Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study

Measurement and Assessment Procedural Manual

Version 1.5

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1. Introduction

This manual describes and provides instructions for the physical measurements and assessments performed in the Glycemic Reductions Approaches in Diabetes: A Comparative Effectiveness (GRADE) Study in the order in which they are first collected. Anthropometric measurements including weight, height, waist and hip circumference measurements are described in the first half of this manual. Assessments such as blood pressure, neuropathy assessment, the Oral Glucose Tolerance Test (OGTT), the Quality of Well Being (QWB) scale, and the Neurocognitive Assessment are described in the second half of this manual. Refer to Table 1.1 for a schedule of the measurements and assessments for the GRADE study. This table is an abbreviated version of the schedule adapted from the GRADE Protocol; it has been revised to only include measurements and assessments discussed in this manual. Following each individual assessment is a certification form that should be completed by research clinic staff, maintained and filed at the clinical site.

A current version of this manual will be maintained and provided on the GRADE study website by the GRADE Coordinating Center. Additional training materials are also available on the GRADE study website including presentations and training videos for certain assessments. Videos posted to the GRADE study website may be accessed via password: grade. Each site will have at least one staff member trained and certified in all procedures at all times (preferably the study coordinator, but may be delegated to another staff person as necessary based on local site operations).

Table 1.1: Abbreviated GRADE Schedule of Measurements and Assessments adapted from GRADE Protocol.

Measurements and Assessments	Screen	Final run-in	Base-line	1 Y	2 Y	3 Y	4 Y	5 Y	6 Y
Anthropometric Measurements									
Weight	√		√*	Q	Q	Q	Q	Q	Q
Height			√*				A		
Waist and hip circumference			√*		A		A		A
Assessments									
Blood Pressure	√		√*	Q	Q	Q	Q	Q	Q
Neuropathy			√*	A	A	A	A	A	A
OGTT			√	A		A		A	
QWB			√*	A	A	A	A	A	A
Neurocognitive Battery			√*				A		A
ECG (read centrally)			√*		A		A		A

A=Performed Annually
Q=Collected Quarterly
*May be completed at Final Run-in visit

2. GRADE Body Weight Measurement

2.1 Introduction

Sites will use locally available and maintained electronic or balance scales for measuring weight. All weight measurements will be taken and recorded in kilograms. The scale should be set to be read in kilograms. Ideally, body weight is measured in the morning after voiding and before breakfast such as at the annual visit. If this is not possible, efforts should be made to weigh each participant under conditions as similar as possible at all visits (e.g., same time of day if possible, same scale). Weight is measured at Screening, Baseline (can be done at Final Run-in based on the site's preference), and all follow-up visits in GRADE.

2.2 Procedures

The participant should be instructed to wear light clothing, remove shoes and to stand still in the middle of the scale platform with head erect and eyes looking straight ahead. Record the weight in kilograms to the nearest 0.1 kg. Participants with amputations (that have occurred since randomization) or participants who are wearing casts should have a weight measure taken and noted as such on the form in the space provided.

2.3 Training

Clinical research staff will be trained locally prior to conducting measurements on participants.

2.3.1 Training Procedures

1. Review Section 2 of the Measurement and Assessment Procedural Manual.
2. Recruit 2 volunteers for initial training and 1 volunteer if re-training.
3. Complete the Body Weight Training Documentation (see section 2.3.2).

2.3.2 Body Weight Training Documentation

GRADE
Body Weight Training

Instructions: Complete this form to document competency and keep on file locally. Staff should be trained initially and at GRADE Study Year 3.

A. Required Materials

- Use locally available and maintained scale, set to be read in kilograms (kg)
- Body Weight Training Form
- 2 volunteers

B. Procedural Checklist

Observe the following procedural steps:

☐ Assemble proper materials and equipment: scale

☐ Greet participant and review procedure

☐ Confirm participant is wearing light clothing, empty pockets and shoes removed

☐ Ask and record on the form any information on amputation, prosthesis or cast (which was not present at baseline)

☐ Position participant correctly on the scale: head erect, eyes looking straight forward, standing still in middle of scale platform

☐ Read and record the weight to the nearest 0.1 kg on the study form

C. Measurements

Record weight measurements

Weight:

	Volunteer #1	**Volunteer #2**
Measurement #1	☐☐☐ . ☐ kg	☐☐☐ . ☐ Kg
Measurement #2	☐☐☐ . ☐ kg	☐☐☐ . ☐ Kg

Comments:_____
_____
_____
_____

Signature of Trainee: _____ Date: _____

Signature of Trainer: _____ Date: _____

3. GRADE Body Height Measurement

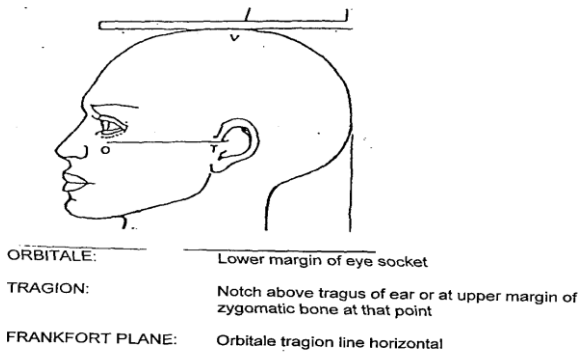
3.1 Introduction

A wall-mounted stadiometer graduated in centimeters with a horizontal measuring block (or fixed angle) is preferable. If the stadiometer is not wall-mounted, you will need a level to ensure that the horizontal measuring block is level. Stadiometers will not be provided by GRADE. Alternatively, a wall mounted measuring stick is acceptable. Sites are responsible for proper mounting and use. Sites will use locally available equipment that has been maintained according to local regulations. Height is recorded at the Baseline visit (can be done at the Final Run-in visit based on site's preference) and at Year 4.

3.2 Procedures

The participant stands erect with his/her back parallel to the vertical mounted measure scale (but not touching the wall), looking straight ahead with his/her head in the Frankfort horizontal plane (the horizontal plane is defined by the lower margin of the bony orbit - the bony socket containing the eye - and the most forward point in the supratragal notch - the notch just above the anterior cartilaginous projections of the external ear). Refer to Figure 3.1 for correct placement of the head during height measurement. The horizontal measuring block is brought down snugly, but not tightly, on the top of the head. The participant's height is recorded in centimeters to the nearest 0.1 cm. The participant should be instructed to stand as straight as possible with feet flat on the floor.

