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Summary of Edits

Summary of changes between Version 1.0 and Version 1.1:

- Corrected schedule for administration of Rose Angina Questionnaire (completed at 3 and 12 months in addition to baseline, 6, and 18 months.)
- Added instructions for allowing a participant to follow PREMIER exercise recommendations for a positive Rose Angina Questionnaire after baseline.
- Added heart rate contraindications for performing treadmill testing.
- Added instructions for cool down following early termination of treadmill testing.
- Added that staff are requested to make at least 3 attempts to reach the participant to determine the resolution of a referral to a personal physician for reaching escape BP.

Summary of changes between Version 1.1 and Version 1.2:

- Systematic review of participants' medical records to detect adverse events is not allowed; however, if a medical record is reviewed for documentation of an adverse event and evidence of an unreported adverse event is found, an AE Form (#30) should be completed and reported to the CC.

Summary of changes between Version 1.2 and Version 1.3:

- Modified section on symptom and AE surveillance to reflect new definitions of AEs.
- An AE form is completed at 18 months for physician confirmed angina
- Added information on NIH requirements for reporting DSMB review of adverse events to IRBs.
- For participants with out-of-range pre-exercise heart rates, the study clinician assesses if the treadmill is performed as scheduled, rescheduled till heart rate is within range, or the participant is referred to his or her personal physician for a safety assessment.

Summary of changes between Version 1.3 and Version 1.4:

- Added referral to physician for further evaluation within two months for BP \geq 140/90 to escape level 1 at the 12-month visit.

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23. Safety Monitoring

Blood Pressure

To prevent a prolonged period of untreated hypertension (outside the eligibility range of PREMIER), several blood pressure safety procedures are implemented.

- At PSV, individuals taking any anti-hypertensive medications are excluded, and those who report having taken them must have been off medication for at least three months.
- Individuals with a history of cerebrovascular or cardiovascular disease are excluded, as are those with congestive heart failure, diabetes, and renal insufficiency.
- Blood pressure is monitored regularly throughout the study, and "escape levels" are established to identify and ensure proper follow-up of individuals with potentially dangerous blood pressure elevation. Participants may also be referred to a physician if deemed appropriate based on symptoms and clinical judgment, even though the BP is below the escape thresholds.
- In addition to the random zero (RZ) measurements required for study data, additional non-RZ (standard mercury sphygmomanometer) measurements may be taken on a more frequent basis at the study clinician's discretion to ensure participant safety.
- In particular, the PREMIER escape limits reflect the fact that although persons with Stage 1 hypertension (SBP 140-159 and/or DBP 90-95) are eligible for PREMIER, persons with Stage 1 hypertension 6 months after randomization should be referred to their personal MD for possible treatment with medication.
- If escape levels are reached, a BP Escape Tracking Record (Form #32, 83, 84, or 52) is filled out. The original is placed in the participant's chart at the site, and a copy is sent to the CC.
- If the participant requires a physician's evaluation and does not have a personal physician, qualified personnel at the clinical center will make a referral.

PREMIER Blood Pressure Escape Criteria

The following blood pressure escape levels and protocols have been established to ensure that participants are offered appropriate evaluation and therapy when clinically indicated. The actions taken when these escape levels are reached vary somewhat for screening and intervention. Participants may be referred for evaluation at any time if a qualified clinician believes such action is appropriate based on his or her own clinical judgment.

All escape blood pressures should be documented by completing the appropriate BP Escape Form (Form #32 for screening; #83 for 3-month, #84 for 12-month, and #52 for 6 and 18 month visits).

In the event that a randomized participant is referred to a clinician for evaluation, the clinical center should try to obtain four sets of end-of-intervention blood pressure measurements prior to treatment. Blood pressure measurements used to define and confirm escape may be used as end-of-intervention measurements, regardless of spacing. Care should be taken, however, that this

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does not delay or otherwise interfere with appropriate clinical care. Regardless of the outcome of the referral, if possible all participants continue in the trial and get all study measurements.

