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Summary of Edits

Summary of changes between Version 1.0 and 1.1:

- p. 13-4: Added: Anthropometric assessments - weight (Form #57) and waist circumference (Form #57)
- Added form numbers throughout when title of form is mentioned and corrected form titles when incorrect
- Corrected form numbers throughout when incorrect
- Titles of Forms #104 and #105 changed to “Food Interview” from “Diet Recall”
- Corrected BP forms numbers
- Corrected form to use for closeout if escape BP is reached (From #28 to #37)
- Added Form #25 (Perceived Questionnaire) to list of questionnaires administered at this visit
- Study clinician does not sign Form #16. Deleted from *Administer Symptoms Questionnaire*
- AE form is filled out if Form #16, Question #17 is “yes” (not question #14)
- AE form is filled out if Form #6, Question #8 is “positive”
- Added sentence that staff completes Form #105, Convenient Times Schedule, in section on completion of 24-hour food interviews by Penn State.
- Corrected statement regarding continuing participation of participants who initiate antihypertensive therapy: they continue in the intervention and continue to provide all study measurements, including blood pressure. These measurements are reviewed by the adjudication committee.

Summary of changes between Version 1.1 and 1.2:

- Added statement regarding how to handle positive Rose Angina questionnaires that were positive at baseline.

Summary of changes between Version 1.2 and 1.3:

- Corrected instructions for follow-up of Rose Angina Questionnaires: Participants with a newly positive Rose Angina Questionnaire at this visit must refrain from exercise until they have a stress test and approval from both their personal physician and a PREMIER clinician.
- Participants with a positive Rose Angina Questionnaire at this visit who had any previous positive Rose Angina Questionnaire refrain from exercise until they have approval from both their personal physician and a PREMIER clinician. The decision to require a repeat stress test in this case is left to the discretion of the participant’s personal physician.

Summary of changes between Version 1.3 and 1.4:

- Form #11, Medication Use Questionnaire, is no longer in use for follow-up visits. Use Form #79, Follow-Up Medication Use Questionnaire.
- Complete Form #79 at every BP visit.
- Use Form #201, Weight Loss Medications that Affect Blood Pressure, when completing form #79, Follow-Up Medication Use Questionnaire.
- Weight is measured at the first visit of the cluster
- The Follow-Up Symptoms Questionnaire (Form #78) is administered at only one of the 4 cluster visits.

Summary of Edits

Summary of changes between Version 1.3 and 1.4 (continued):

- An AE Form (#30) is completed if Follow-Up Symptoms Questionnaire (Form #78) Question #15 = yes.
- For cohorts 2-4, collect additional blood for folate, carotenoids, and Vitamin B12 to be analyzed at CDC
- A blood pressure measurement that is taken as part of the BP escape procedure may be counted as the next “cluster visit” blood pressure measurement for that participant.
- If a follow-up measurement triggers a referral and the participant is not put on blood pressure medications, try to get at least one additional blood pressure measurement in order that the gap between the first and last blood pressures is at least one month.

Summary of changes between Version 1.4 and 1.5

- Reduce the number of 6-month blood pressure measurements from four sets of two to three sets of two

13. 6-Month Visit

Overview

This chapter describes the sequence of activities that comprise the 6-month “visit.” Although we use the term “visit” for simplicity, these activities are actually spread out over a series of at least three visits occurring between 5 ½ and 8 ½ months post randomization.

The purpose of the 6-month visit is to collect the primary study outcomes. Additionally, data collected at the 6-month visit is used for ongoing safety monitoring.

Setting

With the possible exception of the submaximal treadmill test, which may take place at a separate medical facility, all of the 6-month measurements take place at the clinical center and require a quiet, private or semi-private setting where the participant can wait relaxed prior to the random zero blood pressure measurement. Questionnaires also need to be administered and reviewed in a setting that permits privacy for the participant.

Required Materials

- 6 Month Visit Form (#57)
- Study charts for scheduled participants
- Scale
- Tape Measure

Food Interview materials

- Food Interview Instruction Sheet (Form #104)
- Informational Poster
- Food Interview Convenient Times Schedule (Form #105)

Questionnaires

- Quality of Life Questionnaire (Form #23)
- Perceived Stress Questionnaire (Form #25)
- Exercise Confidence Questionnaire (Form #45)
- Eating Habits Confidence Questionnaire (Form #46)
- Social Support and Eating Habits Questionnaire (Form #47)
- Social Support and Exercise Habits Questionnaire (Form #48)
- Perceived Body Image Questionnaire (Form #49)
- Alcohol Intake Questionnaire (Form #22)

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- Rose Questionnaire — Angina (Form #6)
- Follow-Up Symptoms Questionnaire (Form #78)
- 7-Day Physical Activity Recall (Form #18)
- Follow-Up Medication Use Questionnaire (Form #79)
- Weight Loss Medications that Affect Blood Pressure (Form #201)

Treadmill Fitness Test

(Detailed information on conducting the fitness test is included in Chapter 18, Fitness).