Figure 3.1: Placement of head during height measurement



3.3 Training

Clinical research staff will be trained locally prior to conducting measurements on participants.

3.3.1 Training Procedures

1. Review Section 3 of the Measurement and Assessment Procedural Manual.
2. Recruit 2 volunteers for initial training.
3. Complete the Body Height Training Documentation (see section 3.3.2).

3.3.2 Body Height Training Documentation

GRADE
Body Height Training

Instructions: Complete this form to document competency and keep on file locally. Staff should be trained initially and at GRADE Study Year 3.

A. Required Materials

- Stadiometer graduated in centimeters (preferred) or horizontal measuring block (or fixed angle)
- Body Height Training Form
- 2 volunteers

B. Procedural Checklist

Observe the following procedural steps:

☐ Assemble proper materials and equipment

☐ Greet participant and review procedure

☐ Confirm participant has removed shoes

☐ Position the participant correctly parallel to the wall measuring scale: standing straight as possible with feet flat on the floor back parallel to the vertical mounted measuring scale, looking straight ahead, back not touching wall if possible

☐ Read and record the height to the nearest 0.1 centimeters on the study form

C. Measurements

Record height measurements

Height:

	Volunteer #1	**Volunteer #2**
Measurement #1	☐☐☐ . ☐ cm	☐☐☐ . ☐ cm
Measurement #2	☐☐☐ . ☐ cm	☐☐☐ . ☐ cm

Comments:_____
_____
_____
_____

Signature of Trainee: _____ Date: _____

Signature of Trainer: _____ Date: _____

4. GRADE Waist and Hip Circumference Measurement

4.1 Introduction

The Gulick II Tape Measure (model 67020) will be used for accuracy in obtaining duplicate waist and hip girth measurements. The Gulick II Plus Tape Measure (model 67019) will be used to obtain measurements for large individuals when appropriate. The design of the tape measure eliminates the guesswork by applying a known amount of tension (four ounces) to the measuring tape. When used properly, tape tension is always four ounces ensuring accurate measurements. The Gulick II is standardized equipment for GRADE. It is clear that only by applying a constant tension (as the Gulick II does) can accurate and repeatable measurements be taken.

The Gulick II Tape Measure uses a no-stretch, retractable tape with both Metric and English gradations (centimeters and inches). The self-retracting tape is kept at the desired length until the retract button is pushed. The most important part of the Gulick II Tape Measure is the tensioning device attached to the measuring tape. Its function is to provide a known amount of tension while a measurement is being taken. Each individual tensioning device is calibrated to indicate precisely a four-ounce tension. Note that a stainless-steel compression spring is used. This guarantees that the calibration will last a lifetime, since it is impossible to "over-compress" a spring of this type.

4.2 Taking measurements

Ideally, waist circumference would be measured in the morning after voiding and before breakfast. If this is not possible, efforts should be made to measure each participant under conditions as similar as possible at all visits (e.g., same time of day, fasting, limited consumption of fluids).

All measurements are to be made with the participants wearing light clothing, e.g., a short sleeve shirt or blouse (or surgical gown), lightweight pants or shorts, socks and without shoes (for weight and height). A supply of gowns should be maintained at the clinic for participants who forget to wear or bring the appropriate clothes for body size measurements. The pants must be lowered to get an accurate reading as measuring over thick clothing will not be accurate. In some cases where the pants/shorts are extremely light-weight, it may be possible to measure over them, but this is highly discouraged. Body size measurements should always be conducted by study certified staff. If possible, measurements, especially waist and hip circumferences, should be taken by a team of two persons, one acting as observer and the other as recorder. The observer takes the measurements, reporting the results to the recorder, who repeats them. The observer keeps the measuring instrument in place until the recorder repeats the number. The recorder generally checks the examinee's position during the procedure. If a second observer is not available, a mirror can be used to check for the correct position (e.g., whether the tape is horizontal for waist circumferences). If a mirror is not available, the observer must take extra care to employ excellent technique and respect the subject's privacy and comfort level. Waist and hip circumferences will be measured at baseline (or final run-in), Year 2, Year 4, and Year 6. Measurements are taken twice. If the measurements are not within 0.5 cm of each other, a third measurement is needed.

4.2.1 Waist measurements

Participants should stand with their feet at shoulder width (comfortably separated and balanced).The measure should be taken around the abdomen horizontally at midpoint between highest point of the iliac crest and lowest part of the costal margin in the mid-axillary line. Mark the midpoint on both sides using a washable marker. (Participant may be asked to assist in passing the tape around the abdomen by holding the end of the tape in position). The tape should be aligned with the markings and positioned in the horizontal plane at the correct height. At this point, it may be helpful to mark the position of the tape on the participant's back in order to ensure proper placement for the second reading.

Pull an appropriate amount of tape out of the housing. Wrap the tape once around the waist (see instructions below). Align the tape's "zero line" alongside of the tape graduations. Use metric units (cm). Now simply pull on the end of the tensioning mechanism until the **calibration point** is just seen. Read the measurement next to the tape's "zero line". When you pull slightly harder and harder on the tensioning device, two colored beads will be seen separated by a silver disk. When you are pulling with exactly four ounces of force, you will see a silver disk separating the two beads. When you see one of the two beads, you are at the "calibration point". Remember, four ounces is not a great deal of force; in fact, it is approximately equal to the force required to lift a stack of 20 U.S. quarters. Do not pull so hard that the beads start to disappear into the end cap of the tensioning device as that is too much force.

The participant should be asked to keep relaxed arms at the sides and to breathe naturally. Ask the participant to breathe in, out, and hold at the end of a normal exhalation. Record circumference to the nearest 0.1 centimeter. Remove the tape and repeat the procedure. If the tape cannot be made horizontal across the waist markings, default to the right hip marking.

4.2.2 Hip Circumference

With the participant standing, identify the femoral greater trochanters (bony prominence of the hip) on the mid-axillary line for each side of the body. As above, mark at the bony prominence. Measure the hip using the Gulick ll Tape Measure (model 67020 or model 67019) placed horizontally at the level of the markings. Ask the volunteer to have arms at their side. Occasionally, an obese volunteer may have a pendulous abdominal wall which extends (or hangs down) anteriorly to the level of the greater trochanters. In such situations, this pendulous abdomen should not be included in the hip girth and should be held out of the way while the tape is placed beneath it. Measure and record the hip measurement to the nearest 0.1 centimeter.

