study forms for which the data are past due at the Coordinating Center

3. Percentage of participants with missing forms and percent of missing data for each form

4. Form coding errors

These activities will be supplemented by periodic site visits by Coordinating Center staff to the Study Centers.

D. Quality Assessment of the Coordinating Center

The following are some of the activities the REACT Coordinating Center will carry out that will help to enhance the quality of the data and analyses. These activities will be supplemented by periodic site visits by the NHLBI Project Office to the CC.

1. A sample of original process data forms and medical record abstract data forms abstracted during site visits will be compared with the data entered on computer to detect problems with the data entry and editing software and problems with merging the data onto the main study data base.

2. For each variable on the data base, a tabulation of the frequency of occurrence of every distinct value will be obtained. This will help to identify many types of anomalies in the data such as: (1) illegal codes, (2) measurements given to more decimal places than provided by the measuring instrument, (3) digit preferences, (4) bimodality or other bizarre form of a distribution, and (5) outliers, i.e., extreme values distinctly separate from the rest of the distribution. Once an observation has been identified as a true outlier, the first step is to go back to the

original records and determine whether a recording or keying error was made. If such a value is verified as correct, then the question of whether or not to include the value in the data analysis depends upon the nature of each analysis. There is no reason to exclude the value if the analysis is a count of the number of participants having a value exceeding a given cut point. However, if means and standard deviations are being computed, or if correlation or regression analyses are being carried out, and the outlier value is such that it could have an undue impact on the mean and standard deviation, regression analysis, etc., then it should either be excluded or statistically transformed for purposes of the analysis.

3. When preparing data reports, tables developed from a variety of analysis programs will be checked for consistency. A discrepancy of as little as one participant among the denominators in different tables may be an indication of a much larger problem.

X. SAMPLE SIZE, POWER, AND DETECTABLE EFFECTS

A. Units of Analysis: Design and Sampling Constraints

In this community trial the term "sample size" has a dual meaning: first, the number of communities randomized, and second, the number of cases collected within each community. The randomized units are whole communities, geographically distinct and pair-matched for size and demographics. The sample size is limited by practical constraints to 20 randomized communities, comprising 10 pairs, two pairs per field site, one of each pair to be assigned to Intervention and one to Control.

Because 20 units is a relatively small number for a randomized experiment, the following two statistical strategies have been pursued to ensure a high likelihood of detecting the experimental effect with statistical significance. First, the communities have been paired as effectively as possible, so that intra-pair correlation will act to reduce variance and sharpen the comparison between the Intervention community and the Control community in each pair. Second, the community-level endpoint has been defined in such a way that it can be measured with the greatest possible precision. In REACT this means (a) choosing a primary endpoint that is consistently defined and measured at every site and has low random variability among communities; (b) using statistical techniques such as covariate adjustment at the local level to improve precision in estimating the community value (addressed in the Analysis Plan); and (c) collecting a sufficient number of cases in each community to minimize measurement error as a source of variance. The number of cases depends, in turn, on the definition of the endpoint to the degree that eligibility criteria enter into that definition.

The available number of cases in each community is constrained by the local population and demographics as well as the pattern of hospital and emergency-department (ED) usage. Table 4 shows the projected number of cases in each community in three categories: total ED visits for chest pain; hospital discharges with ICD code 410 or 411; and confirmed cases of MI. Although the expected event rates in Table 4 come to 1202 per community for the 22-month trial, that rate is severely diminished by several mechanisms. First, a certain fraction of the patients discharged with 410/411 codes will present at the ED with complaints other than chest pain or will be admitted by some route not captured by the REACT sampling frame. Second, a certain fraction of cases will provide incomplete, invalid, or unusable data. Finally, a certain percentage of 410/411 diagnoses will fail to be validated. Early data showed that these mechanisms when compounded reduced the rate of usable cases by more than two-thirds, from 1202 to 375 per community. The REACT eligibility criteria were therefore revised to include all cardiac-related discharges. Broadening the criteria approximately doubled the expected sample, to 750 per community over 20 months, or a total of 15,000 usable cases.

The logistical demands of REACT measurement suggest, insofar as is compatible with sample-size requirements, that random subsampling of cases be conducted in the larger communities. Rather than lock the REACT design into a fixed subsampling scheme, the study will institute a conservative sampling plan that can be adjusted (without bias) as the data come in. In the smallest communities (two in the Washington field site and all four in the Texas site), 100% sampling will certainly be required throughout REACT. In the intermediate-sized communities, sampling will

begin at 100% but will be monitored by the Coordinating Center to determine whether "mid-course" adjustment to a smaller sampling fraction might be appropriate. In the largest communities (Worcester, MA and Eugene, OR), sampling will begin at 50% and will be similarly monitored and adjusted if necessary.

The mechanism of random sampling will be as follows. Case ID numbers will be generated in bulk at the Coordinating Center. Along with each ID, a random number will be drawn from the uniform distribution between 0 and 1 and coupled with that ID in the permanent database. The ID numbers will be printed on labels and shipped to the field sites for use in case ascertainment, but the random numbers will be retained in the Coordinating Center database. On receiving each batch of ascertained cases (on ED Log Forms) from the field, the Coordinating Center will determine by consulting the random numbers in the database which case ID's should be followed up with REACT Locator Forms, ED Abstract Forms, and Followup Surveys.

This system of random sampling is unbiased and blinded to a high degree, because the field sites will have no access to the random numbers. An important advantage of the system is the possibility of adjusting sampling fractions, either prospectively or retroactively. Any such adjustments will be made solely on the basis of need for a larger or smaller sample. This can be done without bias because the Coordinating Center has no access to medical chart data other than what has already been collected.

At the individual level, with all sites pooled, subsampling will skew the ethnic composition of the overall REACT sample to some degree, slightly raising minority representation. A valid random subsampling scheme would not alter the ethnic balance of the sample collected in any given community. Since all primary and secondary REACT analyses, in keeping with the community randomization design, are planned at the community level, these would not be biased by subsampling. The impact of subsampling is addressed in more detail in Appendix C.

B. Detectable effect, primary analysis

Power calculations for REACT are most informatively framed with sample size, power, Type I error, and variance as fixed parameters (or, in sensitivity analysis, as independent variables) and detectable effect as the dependent variable. The requisite formulas for the primary analysis are summarized in this section. Results for secondary outcomes and further mathematical details are provided in Appendix C.

The primary REACT endpoint is *T*, the delay time between onset of acute symptoms and arrival at the hospital. Because the distribution of delay time is skewed according to all reports from previous studies, the logarithm of delay time will be used in the analysis.

The primary community-level endpoint of REACT is the trend in mean log delay time over the course of the trial. The individual delay times are expected to be sufficiently variable that the trend will be adequately represented by a linear slope β. The null hypothesis of REACT is that on the average β will not differ between the Intervention community and the Control community in each pair.

Delay time will be observed during a four-month baseline period and then over an 18-month intervention period (Figure 6). Each community's trend will be estimated

by simple linear regression, with all baseline observations assigned to time 0. The fitted slope *b* has a standard error asymptotically equal to $\sigma(KV_t)^{-1/2}$, where σ is the residual standard deviation of log delay time; *K* is the total number of cases collected in the community; and V_t is the variance of calendar time at which cases were observed.

The average effect of REACT is estimated by

$$\bar{d} = \sum_{j=1}^{J}\left[b_{j,Intervention} - b_{j,Control}\right] / J$$

where *J*=10 is the number of community pairs. $\bar{d}$ is an unbiased estimator of the truemean difference between Intervention and Control slopes. Its variance is

$$SE^2(\bar{d}) = V(\bar{d}) = 2\sigma_\beta^2(1-\rho)/J + \sigma^2 \sum_{j=1}^{J}\left[K_{j,Intervention}^{-1} + K_{j,Control}^{-1}\right] / V_t J^2,$$

where σ_β^2 and ρ are respectively the random community-to-community variance and the intra-pair correlation betwen community-level linear trends.

The primary null hypothesis of the REACT trial is that there is no population ("true") mean difference between Intervention and Control slopes: $H_0 : \Delta\beta = \langle\beta_{Intervention}\rangle - \langle\beta_{Control}\rangle = 0$, where $\langle\ \rangle$ indicates population expected value. The null hypothesis permits the Control slope to be nonzero and thus allows for secular trend. The alternative hypothesis is that Δβ≠0; this is a two-sided alternative because it is conceivable (though not likely) that the REACT Intervention could prolong the average delay time.

The primary hypothesis will be tested with the conventional Type I error rate of α =5% (two-sided). Sample size estimates are based on a paired *t*-test on the values of *d*, or, equivalently, using a mixed-model ANOVA with REACT group as a fixed effect (1 df). Using the *t*-test formulation, the smallest effect detectable with a specified level of power Π is given approximately by

$$\Delta\beta = SE(\bar{d})(t_{\alpha/2} + t_{1-\Pi}),$$

where $t_{()}$ demarks the specified upper tail area of the central Student distribution. The degrees of freedom for *t* are *J*-1=9.

The net end-trial effect on delay time is related to slope as follows. After *L*=1.5 yr of intervention, the difference in mean log delay time between Intervention and Control communities will be $\Delta y = L\Delta\beta$. The corresponding effect on the median delay time will be a multiplicative reduction by a factor of $10^{-L\Delta\beta}$, or

$$Relative\ reduction = 100\% \times (1 - 10^{-L\Delta\beta}),$$
$$Absolute\ reduction = M \times (1 - 10^{-L\Delta\beta}),$$

where *M* is the median delay time at the end of the trial in the Control communities.

C. Results and Sensitivity Analysis

Detectable effects for the primary endpoint in the primary population are shown in Table 5. Three sample sizes are considered: K=800, 600, or 400 complete, usable cases per community. The figure of 600 represents a conservative estimate, based on the above event rates and attrition parameters. For comparison, a "pessimistic" figure of 400 is included, representing the worst-case parameters with an additional 100 cases subtracted for unforeseen attrition. The "optimistic" figure of 800 per community is probably not attainable but has been included as a benchmark for comparison.

In the conservative case (600 per community), which should be easily attained with the broadened eligibility criteria, the detectable absolute reduction is between 27 and 30 min. if the initial median delay is assumed to be 2.5 hr, as much of the available data suggests. If the initial median is taken as 3.0 hr., the absolute level lies between 32 and 35 min.

The detectable effects shown in Table 5 are not sensitive to the pair correlation of community slopes (ρ). Varying ρ between 0.4 and 0.0 changes the detectable relative reduction by no more than 1% and the detectable absolute reduction by no more than one min., regardless of the other parameters. Sensitivity to the comuunity-level slope variance parameter is also slight. Between 5% and 15% variation in delay time due to random fluctuation of the community trend, the detectable relative reduction varies by 1-2%, which translates to 2-4 min. depending on the initial median.

In summary, Table 5 demonstrates that we can expect to detect a net effect of REACT in the primary population as small as 30-40 min with 80% power, regardless of the strength of pair correlation, the attained sample size, or any magnitude of random trend variability in the plausible range.

Detectable effects for secondary endpoints and for the primary endpoint in secondary populations (sub- or super-groups of the primary population) are discussed in Appendix C.