Screening (Prior to randomization)

Escape Level #1: The mean blood pressure recorded at any single visit, including PSV, SV1, SV2, SV3 or the 4th Baseline Blood Pressure, is SBP \geq 180 or DBP \geq 110 mm Hg.

Action: Participant is excluded immediately and referred to a physician for further evaluation within one week.

Escape Level #2: The mean cumulative blood pressure recorded at SV1, SV2, or SV3 exceeds the established upper limit of eligibility (see Protocol, section 6, Table 3).

Action: Participant is excluded and referred to a physician for further evaluation within one month.

Intervention Period: 3-Month Visit

Escape Level #1: The mean blood pressure recorded at the three-month visit is SBP \geq 160 or DBP \geq 100 mm Hg.

Action: One additional set of RZ blood pressure measurements must be obtained within one week. If the cumulative mean from the two visits is SBP \geq 180 or DBP \geq 110, participant is referred to his/her personal physician for further evaluation within one week. If the cumulative mean from the two visits is SBP \geq 160 or DBP \geq 100, then the participant is referred to his/her personal physician for further evaluation within one month.

Intervention Period: 6-Month and 18-Month Visit Clusters

Escape Level #1: The mean blood pressure recorded at any single visit is SBP \geq 160 or DBP \geq 100 mm Hg.

Action: One additional set of RZ blood pressure measurements must be obtained within one week. If the cumulative mean from the two visits is SBP \geq 180 or DBP \geq 110, participant is referred to his/her personal physician for further evaluation within one week. If the cumulative mean from the two visits is SBP \geq 160 or DBP \geq 100, then the participant is referred to his/her personal physician for further evaluation within one month.

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Escape Level #2: The cumulative mean blood pressure recorded at the end of the six or 18 month cluster of visits is SBP \geq 140 or DBP \geq 90 mm Hg.

Action: Participant is referred to his/her personal physician for further evaluation within two months.

Intervention Period: 12-Month Visit

Escape Level #1: The mean blood pressure recorded at the 12-month visit is SBP \geq 160 or DBP \geq 100 mm Hg.

Action: One additional set of RZ blood pressure measurements must be obtained within one week. If the cumulative mean from the two visits is SBP \geq 180 or DBP \geq 110, participant is referred to his/her personal physician for further evaluation within one week. If the cumulative mean from the two visits is SBP \geq 160 or DBP \geq 100, then the participant is referred to his/her personal physician for further evaluation within one month. If the cumulative mean from the two visits is SBP \geq 140 or DBP \geq 90, participant is referred to a physician for further evaluation within two months.

Escape Level #2: The mean blood pressure recorded at the 12-month visit is SBP \geq 140 mm Hg or DBP \geq 90 mm Hg.

Action: One additional set of RZ blood pressure measurements must be obtained within one week. If the cumulative mean from the two visits is SBP \geq 160 or DBP \geq 100, then the participant is referred to his/her personal physician for further evaluation within one month. If the cumulative mean from the two visits is SBP \geq 140 or DBP \geq 90, participant is referred to a physician for further evaluation within two months.

As information about referrals for blood pressure escape levels is requested by the DSMB, staff are requested to make at least 3 attempts to reach the participant to determine the resolution of the referral.

Morbid Events Affecting Blood Pressure

Participants who suffer a cardiovascular event with a lasting effect on blood pressure (e.g., myocardial infarction, stroke) may continue with the interventions and follow-up clinic visits with the approval of their primary physician and a study clinician. Such events will be detected through the Follow-up Symptoms Questionnaire (Form #78) or the Follow-up Rose Angina

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Questionnaire Form (#7). Follow-up of these events will be monitored via the Adverse Events Form (#30). Whenever staff become aware that such an event has occurred, they should immediately report it to the study clinician. If necessary, permission to continue from both the participant's personal physician and a study clinician should be documented in the participant's chart on the Adverse Events Form, with a copy sent to the coordinating center.