- Treadmill equipment and materials as specified in Chapter 18.
- Fitness Test Form (Form #26)

Central Lab Specimens Collection

(Detailed information on processing lab samples is included in Chapter 21, Central Laboratory Procedures).

- Fasting blood sample kit (analyzed centrally for total cholesterol, LDL-C, HDL-C, VLDL-C, triglycerides, insulin, glucose, and homocysteine)
- CDC kit for folate, carotenoids, vitamin B12
- 24-hr urine processing materials (analyzed centrally for Na, K, phosphorous, creatinine, and nitrogen)
- Central Lab Collection Form – 24hr Urine (Form #62 and Form #68)
- Central Lab Collection Form – Fasting Blood (Form #63 and #65)
- CDC Lab Collection Form – Folate/Carotenoid/VitB12 (Form #77)

Blood pressure assessment

- Random zero sphygmomanometer and stethoscope
- Standard mercury sphygmomanometer
- 6-Month Visit Blood Pressure Forms (#67-69)
- Blood Pressure Escape Form – 6, 18 month visits (Form #52)

Anthropometric assessments

- Weight (Form #57)
- Waist circumference (Form #57)

Other Questionnaires

- Adverse Events Form (Form #30)

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Preprinted ID labels should be available to use on the forms. The number of forms and pieces of equipment are determined by local staffing configurations and the anticipated participant flow. If available, a spare (back up) sphygmomanometer should be accessible.

Conducting the 6-Month Visit(s)

As noted previously, the following activities should be completed between 5 ½ and 8 ½ months post randomization. The exact sequence for the activities, however, as well as the content of any given visit, are left to the discretion of the individual clinical centers. The only requirement is that the visits fall within the windows shown in table 13-1. For most activities, the separate target, allowable, and adjudication windows are listed. In addition, a Visit Windows Report for each participant can be printed from the Data Management System. This gives exact calendar dates for each of the windows based on the participant's randomization date. Staff should always attempt to schedule activities to occur within the target windows, and the CC will report on the success of each site in achieving these target ranges. However, measurements may still be collected outside of the target window provided that they fall within the allowable window range. Measurements taken outside of the allowable windows are evaluated by the adjudication committee to determine if and how they can be used. It is critical that staff make every possible effort to make sure all of the six-month activities occur within the allowable window.

- Confirm participant ID
- Complete the Follow-Up Symptoms Questionnaire (Form #78)
- Complete the Follow-Up Medication Use Questionnaire (Form #79)
- Complete the Rose Questionnaire - Angina (Form #6)
- Complete the 7-Day Physical Activity Recall (Form #18)
- Complete/review the various psychosocial questionnaires and the Alcohol Intake Questionnaire (Forms #45-49, #22 & #23)
- Collect and process the 24-hour urine specimen (Form # 62)
- Collect and process the fasting blood sample (Forms #63 and #77)
- Complete two 24-hour food interviews (by a central diet assessment center)
- Conduct the Treadmill Fitness Test and record the results (Form #26)
- Measure Blood Pressure on Three Separate Occasions (Forms #67-69)
- Measure Weight and Waist Circumference (Form #57)
- Record events on the 6-Month Visit Form (Form # 57)

Table 13-1. 6 Month Visit Measurement Targets and Windows	
RZ BP	Total of three measurement visits with two readings per visit. No two visits less than two weeks apart. When possible, center measurements around 7 months from randomization date <i>Target/Allowable Window</i> <ul style="list-style-type: none"> • 5 ½ months to 8 ½ months <i>Adjudication Window*</i> <ul style="list-style-type: none"> • 3 ½ months to 11 ½ months*
Treadmill, Lab, Questionnaires, Wt, Waist, 24 hr Food Interviews**	May be done in separate visits <i>Target Window</i> <ul style="list-style-type: none"> • 7 months from randomization date \pm 3 weeks <i>Allowable Window</i> <ul style="list-style-type: none"> • 5 ½ months to 8 ½ months <i>Adjudication Window*</i> <ul style="list-style-type: none"> • 3 ½ months to 11 ½ months
*If outside allowed range, collect data, enter forms, and adjudication committee will determine if/how to use. If outside adjudication range, collect but do not enter. Adjudication committee will review.	
** Food Interviews to be completed by Penn State; instructions provided by clinical site staff	

Confirm participant ID

Make sure that the participant’s ID is on the 6-Month Visit Form (#57) and any other forms to be completed as part of the 6-Month visit. Clinical center staff should confirm the accuracy of all IDs. Use of preprinted ID labels is recommended.