Table 4. Expected REACT Events Over 22 Months

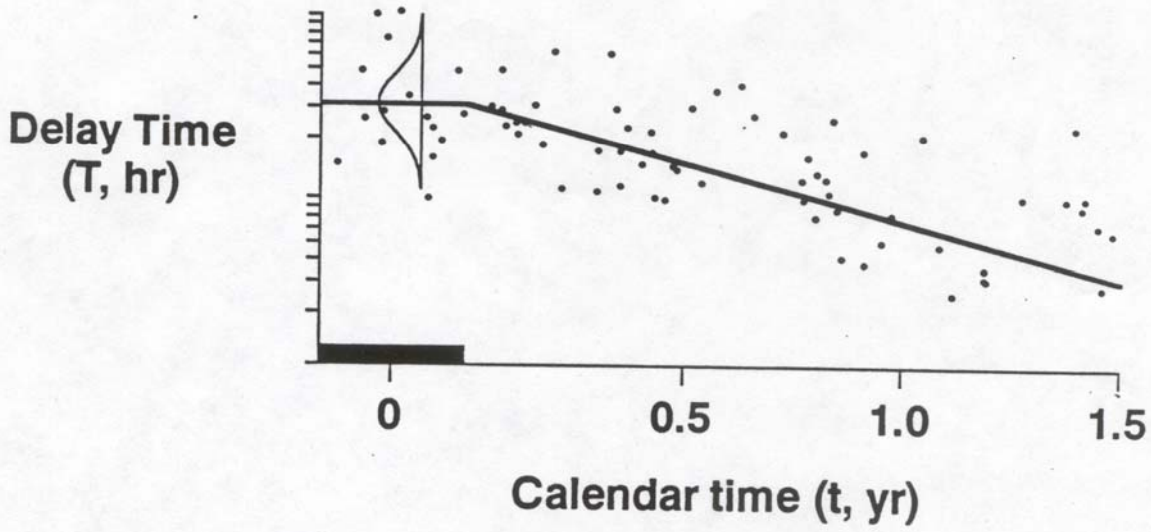
Community	ED Visits	MI Discharges (410)	410/411, All
Alabama			
Anniston (Calhoun Co.)	3667	440	1100
Tuscaloosa (Tuscaloosa Co.)	5500	660	1650
Huntsville (Madison Co.)	3667	440	1100
Opelika (Lee Co.)	4107	499	1247
Massachusetts			
Pittsfield/Dalton	2658	319	726
Westfield/W. Springfield	3343	401	796
Worcester	9686	1162	2578
Lowell	6215	746	1400
Minnesota			
Fargo/Moorhead	6087	733	1833
Sioux Falls	5500	660	1650
Eau Claire	5500	660	1650
LaCrosse	4840	587	1467
Texas			
Brownsville	2420	293	733
Laredo	2420	293	733
Tyler	1833	220	550
Lake Charles	1833	220	550
Washington			
Shoreline	1320	183	345
Olympia	1320	183	352
W. Portland/Beaverton	4620	550	1393
Eugene	4217	935	2179
Total (22mo)	80,752	10,185	24,038
Average per site	16,150	2037	4808
Avg per community	4038	509	1202

Table 5. Detectable Reduction In Delay Time, Primary Population*

Usable cases per community (K)	$R_\beta = 10^{2\sigma_\beta L}$	ρ	Relative (%)	Absolute (min)	
				M=2.5 hr	M=3 hr
800	1.05	0.4	16	24	28
		0.2	16	24	28
		0.0	16	24	28
	1.15	0.4	17	25	30
		0.2	17	26	31
		0.0	18	27	32
600	1.05	0.4	18	27	32
		0.2	18	27	32
		0.0	18	27	32
	1.15	0.4	19	28	34
		0.2	19	29	35
		0.0	20	29	35
400	1.05	0.4	21	32	38
		0.2	21	32	38
		0.0	21	32	39
	1.15	0.4	22	33	40
		0.2	22	34	40
		0.0	23	34	41

*80% power, 5% Type I error (two-sided)

Figure 6. Four-month baseline observation period, followed by linear decline in $\log_{10}$ delay time over 18-month intervention period. REACT hypothesis is that the slope will be systematically steeper in Intervention member of each community pair. Statistical model allows for random variation in slope among communities.



XI. DATA ANALYSIS

A. Methodological considerations

This section reviews the major methodological considerations which affect the analysis of data from REACT, and provides a rationale for the decisions taken for this trial. The major issues include:

- the expected intraclass correlation among observations within a community,
- the lack of comparability between the two study groups expected at baseline,
- the expected lack of balance in the data,
- the distributions of the major dependent variables at the individual level,
- alternative models for the treatment of time,
- the desire for subgroup analyses,
- Type I and II error rates,
- the use of one vs two-tailed tests,
- and the intention to treat principle.

1. Special problems in community trials

The REACT trial belongs to a class of studies often called community trials, a class characterized by the allocation of intact social groups to study conditions. In the case of REACT, whole communities will be randomized to treatment or control conditions. This design is usually chosen because the treatments under study manipulate the social or physical environment, address factors that operate at a group level, or cannot easily be delivered to individuals. In the case of REACT, many of the major interventions will be delivered via mass media and therefore will manipulate the physical environment and cannot be delivered to individuals.

Studies with this nested or hierarchical structure exist in many disciplines and pose a number of design and analysis problems not always present when many individuals are randomized directly to study conditions. These problems are not new (e.g., 82-86), but neither are they widely understood, in spite of a number of recent reviews (e.g., 87,71,88-92). Fortunately, efforts to develop workable solutions to these problems has begun to pay dividends (93,94).

2. Intraclass correlation

The major problem common to community trials is that the observations from the individuals within any intact social group will be positively correlated, reflecting common experiences, selection factors, or both (86). This positive intraclass correlation yields a component of variance attributable to the unit of assignment, above and beyond variation attributable to the individual participants or to the treatments themselves. Since the assignment units are nested within the study conditions in a community trial, the extra variation associated with those units is confounded with variation due to treatment.

Unless the extra variation is accounted for in the analysis, the Type I error rate for the test of treatment will be inflated, often badly (95). Analyses which leave the unit of assignment out of the model altogether will always have an inflated Type I error rate (82,85). Analyses which put the unit of assignment into the model but which treat it as a fixed effect will have an even higher Type I error rate, since that approach will reduce the individual-level error term used to test the treatment effect but will still not account for the positive intraclass correlation (95).

The traditional method to reflect the extra variation inherent in the nested design is to analyze the data in two stages (e.g., 96-98). In the first stage, the data are aggregated at the level of the unit of assignment. At the second stage, the estimated community means or probabilities are analyzed to evaluate the treatment effect, with denominator degrees of freedom (ddf) based on the number of communities; unit level values are often weighted based on the inverse variance of the estimated unit value. Given a sufficient number of assignment units, ANOVA/ANCOVA methods are appropriate for the second stage; where the number of assignment units is small, an exact permutation test can be employed (99).

Mixed-model regression methods often allow this two-stage analysis to be conducted in a single stage, wherein separate variance components are estimated at the observation and assignment levels (e.g., 89,93,94,100). Mixed-model regression methods are now well developed for continuous outcomes, but much work remains before they are ready for common application to binary outcomes; for the later, the two-stage approach is still preferred.

REACT has chosen to employ a two stage procedure for continuous and binary endpoints.

3. Baseline comparability

Because covariates measured on the members of intact social groups also tend to be correlated, it is common for the study conditions included in a community trial to reflect important differences at baseline, especially in trials which involve a limited number of communities (87,101). These differences may exist not only for levels observed at baseline, but also in terms of the underlying individual or community trends. If such differences are ignored in the analysis, misleading estimates of treatment may result, just as misleading estimates may result in small individual-level randomized trials if measurable confounding is ignored.

Several strategies have been suggested to address this expected lack of baseline comparability, including repeated measures on the same subjects over time, stratification or matching on major covariates assessed at the community level, regression adjustment for individual and community level covariates, or some combination of these strategies (e.g., 89,101). While the primary goal with these methods is to limit the influence of confounding variables, these steps may also serve to reduce the natural variation among participants and/or the extra variation attributable to the units of assignment, and these reductions may substantially improve power (e.g., 97). At the same time, care must be taken especially in the selection of matching factors, since ineffective matching can substantially reduce power, especially when there are few communities allocated to each condition (102,103).

Repeated measures on the same subjects is not a possibility for REACT, as the major outcomes will be measured in an ongoing surveillance operation. As a result, REACT has chosen to match on key factors related to the outcome and adjust for selected individual-level covariates. Communities will be pair-matched within field sites for size (population) and sociodemographics (ethnicity, sex, age, education and income).

4. Balance

REACT is perfectly balanced with respect to the randomized units of analysis, the 20 communities. Given the existing imbalance in population size of the proposed pair-matched communities, it is reasonable to expect measurable imbalance in sample size per community for the two study conditions, even after the gross imbalances are mitigated by subsampling. Such imbalance is common in community trials, and may be reduced through matching on population size, through weighting community values according to the estimated inverse variance of the community value, and regression adjustment for individual-level covariates, as described above (c.f., 89,96,98,101).

REACT will use matching on community size, a sampling scheme designed to obtain essentially equal numbers of cases in each community, and regression adjustment for individual-level covariates.

5. Distributions of dependent variables

Community trials may involve outcomes measured as continuous, categorical or time-to-event variables, and these variables may display quite different error distributions at the individual level (87,94). In addition, the error distribution at the community level may not be the same as that observed at the individual level. In the case of REACT, the primary outcome will be delay time, a variable known to have a highly skewed distribution. Other important outcomes include the number of calls per unit time for emergency medical service (also highly skewed), and the proportion of events arriving at the hospital in less than six hours after symptom (binary).

The two-stage approach to analysis of data from community trials accommodates each observation-level distribution through the appropriate selection of the first-stage analysis method, in combination with appropriate transformations. Thus a log-transform could be used to convert delay time to a nearly normal distribution. At that point, the analysis could proceed in several directions. Weighted community means could be analyzed without regard to adjustment for individual or community level factors, or ordinary least squares methods could be used in a first stage to make adjustment for individual-level covariates, followed by ANOVA/ANCOVA at the second stage.

For binary outcomes, weighted community rates could be analyzed without regard to adjustment for individual or community level factors, or logistic regression could be used to estimate adjusted community rates in a first stage, followed by ANOVA/ ANCOVA at the second stage. If measurable confounding is apparent, the methods providing for adjustments will be preferred.

The mixed-model regression approach generally assumes normal distributions for all random variables at both the individual and community level. Thus SAS/STAT MIXED could be used for the analysis of delay time, after a log-

transform is applied to the original data, or for analysis of other variables if the individual-level error distributions can be normalized. SAS/STAT MIXED has a macro which allows the user to specify a binomial, poisson, or other distribution at the individual level, retaining a normal distribution at the community level (94), but this macro remains an experimental procedure and must be used with caution.

REACT will employ a log-transform for the delay time data, followed by analysis as described above.

6. Alternative models for the treatment of time

Each of the REACT field center proposals anticipated that data would be collected at baseline and again at some point after a period of intervention in the treatment communities. This pre-post control group design is of course the mainstay in most clinical and community trials, and will be appropriate for some secondary analyses in REACT where the data will be collected on such a pre-post schedule. Where additional observations are available before or after the intervention (or both), a more efficient analysis may be available if the investigator can specify a particular pattern over time for the expected treatment effect. (e.g., 89,96,97).

