CHAPTER 21

SAFETY MANAGEMENT

Study Documents Referred to in this Chapter

- Outcome Events Questionnaire
- Study Eligibility Review Checklist
- Blood Pressure, Radial Pulse & Weight

- 400 m Walk
- Telephone Screening Interview
- Physical Exam
- Electrocardiogram
- Medical, Hospital Admission History

CHPATER 21

SAFETY MANAGEMENT

21.1. SAFETY MANAGEMENT OVERVIEW

Safety management in LIFE is intended to achieve four objectives: 1) to minimize the occurrence of adverse effects, especially those related to interventions; 2) to effectively manage adverse events as they relate to the study; 3) to identify when LIFE interventions should be suspended because of concerns for participant safety; and 4) to determine when interventions may be resumed after having been suspended.

The study monitors the medical safety of participants. One aspect of this monitoring is to evaluate potential volunteers at screening to determine whether it is safe for them to participate in the planned intervention. Another aspect is monitoring of safety during study assessments. A third area to monitor is safety during physical activity, both supervised and unsupervised.

Each LIFE investigator has primary responsibility for the safety of participants as it relates to the study protocol. The Data Safety Monitoring Board is responsible for monitoring study data for evidence of adverse effects attributable to participation in LIFE.

21.2 DATA SAFETY MONITORING BOARD

A **Data Safety Monitoring Board (DSMB)** is established, with responsibility to monitor all aspects of the study, including those that require access to any blinded data. The DSMB and its chair are approved by the NIA, and consist of 7 experts who are not affiliated with the study. The **Medical Safety Committee** reports to the DSMB for issues related to participants safety. The Chairs of the Steering Committee, the PI of the DMAQC, and designated staff attends the DSMB meeting and are responsible for preparing and presenting data reports from the study but do not vote. The Project Officer and designated NIA staff along with the Chair and Vice Chair of the Steering Committee attend DSMB meetings and participate in *ex officio* capacities. Only voting members of the DSMB, designated NIA officers and the study statistician have access to unmasked outcome data.

The DSMB have the following charges:

- The initial task of the DSMB is to review the entire study protocol, and the informed consent form with regard to recruitment, randomization, intervention, subject safety, data management, plans for auditing of subject records, and quality control and analysis plans, and to identify needed modifications. The DSMB then identifies the relevant data parameters and the format of the information to be regularly reported.
- Review data (including masked data) over the course of the trial relating to efficacy, recruitment, randomization, compliance, retention, protocol

adherence, trial operating procedures, forms completion, intervention effects, gender and minority inclusion and subject safety.

- Identify problems relating to safety over the course of the study. Inform study PI via written report, who, in turn, ensures that all Field Center PIs receive this report.
- Identify needs for additional data relevant to safety issues and request these data from the study investigators.
- Propose appropriate analyses and periodically review developing data on safety and endpoints.
- Make recommendations regarding recruitment, treatment effects, retention, compliance, safety issues and continuation of the study.
- Send the Program Administrator and PI written reports following each DSMB meeting. These reports may address all (blinded) issues reviewed by the DSMB. The PIs then send the DSMB report to their respective IRBs.
- The study PI is responsible for sending the reports to individual site PIs, who in turn are required to distribute the report to their local IRBs.
- At any time, the DSMB may recommend discontinuation of any component of the study for any of the following reasons:
    1) Compelling evidence from this or any other study of an adverse effect of the study treatment(s) that is sufficient to override any potential benefit for the interventions to the target population.
    2) Compelling evidence from this (or any other) study of a significant beneficial effect of the study treatment(s), such that its continued denial to other study group(s) would be unethical.
    3) A very low probability of addressing the study hypothesis within a feasible time frame.
- The DSMB may convene an executive session at any time. The PI, project director, and project officer attend these meetings.
- Finally, the NIA makes the final decision on whether or not to accept the DSMB's recommendation about discontinuation of any component of the study. Any serious adverse event that might be due to the study intervention is reported within 7 days to the DSMB, the IRB and to the Project Office.

21.2.2 The LIFE study has a **Medical Safety Committee** composed of a committee chair, representatives from each site and members of the coordinating center's data management team. The Safety Committee has the following responsibilities.