4.3 Certification Procedures

1. Review Section 4 of the Measurement and Assessment Procedural Manual.
2. Recruit 2 volunteers if initial certification or 1 volunteer if re-certification (Year 3 of GRADE for all staff unless certified within past 6 months).
3. Complete the Waist and Hip Circumference Certification documentation (see section 4.3.1).

4.3.1 Waist and Hip Circumference Certification

GRADE
Waist and Hip Circumference Certification

Instructions: Complete this form to document competency and keep on file locally. Staff should be certified initially and at GRADE Study Year 3.

A. Required Materials

- Gulick ll Tape Measure (model 67020) or Gulick II Plus Tape Measure (model 67019)
- Washable marker
- Alcohol swabs
- Waist Circumference certification form
- 2 volunteers if initial certification, 1 if re-certification

B. Procedural Checklist

Observe the following procedural steps:

☐ Assemble proper materials and equipment

☐ Greet participant and review procedure, ensure participant is wearing light clothing and has removed shoes

☐ Position participant's feet shoulder width apart

Waist:

☐ Determine the midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the mid axillary line and mark the midpoint on both sides with a washable marker

☐ Position tape around the abdomen in the horizontal plane at the correct height indicated by the markings

Hip:

☐ Determine the site of the greater trochanter of the femur by locating the bony prominence on the mid-axillary line of the lower hip and mark the bony prominence with a washable marker, repeat process on other side

☐ Position tape around the hips in the horizontal plane at the correct position indicated by the markings, if abdomen is pendulous, hold it out of the way of the measurement

Both waist and hip:

☐ Instruct participant to keep hands at side and breathe normally

☐ Ask participant to breathe in, out and hold at the end of a normal exhalation

☐ Pull with just enough force on the Gulick II tape to visualize one red bead (the calibration point), read and record circumference to the nearest 0.1 cm

☐ Remove the tape

☐ Repeat the measurement

☐ Thank the participant

Site Number __ __ - __ Name of Clinical Staff Member ______ Staff ID __ __ __ Certification Date __/__/____ (month day year)

C. Measurement

Record waist and hip circumference

Volunteer # ☐

	Waist:	Hip :
Measurement #1	☐☐☐ . ☐ cm	☐☐☐ . ☐ Cm
Measurement #2	☐☐☐ . ☐ cm	☐☐☐ . ☐ Cm

Record measurement #3 only if first two measurements are not within 0.5cm.

Measurement #3	☐☐☐ . ☐ cm	☐☐☐ . ☐ Cm

Volunteer # ☐

	Waist:	Hip :
Measurement #1	☐☐☐ . ☐ cm	☐☐☐ . ☐ Cm
Measurement #2	☐☐☐ . ☐ cm	☐☐☐ . ☐ Cm

Record measurement #3 only if first two measurements are not within 0.5cm.

Measurement #3	☐☐☐ . ☐ cm	☐☐☐ . ☐ Cm

Volunteer # ☐

	Waist:	Hip :
Measurement #1	☐☐☐ . ☐ cm	☐☐☐ . ☐ Cm
Measurement #2	☐☐☐ . ☐ cm	☐☐☐ . ☐ Cm

Record measurement #3 only if first two measurements are not within 0.5cm.

Measurement #3	☐☐☐ . ☐ cm	☐☐☐ . ☐ Cm

Comments:____

____

Signature of Trainee: ______________________ Date: __________ Certification ☐

Signature of Trainer: ______________________ Date: __________ Re-certification ☐

5. GRADE Blood Pressure Assessment

5.1 Introduction

Blood Pressure (BP) will be measured by site personnel at specified time points. The GRADE study will not provide standardized equipment for the procedure. Sites will use equipment available at their local setting. The equipment used must be maintained as per local guidelines. Documentation of local policy for equipment maintenance and inspection/maintenance records if applicable must be kept on hand by the study coordinator. Mercury, aneroid, and automated/digital equipment are all acceptable for use. Every attempt must be made to use the same equipment for all study visits. However, if extenuating circumstances prevail, alternate equipment may be used but should be noted in the study source documentation.

5.2 Schedule of Administration

Blood pressure will be measured by GRADE personnel at Screening, Baseline (can be done at Final Run-in based on the site's preference), and all follow-up visits. It is suggested that the blood pressure be done at the beginning of a visit if possible. Always do the measurements after the participant has been sitting quietly for at least five minutes. A five-minute rest preceding the first measurement will allow blood pressure to stabilize after movement or activity, such as walking. ***During this five-minute resting period, participants should NOT be engaging in any of the following: reading, filling out forms, talking, or crossing their legs or ankles.***

Clinic staff should explain the blood pressure procedures to the participant prior to the five-minute rest period. Participants should be educated about how blood pressure can be affected by any of the above and told that the five-minute resting period helps the GRADE study obtain more accurate measurements. Making it the first procedure done in a participant's visit will help to avoid any physiological response which might occur due to stress related to anthropometric measurements, phlebotomy, or questionnaires.

5.3 Required Equipment, Materials & Personnel

All GRADE locations will use locally available devices for the blood pressure measurement.

5.3.1 Cuffs

Cuff size will be determined by arm circumference. Each of the following cuff sizes should be available: Adult, Large Adult, and Thigh.

5.3.2 Stethoscope

A standard stethoscope should be utilized, preferably with a bell.

5.3.3 Participant position

The participant should be seated comfortably with feet resting on the ground, without legs/ankles crossed and with their right arm available for measurement. The right arm should be used for measurement unless contraindicated.

5.3.4 Number of readings at each visit

One measurement is taken at the Screening Visit. For all subsequent visits, two repeated measurements are taken.

5.4 Procedures

5.4.1 Preparation

First it is necessary to determine the appropriate size of cuff to be used. The following guideline can be used to determine the cuff size as needed. It is not mandatory to measure the arm. This is suggested if the operator is unsure of the cuff size that would be most appropriate.

Arm Circumference *	Cuff Size
17-25 cm	Small Adult
23-33 cm	Adult
31-40 cm	Large Adult
38-50 cm	Thigh (or Large Adult Long, see text)
* Circumference measured at midpoint between shoulder and elbow	

The sizes for cuffs are overlapping in order to have some flexibility in choice. The first choice for cuff should always be the larger size. However, if the participant is small in stature, the smaller cuff size might be used to avoid having the cuff slide down the antecubital fossa.