REACT presents an unusual study in that the primary events of interest will occur at times randomly distributed throughout both the baseline period and the intervention period. For each event, a record will become available that classifies the event as to its community, its patient characteristics, and its values for each outcome measure. This will give the dataset an uncommon richness in terms of time-dependent observations, and will allow the analysis to model time in ways not commonly available to community trials.

REACT will follow the pattern employed in the analysis of the Minnesota Heart Health Program risk factor and morbidity and mortality data (97), and adapted for the joint analysis of data from the three major U.S. trials of community heart health promotion in the 1980's (71). Pre-intervention data from all 20 communities will be combined with postintervention data from the comparison communities to model a single secular trend. The intervention effect will then be estimated as a departure from that secular trend.

7. Subgroup analyses

Subgroup analyses are often desirable to provide insight into how and for whom an intervention achieved its effect. REACT plans a number of subgroup analyses, all secondary to the primary analyses. These include assessment of the treatment effect on delay among subgroups defined by sex, ethnicity/race, age, history of previous CHD, risk status, and other variables listed in Section IV. These analyses will be patterned after the primary analyses, with appropriate caution added to their interpretation.

8. Inferential parameters

All primary and secondary analyses will employ two-tailed tests with a nominal Type I error rate of 5%.

9. Intention to treat

A commonly followed principle in rigorously evaluated trials is the intention-to-treat principle, which states that participants allocated to each condition must be

retained in the primary analyses, even if that requires conservative procedures to estimate data for subjects lost to followup. REACT will be relatively protected in this regard, as it is not based on a cohort design and so will not be subject to the usual loss to followup problems. At the community level, the intention-to-treat principal implies that a community must be analyzed as belonging to the treatment condition to which it was randomized, regardless of how well the intervention was implemented (in the case of an intervention community) or how much the community may have been influenced by independent REACT-like messages (in the case of a control community).

B. Analytic Methods

1. Analysis of delay time in the primary population

The primary population for whom delay times in each community will be assessed consists of all patients with confirmed MI or unstable angina. This group will be referred to as *primary patients*. For the primary endpoint, delay time is defined to be the time between onset of symptoms and arrival at the hospital.

The logarithm base 10 of delay times will be used in the analysis to make the distribution less skewed and reduce the impact of a few extreme values. A two stage procedure described by (98) will be adopted. In the first stage, delay times within each community are adjusted for individual level covariates such as the patient's age and gender, and then a community level summary is obtained. The second stage consists of analyzing the community level summaries using analysis of variance. The following linear model will be fit in the first stage:

$$Y_{ijk} = \mu_i + P_{j(i)} + \mathbf{q}^T(\mathbf{x} - \bar{\mathbf{x}}) + \beta_i t + \varepsilon_{ijk}. \qquad (1)$$

The terms in the model are explained below. References will be made to "true" means. This refers to the theoretical mean if an unlimited amount of data could be obtained.

Y_{ijk} =log(delay) for the *k*th observation on the *j*th patient in the *i*th community (there may be more than one observation on the same patient).

μ_i =intercept for the *i*th community. This is the true mean baseline value of log(delay) in the ith community for a patient with average covariate values.

$P_{j(i)}$ =random patient effect. This is the difference between the true log(delay) for the *j*th patient of the *i*th community and the true mean of all patients in the *i*th community with the same covariate values.

$\mathbf{x} = \mathbf{x}_{ijk}$ =column vector of individual level covariates for the *k*th observation on the *j*th patient in the *i*th community. These covariates are gender, history of MI, and age.

$\bar{\mathbf{x}}$ =column vector of average covariate values for all observations in the study.

$\mathbf{q}$ =column vector of regression coefficients associated with $\mathbf{x}$.

t=calendar time (time since beginning of study).

β_i=slope associated with log(delay) versus time in the *i*th community (reflects how rapidly delay times change as the study progresses). A negative value means delay times are decreasing.

ε_{ijk}=a random error term.

In this first stage all parameters except $P_{j(i)}$ will be treated as fixed effects, and they will be estimated by maximum likelihood. The $P_{j(i)}$ are random effects. The patients in this study in a given community are regarded as a random sample from all potential MI patients in the community. The above model reduces residual variability by adjusting log(delay) for a limited number of patient specific covariates. The estimates, b_i, of β_i will be used as summary measures in the second stage of the analysis. These are the best estimates of the relationship between log(delay) and calendar time in the *i*th community, adjusted for covariates. For the *k*th community pair, the difference d_k between the intervention and control *b*′s will be computed. A two-tailed, single sample *t*-test of these 10 d_k's will be performed at α=.05.

The relative improvement in end-of-study delay time for an intervention community compared to a control community with the same intercept will be estimated using a 95% *t*-interval for $\Delta\beta$. Specifically, the confidence interval is

$$\left[10^{2(LL)}, 10^{2(UL)}\right], \qquad (2)$$

where *LL* and *UL* are the lower and upper confidence limits for $\Delta\beta$ based on a *t*-interval with nine degrees of freedom.

Analysis will follow the intention-to-treat principle as described in the last section. Every effort will be made to obtain, for each patient, complete information necessary to carry out the primary analysis. It is anticipated that this information will be available on the great majority of patients. For this reason the primary analysis will use the available data only. However, sensitivity analyses will be conducted to determine the effect of missing observations on the results of the study.

The justification for adjustment for the covariates (gender, age, and history of myocardial infarction) in REACT is as follows. The primary analysis for REACT consists of two stages. In the first stage, a single slope will be computed in each community reflecting the relationship between delay time and time since baseline. In the second stage, a paired t-test will be performed on the 10 (control, intervention) pairs. Adjustment of delay time for a few patient-specific covariates will occur only in the first stage. This will allow different intercepts (baseline median delay times) for different subgroups of patients. Only a limited number of variables for which there is prior evidence or strong suspicion of differential delay times will be included.

Failure to account for different intercepts would not be catastrophic because the primary outcome (slope) would still be reasonably accurate in most cases. However, the variance of the estimated slope would increase, resulting in lower power. This is a very important consideration in a community trial which, of necessity, can randomize only a relatively small number of communities. Failure to account for different intercepts could also yield a biased estimate of slope. To see this, suppose that the mean delay time for women at time x relative to the beginning of the study is

a_1+bx, where $a_1<a_2$. If a single line is fit through all of the data, the expected value of the slope estimate can be shown to be

$$b+(a_2-a_1)\frac{\Sigma_{men}(x_i-\bar{x})}{\Sigma_{all}(x_i-\bar{x})^2}$$

where $\bar{x}$ is the mean of all patients' times since baseline. Thus, the slope estimate is biased, the degree to which depends on the times since baseline for men relative to the average for all patients. If the men's times since baseline are very close to those of the entire group, the bias will be quite small. Otherwise, it could be large. Allowing for different intercepts provides an estimate of slope which is unbiased regardless of the times since baseline.

2. Secondary analyses of delay time

Three secondary analyses of delay time defined as above will be performed.

a. A one-stage analysis will be conducted using a (104) model. Specifically, the model will be

$$Y_{ijkmn}=\mu+\gamma_i+M_{j(i)}+\alpha_k+P_{m(ijk)}+\mathbf{q}^T(\mathbf{x}-\bar{\mathbf{x}})$$
$$+(\beta+\lambda_i+Q_{j(i)}+\tau_k+V_{jk(i)})t+\varepsilon_{ijkmn} \qquad (3)$$

The terms in the model are as follows.

Y_{ijkmn} = log(delay) for the *n*th observation on the *m*th patient in the *k*th treatment group of the *j*th pair of the *i*th site.

μ= overall intercept. This is the true mean log(delay) at baseline for a patient whose covariate values are average. This is a fixed effect.

γ_i = the effect on the intercept of the *i*th site. For fixed values of covariates, this is the difference between the true mean baseline log(delay) in the *i*th site and that of all 5 sites. This is a fixed effect.

$M_{j(i)}$ = the effect on the intercept of the *j*th matched pair in the *i*th site. For a given set of covariate values, this is the difference between the true mean log(delay) at baseline in the *j*th matched pair of site *i* and that for all possible matched pairs in the *i*th site. This is a random effect.

α_k = the effect on the intercept of treatment assignment. For a given set of covariate values, this is the difference between the true mean log(delay) in treatment *k* and that of all intervention and control communities combined.

$P_{m(ijk)}$ = the effect on the intercept of the *m*th patient within the *k*th treatment group of the *j*th pair of the *i*th site. For a given set of covariate values, this is the difference between the true log(delay) of patient *m* and that of all possible patients within the *k*th treatment group of the *j*th pair of the *i*th site. This is a random effect.

$\mathbf{x} = \mathbf{x}_{ijkmn}$ = column vector of patient-level covariate values for the *n*th observation on the *m*th patient in the *k*th treatment group of the *j*th pair of the *i*th site.

$\mathbf{q}$ = column vector of regression coefficients associated with the covariates. These are fixed effects.

β= true mean slope of log (delay) versus calendar time in all communities for a patient whose covariate values are average. This is a fixed effect.

λ_i = the effect on slope of the *i*th site. This is a fixed effect.

$Q_{j(i)}$ = the effect on slope of the *j*th pair of the *i*th site. This is a random effect.

τ_k = the effect on slope of intervention. This is a fixed effect.

$V_{jk(i)}$ = the additional random effect on slope of intervention on the *j*th pair of the *i*th site.

ε_{ijkmn} = a random error term.

The effect of intervention on reducing delay time will be declared significant if the two-tailed significance of the τ_k term is less than 0.05. This model is comprehensive enough to include the most important factors related to delay time, without being overly complicated.

b. A simpler two stage procedure will be performed in which the model in the first stage will be identical to (1), except there will be no adjustment for covariates. That is, the term $\mathbf{q}^T(\mathbf{x} - \bar{\mathbf{x}})$ will be dropped from (1). Other than this change the analysis will be conducted exactly as in the primary analysis.

c. A further analysis will dichotomize delay time into ≤ six hr. vs. ≥six hours. The result will be correlated binary data because some patients may have more than one observation. The Generalized Estimating Equation (GEE) approach (105) with an exchangeable working correlation matrix will be used to model the logit of *p* = the probability of arriving within 4 hours:

$$\ln\left(\frac{p}{1-p}\right) = \mu_i + \theta^T(\mathbf{x} - \bar{\mathbf{x}}) + \beta_i t + \varepsilon_{ijk} \qquad (4)$$

The terms on the right side of (4) are as defined after (1), and ln denotes the natural logarithm. The estimates, b_i, of the slopes β_i, will be computed in each community. The 10 intervention slopes will be compared to those of the matching control communities using a two-tailed, paired t-test at α=0.05.

3. <u>Secondary definitions of delay time</u>

The same analysis as for the primary endpoint will be conducted in a random sample of the primary population, using data collected by telephone interview and record abstraction, for alternative definitions of delay time, as follows.

a. Time from onset of symptoms to when emergency care is sought. Because this could be 0, log(delay+.1 hr) will be used in the analysis.

b. Time from onset of symptoms to treatment by emergency personnel (including ambulance personnel).

c. Time from onset of symptoms to "definitive treatment" among those who receive definitive treatment.