- Develop safety policies and procedures for the LIFE study for review by the Steering Committee and DSMB.
- Develop, implement and monitor a reporting system for adverse events and threats to participant safety including forms, policies, and notification systems.
- Review reports of individual adverse events on a scheduled basis
- Review reports of serious and unexpected adverse events, especially deaths and onsite events during monthly meetings of the committee and on an as needed basis.

- Propose guidelines and clarifications on a case by case basis regarding categories of rare conditions (defined as “other” conditions for purposes of temporary or permanent exclusion) that may confer unacceptable risk to participation.
- Propose revised policies and procedures as needed based on issues that develop during the course of the study.

MEDICAL HISTORY
1. Severe visual impairment, hearing loss, or a speech disorder?
2. Progressive, degenerative, neurologic disease (i.e. Parkinson's disease, multiple sclerosis, ALS, dementia).
3. Severe rheumatologic or orthopedic disease (i.e. awaiting joint replacement or active inflammatory arthritis).
4. Terminal illness with life expectancy less than 12 months.
5. Severe pulmonary disease (i.e. on home oxygen or on chronic steroids).
6. Severe cardiac disease (NYHA Class III or IV heart failure, clinically significant aortic stenosis, history of cardiac arrest, implanted defibrillator, uncontrolled angina
7. Severe psychiatric disorder (i.e. bipolar or schizophrenia).
8. Alcohol use > 14 drinks per week.
9. Cancer other than nonmelanoma skin cancer that has received chemotherapy or radiation in the last year
10. Severe Kidney disease
11. Uncontrolled diabetes
12. Lower extremity Fracture in past six months
13. Hip or knee replacement in past six months.
14. MI within the past six months.
15. Major heart surgery (including valve replacement or coronary artery bypass surgery) in last six months.
16. Stroke (not including TIA) in last six months.
17. Spinal surgery in last six months.
18. DVT or PE in last six months.
19. Currently receiving physical therapy or cardiopulmonary rehabilitation (specify when it will end).
20. Other significant health condition (describe)
PHYSICAL EXAMINATION
21. Blood pressure >200/110 or systolic less than 90 (systolic in standing)
22. Open ulcers on feet.
23. Crackles/wheezes on lung exam associated with dyspnea at rest or minimal exertion
24. Grade 4 cardiac murmur
25. Lower extremity limited range of motion or contracture that would limit ability to walk for exercise.
26. Pulsatile abdominal mass consistent with an abdominal aortic aneurysm.
27. Gross neurologic abnormalities or > 5 falls with falls in the last 3 months
28. Other (describe)
ELECTROCARDIOGRAM
29. 3rd degree AV block.
30. Uncontrolled arrhythmia
31. Q waves without evidence of stability from prior EKG > 6 months OR with evidence of ischemia or conduction abnormality
32. ST-segment depressions > 3 mm

21.3 MEDICAL PROBLEMS DETECTED DURING STUDY ASSESSMENTS

Medical problems that would increase risk of study participation are assessed through structured telephone interviews and in person physical examinations during initial subject evaluation, prior to randomization. The goal of these assessments is to detect conditions by history, such as recent major surgery, symptomatic conditions such as angina and asymptomatic conditions, such as valvular heart disease or abdominal aortic aneurysms. Such persons are excluded from further participation and are referred to their primary physician for further care. Telephone screens can be carried out by site staff using scripts and permanently exclude participants based on self report of arthritis so severe it prevents exercise, lung disease requiring oxygen or steroids, heart disease so severe it prevents exercise, Parkinsons disease, kidney disease on dialysis, heavy ethanol use and residence in a nursing home. Temporary exclusions include self report of the following events in the last six months; hip fracture, joint replacement, heart attack, heart surgery, stroke, spinal surgery, blood clot or current physical or cardiopulmonary therapy. See Telephone Screen Form.
Physical examinations are carried out by qualified health care professionals, either nurses or physicians using the Physical Exam Form.
Based on the history, medication review and physical examination, the following guidelines are used by the study physician to determine eligibility.

The purpose of the Study Eligibility Review Checklist is to serve as a guide to medical evaluation for safety of participants in the life study. These guidelines cannot be comprehensive since older adults have innumerable potential health problems. Health professional must apply clinical judgment to make these determinations.

Severe visual impairment, hearing loss, or a speech disorder? Determined primarily from interaction with the participant. The disorder should be sufficiently severe to limit ability to participate in the study. For example, inability to walk for exercise without supervision or inability to participate in the health education program.