If a participant's upper arm circumference indicates use of the thigh cuff, but the arm is too short for the cuff, or the cuff does not remain secured when inflated, the Large Adult Long arm cuff should be used. Difficulty with placement is often a problem with obese participants and may result in inaccurate readings.

5.5 Taking the seated blood pressure:

The participant should be seated with both feet flat on the floor and the right forearm resting comfortably on a table or surface at approximately heart level. Have the participant rest for five minutes prior to taking the first measurement. Palpate the antecubital fossa and position the cuff around the arm so that the midpoint of the bladder length is at heart level, and the cuff arrow marked "artery" is aligned with the brachial artery. Cuffs are labeled with range and index lines. The correct cuff has been selected if the index line is within the range as the cuff is wrapped around the arm. The cuff should be wrapped snugly enough so that no more than one finger-width distance exists between cuff and skin.

If not using a digital/automated system, a stethoscope will be needed. Stethoscope earpieces should be pointing forward and comfortable. The bell (or diaphragm, but bell is preferred) of a high quality stethoscope should be placed over brachial artery, below the cuff and held by hand.

Inflate the cuff and initiate the first reading. Rapidly inflate the cuff above the participant's systolic value (usually 180 is sufficient but may vary). Hold for 3 seconds then steadily and slowly decrease the pressure until you are able to hear a beat (systolic) and keep listening until the beat disappears (diastolic). Once the reading is obtained, wait one minute before initiating reading # 2.

Record the blood pressure on the data forms.

Clean cuffs and equipment as per local regulations.

5.6 Training

Clinical research staff will be trained locally prior to conducting measurements on participants.

5.6.1 Training Procedures

1. Review Section 5 of the Measurement and Assessment Procedural Manual.
2. Recruit 2 volunteers for initial training and 1 volunteer if re-training.
3. Complete the Blood Pressure Training Documentation (see section 5.6.2).

5.6.2 Blood Pressure Training Documentation

Site Number ☐☐ - ☐ | Name of Clinical Staff Member _____ | Staff ID ☐☐☐ | Certification Date ☐☐ / ☐☐ / ☐☐☐☐ (month / day / year)

GRADE
Blood Pressure Training

Instructions: Complete this form to document competency and keep on file locally. Staff should be trained initially and at GRADE Study Year 3

A. Required Materials

- Use locally available devices for blood pressure measurement
  - Mercury, aneroid, or automated/digital equipment acceptable
  - Blood Pressure cuff sizes: Adult, Large Adult, Thigh
- Measuring tape if needed
- Standard stethoscope preferably with a bell if not using automated device
- Chair
- Table, bench or other support to rest participant's forearm
- Blood Pressure Training Form
- 2 volunteers

B. Procedural Checklist

Observe the following procedural steps:

☐ Assemble proper materials and equipment: blood pressure monitor, cuff sizes, measuring tape if needed

☐ Greet participant and reviews purpose, time requirement and procedure

☐ Determine appropriate cuff size and measure arm circumference if necessary

☐ Seat participant in proper position: both feet flat on floor, right forearm resting on table or surface at approximately heart level

☐ Confirm participant is relaxed and comfortable and remind of the need to be seated quietly for 5 minutes prior to the measurement

☐ Palpate brachial artery

☐ Place cuff properly with center of bladder over the brachial artery and cuff at the level of participant's heart

☐ Obtain 2 blood pressure measures with a 1 minute interval between end of first reading and beginning of second reading

☐ Record blood pressure readings

☐ During procedure:
- Keep participant warm, relaxed and comfortable
- Discourage participant from talking except to voice discomfort or confusion about instructions

C. Measurements

Record blood pressure measurements

	Volunteer #1		Volunteer #2	
1st measurement	☐☐☐ / ☐☐☐	mmHg	☐☐☐ / ☐☐☐	mmHg
2nd measurement	☐☐☐ / ☐☐☐	mmHg	☐☐☐ / ☐☐☐	mmHg

Comments:_____

_____

Signature of Trainee: _____ Date: _____ Certification ☐

Signature of Trainer: _____ Date: _____ Re-certification ☐

6. GRADE MNSI (Peripheral neuropathy) assessment

6.1 Introduction

Evaluation of peripheral neuropathy in GRADE will be conducted using the Michigan Neuropathy Screening Instrument (MNSI). The first part of this instrument consists of 15 self-administered "YES or NO" questions (Neuropathy, or MNSI Questionnaire). These questions were chosen from the Neuropathy Screening Profile that showed the highest degree of specificity and sensitivity for diabetic neuropathy. The questions address foot sensation, including pain, numbness, and temperature sensitivity. The second part of the MNSI is a brief physical assessment that includes a foot exam and specifically addresses the following:

1. Inspection of the feet for deformities, excessive dry skin, hair or nail abnormalities and callus, ulcer or infection.
2. Semi-quantitative assessment of vibration sensation at the dorsum of the great toe.
3. Grading of ankle reflexes.

The third part of the peripheral neuropathy assessment is the monofilament test. This is not a part of the MNSI exam, but is included in an overall evaluation for neuropathy. **Note that the MNSI Questionnaire is to be completed at the same visit as the peripheral neuropathy assessment (foot exam).**

6.2 Background

The incidence of diabetic neuropathy is reported to be as high as 60% in both type 1 and type 2 diabetes. Incidence increases with age and with duration of diabetes. The Diabetes Control and Complications Trial (DCCT) showed that near-normal glucose control could reduce the incidence of neuropathy by as much as 60%. Neuropathy will be evaluated in GRADE as a secondary outcome.

6.3 Schedule

The MNSI and monofilament test is completed yearly to track the presence of neuropathy, identify foot problems, and assess sensory function. Neuropathy screening is conducted during baseline (or final run-in) and annual visits for all participants.

6.4 Administration of the Neuropathy Questionnaire, the MNSI, and the Monofilament Test

6.4.1 Neuropathy Questionnaire

The questionnaire is completed by the participant before the foot exam. The instrument is designed as a self-administered questionnaire. Therefore, staff should avoid prompting or interpreting questions, unless the participant specifically asks for clarification or assistance. To reduce errors, encourage participants to read each item carefully before answering.