4. Analysis of delay time in secondary populations

The intervention effect on delay time will be assessed in a random sample of patients presenting at the ED with chest pain, but not admitted to the hospital. The same primary analysis that was used for the primary population will be used for this population.

An important subgroup of the primary population for whom we would like to assess the intervention effect is those patients with confirmed MI. Additional subgroups are defined by the individual level covariates **x** (age, gender, and history of MI). Additional subgrouping variables are listed in Section IV. The primary analytic method will be carried out in each subgroup defined by these variables.

Differential intervention effects among subgroups will be tested using model (3), except that instead of $\beta + \lambda_i + Q_{j(i)} + \tau_k + V_{jk(i)}$, the coefficient in front of *t* will be $\beta + \lambda_i + Q_{j(i)} + \tau_k(1 + \mathbf{f}^T(\mathbf{x} - \bar{\mathbf{x}})) + V_{jk(i)}$. A significant value of a φ coefficient (using a two-tailed test at α=.05) indicates a differential effect of intervention for different values of covariates. If this happens, the model will be used to compute estimates of the difference in slopes between intervention and control communities for the different subgroups defined by the covariate. The other covariates will be set to their average values.

5. Secondary endpoints

Several secondary analyses will attempt to assess the clinical consequences of decreased delay time. The hypotheses, discussed in Section X., are that reducing delay time will result in

a. more frequent delivery of early revascularization;

b. less severe disease;

c. shorter hospitalization;

d. lower mortality from MI and acute ischemia; and

e. increased emergency department utilization (both appropriate and inappropriate).

Among the measures addressing these outcomes, many are proportions; for example,

a. proportion of primary patients who receive thrombolytic therapy or PTCA;

b. proportion of primary patients who die in the hospital;

c. proportion of primary patients who incur ventricular fibrillation within 24 hours of admission;

d. proportion among ED patients with chest pain who turn out not to have MI or unstable angina.

For these dichotomous endpoints, the two-step procedure beginning with (4) will be used, with p denoting the probability of interest (for example, the probability that a patient will die in the hospital).

Other secondary questions are addressed by continuous measures; for example,

a. average daily number of patients presenting in the emergency department with chest pain;

b. average daily number of 911 calls for chest pain;

c. average peak CPK in primary patients in whom it is measured;

d. number of patients dismissed to home from the ED after presenting with complaint of chest pain or discomfort ("false positives");

e. number of patients discharged from the hospital with confirmed acute ischemic heart disease ("true positives").

For each continuous measurement Y, linear regression will be performed in each community. The dependent variable will be Y, and the independent variable will be calendar time. As with the primary analysis, the first six months of baseline values will be considered to have occurred at time 0. The 10 slope estimates for intervention communities will be compared to those of the control communities using a two-tailed paired t-test at $\alpha=0.05$.

XII. PUBLICATIONS, PRESENTATIONS, AND ANCILLARY STUDIES POLICY

The REACT Study is an important scientific investigation impacting public education and health care. Because of the great effort that goes into such a study and the large amount of resources used, study investigators have the right and responsibility to communicate their findings to the scientific community and to the public at large.

To minimize the probability of inaccurate data in published materials, it is the policy of REACT that all data and text considered for all papers, and all abstracts for presentation at scientific meetings, be submitted to the Publications, Presentations and Ancillary Studies (PPAS) Committee for review and approval prior to presentation or publication. Also, the Coordinating Center shall review these materials to verify that they are accurate in nature and are consistent with data used in other REACT documents and papers. (Specific procedures to achieve this policy are delineated in Appendix B: REACT Publications, Presentations, and Ancillary Studies Procedures)

The objectives of the REACT PPAS policy are:

1. To assure and expedite orderly and timely presentations to the scientific community of all pertinent data resulting from the REACT study.
2. To assure scientifically accurate presentations and papers from REACT investigators.
3. To assure that all investigators, particularly those of junior rank, have the opportunity to participate and be recognized in the study-wide presentations and publications of REACT data.
4. To assure that press releases, interviews, presentations, and publications of REACT materials are accurate and objective, and do not compromise the scientific integrity of this collaborative trial.
5. To establish procedures that allow the REACT Steering Committee and the NHLBI to exercise review responsibility in a timely fashion for REACT publications and presentations.
6. To maintain a complete up-to-date list of REACT presentations and publications, and to distribute such lists to all REACT investigators and the REACT DSMB on a regular basis.
7. To provide an orderly process of approval for ancillary studies stemming from the overall REACT study.
8. To clarify the acknowledgment of non-NHLBI support of REACT studies and publications.
9. To encourage ancillary studies which enhance the value of REACT.
10. To assure that ancillary studies are scientifically sound and do not interfere with the conduct of the project or jeopardize the main goals.

APPENDIX A: REFERENCES

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APPENDIX B: PUBLICATIONS, PRESENTATIONS AND ANCILLARY STUDIES PROCEDURES

A. Definitions

1. Main Papers and Presentations

Main papers and presentations are those reporting results dealing with the main hypotheses of the randomized controlled trial (i.e., primary and secondary end points, the design of the trial) as well as papers and presentations using the common data set. In general, main papers and presentations refer to use of data from all five sites.

2. Other Papers and Presentations

Other papers and presentations are those not encompassed by the above category; they relate to work done in ancillary studies (studies not relating to the original main hypothesis) or by a single center or a limited number of centers (using data not from all five sites).

B. Proposal and Approval Process

1. To initiate the process that might lead to a presentation at a scientific meeting, or writing a paper for publication, all REACT investigators and professional staff are invited to submit written proposals for abstracts or for papers to the REACT PPAS Committee.

2. The proposal should clearly state the research question or hypothesis and include a brief background statement to clarify the purpose and importance of the research question. If approved to go forward, a writing group will be formed, as specified below.

C. Selection of Writing Group Members and Writing Group Chairperson

1. As soon as the concept for an abstract or paper has been identified and approved by the PPAS Committee, the chairman of the committee will communicate with all centers requesting nominees of qualified and interested investigators to participate as members of a writing group for that paper, as well as seeking the rationale for each nominee for the writing group. The request for nominees will include a specific date (deadline) for submission of nominations.

2. The PPAS committee will select from the submitted list of nominees the membership of the writing group for each paper and will also identify a lead person for that writing group, so that the group may expeditiously proceed with the task. In general, the proposer of the idea for the paper or abstract will be the lead person.

3. It is the responsibility of the lead person to communicate with other writing group members, to develop a detailed manuscript outline, to identify data and analysis needed from the Coordinating Center, and to assume leadership in writing the manuscript. In general, the lead person will be the first author of the paper.

4. To expedite publication, one or more meetings of the writing group may be necessary, but in view of cost limitations, it is recommended that such meetings be kept to a minimum or, to the degree possible, be incorporated as part of other

scheduled meetings, such as REACT Steering Committee meetings or national scientific meetings.

5. The PPAS Chair and Committee are charged with the task of periodic systematic review of the work of all writing groups, aiding and encouraging members as appropriate, revising their membership or reconstituting the group membership, with written notification, when indicated. It is the intent that selection of writing committee members be equitable and fair to all groups and individuals participating in this collaborative program, including encouragement of participation by younger professional colleagues, with due regard paid to exceptional efforts of groups or individuals.

D. Preparation and Submission of Papers

The following steps should be followed in the preparation of REACT manuscripts. The lead person of each writing group should:

1. Contact each writing committee group and review the specific charge to the group;
2. Draft dummy tables which each member of the writing group would consider appropriate and needed for writing the manuscript;
3. Be aware that the Coordinating Center will process all requests for data and analysis according to the overall priorities of the REACT study.
4. Collate comments and dummy tables, solicit opinions of the writing group members, and when a consensus is reached, will submit the dummy tables (or data and analysis requests) to the Coordinating Center with copies to the Chairman of the PPAS Committee;
5. Obtain the input from every member of his/her group. If any member of the writing group does not respond to the lead person's request, or does not contribute to the writing of the paper, the lead person may request a replacement from the PPAS Committee. Members of each REACT writing group should participate actively in the writing, and review of the paper assigned to that group. Input from every member of the writing group should be encouraged and adhered to by all groups.
6. Approve the final version of the paper before its submission to the PPAS Committee. All members of the writing group should have seen the final draft before its submission to the PPAS Committee;
7. Perform his/her duties under the review of the PPAS Committee. If in the judgment of the PPAS Committee a writing group is not working well, and if there is an unjustifiable delay in writing the paper assigned to it, the PPAS Committee may change either the lead person or the entire membership, if in the Committee's judgment this action will expedite the writing of that particular paper.
8. Ensure that, in general, membership of writing groups is restricted to REACT investigators and professional staff, including the Coordinating Center and the project office at the NHLBI. Others not formally associated with REACT may become involved in some aspects of data analysis and publication if sponsored

by a REACT principal investigator, and approved by the REACT PPAS Committee.

E. Authorship and Clearance

1. For main papers and presentations, names of members of the writing group shall be listed as authors in the masthead, with the addition of the phrase "for the REACT Study Group." The lead person of the writing group, with the concurrence of other members of the group, should determine the order of authorship. The lead person may choose to add REACT investigators to the authorship who are not on the writing group. A major criterion for order of authorship shall be the effort and contribution made by the members of the writing group in preparation of the manuscript. Disagreement about the order of authors which cannot be resolved by the chairman of the writing group will be resolved by the REACT PPAS Committee.

2. The phrase "for the REACT Study Group" added after the names of the authors in the masthead is optional in papers reporting local data, or ancillary studies using local data.

3. A credit roster of all major committees, units, and REACT centers with their members (generally no more than ten persons from each center) is to appear at the end of each main paper (printed as an appendix). It is the responsibility of the Coordinating Center to solicit, obtain and prepare the final list for inclusion in each REACT paper. Reprints should be ordered and supplied to the Coordinating Center.

4. All requests for reprints of main papers should be directed to the REACT Coordinating Center. Requests for reprints of other papers reporting data from a limited number of centers (less than the five sites) should be directed to the lead author (or the author's designee).

5. The REACT Steering Committee shall have the final authority to review and approve all REACT papers including papers on ancillary studies, substudies, or local center data. It is the responsibility of the chairman of the PPAS Committee to present the recommendation of the Committee to the REACT Steering Committee in a timely fashion, and to solicit the approval of that body without delay.

6. If an NHLBI staff member is listed as an author on a REACT article, approval of the article must be obtained by the NHLBI. To expedite the approval, it is recommended that the article be submitted simultaneously to the PPAS Committee and the NHLBI.

7. The chairman of the PPAS Committee will be required to submit a final draft of each REACT paper to the REACT Coordinating Center for final check on accuracy of the data. This will be done simultaneously as the paper is submitted to the REACT Steering Committee for review.

8. The Coordinating Center staff will be requested to submit their review within a reasonable time limit (generally not to exceed one month), and provide feedback to the chairman of the PPAS Committee as soon as possible.

9. Since not all circumstances that might cause disagreement among REACT investigators on the merit of a given paper can be foreseen, these disagreements should be resolved by the REACT PPAS Committee, and ultimately by the Steering Committee, if the PPAS Committee remains divided on the issue.