Dementia diagnosis or 3ms< 80

Severe rheumatologic or orthopedic disease (i.e. awaiting joint replacement or active inflammatory arthritis). Also weight bearing pain so severe that it would seriously limit ability to walk for exercise.

Cardiac- chest pain at rest or with minimal activity or a change in pattern in the last 6 months

Pulmonary – daily use of O2 or oral steroid medications (not just inhalers)

Psychiatric disorder that has required hospitalization in the last year or limits ability to respond to questionnaires

Cancer other than nonmelanoma skin cancer if it has received active treatment using chemotherapy or radiation in the last year. Hormone modulation is eligible.

Kidney disease on dialysis or with active plans for dialysis such as shunt placement

Uncontrolled diabetes defined by hospitalization or episodes of syncope due to hypoglycemia in the last year.

Loss of Rom or contracture severe enough to limit ability to walk for exercise

Any gross neurologic abnormalities? Severe paresis, spasticity or instability that would limit participation in exercise. Poor balance is demonstrated by needing stabilization by another person at any time during the intake process, especially 400 meter walk, they are excluded at least temporarily.

Uncontrolled arrhythmia : any rate under 40 or over 100, junctional or ideoventricular rhythm, > 10 beats of ventricular tachycardia

A physician is available at each site to review any significant health issues detected. See Chapter 16 for further description of the Physical Examination.

After enrollment, participants are queried about health events and undergo on site assessments every six months. Participants who report significant symptoms such as chest pain, dyspnea at rest, focal neurological deficits or loss of consciousness are queried to confirm that symptoms have been reported to the primary care provider. Persons who are found to have alert values (see table section 21.6) have actions taken as described.

21.4 SAFETY CONSIDERATIONS FOR STUDY ASSESSMENTS

It is anticipated that some medical problems occur during the course of the study while some participants are in the LIFE study clinic. The following is a summary of a plan of action based on level of acuity of the problem.

Emergent problems and problems that are life threatening or require life saving attention should be dealt with using the local Emergency Medical System (EMS). Clinical staff may provide basic life support as an interim measure when appropriate until EMS personnel arrive. CPR training is recommended but is not required. The study staff is responsible for notifying

the participant's family or designated contacts and the participant's primary care provider.

Urgent medical problems and problems that require immediate attention but that do not require life saving attention should be dealt with by taking measures to ensure the participant's comfort and offering first aid, as appropriate. Disposition plans should be made with the participant, clinic staff, investigators, family, and primary care provider. The clinic staff may arrange transportation of the participant to another medical care site for definitive care. The primary care provider and family or designated contacts should always be notified.

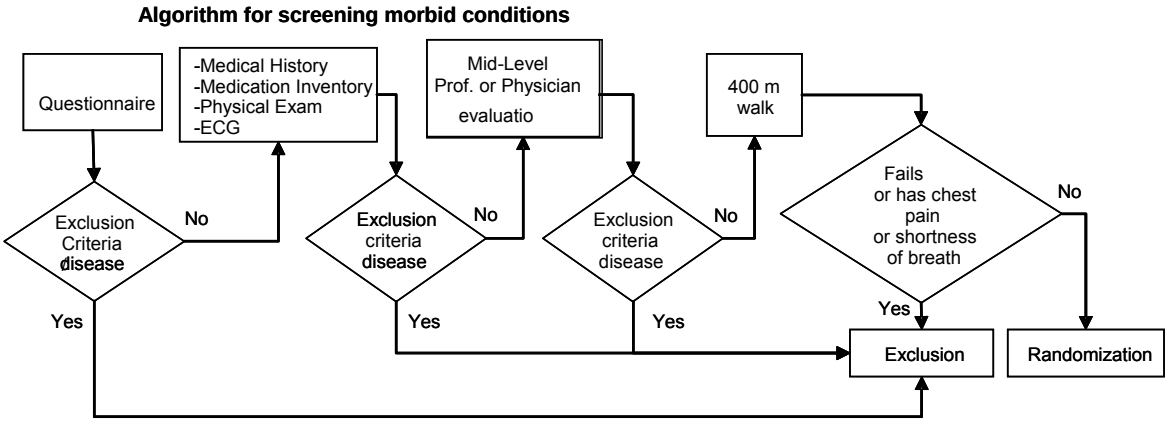
General medical problems or those problems that require attention when feasible should be dealt with by contacting the primary care provider. The clinic staff should follow the primary care provider's directions regarding disposition and follow-up. The participant should be advised regarding the primary care provider's instructions and documentation of the problem and actions should be placed in the participant's record on a progress note. A follow-up letter to the primary care provider documenting the problem and actions taken should be sent by clinic staff.