Once the questionnaire has been completed, staff should review the form, paying particular attention to the following common errors:

1. Questions #7 ("…able to tell the hot water from the cold water?") and #13 ("…sense your feet when you walk?") are frequently answered incorrectly. As most of the preceding items are answered "no", there is a tendency for the participant to scan the questions, and answer "no" to these items as well. A "no" response to items 7 and 13 would be indicative of advanced sensory loss, and would not be common in the absence of other signs of advanced neuropathy or other neurologic disorder. If the participant does check "no", ask the participant to review the item (or read the item to the participant) and confirm their response. You can preface the review with a phrase like "I just wanted to double check a couple of your answers. On this item, are you able to tell the hot water from the cold? Did you mean to say no?"
2. Question #11 ("…symptoms worse at night?"). Many patients misunderstand the question, especially if they have responded in the negative to preceding items, and will ask for clarification. If the patient asks, for example, "What symptoms," then an appropriate response is "any of the symptoms previously asked on this survey." If the patient says, "I don't have any symptoms", then an appropriate response is "if you don't have any symptoms, then you can answer no."

6.4.2 The Michigan Neuropathy Screening Instrument (MNSI) and Monofilament Test

Foot Inspection:
The feet are inspected for excessively dry skin, calluses, fissures, ulcerations, or deformities.

Please pay particular attention to the following:

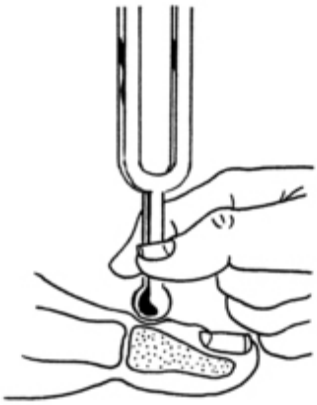
1. The room is comfortable and the foot is warm.
2. Note only significant dry skin (peeling, flaking, cracking) and callus formation.
3. Report findings such as fungal nails, thickened nails, etc. in the "Other" category.
4. Deformities include flat feet, hammer toes, overlapping toes, hallux valgus, joint subluxation, prominent metatarsal heads, medial convexity (Charcot foot), and amputation.

6.4.3 Vibratory Sensation:

Please pay particular attention to the following:

1. Vibratory sensation is tested bilaterally using a 128 Hz tuning fork (provided locally).
2. The great toe is unsupported during the test.
3. The tuning fork is placed over the dorsum of the great toe on the bony prominence of the last joint (see Figure 6.1 below).

Figure 6.1: Tuning fork placement during testing of vibratory sensation



4. A trial is conducted when the tuning fork is not vibrating and when the tuning fork is vibrating to ensure that the participant is responding to vibration and not pressure from the tuning fork.
5. The participant closes his or her eyes before the vibrating tuning fork is applied and indicates when they can no longer sense the vibration from the tuning fork.
6. Examiner's fingers do not touch the prongs of the tuning fork during the test. This will attenuate the vibration that the participant detects and result in an inaccurate test.
7. Examiner should be able to feel vibration from the tuning fork for 5 seconds longer on his/her distal forefinger than a normal subject can on his/her great toe. If the examiner feels vibration for >10 seconds longer than the participant, then vibration sensation is considered to be reduced.
8. Vibration sensation is scored as:
    - Present, if the examiner senses the vibration on his/her distal forefinger for ≤10 seconds longer than the participant
    - Reduced, if sensed by examiner for > 10 seconds after vibration no longer felt by participant
    - Absent, if no vibration detected by the participant
9. A timing device is used to determine the length of time vibration is present on the examiner's finger.

6.4.4 Ankle Reflexes:

Please pay particular attention to the following:

1. Use a reflex hammer (Tromner, Queen Square, or Tomahawk style; provided locally) to assess ankle reflexes. Each type of reflex hammer is acceptable and choice is based on user preference. Ankle reflexes can be difficult to elicit and some users find the Tromner or Queen Square easier to use than the tomahawk type.

2. Elicit the reflex by sitting the participant on a firm surface so the leg is hanging freely and the foot is in a passive position; slightly dorsiflex the foot to obtain optimal stretch of the muscles. The Achilles tendon should then be percussed directly with the reflex hammer.
3. Note that if the reflex is obtained, it is graded as present. If the reflex is absent, the participant is asked to perform the Jendrassic maneuver (hooking the fingers together and pulling) while checking the reflex.
4. Reflexes are scored as:
   - Present, if elicited without reinforcement
   - Present with reinforcement, if only elicited with the Jendrassic maneuver
   - Absent, if there is no reflex elicited without or with the Jendrassic maneuver.

6.4.5 10-Gram Monofilament:

Please pay particular attention to the following:

1. The participant's foot is supported by allowing the sole to rest on a warm flat surface.
2. Use a 10 gram monofilament (provided centrally). We will use the Owen Mumford device as it is considered the most reliable in applying a 10 g pressure, and is the device others are using in both clinics and trials. Each clinic will use the monofilament with a pen holder device and will replace the monofilament at least after every 100 uses per the manufacturer or if bent or buckled. Sites will need to keep track of this and replace at the appropriate interval.
3. The filament is pre-stressed by pressing it 4 to 6 times against the dorsum of the examiner's first finger.
4. The filament is applied to the dorsum of the great toe midway between the nail fold and the DIP joint (see Figure 6.2). Do not hold the toe directly. The filament is applied perpendicularly and briefly (<1 second) with an even pressure. The filament will bend when a force of 10 grams has been applied and forms a "C" shape. The participant, whose eyes are closed, is asked to respond "Yes" if he or she feels the filament.
5. Repeat step 4, nine more times for a total of 10 pricks on the dorsum of the big toe.
6. Vary the interval between pricks to ensure that the participant actually feels the filament and is not just responding in a rote manner.
7. The monofilament test (light touch sensation) is graded as:

   Normal if 8 or more pricks out of 10 monofilament pricks are detected.

   Reduced if 1 to 7 pricks are detected.

   Absent if no pricks are detected.
8. The examiner will document the number of pricks detected out of 10.

Please note that this test is conducted by applying the monofilament 10 times on the dorsum of the great toe, not by testing different locations on the foot, as in other neuropathy exams.

Figure 6.2: Between the cuticle of the great toenail and the DIP

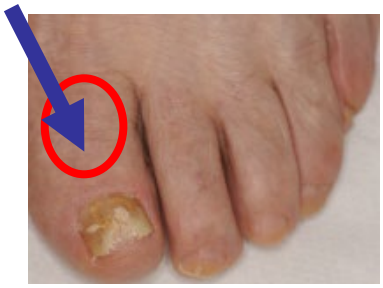


Image: Courtesy C Martin, U Michigan

6.5 Certification

6.5.1 Timeline

Initial certification†: GRADE staff performing this assessment should correctly perform the MSNI on 2 volunteers in order to be certified. Ideally, the group of volunteers used for certification should have a range of duration of diabetes and/or degree of neuropathy so that a variety of possible responses can be measured. If volunteers with diabetes are not available, normal volunteers are acceptable.