10. Every effort should be made to accommodate the expression of differing interpretations and alternate analyses within the body of each manuscript, so that all points of view are represented to the satisfaction of every participant.

F. Preparation and Submission of Abstracts for National and International Meetings

1. The Coordinating Center will maintain a current list of all relevant meetings and their deadlines for submission of abstracts.

2. All abstracts of main, other, and ancillary study papers must be approved by the PPAS Committee before they are submitted to any national or international organizations. Abstracts submitted to the Committee for review should be accompanied, if appropriate, by copies of tables and graphs to support the conclusions of the abstract. It is understood that some descriptive abstracts may not require data submission or the data may be contained in the abstract. In order for the Coordinating Center to meet the request of REACT investigators for data analysis for abstracts, and allow sufficient time for writing the abstract, the writing groups, or individuals submitting the abstract, should be selective and timely in their data requests. That is, only tables which relate to the major topics of the abstract should be requested. Detailed tabulations dealing with special topics should be reserved for the preparation of the text for meeting presentations or for the manuscript for publication. Generally, five or six tables should be sufficient. On rare occasion, examination of these five or six tables may necessitate one or two additional tables. In these situations, the Coordinating Center should meet these additional requests in a timely basis, if at all possible.

3. Any member of the REACT Study Group may prepare an abstract on a subject appropriate to the REACT investigation. Such an abstract may be based on the topic already assigned to a writing group, in which case the person preparing the abstract should be a member of that writing group or, the abstract may be on an entirely new topic, in which case it could originate from any investigator member of the REACT Study Group.

   If an abstract is submitted for a topic for which there is no writing group, and if the topic and the abstract is approved, a writing group will be activated. Regardless of the nature of the abstract, it must be approved by:

   a. a REACT writing group if that abstract deals with the topic assigned to that group; and

   b. the REACT PPAS Committee.

4. In general no abstract shall be submitted to any national or international organization for consideration prior to approval of the PPAS Committee. If the REACT PPAS Committee disapproves of an abstract already submitted, the author(s) will be required to withdraw that abstract immediately. The time limit

for review and approval of an abstract by the PPAS Committee should not exceed 2-3 weeks after the PPAS chairman has received the abstract.

5. If an abstract is prepared on a topic for which a writing group has not yet been selected, it is the responsibility of the PPAS Committee to select a writing group as soon as the content of the abstract is approved. The REACT Coordinating Center should have a representative on this writing group, as in most REACT writing groups, to expedite communication with the Coordinating Center and facilitate timely analysis of data and preparation of art work and slides for presentation.

6. The selection of the person who will present the material in the abstract at the respective national or international meeting will be at the discretion of the respective writing group (if any). If a writing group has not been constituted, the PPAS Committee will make the selection of the presenter. In general, this will be the person proposing the abstract. Regardless of who selects the presenter, the selection must be approved by the PPAS Committee.

G. Dissemination of Information

1. Prior to abstract presentation, the responsible writing group is required to submit a copy of visual aids, including tables and graphs, of the paper to be presented, to the PPAS Committee for review, prior to the date of the particular meeting. Unless these tables and graphs are approved by the PPAS Committee, that paper shall not be presented, even though its abstract may have been approved for presentation. Also, it is desirable to submit to the PPAS Committee a copy of the text for presentation, if available. Each presentation shall have a sentence at the beginning identifying it as the work of the REACT Study GROUP, and that it is presented by that particular member "for the REACT Study Group". Likewise, the presenters of REACT ancillary studies or local center data, are encouraged to share their visual aids and text of their presentations with the PPAS Committee. These presentations need not include the phrase "for the REACT Study Group."

2. Once a main paper has been presented at a scientific meeting, the tables used should be available to REACT investigators and may be used by them at other scientific meetings. However, such subsequent presentations should not appear in published form unless the data in the original paper are already published.

3. In the case of papers scheduled for presentation before an organization issuing press releases, the presenter may submit, for release to the press, the text of the presentation after it has been approved by the PPAS Committee . If the presentation is based on a manuscript not yet accepted for publication in a peer review journal, a sentence must be included on the front page indicating the preliminary nature of the results.

4. Slides for use at national or international meetings or for publications will be sent to REACT Principal Investigators by the Coordinating Center.

5. A standard set of slides, representing the major results of REACT will be produced by the Coordinating Center for each study center.

H. Invitations to REACT Investigators for Presentation of REACT Materials

The REACT Study Group welcomes opportunities to participate and present reports at national and international scientific meetings. When an invitation is received by a member of the REACT Study Group, REACT policies with regard to publications and presentations must be followed.

1. When a personal invitation is received by a REACT investigator to make a presentation, this invitation shall be sent to the PPAS Committee for review and approval.

2. When an invitation is extended to more than one investigator, or if it comes to the chairperson of the Steering Committee or the chairperson of the PPAS Committee, requesting a representative of the REACT study, the PPAS Committee shall decide who is to represent REACT.

3. All presentations in response to such invitations are to be based on published REACT reports unless approved beforehand by the PPAS Committee.

4. Any presentation of unpublished REACT data must be reviewed and approved by the PPAS Committee prior to the date of presentation.

5. Requests received by Principal Investigators or their staff, to present or discuss at local meetings (city, state or regional) any previously published REACT data, need no prior clearance by the PPAS Committee. All local presentations must be reviewed and approved by the principal investigator for the center making the presentation. REACT Investigators should be encouraged to accept such invitations. It is requested that principal investigators receiving such requests notify the Coordinating Center so the Center can keep record of these presentations.

I. Use of REACT Material for Graduate Student Theses or Dissertations

1. All requests for use of REACT data by students will be reviewed by the PPAS Committee.
2. The student requesting REACT data must be associated with an investigator in the REACT study. The REACT investigator shall act as the student's "sponsor" with regard to the data request.
3. REACT data may not be used by students if the data related to the REACT main paper are in progress or if the PPAS Committee deem the data necessary for a future paper.
4. If the PPAS Committee recommends approval for the use of the requested data, a review group will be established and will include the student as convener of the group.
5. The review group will take no action regarding the paper until the student has completed and defended the thesis or dissertation, provided this occurs in a reasonable length of time. (The student's sponsor will be requested to report on the student's progress to the PPAS Committee).
6. The students must include in the completed thesis the following:
   a. a statement acknowledging REACT study for use of the data;
   b. a statement indicating that opinions, ideas, and interpretations included in the thesis or dissertations are those of the student alone and not necessarily those of the REACT Investigators.
7. When the thesis or dissertation has been completed as determined by the sponsor, the dissertation review group will proceed to prepare the paper(s) for publication. A writing group will be formally constituted and will be composed primarily of review group members. The student should be given the opportunity to take the lead on the paper.
8. The standard REACT publication policy will apply to any material published from the thesis or dissertation.
9. The REACT Study Group reserves the right to proceed with preparing a paper for publication on the thesis or dissertation topic if, in the view of the PPAS Committee, the student has not made reasonable progress on completing the thesis or dissertation.

J. Other Papers and Presentation, and Other Matters

1. Members of REACT centers who identify additional papers that draw on data collected by all REACT centers should communicate in writing the general topic or title of the paper they wish to have considered for publication to the chairperson of the PPAS Committee. The proposal should state the rationale, background, hypothesis or purpose, and methods. Upon receipt, the policy and procedures described above shall apply.
2. If a specific writing group decides that the topic or charge to that writing group is too broad and should be divided into two or more papers rather than the one paper originally assigned, the writing group (through its lead person) shall

communicate with the chairperson of the PPAS Committee indicating the writing group's recommendation for the division of the paper into two or more components. The writing group is to identify which of the components it believes are its responsibilities, and to suggest titles and outlines for the other components. The PPAS Committee shall consider these recommendations and, when appropriate, redefine the charge to the respective writing group, following which the above specified policy and procedure will apply.

3. If, in its deliberation, any writing group identifies other topics, titles, or papers, either directly or indirectly related to the charge of that specific writing group, the lead person of the writing group is to communicate these suggestions to the chairperson of the PPAS Committee, following which above specified policy and procedures are to apply.

4. Papers and presentations being developed, based on special data sets by centers involved in substudies or ancillary studies, are to be reviewed by the PPAS Committee. In general, the writing group, which will prepare such a report, must consist of individuals designated by the participating center(s). The authorship of such a report is to be designated in the usual manner for a scientific report, with the order of names appearing after the title to be decided upon by the participating center(s). The PPAS Committee may act as referee, if requested, to help resolve the order of names of authors. In addition to a statement of authorship, such a paper is to have a clear statement that this work was a substudy or ancillary study of REACT and the appropriate grant support is to be acknowledged.

5. At the end of the list of the paper's authors, an asterisk is to appear for a footnote designating that this work was performed as part of REACT, as a substudy, an ancillary study or an analysis of local data. Where appropriate, a listing of participating centers and participants who are not authors (generally not more than three persons from each center) is to be included. This decision is to be made by the participating centers and is to be referred by the PPAS Committee.

6. Local REACT centers are permitted, indeed encouraged, to write papers on local data and experience. A local paper dealing with a matter of a mainstream paper should be prepared only after the respective mainstream paper, based on national experience, has been published or has been officially accepted for publication. The authorship of a local paper is to be dealt with at the discretion of the Principal Investigator of the respective center.

K. REACT Ancillary Studies and Presentations

1. Proposals for ancillary studies will be submitted in writing to the PPAS Committee for review and recommendation for approval by the Steering Committee. The responsible proposer must be identified.

2. Proposals will be considered for two types of Ancillary studies: 1) "Data Analysis" studies which require additional analytical resources beyond those already available in the main REACT grant, and 2) "New Data Acquisition" studies which require the collection of data which is <u>in addition</u> to that collected for the overall study. Proposals may be reviewed concurrently with the Design

and Analysis and/or Measurement Committee as deemed appropriate by the PPAS Committee.

Ancillary studies which enhance the value of the REACT study are encouraged but must not interfere with the conduct of the project or in any way jeopardize the main goals. Funding may be needed and is the responsibility of the proposer. The PPAS Committee is charged with the evaluation of the desirability of ancillary study results, assessment of the acceptability of additional demands on staff and patients, adequacy of estimates of funds and their likelihood/availability risk to the participants, and to the primary REACT goals, and the overall chances for success.

3. The principal proposer of the ancillary study will serve as the lead person of the writing group for papers based on approved ancillary studies. The proposer will notify the PPAS Committee of the intent to prepare a paper or presentations on the ancillary study.

4. The selection of a writing group, the preparation and submission of papers, and the submission of abstracts will follow the guidelines for other REACT papers as outlined in the preceding sections.

L. The PPAS Committee and REACT Study will adhere to NHLBI guidelines regarding private sector participation in a clinical trial

M. Administrative Procedures

1. Committee Meetings: The PPAS Committee will hold interim meetings via conference call to:

   a. monitor the status of REACT publication and presentations

   b. approve requests for new papers, presentations, publications or abstracts

   c. formulate the content of reports to the Steering Committee on the status of REACT publications and presentations

2. The PPAS Committee will have a vice-chairman who will act on behalf of the chairman in his/her absence to expedite flow of activities with regards to presentations and publications of REACT materials.