All study assessments are done by trained and certified staff. Safety precautions are taken during the 400 m walk test by applying standardized stopping criteria. If the participant reports chest pain, tightness or pressure, significant shortness of breath or difficulty breathing, or feeling faint, lightheaded or dizzy the test is stopped. During the 400 m walk tests a defibrillator is available. Onsite staff are trained to provide basic life support and to provide immediate care when faced with medical emergencies. Also, institutional and community EMS services are activated if needed. (See further Study Protocol Section 8.3 Safety Considerations for Study Assessments for further detail.)

We are aware of the potential for overburdening participants with an outcomes assessment that is unduly long. We take several precautions to minimize participant burden and fatigue.. All assessment instruments are prioritized and those with the lowest priority are omitted, as indicated, from the final outcomes assessment.

21.5 PRE-EXERCISE SAFETY SCREENING

Figure 21.5



Appropriately designed and implemented moderate-intensity physical exercise interventions, as are being utilized in this study, have been shown to be safe and efficacious in older adults. To maximize the **participants' safety,** we follow a standardized screening protocol (Figure 21.5.). Accordingly, all potential participants undergo **screening for cardiovascular and other major diseases** by means of a screening health questionnaire (Telephone Screening Interview form). Those with overt cardiovascular diseases (or other severe diseases) that meet the exclusion criteria are excluded. Next, otherwise eligible persons who are not excluded undergo the **400 m walk** test. Persons who develop chest pain or substantial shortness of breath during the 400 m walk test and those who fail the test are excluded. Those who are not excluded undergo a physical examination by a nurse or a physician, an electrocardiogram and a more detailed health questionnaire (Medical and Hospital Admission History form). All inclusion and exclusion criteria are reviewed in the Study Eligibility Checklist form. Criteria for exclusion based on the physical examination are described in Chapter 3 (Eligibility), on the Physical Exam form, and on the Study Eligibility Checklist form. Major permanent exclusions include inability to exercise due to loss of range of motion in the lower extremities, or abdominal examination consistent with aortic aneurysm. Temporary exclusions include systolic blood pressure over 200 mmHg, diastolic pressure over 110 mmHg, or evidence of poorly controlled CHF such as a pattern of bilateral rales AND lower extremity edema. Electrocardiographic findings leading to temporary exclusion include undiagnosed atrial fibrillation, ventricular tachycardia, third degree AV block, acute ischemia or infarction. This set of data is reviewed by a study physician for final approval of participation prior to randomization and the data are recorded on the Study Eligibility Review Checklist. After approval, participants may be randomized to the physical exercise intervention group or to the health education control group.

Participants do not undergo exercise stress testing. The Planning Group decided by unanimous vote that including an exercise stress was not necessary and would not add additional information for the study or protection to the human subjects. This decision was based on the following considerations:

- The **recommendations** published in by Gill et al. advised that a screening

protocol based on a simple cardiovascular reserve test, similar to the one described above is more suitable for screening older adults than a protocol based on stress exercise testing.

- The American Heart Association (AHA) and the American College Sports Medicine (ACSM) **joint position statement** advised that "apparently healthy persons of all ages and asymptomatic persons at increased risk may participate in moderate-intensity exercise without first undergoing a medical examination or a medically supervised, symptom-limited exercise test".
- The **AHA Scientific Statement** on Exercise Standards for Testing and Training by Fletcher et al., advised that "for older, apparently healthy persons desiring to participate in a low to-moderate intensity activity such as walking, an exercise test may not be required", and that "the role of exercise testing among the elderly (>75 years) as a guide to identifying the high-risk patient for primary prevention requires further study".
- The majority of older persons (>75%) are **unable to satisfactorily complete** a treadmill exercise test, which makes its utility as a screening tool in the elderly population questionable.
- Older persons have a **high prevalence of ECG abnormalities**, which diminish the diagnostic accuracy of treadmill exercise testing.
- Participants with potential cardiac contraindications to the physical activity program are identified and excluded by means of the **screening** process described above.
- Physical activity of **moderate intensity** is conducted in a **supervised environment**.
- We have found that a maximal or near maximal exercise test on a treadmill is an **unpleasant, if not frightening experience**, for sedentary and unfit adults (unpublished data from WFUHS and Cooper Institute). Requiring an exercise stress test may deter older persons from participating in the trial.
- Regular exercise and physical activity **may actually reduce the overall risk of MI and death** among older persons, possibly through improvements in cardiac risk factors and overall fitness.