Participants complete a Baseline Rose Angina Questionnaire at SV1 and a Follow-up Rose Angina Questionnaire at 3, 6, 12, and 18 months.

At baseline, participants with a positive Rose Angina Questionnaire (Form #6, question #8 answered "positive") must be referred to a personal physician for evaluation and cannot participate unless approved to do so by both the personal physician and a study clinician. The participant's personal physician will be asked to confirm that the participant has had a negative exercise stress test within the last 6 months (defined as 6 months prior to the date the physician contacts PREMIER with the information), and that the physician approves of the patient participating in the PREMIER interventions. A study clinician must review the study chart and also agree that the participant may continue in the study.

At 3, 6, and 12 months, individuals with a positive Rose Angina Questionnaire are immediately referred to their personal physician for evaluation.

If **all prior** Rose Angina Questionnaires were **negative**, the participant is asked to refrain from further exercise until they have a stress test, and approval from both their personal physician and a PREMIER clinician.

If **any prior** Rose Angina Questionnaire was **positive**, the participant is asked to refrain from further exercise until they have approval from both their personal physician and a PREMIER clinician. A repeat stress test is not automatically required in this case; the decision to perform one is left to the discretion of the participant's personal physician. If the participant does not have a personal physician, she is given a referral to a physician whom she is advised to consult.

In either case, if angina is confirmed, they are advised to follow their physician's advice regarding exercise. Otherwise, they can restart exercise per PREMIER recommendations. In cases of physician-confirmed angina, an AE Form (#30) is completed.

At 18 months, individuals with a positive Rose Angina Questionnaire are immediately referred to their personal physician for evaluation and advised to follow that physician's advice regarding further exercise. Since the intervention is completed, the need for study clinician review is now moot. If the participant does not have a personal physician, a recommendation regarding further exercise may be made by a study clinician. However, the participant is also given a referral to a physician whom they are advised to consult. In cases of physician-confirmed angina, an AE Form (#30) is completed.

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Hyperlipidemia and the Use of Lipid Lowering Medications

Hyperlipidemia is not an exclusionary criterion. However, lipid values outside of normal ranges are flagged for the participant, and a local clinician reviews these results and makes recommendations for referral as appropriate based on National Cholesterol Education Program (NCEP) guidelines. Participants who are placed on lipid lowering drugs, whether before or after randomization, may continue in PREMIER.

NCEP Guidelines for Treatment Decisions Based on LDL-Cholesterol		
	Dietary Therapy	
	<i>Initiation Level</i>	<i>LDL Goal</i>
Without CHD and with fewer than 2 risk factors	≥ 160 mg/dL	< 160 mg/dL
Without CHD and with 2 or more risk factors	≥ 130 mg/dL	< 130 mg/dL
With CHD	> 100 mg/dL	≤ 100 mg/dL
	Drug Treatment	
	<i>Initiation Level</i>	<i>LDL Goal</i>
Without CHD and with fewer than 2 risk factors	≥ 190 mg/dL*	< 160 mg/dL
Without CHD and with 2 or more risk factors	≥ 160 mg/dL	< 130 mg/dL
With CHD	> 130 mg/dL**	≤ 100 mg/dL
* In men under 35 years of age and premenopausal women with LDL-cholesterol levels 190-219 mg/dL, drug therapy should be delayed except in high-risk patients such as those with diabetes.		
** In CHD patients with LDL-cholesterol levels 100-129 mg/dL, the physician should exercise clinical judgment in deciding whether to initiate drug treatment.		

Laboratory evidence of diabetes or renal insufficiency

Participants who are excluded because of previously undetected diabetes or renal insufficiency are informed that this lab abnormality is potentially clinically significant and are encouraged to discuss the test result with their physician. Written documentation of the laboratory result is provided to the participant.