APPENDIX C: SAMPLE SIZE, POWER, AND DETECTABLE EFFECTS: ADDITIONAL CONSIDERATIONS

In this Appendix the details of sample size, statistical power, and magnitude of detectable effects will be addressed within a comprehensive theoretical framework, closely linked to the Analysis Plan. In Section A two schemes of subsampling are examined and evaluated as to their impact on statistical power and their potential for skewing the ethnic composition of the REACT sample.

The theoretical basis for the power calculation is developed in Section B, in regard to the primary analysis. Parameter values and mathematical assumptions that go into the model are detailed and documented in greater detail than was provided in Section X.B. In Section C, the theory is extended to cover detectable effects in secondary populations (subgroups or supergroups of the primary population), and in Section D it is extended to cover binary endpoints in the primary population, which comprise many of the secondary endpoints of interest.

The results of the detectable effect calculation for the primary analysis were presented in Section X.C. The analogous results for secondary analyses are presented in Section E, with a discussion of sensitivity to key parameters.

A. Subsampling and Minority Representation

In the early design phase of REACT, the prospect of a demanding logistical effort raised the question of random subsampling of cases in the larger communities. Three schemes for sampling are detailed in Table 6. Scheme A ("All") is complete sampling. IN Scheme B ("Biggest/2"), only the two largest communities (Worcester, MA, and Eugene, OR) are subsampled, at 50%. This is the closest scheme to what we expect will be required for adequate sample size, and it is the scheme that will be implemented initially. In Scheme C ("Catch 700") the target is to collect approximately 700 cases in each community. In the smallest communities, where fewer than 1000 cases are expected, 100% sampling is required. In the intermediate-sized communities (1100-2000 cases expected), 50% sampling would be employed. In the larges communities (2100-2600 cases expected), the sampling fraction would be 25%. This scheme might be adopted if event rates are higher than the current projection.

At the individual level, if all sites are pooled, subsampling skews the ethnic composition of the overall REACT sample to some degree. These effects are detailed in Table 7. It should be emphasized, however, that a valid random subsampling scheme would not alter the ethnic balance of the sample collected in any given community. Since all primary and secondary REACT analyses, in keeping with the community randomization design, are planned at the community level, these would not be biased by subsampling.

B. Detectable effect, primary analysis

Sample size is essentially fixed in advance at both levels of REACT, on the community level at 10 pairs and at the individual level by the available number of cases or some convenient sampling fraction. The effect of the REACT Intervention in reducing delay time is by contrast difficult to predict, because comparable interventions have not previously been conducted. As a consequence, power calculations for REACT are most informatively framed with sample size, power, Type I error, and variance as fixed parameters (or, in sensitivity analysis, as independent variables) and detectable effect as the dependent variable. The requisite formulas are derived in this section. The results are tabulated and discussed in

Section E. The sources and choices of operating parameters that enter into the formulas are detailed along with the mathematical derivation. A parameter summary is provided in Table 8.

The primary REACT endpoint is T, the delay time between onset of acute symptoms and arrival at the hospital. Because the distribution of T is skewed according to all reports from previous studies, the primary endpoint for analysis will be $y = \log_{10} T$. All other factors being equal, y will be assumed to have a normal distribution with mean μ and variance σ^2. Thus T is log-normally distributed with median $M = 10^{\mu}$. In the log-normal distribution, approximately 95% of cases fall within a multiplicative range of $10^{\mu \pm 2\sigma}$. The multiplicative factor $R = 10^{2\sigma}$, according to pertinent data (Section II), is approximately 9. That is, 95% of delay times fall between 1/9 of the median value and 9 times the median value (Figure 7).

In the course of REACT, y will be observed first during a four-month baseline period and then over an 18-month intervention period. Assigning all baseline observations to time t=0, where t indicates calendar time, an approximately linear decline in the mean log delay time may be assumed in each community over the course of the trial:

$$\mu(t) = \mu(0) + \beta t, \quad 0 \le t \le 1.5 \text{ yr.}$$

(The word "decline" is adopted for convenience; in any community the mean log delay time could conceivably go either up or down.) The slope β is the primary community-level parameter of REACT, the null hypothesis being that the population mean slope, $\langle \beta \rangle$, does not differ between the Intervention community and the Control community in each pair. The null hypothesis specifies $H_0: \langle \beta_{Intervention} \rangle = \langle \beta_{Control} \rangle$ but does not require that the common slope be zero; i.e., it allows for secular trend.

The community-level parameter β is to be estimated by simple linear regression. The regression slope b, fitted to one community's data, is an unbiased estimator of β and has a standard error asymptotically equal to $\sigma(KV_t)^{-1/2}$, where σ is the residual standard deviation of log delay time (y) as defined above; K is the number of cases collected in the community; and V_t is the variance of calendar time at which cases were observed. According to the study timeline described above, the observation times are expected to be uniformly distributed over an interval of L=1.5 yr, with an additional cluster at t=0 accumulated from the preceding baseline period of B=0.333 yr. The variance of this distribution is

$$V_t = \frac{L^3}{3(B+L)} - \frac{L^4}{4(B+L)^2} = 459/1936 = 0.237 \text{ yr}^2.$$

Measurement error is not the only source, and possibly not even the dominant source, of random variability in the measured slope b. The underlying "true" slope in the community will differ in a systematic way, if the experiment is successful, between the Intervention group and the Control group, but it will undoubtedly vary as well from one community to another within each group. This variability may be modeled by a random effect superimposed on the fixed effect of REACT Intervention. Assuming the true slopes are normally distributed about their REACT-group means $\langle \beta_{Control} \rangle$ and $\langle \beta_{Intervention} \rangle$ with

variance σ_β^2, the total variance of estimated slope is

$$SE^2(b) = \sigma_\beta^2 + \sigma^2 / KV_t$$

in each community.

To aid in determining reasonable values for σ_β, it is most convenient to relate that parameter, which directly influences slope variability, to its indirect effect on delay time. The net effect of slope variability on y by the end of the trial will be a perturbation of magnitude $\pm 2\sigma_\beta L$ (95% confidence interval). The corresponding effect on delay time T will be a multiplicative perturbation of magnitude $R_\beta = 10^{2\sigma_\beta L}$ (Figure 8). To cover a reasonable range of R_β, the values 1.05 and 1.15 have been entered into sensitivity analysis, representing respectively 5% and 15% net variability of mean log delay time among nominally identical communities attributable to random variation in the slope.

Mitigating the random variability among communities is the correlation ρ in true slopes between members of a pair, attributable to matching. Community matching, for all the investigators' careful choices, is at best an imperfect method for achieving comparable intervention and control groups, compared with the randomization of large numbers of subjects in a conventional clinical trial. The two-year time course of a phenomenon determined by several thousand individual actions cannot be expected to have more than a weak correlation within pairs, and the numerical value of even a weak correlation must be speculative. Values of ρ=0, 0.2, and 0.4 have therefore been entered into the detectable effects calculation and sensitivity analysis, in order to cover the plausible range.

Comparison within pairs will be accomplished by taking the difference

$$d = b_{Intervention} - b_{Control}$$

in each pair. The variance of d is

$$V(d) = 2\sigma_\beta^2(1-\rho) + \frac{\sigma^2}{V_t}\left[K_{Intervention}^{-1} + K_{Control}^{-1}\right],$$

where ρ is intra-pair correlation as discussed above, and the calendar variance V_t is assumed equal in both members of the pair.

Combining all 10 pairs (two from each of five sites), the average effect is

$$\bar{d} = \frac{1}{J}\sum_{j=1}^{J}\left[b_{j,Intervention} - b_{j,Control}\right],$$

where J=10 is the number of pairs. $\bar{d}$ is an unbiased estimator of the true mean difference between Intervention and Control slopes. Its variance is

$$SE^2(\bar{d}) = V(\bar{d}) = \frac{2\sigma_\beta^2}{J}(1-\rho) + \frac{\sigma^2}{V_t J^2}\sum_{j=1}^{J}\left[K_{j,Intervention}^{-1} + K_{j,Control}^{-1}\right].$$

The primary null hypothesis of the REACT trial is that the true mean difference between Intervention and Control slopes, $\Delta\beta = \langle\beta_{Intervention}\rangle - \langle\beta_{Control}\rangle$, is zero. The

alternative hypothesis is that $\Delta\beta \neq 0$; this is a two-sided alternative because it is conceivable (though not likely) that the REACT Intervention could prolong the average delay time.

The primary hypothesis will be tested with the conventional critical value (Type I error rate) of α=5% (two-sided), using a paired *t*-test on the values of *d*, or, equivalently, using a mixed-model ANOVA with REACT group as a fixed effect (1 df). Using the *t*-test formulation, the smallest effect detectable with a specified level of power Π is given approximately by

$$\Delta\beta = SE(\bar{d})(t_{\alpha/2} + t_{1-\Pi}),$$

where $t_{()}$ demarks the specified upper tail area of the central Student distribution. The degrees of freedom for *t* are *J*–1=9. (In the equivalent ANOVA formulation, denominator df for the Intervention effect are [Communities – (Treatment Groups–1) – (Sites–1) – Sites × (Pairs per site–1) – 1] = 20 –1 –4 –5×1 –1 = 9.)

Power has been fixed at Π=80% for the primary analysis on the premise that a large-scale trial can afford no more than 1 chance in 5 of achieving a result and then failing, because of random chance alone, to prove its success to the scientific community. For secondary populations and endpoints, the calculations have likewise been performed at 80% power.

It is desirable to address the detectable effect on delay time directly, rather than indirectly through the detectable slope difference. Slope is related to the net end-trial effect on delay time as follows. After *L*=1.5 yr of intervention, the difference in mean log delay time between Intervention and Control communities will be $\Delta y = L\Delta\beta$. The corresponding effect on the median delay time will be a multiplicative reduction by a factor of $10^{-L\Delta\beta}$, or

$$\textit{Relative reduction} = 100\% \times (1 - 10^{-L\Delta\beta}),$$

$$\textit{Absolute reduction} = M \times (1 - 10^{-L\Delta\beta}),$$

where *M* is the median delay time at the end of the trial in the Control communities.

C. Detectable Effect, Secondary Populations

Many of the secondary questions in REACT concern the primary endpoint as measured in populations, smaller or larger, that differ from the primary group of patients with confirmed MI or acute ischemia presenting with chest pain. Smaller groups of interest include the two sexes; ethnic subpopulations; and MI patients alone. Larger groups include all patients presenting at the ED with chest pain.

Two distinct questions may be formulated with respect to a subgroup: (1) Did REACT Intervention have an effect in that subgroup, considered alone? (2) Did REACT Intervention have a different effect in that subgroup compared with the complementary subgroup?

To calculate detectable effects in answer to the first question, it is necessary merely to increase or decrease the overall sample sizes in the calculation for the primary endpoint, in proportion to the size of the group. This assumes that all design and variance parameters are unaffected by moving to a larger or smaller group; for example, that inter-pair slope correlation (ρ) is the same for women as for the primary sample as a whole.