21. 6 SAFETY CONSIDERATIONS FOR EXERCISE INTERVENTION

The General policy is the same as section 21.3
Details of staff guidelines for managing intercurrent medical problems and staff training for monitoring participant safety during physical exercise are described in chapter 10 on Physical Activity and Successful Aging Interventions.

LIFE staff, including interventionists, should be familiar with the warning signs of heart attack and stroke. If a participant reports to the study staff, either at a regularly scheduled visit or otherwise, symptoms consistent with cardiac disease, stroke or transient ischemic attack (TIA), or develops such symptoms during LIFE activities, these symptoms should be evaluated either by LIFE medical staff, by the participant's PCP, or by sending the participant to the emergency room. The decision as to who should evaluate these symptoms should be based on the location of the participant at the time of the report and the nature of the

complaint. If the LIFE physician or other medical staff concludes that the symptoms, exam findings or electrocardiogram may be due to cardiac disease or cerebrovascular disease, physical activity is suspended and the participant is referred to his or her PCP for a more complete evaluation. The exercise intervention should not be resumed until the safety criteria described below have been addressed.

21.6.1 Safety Recommendations for Resumption of Exercise after a CVD Event

LIFE recognizes the guidelines of the American College of Sports Medicine (ACSM), the American Heart Association (AHA), and the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) when considering resumption of exercise for a participant following a CVD event. These guidelines provide criteria for risk stratification and recommendations for medical supervision during exercise training. Nevertheless, no set of guidelines for risk stratification, exercise testing, and exercise training cover all potential participant circumstances. These guidelines, for the most part, are based on the results of exercise testing and structural and functional assessment of the cardiovascular system. However, they do not consider co-morbidities such as diabetes, hypertension, obesity, and hypercholesterolemia that further adversely affect risk during exercise.

It is recommended that all participants join a cardiac rehabilitation program after an event. After a period of recovery, usually two to three months for uncomplicated myocardial infarction, two to three months for coronary artery bypass surgery, and one to two months for PTCA, participants should be evaluated by the PCP, cardiologist or LIFE medical staff for resumption of the intervention. It is recommended that the PCP determine if an exercise stress test is needed to assess the participant's ability to resume a mild to moderate intensity exercise program without medical supervision. In most cases, the PCP or cardiologist caring for the participant is responsible for conducting this test.

Unsupervised exercise interventions may also be stopped by the LIFE medical staff for reasons of increased angina, dyspnea, fatigue or other symptoms for which medical evaluation is deemed appropriate. If a CVD event has not occurred, unsupervised exercise can be resumed without the need for a repeat treadmill test. One example might be an increased frequency of angina but without evidence of MI. <u>After participants have completed a medical evaluation by their PCP, LIFE medical staff should obtain written approval from the PCP for the participant to resume unsupervised physical activity.</u>

<u>LIFE staff should not resume unsupervised physical activity without the permission of the cardiologist or PCP. A letter should be sent to the cardiologist</u>

and or PCP with Guidelines for Resuming Physical Activity after a Cardio-Vascular Disease Event (Appendix A and B, found at the end of this chapter). The letter provides the following check boxes for the physician:

Resume prior unsupervised physical activity program

Discontinue unsupervised physical activity program

Modify physical activity program in the following manner.

Since after an event, participants might be at increased risk for another event, the LIFE medical staff should consider one or more of the following options to safely re-introduce exercise. First, participants should be re-instructed on self-monitoring (pulse and RPE) and to promptly re-contact their PCP and halt exercise if symptoms recur on resuming exercise. Second, LIFE staff may decide to have a participant resume exercise under supervised conditions, such as one or two sessions at the LIFE site. Third, depending on the individual circumstances, participants may be instructed to resume exercise on a more restricted basis and to gradually increase duration or intensity of exercise. Fourth, LIFE medical staff may decide to contact the participant several weeks after exercise is resumed in order to monitor whether there has been recurrence of prior symptoms.