Other laboratory abnormalities

Participants receive copies of clinically relevant local and central lab results and are encouraged to share these data with their personal physicians. The central lab notifies sites immediately when an alert value is reached. In addition, a local clinician reviews all laboratory measurements and makes recommendations for referral as appropriate prior to sharing these laboratory measurements with the participants. If urgent referral is indicated, the participant will be informed and referred as soon as possible. Otherwise, local lab reports are provided to the participant to review with the personal physician at the participant's discretion.

The mere occurrence of an abnormal laboratory measurement is not considered to be an adverse event. Such measurements only trigger an AE form if the participant reports a diagnosis made by a health-care professional on the basis of the abnormal result. This report by the participant is

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done through the completion of the Follow-up Symptoms Questionnaire Form (#78). Discussion of PREMIER laboratory measurements with ones physician as part of a routine clinic visit is not considered an adverse event.

Pregnancy and Other Exclusions

If a participant becomes pregnant during the study, she is excluded immediately from further participation in all study activities and her data are considered censored as of the date of conception, which is measured based on self-report. If she has not yet seen a physician, she is immediately referred for standard prenatal care. If a participant develops any other exclusionary condition (e.g., cancer) following randomization, further participation is determined by a study clinician in conjunction with the participant's personal physician.

Symptoms and Adverse Events (AE) Surveillance

The Follow-Up Symptoms Questionnaire (Form #78) is administered at the 3, 6, 12 and 18 month follow-up visits. A separate Baseline Symptoms Questionnaire (Form #16) is administered at SV3. Participants are specifically queried about gastrointestinal, musculoskeletal, and cardiovascular symptoms. Questionnaire responses are reviewed by study clinicians and referred for additional care as needed.

Participants are also queried using Form #78 at the 3, 6, 12 and 18-month follow-up visits about possible adverse events (defined below). Positive responses trigger an Adverse Events Form (#30), which is completed by an unblinded study clinician at the local site and then reviewed by a clinician at the coordinating center and classified as either gastrointestinal, cardiovascular, musculoskeletal, or "other" in nature. This information is then reported to the DSMB by site and treatment arm. Similar information reported by participants at other times (e.g., during intervention classes) is noted on the Safety Review Form (#31) and followed up with as needed to assure participant safety. To avoid possible reporting bias, such events do not constitute AEs unless they are reported at the regularly scheduled clinic visits.

The following constitute adverse events (AEs): heart attack, stroke, transient ischemic attack, heart failure, coronary angioplasty or bypass surgery, angina pectoris, broken bone, torn ligament, or any other serious injury to the bone or muscle. Evidence of the occurrence of these events is based on participant self-report that a health care professional has diagnosed the condition (Ques 15 on Form #78), and no attempt is made to verify the diagnosis. Physician confirmed angina following a positive Rose Angina Questionnaire also constitutes an adverse event and triggers the completion of Form #30.

Cancer, gallbladder disease, hyperlipidemia and diabetes are not considered AE's in PREMIER, but are tabulated and reported to the DSMB in a separate table.

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All other outcomes that may be construed as being an adverse consequence of study participation, such as an injury while performing a study measurement, are documented on Form #31, reviewed, and followed up on as needed by a study clinician.

At all times, the paramount concern is the safety of the participant. If a symptom or AE seems likely to lead to termination of participation in the intervention, to the extent possible staff should collect end-of-intervention measurements before termination, giving highest priority to the four end-of-intervention blood pressure measurements.

Review of a participant's medical record to confirm adverse events is not required and should not be done. However, during the course of a medical record review for some other purpose a staff member may find evidence of a previously unreported adverse event. In this case, a Safety Review Form (#31) should be completed and reviewed locally to determine if the condition should affect the participant's further involvement in the study.