Re- certification†: GRADE staff should correctly perform the MSNI on 1 volunteer in order to be recertified.

6.5.2 Certification Procedures

1. Review Section 6 of the Measurement and Assessment Procedural Manual.
2. Recruit 2 volunteers if initial certification or 1 volunteer if re-certification.
3. Complete the MNSI (Peripheral Neuropathy Certification Documentation (see section 6.5.3). Staff are certified initially and at GRADE year 3.

6.5.3 MNSI (Peripheral Neuropathy Certification Documentation

† Adapted from the Epidemiology of Diabetic Interventions and Complications (EDIC) and Diabetes Prevention Program Outcomes Study (DPPOS) Manual of Operations.

GRADE
MNSI (Peripheral Neuropathy) Certification

Instructions: Complete this form to document certification and keep on file locally. Staff should be certified initially and at GRADE Study Year 3.

A. Required Materials

- 128 Hz tuning fork
- Tromner, Queen Square, or Tomahawk reflex hammer
- 10 gram monofilament
- Black pen to record measurements
- Neuropathy Questionnaire
- MNSI certification form
- 2 volunteers if initial certification, 1 if re-certification

B. Procedural Checklist

Observe the following procedural steps (refer to the MAP Section 6.4 for details):

- ☐ Assemble proper materials and equipment, check room temperature
- ☐ Greet participant and review procedure
- ☐ Have the participant complete the self-administered neuropathy questionnaire
- ☐ Review the questionnaire for common mistakes on Questions 7 & 11
- ☐ Ensure room is comfortable and foot is warm and complete the foot inspection
- ☐ Perform vibratory test of feet
- ☐ Perform Achilles tendon reflex
- ☐ Perform monofilament exam of feet

C. Assessments

Record completion of assessments

	Completed Neuropathy Screening Instrument/Foot Exam & Questionnaire
Volunteer #1	☐
Volunteer #2	☐

Comments:_____

_____

_____

Signature of Trainee: _____ Date: _____ Certification ☐

Signature of Trainer: _____ Date: _____ Re-certification ☐

Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

Michigan Neuropathy Screening Instrument - MNSI FORM

Volunteer #1

INSTRUCTIONS: This form is to be completed by the person with diabetes (self-administered). Please take a few minutes to answer the following questions about the feeling in your legs and feet. Check yes or no based on how you usually feel. Thank you.

A. History

1.	Are your legs and/or feet numb?	1 Yes	2 No
2.	Do you ever have any burning pain in your legs and/or feet?	1 Yes	2 No
3.	Are your feet too sensitive to touch?	1 Yes	2 No
4.	Do you get muscle cramps in your legs and/or feet?	1 Yes	2 No
5.	Do you ever have any prickling feelings in your legs or feet?	1 Yes	2 No
6.	Does it hurt when the bed covers touch your skin?	1 Yes	2 No
7.	When you get into the tub or shower, are you able to tell the hot water from the cold water?	1 Yes	2 No
8.	Have you ever had an open sore on your foot?	1 Yes	2 No
9.	Has your doctor ever told you that you have diabetic neuropathy?	1 Yes	2 No
10.	Do you feel weak all over most of the time?	1 Yes	2 No
11.	Are your symptoms worse at night?	1 Yes	2 No
12.	Do your legs hurt when you walk?	1 Yes	2 No
13.	Are you able to sense your feet when you walk?	1 Yes	2 No
14.	Is the skin on your feet so dry that it cracks open?	1 Yes	2 No
15.	Have you ever had an amputation?	1 Yes	2 No

Signature of Trainee: _____ Date: _____ Certification ☐

Signature of Trainer: _____ Date: _____ Re-certification ☐

GRADE
MNSI Certification: Neuropathy Screening Instrument/Foot Exam
Volunteer #1

1. RIGHT FOOT

a. Appearance

☐ 1 Normal ☐ 2 Abnormal

If ABNORMAL, check all that apply:

☐ 1) Deformities ☐ 3) Dry skin, callus
☐ 2) Infection ☐ 4) Fissure
☐ 5) Other: _____

b. Ulceration

☐ 1 Absent
☐ 2 Present

c. Ankle Reflexes

☐ 1 Absent
☐ 2 Present / Reinforcement
☐ 3 Present

d. Vibration (perception at great toe)

☐ 1 Absent
☐ 2 Reduced (>10 sec)
☐ 3 Present (≤10 sec)

e. 10 gm Filament (number of applications detected)

☐ 1 Absent
☐ 2 Reduced (1-7)
☐ 3 Present (≥ 8)

2. LEFT FOOT

a. Appearance

☐ 1 Normal ☐ 2 Abnormal

If ABNORMAL, check all that apply:

☐ 1) Deformities ☐ 3) Dry skin, callus
☐ 2) Infection ☐ 4) Fissure
☐ 5) Other: _____

b. Ulceration

☐ 1 Absent
☐ 2 Present

c. Ankle Reflexes

☐ 1 Absent
☐ 2 Present / Reinforcement
☐ 3 Present

d. Vibration (perception at great toe)

☐ 1 Absent
☐ 2 Reduced (>10 sec)
☐ 3 Present (≤10 sec)

e. 10 gm Filament (number of applications detected)

☐ 1 Absent
☐ 2 Reduced (1-7)
☐ 3 Present (≥ 8)

Signature of Trainee: _____ Date: _____ Certification ☐

Signature of Trainer: _____ Date: _____ Re-certification ☐

Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

Michigan Neuropathy Screening Instrument - MNSI FORM

Volunteer #2

INSTRUCTIONS: This form is to be completed by the person with diabetes (self-administered). Please take a few minutes to answer the following questions about the feeling in your legs and feet. Check yes or no based on how you usually feel. Thank you.