21.6.2 Additional Safety Considerations for Exercise

Foot Care

Because persons with diabetes or peripheral vascular disease may be participants in the LIFE trial, and these conditions increase the risk for foot ulceration, use of proper footwear during exercise is essential for all participants. Where applicable, affected participants should also be taught to inspect their feet. The use of silica gel or air midsoles is to be encouraged, as is the use of polyester or cotton-polyester blend socks to keep the feet dry and prevent blisters. Participants should also be taught to inspect their feet for blisters and other damage daily. For participants with severe peripheral neuropathy, or the presence of a foot ulcer, non-weight-bearing exercise is recommended, such as swimming and bicycling. For participants with severe neuropathy, walking for more than 30 minutes should be avoided.

Hypoglycemia

Physical activity can provoke hypoglycemia in individuals with type 2 diabetes although this risk is limited to those receiving insulin, sulfonylurea, repaglinide or nateglinide. All participants in LIFE who have diabetes receive education on the risk of hypoglycemia. Participants who have diabetes are encouraged, though not required, to perform self-monitoring of blood glucose before and following exercise sessions to determine the effect of exercise on blood glucose.

Participants are encouraged to review this information with their PCP or with the LIFE medical staff. Persons on these medications are noted by intervention staff. In the event of an episode of faintness or altered mental status, immediate safety procedures include supervised assistance to a seated or lying state, offer sweetened beverage and provide constant observation until episode has resolved. Field sites have the option to provide glucometers and training on their use to intervention staff.

21.7. LIFE ALERTS

There are several types of alerts in LIFE. The table below describes a summary of alerts and the appropriate action.

ALERT	ACTION
Blood Pressure SBP > 140mm/Hg or DBP > 90mm/Hg	Clinic staff inform the participant
Blood Pressure SBP > 170mm/Hg or DBP > 100mm/Hg	Qualified staff should talk to participant, and encourage participant to seek additional follow-up and/or evaluation.
Resting Pulse Rate > 100 or < 40 beats/min	Qualified staff should talk to participant, and encourage participant to seek additional follow-up and/or evaluation.
Mood questionnaire score >= 24 or 3MSE score < 80	Qualified staff should talk to participant, and encourage participant to seek additional follow-up and/or evaluation.
ECG meets exclusion criteria. Serious conduction disorder (e.g., 3rd degree heart block), uncontrolled arrhythmia, or new Q waves or ST-segment depressions (>3 mm) on ECG.	Qualified staff should talk to participant, and encourage participant to seek additional follow-up and/or evaluation.
Ankle Brachial Index <0.90	The participant will receive a letter that provides the ABI result and suggests that the participant share the letter with their physician.
No posterior tibial arterial signal present in either leg	The participant will be examined by a qualified staff member who will evaluate the participant for signs of critical limb ischemia. The qualified staff member will re-check for presence of a posterior tibial artery signal and will check for presence of a dorsalis pedis arterial signal. Appropriate follow-up will be recommended. If critical limb ischemia is determined to be present, the study physician will be notified.
Forced Expiratory Volume in 1-Second (FEV1) <80% Predicted but >50% Predicted.	The participant will receive a letter that provides the spirometry result and suggests that the participant share the letter with their physician.
FEV1 < 50% Predicted	The participant will be examined by a qualified staff member who will evaluate the patient for signs of respiratory distress (i.e., severe shortness of breath).
Serum glucose < 60 during intervention session in diabetic on hypoglycemic agent	Intervention staff provide immediate care such as offering beverage with sugar and advise participant to contact PCP regarding adjustment of hypoglycemia medication