Administer the Follow-Up Symptoms Questionnaire (Form #78)

Ask the participant to complete the Follow-Up Symptoms Questionnaire (Form #78). If the participant answers “yes” to question #15, an Adverse Events Form (#30) is required. Administer this questionnaire at only one of the 4 cluster visits. Check the appropriate box on the 6-Month Visit Form to indicate that the Follow-Up Symptoms Questionnaire was administered.

Complete the Follow-Up Medication Use Questionnaire (Form #79)

This form is administered at every blood pressure visit. Confirm that the participant has brought in all medications, over-the-counter products, or nutritional supplements that they are currently using. Check the participant’s medication containers and complete the Follow-Up Medication Use Questionnaire (Form #79). If the participant has started taking any additional medications, a PREMIER clinician must review the form. If the participant fails to bring her current medications, it will be necessary to call the participant at home to review her medications. Use Form #201, Weight Loss Medications that Affect Blood Pressure, to check weight loss medications.

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Complete Rose Angina Questionnaire (Form #6)

Administer the Rose Angina Questionnaire (Form #6) to the participant. Individuals with a positive Rose Angina Questionnaire (question #8 answered “positive”) are immediately referred to their personal physician for evaluation.

If **all previous** 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 the PREMIER clinician.

If **any previous** 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.

An AE form is to be completed if the answer to question #8 is “positive.” Check the appropriate box on the 6 Month Visit Form (#57) to indicate that the Rose Angina Questionnaire was administered. Use the worksheets attached to the Rose Questionnaire to document the follow-up process.

Administer 7-Day Physical Activity Recall (Form #18)

Staff are specially trained to administer this form. Complete the 7-Day Physical Activity Recall (Form #18). Check the appropriate box on the 6-Month Visit Form indicating the recall was completed. See Chapter 22 for more details.

Complete/review the various psychosocial questionnaires and the alcohol intake questionnaire

A number of self-administered questionnaires must be completed during the 6-month visit window period. These include an alcohol intake questionnaire (Form #22) and six psychosocial questionnaires (Forms # 45-49, #23). These may either be completed at home and brought to the clinic, or else completed in the clinic. In either case clinic staff should review all of the forms for completeness and resolve any missing or ambiguous responses.

Collect the 24-hour urine sample (Form #62)

In order to maximize quality control for urine collections, the collections should ideally begin on a Monday through Thursday when the participants come in to pick up their collection materials, and

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participants should be instructed to return the collections the next day. This enhances the likelihood that the initial voiding to start the interval is discarded and that a final voiding is obtained at the end of the collection interval. It should also maximize the likelihood that the collection duration falls within the allowable limits (22-26 hours). If, in the opinion of clinic staff, the participant is unlikely to comply with the collection regimen due to this weekday collection, the participant may be allowed to collect the specimen over the weekend. In this case it is still preferable to either begin or end the collection in the clinic, so that at least some level of quality assurance is achieved.

To begin the collection, distribute the 24-hour urine container and instructions to the participant and review the instructions. Stress the importance of strictly adhering to the collection protocol, and remind the participant that the sample needs to be returned to the clinic within 24 hours of the final voiding. Begin completing Form #62.

Make sure that a label is affixed to the collection jug. Refer to the Interim Visit Chapter (Chapter 10) of the MOP for detailed instructions. (See Chapter 21, Central Lab Procedures, regarding requirements for acceptability and repeat samples and for instructions on sample handling and processing.) Note: Instruct pre-menopausal women to collect the 24-hour urine specimen when they are not menstruating.

Collect and process the 12-hour fasting blood sample (Forms #63 and #77)

Part of the 6-month visit includes a fasting blood draw. Participants should be instructed to fast for 12 hours prior to the clinic visit (an overnight fast with an early morning clinic visit is suggested for this purpose). Clinic staff should also provide the participants with light snacks and juice immediately after the blood draw.

The blood specimen should be processed immediately following collection using the procedures outlined in Chapter 21, Central Lab Procedures. See Chapter 21 regarding requirements for acceptability and repeat samples. Complete the Central Lab Collection Form (#63), and the CDC Lab Collection Form – Folate/Carotenoid/B12 (Form #77). Document the collection on the 6-Month Visit Form (#57).

Completion of two 24-hour food interviews

Two unannounced 24-hour food interviews occur between 5 ½ months and 8 ½ months post randomization. These interviews, conducted by telephone by the Diet Assessment Center of Pennsylvania State University, are meant to take place within a 3-week period on nonconsecutive days. The procedure for administration of the interviews is presented in Chapter 19. Complete Form #105, Convenient Times Schedule, for appropriate time zone. Penn State will notify the clinical centers once the two interviews have been completed so that this information can be noted in the data management system using Form #57.