A. History

1.	Are your legs and/or feet numb?	1 Yes	2 No
2.	Do you ever have any burning pain in your legs and/or feet?	1 Yes	2 No
3.	Are your feet too sensitive to touch?	1 Yes	2 No
4.	Do you get muscle cramps in your legs and/or feet?	1 Yes	2 No
5.	Do you ever have any prickling feelings in your legs or feet?	1 Yes	2 No
6.	Does it hurt when the bed covers touch your skin?	1 Yes	2 No
7.	When you get into the tub or shower, are you able to tell the hot water from the cold water?	1 Yes	2 No
8.	Have you ever had an open sore on your foot?	1 Yes	2 No
9.	Has your doctor ever told you that you have diabetic neuropathy?	1 Yes	2 No
10.	Do you feel weak all over most of the time?	1 Yes	2 No
11.	Are your symptoms worse at night?	1 Yes	2 No
12.	Do your legs hurt when you walk?	1 Yes	2 No
13.	Are you able to sense your feet when you walk?	1 Yes	2 No
14.	Is the skin on your feet so dry that it cracks open?	1 Yes	2 No
15.	Have you ever had an amputation?	1 Yes	2 No

Signature of Trainee: _____ Date: _____ Certification ☐

Signature of Trainer: _____ Date: _____ Re-certification ☐

GRADE
MNSI Certification: Neuropathy Screening Instrument/Foot Exam
Volunteer #2

1. RIGHT FOOT

a. Appearance

☐ 1 Normal ☐ 2 Abnormal

If ABNORMAL, check all that apply:

☐ 1) Deformities ☐ 3) Dry skin, callus
☐ 2) Infection ☐ 4) Fissure
☐ 5) Other: _____

b. Ulceration

☐ 1 Absent
☐ 2 Present

c. Ankle Reflexes

☐ 1 Absent
☐ 2 Present / Reinforcement
☐ 3 Present

d. Vibration (perception at great toe)

☐ 1 Absent
☐ 2 Reduced (>10 sec)
☐ 3 Present (≤10 sec)

e. 10 gm Filament (number of applications detected)

☐ 1 Absent
☐ 2 Reduced (1-7)
☐ 3 Present (≥ 8)

2. LEFT FOOT

a. Appearance

☐ 1 Normal ☐ 2 Abnormal

If ABNORMAL, check all that apply:

☐ 1) Deformities ☐ 3) Dry skin, callus
☐ 2) Infection ☐ 4) Fissure
☐ 5) Other: _____

b. Ulceration

☐ 1 Absent
☐ 2 Present

c. Ankle Reflexes

☐ 1 Absent
☐ 2 Present / Reinforcement
☐ 3 Present

d. Vibration (perception at great toe)

☐ 1 Absent
☐ 2 Reduced (>10 sec)
☐ 3 Present (≤10 sec)

e. 10 gm Filament (number of applications detected)

☐ 1 Absent
☐ 2 Reduced (1-7)
☐ 3 Present (≥ 8)

Signature of Trainee: _____ Date: _____ Certification ☐

Signature of Trainer: _____ Date: _____ Re-certification ☐

7. GRADE Oral Glucose Tolerance Test (OGTT)

7.1 Background and rationale

The oral glucose tolerance test (OGTT) is the standard test to determine whether diabetes or a milder abnormality of glucose tolerance is present. It also allows assessments of insulin secretion and insulin sensitivity. In GRADE, OGTTs are performed at baseline and Year 1. Year 3, and Year 5 to compare the effects of the different drug combinations over time.

The test will involve obtaining fasting blood samples followed by timed draws after consumption of a standard glucose-containing drink (75 gm Fisher Brand glucose drink). The Fisher Brand glucose drink is available in 3 flavors for the GRADE study (lemon-lime, orange, and fruit punch).

7.2 Participant Preparation and Instructions

Because a large number of factors may affect the OGTT, care must be taken to properly prepare participants for the test. Please refer to the Manual of Procedures (MOP) for detailed instructions regarding participant preparation and instructions.

7.3 Eligibility

The participant must meet the following criteria in order to be eligible for the OGTT:

1.	No major surgery or illness (e.g. flu, fever, vomiting) in the 7 days prior to the test.
2.	Nothing to eat or drink (other than water) within 8 hours before the test.
3.	Eaten a normal diet over the 3 days before to the test.
4.	No vigorous exercise within 8 hours before the test.
5.	No alcohol consumed within 8 hours before the test.
6.	No smoking within 1 hour before the test.
7.	Worked a typical or usual schedule the day/night before the test.
8.	No oral steroids (glucocorticoids, like prednisone) or steroid injections within two weeks of the test.
9.	No diabetes medications on the morning of the test.
10.	Local fasting finger-stick blood glucose of <350 mg/dl.

7.4 Specific Procedures

1. Confirm eligibility for OGTT (see above Section 7.3) using Section A: Eligibility Assessment for Oral Glucose Tolerance Test on the OGTT forms used at Baseline (BASEOGTT) and Annual (ANNOGTT) visits.
2. Obtain fasting samples
    - An intravenous line is preferred for the blood sampling. If the clinical site is unable to establish an IV due to poor venous access, lack of IV experienced staff available, or based on patient preference, individual sticks will be acceptable but are highly discouraged. If a heparin or saline lock is used, a small volume of blood MUST be discarded to clean the line as per local institutional policy

(usually 2 ml or less or are approximately three times the dead space). *It is essential that blood samples not be diluted by heparin or saline. The use of saline or heparin is based on local policy.*