To calculate detectable effects for a comparison between two complementary subgroups, the fraction f of each community to be compared to the complementary fraction $(1-f)$ will be assumed the same in each community, although this is clearly not true for certain subgrouping factors such as ethnicity. The 20 community-level endpoints become 40, as slope can be measured separately in each subgroup in each community. The contrast of interest is a second-order difference in each community pair:

$$d' = \left[b_{Subgroup\#1,Intervention} - b_{Subgroup\#1,Control}\right] - \left[b_{Subgroup\#2,Intervention} - b_{Subgroup\#2,Control}\right].$$

The average contrast over all 10 pairs, $\overline{d'}$, is an unbiased estimate of the differential effect of REACT Intervention by subgroup. Its variance is

$$SE^2(\overline{d'}) = V(\overline{d'}) = \frac{4\sigma_\beta^2}{J}(1-\rho-\rho^*)$$

$$+\frac{\sigma^2}{V_t J^2}\sum_{j=1}^{J}\left[(fK_j)^{-1}_{Intervention} + (fK_j)^{-1}_{Control} + ((1-f)K_j)^{-1}_{Intervention} + ((1-f)K_j)^{-1}_{Control}\right],$$

where $\rho+\rho^*$ is the correlation between two subgroup slopes drawn from the same community. ρ^* may be considered the *additional* correlation attributable to two slopes' coming from the same community, rather than merely from the same matched pair. It is reasonable that ρ^* should be at least as large as ρ. To be conservative we shall assume ρ^* equal to ρ.

The contrast $\overline{d'}$ serves to test the hypothesis of Intervention × Subgroup interaction. The detectable slope differential between complementary subgroups is

$$\Delta'\beta = SE(\overline{d'})(t_{\alpha/2} + t_{1-\Pi}).$$

In this case the t-statistic has 9 df.

D. Detectable Effect, Binary Endpoints

Many of the secondary endpoints of REACT are yes/no variables, such as receipt of thrombolytic therapy or use of 911 service. Accordingly the power analysis for secondary variables will be presented in terms of dichotomous outcomes.

A statistical model for binary endpoints can be formulated similarly to that presented above for the continuous, log-transformed primary endpoint. The prevalence of the binary endpoint at any point in time will be denoted p. To cover the wide range of binary endpoints of interest, the calculation has been performed for p=0.01, 0.05, 0.10, 0.20, 0.30, and 0.50. The numerical results are identical for the complementary cases p=0.99, 0.95, 0.90, 0.80, and 0.70.

The transformed prevalence $y = \text{logit}(p) = \ln[p/(1-p)]$ is assumed to follow an approximately linear time course:

$$y(t) = y(0) + \beta t, \quad 0 \le t \le 1.5 \text{ yr.}$$

The slope estimate b is again the community-level measure of interest. As derived from simple logistic regression, the variance of b is approximately $1/\pi(1-\pi)KV_t$, where π is the "average" prevalence over the time range (105).

The mean difference between Intervention and Control slopes has variance identical to the continuous case except for substitution of $1/\pi(1-\pi)$ for σ^2. The random variance component σ_β^2 is related to the binary endpoint by $R_\beta = e^{2\sigma_\beta L}$, R_β being the Odds Ratio for the outcome in a community at the outer 95% limit of slope variation as compared to a community in the center of the slope distribution at the end of the L-year trial. The values R_β = 1.05 and 1.15 were used for sensitivity analysis as in the previous case.

The detectable slope difference,

$$\Delta\beta = SE(\bar{d})(t_{\alpha/2} + t_{1-\Pi}),$$

leads to a detectable prevalence effect in logit-transformed units given by

$$\Delta y = L\Delta\beta.$$

To express the detectable effect directly in terms of the binary outcome, the appropriate re-transformation is

$$OR = e^{\pm\Delta y},$$

indicating the least detectable odds ratio for the outcome in Intervention communities as compared to Controls at the end of the trial. If the starting prevalence in both Intervention and Control communities is written as $p = e^y/(1+e^y)$, then a decrease in the Intervention prevalence would be detectable if it were as low as $p_{Lo} = e^{y-\Delta y}/(1+e^{y-\Delta y})$ at the end of the trial. An increase in the proportion would be detectable if it were as high as $p_{Hi} = e^{y+\Delta y}/(1+e^{y+\Delta y})$. An approximate detectable Risk Ratio (Relative Risk) is therefore given by

$$RR = \sqrt{\frac{p_{Hi}}{p_{Lo}}} \approx \frac{p_{Hi}}{p} \approx \frac{p}{p_{Lo}}.$$

For small effects, *OR* and *RR* are numerically close.

E. Results and Sensitivity Analysis

Detectable effects for the primary endpoint in secondary subpopulations are displayed in Table 9. Two cases are examined for sensitivity analysis: the "best" case, with high intra-pair correlation and low slope variance, and the "worst" case, with low intra-pair correlation and high slope variance. The expected sample size, K=600 per community, is used for both cases.

Clearly, the effect in a small subpopulation will have to be larger to achieve detectability (at a given probability level) than an effect in the full population. Table 9 shows, for example, that in a 5% subpopulation (e.g., a small ethnic minority), the reduction in delay time would have to be dramatic — over 50% — to stand any chance of being statistically confirmed. In larger subgroups, however, the detectability is not substantially worse than in the full sample. In women, for example, who are expected to make up about 40% of eligible REACT subjects, a 27% relative reduction would be detectable with 80% power in the best-case scenario.

Sensitivity to the model parameters is as modest in the secondary populations as in the primary, as Table 9 shows. Between the "best" and "worst" cases, for a given population

fraction, the difference in relative reduction detectable with 80% power is 1-2%, or 1-3 min in absolute reduction.

Table 10 shows the detectable levels of effect modification that might be ascribable to subgroup membership. These are second-order contrasts in delay-time slope between complementary subgroups. Again the "best" and "worst" parameter combinations are examined. These effects will be difficult to detect, as is often the case with subgroup comparisons. Even in the best case of parameter values, with the optimal subgroup split for precision (50/50), the second-order contrast would have to be 30% in relative reduction, or 44 min. in abolute reduction, to be detected with 80% power. This is an effect modification larger than the anticipated average effect itself, and is not likely to occur even in a highly responsive subpopulation such as medical professionals or patients with prior history of coronary disease.

Secondary endpoint effects are shown in Table 11, again at levels detectable with 80% power. This calculation was performed for binary endpoints, which dominate the list of secondary outcomes of interest in the primary population. The "best-case" and "worst-case" variance parameters are used with the expected sample size (K=600 per community).

The most readily detectable effects are perturbations of an initial 50% prevalence; relative risk of 1.17 (best case) or 1.18 (worst case between the expected full samples in REACT intervention and control communities will be demonstrable with 80% power. For less prevalent events (or more prevalent ones), the relative risk would have to be closer to 1.5 to stand a good chance of detection, and for rare (or common) events an extreme effect, on the order of RR=5, would be necessary to ensure a high likelihood of detection.

Binary endpoints are examined for subsamples as well in Table 11. Because the detectable effects for the full sample appear insensitive to variance parameters, only the "best" case is shown for subsamples. Subsample sizes are examined for K=200 and K=100, as are planned for random-sample telephone surveys, and for the "pessimistic" full-sample case of K=400. The detectable effects for these smaller samples are considerably larger than for the full sample, with RR in the range of 1.5-3.0 for common events and above 5.0 for rarer events.

In summary, Tables 9-11 suggest that the REACT study as designed has good power to demonstrate a significant primary outcome effect in major subgroups, as well as significant secondary outcomes if their initial prevalence is not extremely high or low. Power is probably not adequate to demonstrate differences between complementary subgroups in the magnitude of the REACT effect.

In this Appendix the details of sample size, statistical power, and magnitude of detectable effects will be addressed within a comprehensive theoretical framework, closely linked to the Analysis Plan. In Section A two schemes of subsampling are examined and evaluated as to their impact on statistical power and their potential for skewing the ethnic composition of the REACT sample.

The theoretical basis for the power calculation is developed in Section B, in regard to the primary analysis. Parameter values and mathematical assumptions that go into the model are detailed and documented in greater detail than was provided in Section X.B. In Section C, the theory is extended to cover detectable effects in secondary populations (subgroups or supergroups of the primary population), and in Section D it is extended to cover binary endpoints in the primary population, which comprise many of the secondary endpoints of interest.

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A. Subsampling and Minority Representation

In the early design phase of REACT, the prospect of a demanding logistical effort raised the question of random subsampling of cases in the larger communities. Three schemes for sampling are detailed in Table 6. Scheme A ("All") is complete sampling. In Scheme B ("Biggest/2"), only the two largest communities (Worcester, MA, and Eugene, OR) are subsampled, at 50%. This is the closest scheme to what we expect will be required for adequate sample size, and it is the scheme that will be implemented initially. In Scheme C ("Catch 700") the target is to collect approximately 700 cases in each community. In the smallest communities, where fewer than 1000 cases are expected, 100% sampling is required. In the intermediate-sized communities (1100-2000 cases expected), 50% sampling would be employed. In the largest communities (2100-2600 cases expected), the sampling fraction would be 25%. This scheme might be adopted if event rates are higher than the current projection.

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Sample size is essentially fixed in advance at both levels of REACT, on the community level at 10 pairs and at the individual level by the available number of cases or some convenient sampling fraction. The effect of the REACT Intervention in reducing delay time is by contrast difficult to predict, because comparable interventions have not previously been conducted. As a consequence, power calculations for REACT are most informatively framed with sample size, power, Type I error, and variance as fixed parameters (or, in sensitivity analysis, as independent variables) and detectable effect as the dependent variable. The requisite formulas are derived in this section. The results are tabulated and discussed in

Table 6. Expected Events, 22 months, and Subsampling Schemes

Community	410/411, Scheme A ("All")	410/411, Scheme B ("Biggest/2")	410/411, Scheme C ("Catch700")
Alabama			
Anniston (Calhoun Co.)	1100	1100 (100%)	550 (50%)
Tuscaloosa (Tuscaloosa Co.)	1650	1650 (100%)	825 (50%)
Dothan (Houston Co.)	1100	1100 (100%)	550 (50%)
Opelika (Lee Co.)	1247	1247 (100%)	623 (50%)
Massachusetts			
Pittsfield/Dalton	726	726 (100%)	726 (100%)
Westfield/W. Springfield	796	796 (100%)	796 (100%)
Worcester	2578	1289 (50%)	645 (25%)
Lowell	1406	1406 (100%)	703 (50%)
Minnesota			
Fargo/Moorheadd	1833	1833 (100%)	917 (50%)
Sioux Falls	1650	1650 (100%)	825 (50%)
Eau Claire	1650	1650 (100%)	825 (50%)
LaCrosse	1467	1467 (100%)	733 (50%)
Texas			
Brownsville	733	733 (100%)	733 (100%)
Laredo	733	733 (100%)	733 (100%)
Tyler	550	550 (100%)	550 (100%)
Lake Charles	550	550 (100%)	550 (100%)
Washington			
Shoreline	345	345 (100%)	345 (100%)
Olympia	352	352 (100%)	352 (100%)
W. Portland/Beaverton	1393	1393 (100%)	697 (50%)
Eugene	2179	1090 (50%)	545 (25%)
Total (22mo)	24,088	21,660	13,223
Average per site	4808	4332	2645
Avg per community	1202	1083	661

Table 7. Impact of Subsampling on Minority Representation

	Scheme A ("All")	Scheme B ("Biggest/2")	Scheme C ("Catch1000")
White	82.2	81.3	77.3
Black	7.5	8.0	8.2
Hispanic	8.5	8.7	12.6
Native American	0.5	0.5	0.5
Asian/Pacific Islander	2.5	2.5	2.3
Other	1.1	0.9	0.8