Conduct the treadmill fitness test and record the results

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Baseline cardiorespiratory fitness is determined by submaximal treadmill stress testing. (This procedure is described in Chapter 18). Note the completed test on Form #57.

Measure blood pressure on three separate occasions

Three random zero blood pressure measurements must be obtained between 5 ½ months and 8 ½ months after the randomization visit. No two sets of measurements may be less than two weeks apart. It is recommended that timing of these measurements center around 7 months from the randomization date.

Take the participant's blood pressure using the random zero sphygmomanometer and the procedures described in MOP Chapter 17 (Blood Pressure Assessment). **Re-measure the cuff size for the first of the three measurements of the cluster. Be sure to use this same cuff size for all measurements in this cluster.** Record the outcome of the measures on the 6-Month Visit Blood Pressure Form (#53).

If the mean blood pressure recorded at any single visit is \geq either SBP of 160 mmHg or DBP of 100 mmHg, one additional set of RZ measurements must be obtained within one week. If the cumulative mean from the two visits is \geq SBP 180 or DBP 110, the participant is referred to his/her personal physician for further evaluation within one week. If the cumulative mean from the two visits is \geq SBP 160 or DBP 100, then the participant is referred to his/her personal physician within one month. If the cumulative mean blood pressure recorded at the end of the three six month visits $>$ either a SBP of 140 mmHg or a DBP of 90 mmHg, participant is referred to his/her personal physician within two months.

A blood pressure measurement that is taken as part of the BP escape procedure may be counted as the next "cluster visit" blood pressure measurement for that participant. Note that the reports showing progress through the 6-month visit will not include BP measurements that are done as part of the escape procedure. For this reason, sites must track this locally. If the follow-up measurement triggers a referral and the participant is not put on blood pressure medications, try to get at least one additional blood pressure measurement, even if you have already obtained a full set of end-of-study blood pressures, in order that the gap between the first and last blood pressures is at least one month.

The timing of the referral, within one week, within one month, or within 2 months, depends on the threshold level that is reached (see Chapter 23, Safety Monitoring). These threshold levels are also shown on the 6-Month Visit Blood Pressure Form. If the threshold levels are exceeded, the Blood Pressure Escape Form-6, 18 Month Visits (Form #52) needs to be completed, with one copy placed in the participant's study chart and one copy sent to the CC. The participant may also be referred to a physician if deemed appropriate based on symptoms and clinical judgment even if the BP is lower than the above limits.

Participants who initiate antihypertensive therapy as a result of hitting an escape level, or for any other reason, continue in the intervention and continue to provide all study measurements, including blood pressure. The adjudication committee makes a determination as to how subsequent measurements

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should be used for analysis. Enter the 6-Month Visit Blood Pressure Form (#53), and, if applicable, a BP Escape Form—6, 18 Month Visits (Form #52).

Measure Weight and Waist Circumference

At the first visit of the cluster, measure the participant's weight and waist circumference according to the procedures in Chapter 20. Record on the 6-Month Visit Form (#57).

Record events and visit outcome on the 6-Month Visit Form (#57)

Review the 6-Month Visit Form and all other forms to make sure the data collection is complete and each item has been checked off on the checklist.

Ending the 6-Month Visit(s)

Once all items on the 6 Month Visit Form are complete, enter the following items. The order of entry is not important, except that the 6-Month Visit Form must be entered last.

- 6-Month Visit Blood Pressure Form (#67-69)
- BP Escape Form—6, 18 Month Visits (#52) (if any)
- Rose Questionnaire—Angina (Form #6)
- Follow-Up Symptoms Questionnaire (Form #78)
- Adverse Events Form (#30) (if any)
- Central Lab Collection Form—6-Month 24hr Urine (Form #62)
- Central Lab Collection Form—6-Month Fasting Blood (Form #63)
- CDC Lab Collection Form – Folate/Carotenoid/B12 (form #77)
- Fitness Test Form (#26)
- 7-Day Physical Activity Recall (Form #18)
- Follow-Up Medication Use Questionnaire (Form #79)
- Quality of Life Questionnaire (Form #23)
- Perceived Stress Questionnaire (Form #25)
- Exercise Confidence Questionnaire (Form #45)
- Eating Habits Confidence Questionnaire (Form #46)
- Social Support and Eating Habits Questionnaire (Form #47)
- Social Support and Exercise Habits Questionnaire (Form #48)
- Perceived Body Image Questionnaire (Form #49)
- Alcohol Intake Questionnaire (Form #22)
- 6-Month Visit Form (#57)