3. The OGTT test uses a consumption of a standard glucose-containing drink (75 gm Fisher Brand glucose drink), composed of liquid glucose.
    - Fisher Brand glucose drink size = 1 bottle [75gm]
4. Start the OGTT between 6:00 AM and 10:30 AM.
    - If the OGTT is performed after 10:30 AM due to unforeseen circumstances such as difficulty with IV insertion or parking issues, the site will be required to notify their protocol liaison and complete a Protocol and Operational Deviation (PROTDEV) Form for the operational deviation (noting the reason for the deviation). If the participant is unable to schedule the OGTT for a 10:30 AM start time at the visit, the OGTT should be rescheduled. Special circumstances, such as alternate shift work may warrant a late start as long as it is consistent at each of the participant's OGTT visits.
    - Be sure to have a digital time piece available (timer or digital clock).
    - Start the timer as the participant *begins* to drink the Fisher Brand glucose drink. This is the "0 minutes" time point. Actual clock time of this "0 minutes" point should be recorded. NOTE: The fasting sample needs to be drawn before the participant starts to drink the glucose drink and the timer is set to zero. The participant must begin drinking the glucose drink within 15 minutes of the fasting sample.
    - The glucose drink should be consumed in its entirety in 5 minutes or less. If not consumed within 10 minutes, the OGTT must be re-scheduled (with the exception of the Baseline Randomization visit).
    - If the full contents of the glucose drink are not consumed, or if any is vomited, reschedule the test except for the Baseline Randomization visit. At the Baseline Randomization visit, the only reason to reschedule the OGTT is if the participant is not eligible for OGTT based on screening questions (for example BG ≥350 mg/dl, illness, ate carbohydrate restricted diet, etc.).
5. Mild physical activity (e.g. walking within the clinic area) is permissible during the OGTT. More vigorous exercise is not allowed.
6. Obtain all subsequent samples according to the timer. For example, the 15 minute sample is drawn 15 minutes from 0, 30 at 30 minutes from 0 and so on. Record the actual clock time of blood drawing (see intervals for collections on the BASEOGTT or ANNOGTT Form).
7. A snack may be given to the volunteer soon after the last samples are drawn.
8. Participants may take their diabetes and study medications after all blood samples have been collected.
9. If venous access problems are experienced during the OGTT, priority is given to collecting the fasting and 120 minute samples whenever possible.
10. If a participant was eligible for the OGTT based on the eligibility questions on the ANNOGTT form, but is found to be ineligible later in the visit (e.g., taking steroids, eating that morning, etc.), the OGTT should be discontinued immediately upon

determining the participant is ineligible. In addition, sites should hold off on shipping any OGTT samples that were collected. Contact the Coordinating Center for further guidance on documentation, whether the OGTT can be recollected, and handling of the OGTT samples that were collected.

7.4.1 Blood Collection Times and Processing

Refer to the Central Biochemistry Laboratory (CBL) Biospecimen Collection and Processing Manual for the OGTT visit chart with detailed information on required tubes. Also refer to the CBL manual for detailed instructions on specimen processing, supplies required, shipping and handling. In addition, follow all local requirements for blood draws, IV insertion, processing and shipping.

7.5 Training

Clinical research staff will either attend a study meeting where the OGTT procedures will be reviewed, independently review the OGTT training materials available on the GRADE study website, or be trained locally by another trained staff member prior to conducting an OGTT on a GRADE participant. Although there is no central tracking of the completion of OGTT training, it is expected that sites will track and maintain these informal trainings locally.

7.5.1 Training Procedures

1. Review Section 7 of the Measurement and Assessment Procedural Manual.
2. Review CBL Biospecimen and Collection Processing Manual.
3. Complete the OGTT Training Documentation (see section 7.5.2).

7.5.2 OGTT Training Documentation

Site Number ☐☐ - ☐ | Name of Clinical Staff Member _____ | Staff ID ☐☐☐ | Certification Date ☐☐ / ☐☐ / ☐☐☐☐ (month / day / year)

GRADE
Oral Glucose Tolerance Test (OGTT) Training Documentation

Instructions: Complete this form to document competency and keep on file locally. Staff should be trained initially and at GRADE Study Year 3.

A. For detailed review

- ☐ Review OGTT section in MAP, MOP and CBL Manuals
- ☐ Required materials
- ☐ Participant preparation and exclusions
- ☐ Sample collection at specified time points
- ☐ Specimen collection, handling, processing, storage and shipping procedures

B. Training Documentation

- ☐ Attended central GRADE study meeting presentations on OGTT methods, best practices etc.
- ☐ Trained by local staff or other

Description of training:

_____
_____
_____
_____
_____
_____
_____

Comments: _____
_____
_____

Signature of Trainee: _____ Date: _____ Central Training ☐

Signature of Trainer: _____ Date: _____ Local Training ☐

8. GRADE Quality of Well-Being (QWB) Assessment

8.1 Introduction

The QWB assessment consists of a self-administered survey that obtains information about a participant's health problems that occurred in the last three days, not including the day the questionnaire is administered. The QWB is completed at baseline (or final run-in) and at all annual visits. Refer to the QWB Manual of Procedures available on the GRADE study website for further details.

8.2 Procedures

Refer to the QWB Manual of Procedures and presentation available on the GRADE study website for detailed procedures.

8.3 Certification

Refer to the QWB Manual of Procedures and presentation available on the GRADE study website for detailed certification procedures.

8.3.1 QWB Certification Documentation

Refer to the QWB Manual of Procedures available on the GRADE study website for any required certification documentation. In addition, certification of study staff must be documented and tracked locally.

9. GRADE Neurocognitive Assessment

9.1 Introduction

Participants will be administered a brief battery of neurocognitive tests in the baseline GRADE examination, after completion of the baseline OGTT (if not completed at the Final Run-in visit), and again at years 4 and 6. A snack or meal may be offered to the participant prior to completion of the neurocognitive assessment (and after completion of the OGTT). The first assessment will establish a baseline for cognitive functioning in GRADE participants, which with repeated cognitive measurements in the subsequent exam will provide the opportunity to identify risk factors associated with change in cognitive functioning over time.

9.2 Procedures

The Neurocognitive assessment is conducted at Baseline and at Years 4 and 6 for all participants. Refer to the Cognitive Assessments Manual available on the GRADE study website for specific procedural details.

9.3 Training and Certification

Refer to the Cognitive Assessments Manual available on the GRADE study website for detailed instructions and a certification flowchart as well as a training video provided by the Neurocognitive Center (NCC) at Columbia University for specific procedural details. The neurocognitive assessment training video is available on the GRADE study website (video password: grade). Certification is required at study start and recertification will be required for the Years 4 and 6 assessments.

9.3.1 Training and Certification Procedures

Refer to the Cognitive Assessments Manual available on the GRADE study website for detailed procedures.

9.3.2 Neurocognitive Certification Documentation

Refer to the Cognitive Assessments Manual available on the GRADE study website for certification documentation. In addition, certification of study staff must be documented and tracked locally.

10. Electrocardiogram (ECG) Assessment

10.1 Introduction

Refer to the ECG Assessment Manual available on the GRADE study website for background information. ECG assessments will be collected at the Baseline Randomization Visit (or Final Run-In), Year 2, Year 4, and Year 6.

10.2 Procedures

Refer to the ECG Assessment Manual available on the GRADE study website for detailed procedures.

10.3 Certification Procedures

Refer to the ECG Assessment Manual available on the GRADE study website for detailed certification procedures.

10.4 ECG Certification Documentation

Refer to the ECG Assessment Manual available on the GRADE study website for certification documentation. In addition, certification of study staff must be documented and tracked locally.