Table 8. Fixed Parameters and Parameter Values Used in Sensitivity Analysis

B	Baseline period	0.333 yr
L	Intervention period	1.5 yr
J	Community pairs	10
R	Residual 95% multiplicative range = $10^{2\sigma}$	9
R_β	End-trial variability factor due to random slope = $10^{2\sigma_\beta L}$	1.05, 1.15
ρ	Pair correlation of slope	0, 0.2, 0.4
ρ^*	Intra-community, inter-subgroup correlation of slope	Equal to ρ
α	Type I error (two-sided)	5%
Π	Power = 1 – [Type II error]	80%
	Case mix in primary population	50% 410, 50% 411
	Validation rate, 410 discharge	90%
	Validation rate, 411 discharge	60%, 80%
	Participation rate (response and good data)	85%
	ED presentation with REACT-related symptoms	85% of 410/411 discharges

Table 9. Detectable Reduction in Delay Time, Secondary Populations*

	Subpopulation (%)	Relative (%)	Absolute (min)	
			M=2.5 hr	M=3 hr
	100	18	27	32
Best case:	75	20	30	36
R_β=1.05	50	24	36	43
ρ=0.4	40	27	40	48
	30	30	45	54
	20	35	53	64
	10	46	69	83
	5	58	87	105
	1	86	129	154
	100	20	29	35
Worst case:	75	22	33	39
R_β=1.15	50	25	38	46
ρ=0.0	40	28	41	50
	30	31	46	55
	20	36	54	65
	10	46	70	83
	5	58	88	105
	1	88	129	154

*80% power, 5% Type I error (two-sided), K=600 per community.

Table 10. Detectable Reduction in Delay Time, Secondary Comparison Between Complementary Subgroups*

	Subgroup split (%)	Relative (%)	Absolute (min)	
			M=2.5 hr	M=3 hr
Best case:	10/90	48	72	86
R_β=1.05	20/80	39	58	69
ρ=0.4	30/70	35	52	62
	40/60	33	49	59
	50/50	32	48	58
Worst case:	10/90	49	73	87
R_β=1.15	20/80	40	60	71
ρ=0.0	30/70	36	54	65
	40/60	34	52	62
	50/50	34	51	61

*80% power, 5% Type I error (two-sided), K=600 per community.

Table 11. Detectable Effects on Secondary Binary Endpoint, Primary Population*

Sample per community (K)		Prevalence (%)	Detectable effects			
			P_{Lo} (%)	P_{HI} (%)	OR	RR
600	*Best case:*	1 or 99	0.2	4.7	4.87	4.76
	R_β=1.05	5 or 95	2.5	9.8	2.06	1.98
	ρ=0.4	10 or 90	6.2	15.8	1.69	1.60
		20 or 80	14.4	27.1	1.48	1.37
		30 or 70	23.3	37.7	1.41	1.27
		50	42.2	57.8	1.37	1.17
	Worst case:	1 or 99	0.2	4.7	4.88	4.77
	R_β=1.15	5 or 95	2.5	9.8	2.07	1.99
	ρ=0.0	10 or 90	6.1	15.9	1.70	1.61
		20 or 80	14.3	27.2	1.50	1.38
		30 or 70	23.1	37.9	1.43	1.28
		50	41.9	58.1	1.39	1.18
400	*Best case:*	1 or 99	0.1	6.6	6.96	6.73
	R_β=1.05	5 or 95	2.1	11.3	2.48	2.31
	ρ=0.4	10 or 90	5.5	17.5	1.90	1.78
		20 or 80	13.4	28.8	1.62	1.47
		30 or 70	21.9	39.5	1.52	1.34
		50	40.5	59.5	1.47	1.21
200	*Best case:*	1 or 99	0.1	13.6	15.53	14.45
	R_β=1.05	5 or 95	1.5	15.6	3.50	3.24
	ρ=0.4	10 or 90	4.3	21.6	2.42	2.25
		20 or 80	11.2	33.1	1.98	1.72
		30 or 70	19.1	43.8	1.81	1.51
		50	36.7	63.3	1.73	1.31
100	*Best case:*	1 or 99	0.0	32.8	48.39	39.66
	R_β=1.05	5 or 95	0.9	23.6	5.88	5.16
	ρ=0.4	10 or 90	3.0	28.7	3.62	3.10
		20 or 80	8.7	39.6	2.63	2.13
		30 or 70	15.6	49.9	2.32	1.79
		50	31.6	68.4	2.16	1.47

*80% power, 5% Type I error (two-sided).

Figure 7. Distribution of delay time (T). *Left*: In natural units, T is assumed log-normal, with median M and 95% of residual variation lying between M/R and MxR. *Right*: $\log_{10} T$ is normally distributed with mean $\mu=\log_{10} M$ and standard deviation $\sigma=1/2\log_{10}$ R; 95% of residual variation lies in the range $\mu\pm2\sigma$.

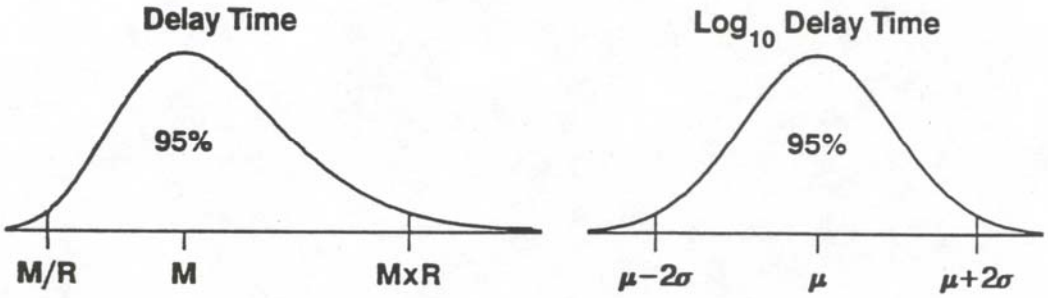
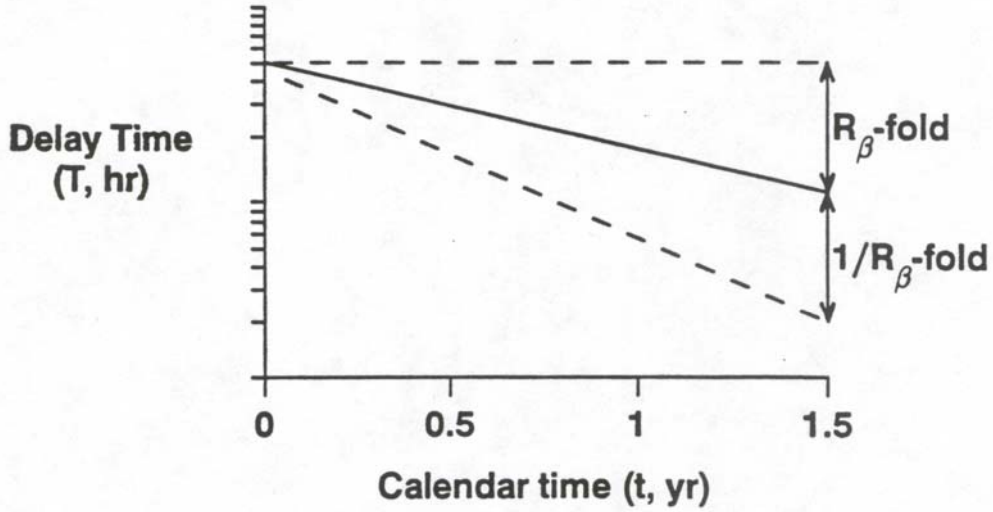


Figure 8. Random variation in slope results in R_β-fold variation in delay time at the end of the trial (95% limits), given the same starting point. Parametrization is $R_\beta=10^{2\sigma_\beta L}$, where L is length of trial and σ^2_β is variance of slopes.



APPENDIX D: STATISTICAL ANALYSIS POLICY

The policy adopted by the REACT investigators regarding statistical analyses reflects the shared view that the Coordinating Center should be responsible for data quality, consistency of analytic approaches, and documentation. This model is similar to those implemented successfully by investigators associated with other multi-center trials. This model may be dissimilar in the specific identification, a priori, of extenuating circumstances, whereby analysis may be performed at locations other than the Coordinating Center.

1. Responsibility for analysis and location of analysis

   The Coordinating Center is responsible for the execution of all statistical analyses, and the dissemination of the results to all field sites. Ideally, all analyses are to be performed at the Coordinating Center. In the specific identification, a priori, of extenuating circumstances (as defined below), an analysis may be performed at a field site. Such exceptions require prior approval from the Steering Committee. In such circumstances the Coordinating Center will oversee the analysis and will have ultimate responsibility for the analysis.

   "Extenuating circumstances" are defined as one or more of the following:

   a. A statistician at a field site has expertise in a specific analytic approach that cannot be communicated to the Coordinating Center.

   b. The analysis in question, part of a substudy, an ancillary study, or a request by an individual investigator, (a) cannot be performed at the Coordinating Center in a timely manner due to other priorities, or (b) requires the inclusion of data not available at the Coordinating Center.

2. Prioritization of analyses

   a. First priority is for the analyses listed in Section XI. These will form the basis of the principal REACT publications. If, due to time constraints, prioritization is required within this set of analyses, the Steering Committee will determine priorities, in consultation with the Coordinating Center, the Publications Subcommittee, and other interested Subcommittees.

   b. Second priority is for unscheduled analyses requested by REACT Subcommittees.

   c. Third priority is for specific analyses requested by individual REACT investigators.

   Within each priority group, the order in which analyses are performed will be the order in which they are received at the Coordinating Center, unless the Steering Committee assigns a higher priority to the request.

   Analysis requests should be sent to the Coordinating Center where they will be assigned a job number and an estimated begin and completion date. If the proposed dates will result in an unacceptable delay, a request may be made to the Steering Committee to allow access to the REACT data for analysis at a field site. Alternatively, if an extended backlog of work has already developed, the Coordinating Center may decide to release a data set to a field site, subject to approval by the Steering Committee. The Coordinating Center will prepare an analysis request form and a data request form to standardize request format.

3. Protocol for field site access to REACT data for data analysis

   a. Data requests, on the standard form, should be forwarded to the Coordinating Center where they will be assigned a job number and an estimated begin and completion date. (Data requests should not involve a serious time lag.)

   b. The Coordinating Center will generate a data file in an appropriate format and mail a diskette and a standard documentation section to the field site. It will be the responsibility of the field site to write computer programs, preferably using a standard statistical package, and perform statistical analyses.

   c. At the completion of the analysis, field sites will return the diskette with the data file, a copy of the programs used for the analysis, and a copy of the final output.

   d. The coordinating center will review the output, give final approval, and archive the diskette. It is the responsibility of a field site conducting an analysis to obtain final approval of the analysis from the coordinating center. It is the responsibility of the Coordinating Center to review and give final approval of analyses carried out by field sites.

   e. Following completion of the REACT study, a complete copy of the REACT data base will be distributed to each of the five field sites involved in the REACT study. This will be done in a manner consistent with NIH policy and the wishes of the REACT Steering Committee.