Alert criteria for blood tests

Test	**Value out of reference range:** **Participant should be notified at a routine visit or within two weeks by a qualified staff member that the value is out of the normal range for all adults but may or may not be medically important and could be discussed with PCP.**	**Value may be medically significant** **Participant should be notified at a routine visit or within two weeks by a qualified staff member that the value is potentially medically significant and strongly recommend that it be discussed with PCP**	**Value requires immediate notification** **A qualified staff member should contact the participant within one working day and request permission to contact a PCP. Assuming that the participant has normal vital signs and is feeling well, there is no need to invoke emergency medical systems.**
Triglycerides	>199		
Total cholesterol	>199		
HDL	<40		
Hemoglobin	M <13 or > 16 F <12 or > 15	M < 12 or > 16.5 F < 11 or > 16	< 8 or > 18
WBC count	< 4000 or >11000	< 3000 or > 12000	< 2000 or > 20000
Platelet count	< 130000 or > 400000	< 100000 or > 500000	< 30000 or > 1000000
Sodium	< 135 or > 146	< 130 or > 155	< 125 or > 160
Potassium	< 3.5 or > 5.3	< 3.0 or > 5.7	< 2.6 or > 6.2
Calcium	<8.5 or > 10.3	< 8.0 or > 11.5	< 7.0 or > 13.0
Glucose	< 70 or > 125	< 60 or > 140	< 50 or > 400
BUN	> 30	> 40	> 80
Creatinine	> 1.4	M >2.0 F > 1.6	> 3.5
Albumin	< 3.5	< 3.0	

For values that are only out of the reference range, participant should be told by qualified staff in person or by letter that the value is out of the normal range for all adults but may or may not be medically important and could be discussed with PCP.

For values that meet criteria for potential medical significance, participant should be told in person or by telephone by qualified staff that the value is potentially medically significant and strongly recommend that it be discussed with PCP

For values that meet criteria for requiring immediate notification of the site, a qualified staff member should contact the participant within one working day and request permission to contact a PCP. Assuming that the participant has normal vital signs and is feeling well, there is no need to invoke emergency medical systems.

A study physician should review all medically significant values and be notified within 24 hours of all values that require immediate notification. .

21.8. CLINICALLY SIGNIFICANT EVENTS

All clinically significant events should be documented using the adverse event reporting forms and reported to the Coordinating Center and the local IRB. See Chapter 22 for these procedures.

21.8.1. Myocardial Infarction

If a participant gives a history of new myocardial infarction, LIFE interventions involving physical activity are suspended until evaluation for resumption of exercise is completed. See safety recommendations for resumption of physical activity after a CVD event (Section 21.5.1).

21.8.2. Angina Pectoris

If a participant develops new symptoms consistent with angina (e.g., pressure, fullness or squeezing pain in the chest related to exercise and relieved by rest; pain in the shoulders, neck or arms related to exercise and relieved by rest; shortness of breath inappropriate for level of exercise), the participant should be immediately referred to his/her PCP. If such a referral is not possible, then a LIFE physician should make an immediate referral. If a physician concludes that the symptoms, exam findings or electrocardiogram suggest angina pectoris, LIFE interventions involving exercise are suspended and the participant be referred to his or her PCP for further evaluation. Interventions involving physical activity are not resumed until the PCP has evaluated the participant and approved resumption of physical.

21.8.3. Congestive Heart Failure

If a participant develops new symptoms consistent with congestive heart failure (e.g., increased dyspnea on exertion, nocturnal dyspnea, ankle edema), LIFE interventions involving physical activity are suspended and the participant is referred to her or his PCP for further evaluation. Interventions involving physical activity are not resumed until the PCP has evaluated the participant and approved resumption of exercise.

21.8.4. Re-vascularization Procedures

If a participant undergoes a revascularization procedure (e.g., coronary artery bypass surgery, percutaneous transluminal coronary angioplasty or stent placement, carotid endarterectomy, peripheral vascular surgery), LIFE interventions involving physical activity are suspended until the PCP has approved resumption of exercise.

21.8.5. Atrial Fibrillation or Other Arrhythmia

If a participant is found by examination to have irregular heart rate, and/or electrocardiogram reveals new atrial fibrillation, or if heart rate is < 110 beats/minute and the participant is asymptomatic, the participant should be instructed to see his or her PCP as soon as possible for further evaluation and treatment. If the heart rate is > 110 beats per minute or if the participant has dyspnea, chest pain, light headedness or other symptoms that the LIFE physician considers secondary to arrhythmia, the participant should be sent to an emergency room for further evaluation. Other significant arrhythmias are referred to the PCP or emergency room as appropriate for evaluation. LIFE interventions involving physical activity are suspended until the PCP has provided written approval for the resumption of physical activity.

21.8.6. Stroke

If a participant experiences a stroke (focal neurologic deficit lasting more then 24 hours or brain infarct by CT or MRI scan), any LIFE interventions involving physical activity are suspended until the PCP has approved resumption of exercise.

Physical activity interventions may be modified to take into account the participant's neurologic deficit.