Musculoskeletal Injuries

Questions on the Prescreen Eligibility Form (#1) determine whether the participant has orthopedic or rheumatologic problems that might limit his/her ability to participate in the physical activity component of the intervention. Potential problems are reviewed by the PI or interventionist to determine whether the problem would make participation in the physical activity component of PREMIER unsafe. Once they are randomized, participants in Groups B and C are taught techniques for stretching, warm-up, and cool-down as a component of the intervention to reduce risk of musculoskeletal injuries. Musculoskeletal symptoms or injuries are reported on the Follow-up Symptoms Questionnaire (Form #78) or the Safety Review Form (#31). Severe or potentially clinically significant symptoms are brought to the attention of a PREMIER clinician who determines 1) if the physical activity portion of the intervention should be terminated either permanently or pending a clinical evaluation; and 2) whether referral for further evaluation or treatment is warranted. In some situations where there are musculoskeletal symptoms, or an injury has occurred, it may be appropriate for the interventionist to advise the participant on adapting his/her physical activity program. (For example, an individual who has sustained a leg injury may be advised about alternatives to walking.) An unblinded clinician is available to advise the interventionists.

If a musculoskeletal injury seems likely to lead to termination of participation in the intervention, to the extent possible staff collect end-of-intervention measurements before termination, giving highest priority to the four end-of-intervention blood pressure measurements.

Treadmill Testing

If a pre-exercise heart rate is <40 or >110 beats/minute, the study clinician is contacted and reviews the situation focusing on participant safety. The participant is not necessarily ill, and might still be a candidate for the test. The study clinician has the following options:

1. If the clinician determines that the abnormal heart rate is not pathological (e.g., a very slow rate in a trained athlete), the participant may perform the test as scheduled

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2. If the clinician determines that the abnormal heart rate is not pathological but that the test would be safer if performed when heart rate is in the normal range, the participant will be asked to reschedule the test for a later time (later that day or on another day) when the participant's heart rate is within the acceptable range
3. If a reason for the slow or fast pulse is not self-evident and is potentially of concern, the study clinician may advise the participant to seek a medical evaluation. Treadmill will be performed only with MD permission after that evaluation.

If any criteria for discontinuing the treadmill test early are met (see Chapter 18, Fitness), examiners must proceed directly to the cool down stage of the procedure. If the test is discontinued because a participant is experiencing chest pain, the cool down procedure is accelerated by slowing the treadmill as rapidly as possible so that participants can dismount safely and staff can attend to their symptoms.

Data and Safety Monitoring Board (DSMB)

The DSMB provides independent oversight of safety monitoring. Clinical centers send copies of all AE forms to the Coordinating Center, where an unblinded clinician reviews the data and adjudicates the nature and severity of the event for reporting to the DSMB. AEs are classified as being either cardiovascular (cardiac or cerebrovascular), musculoskeletal, gastrointestinal, or other in nature, and this information is reported in aggregate to the DSMB, broken down by site and intervention arm. Symptom data from Form #78 are reported separately. The DSMB reviews safety data annually and can recommend that NHLBI terminate the trial early if participants are being subjected to undue risk or if the trial's objectives are met and further follow-up would serve no added scientific purpose.

The NIH "Guidance on Reporting Adverse Events to Institutional Review Boards" of June, 1999, requires all multi-site clinical trials with a DSMB to forward summary reports of Adverse Events to each IRB associated with the trial. Each summary report includes:

- A statement that a DSMB review of data and outcomes across all centers took place, and the date of the review
- A summary of the DSMB review of the cumulative adverse events reports from all participating sites without specific disclosure by treatment arm, unless safety considerations require such disclosure, or a statement indicating that no adverse events were reported from participating sites
- The DSMB's conclusion with respect to progress or need for modification of the protocol.

These summary reports are in addition to all other adverse event reporting procedures required by NHLBI, the trial protocol, each organization, and each local IRB, and are distributed to each Principal Investigator by the Coordinating Center within 30 days after each DSMB meeting. Principal Investigators are required to forward Summary Reports of Adverse Events to their local IRBs.

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Local oversight

Originals of all AE forms remain stored at the clinical site, while copies are sent to the CC for review. The coordinating center annually sends a summary of adverse events to each site for distribution to that institution's IRB as required by local regulations.