21.8.7. Transient Ischemic Attack (TIA)

If a participant reports new symptoms consistent with TIA (focal neurologic deficit lasting less than 24 hours), the participant should be instructed to see her or his PCP immediately or advised to go to an emergency room as appropriate. LIFE interventions involving physical activity are suspended until the PCP has approved resumption of exercise.

21.8.8. Claudication

If participant reports new symptoms consistent with claudication (e.g., calf pain with exercise that is relieved by rest) the participant is asked to see his or her PCP for evaluation. LIFE physical activity interventions do not need to be stopped but may need to be modified to take into account the symptoms.

21.8.9. Foot Ulcers

If a participant develops foot ulceration, any physical activity program that involves walking or other weight bearing activity is suspended until the foot ulcer is healed.

21.8.10. Depression

Participants with a total depression score ≥ 24 on the MOOD questionnaire (CES-D) should be informed of the possibility that they are depressed and referred to their PCP for further evaluation and treatment. See Appendices B and C for sample scripts to follow when contacting participants with their results. After the depression has been evaluated and treated, a determination about the safety of continued participation in LIFE should be made. The PCP and any mental health professional involved in the participant's care should help with this determination.

21.8.11. Other Events

The occurrence of any medical event that, in the judgment of the participant's PCP or a LIFE clinician, makes application of a LIFE intervention unsafe for that participant require that the intervention in question be discontinued for that participant.

In the case of any clinically significant event such as MI, stroke, or those alerts described above, and the participant is in the Physical Activity Intervention group, unmasked staff should complete the Adverse Event form.

Appendix A

Date: _____

Dear Dr. _____,

Your patient _____ (DOB _____) is a participant in the LIFE research study, a multi-center NIH-funded clinical trial examining the effects of physical activity on mobility disability. The exercise advocated for participants in LIFE is approximately 30 minutes or more of daily, moderate intensity, unsupervised physical activity, with the most common form being brisk walking. We understand that _____ experienced a _____ on _____. He or she may have been asked to suspend exercise following the event. We would now like to evaluate whether it is appropriate for your patient to resume the LIFE exercise intervention and we need your assistance and medical opinion in this regard.

At the bottom of this letter are several questions seeking your opinion of whether it is appropriate for _____ to resume physical activity as previously recommended by the LIFE research study. We have also attached a summary of contemporary recommendations regarding the resumption of a physical activity program following various types of cardiovascular events. We hope this information might be useful for you.

We greatly appreciate your timely response, as we will not advise _____ regarding resumption of LIFE exercise interventions until we hear from you. If you have any questions or concerns, please do not hesitate to contact us.

Sincerely,

Yes_____ No_____ Resume prior unsupervised physical activity program
Yes _____ No_____ Discontinue unsupervised physical activity program
Yes _____ No _____ Modify physical activity program in the following manner:
_____
_____

Signature of M.D. _____ Date: _____

Printed name of M.D. _____ Phone #: ( )_____

Please fax this form to LIFE study nurse at ( ) _____- _____.

APPENDIX B

Script for Depression Known

Hello,

My name is _____. I am the nurse working with the LIFE Study.

I am contacting you regarding your last visit to the clinic. I want to inform you that at your last visit you answered a number of questions we use to describe the health status of our participants including information on mood. Your results from these questions indicate that at the present time you show signs or symptoms that could be from depression. I note that you already have a diagnosis of depression AND/OR you are on a medication that treats depression. Even with that, there is some evidence of continued symptoms.

These tests are not intended to replace any test or treatment your doctor may order for a specific reason, but do provide important information about your health. This information is collected for research purposes and cannot make a diagnosis. Further discussion with your physician is recommended and only from such a discussion can you know whether you would benefit from additional attention to your mood.

Do you have any questions about this?

Thank you for your participation.

APPENDIX C
Script for Depression not Known

Hello,

My name is _____. I am the nurse working with the LIFE Study.

I am contacting you regarding your last visit to the clinic. I want to inform you that at your last visit you answered a number of questions we use to describe the health status of our participants including information on mood. Your results from these questions indicate that at the present time you show signs or symptoms that could be from depression.

These tests are not intended to replace any test or treatment your doctor may order for a specific reason, but do provide important information about your health. This information is collected for research purposes and cannot make a diagnosis. Further discussion with your physician is recommended and only from such a discussion can you know whether you would benefit from additional attention to your mood.

Do you have any questions about this?

Thank you for your participation.