Quantitative Myasthenia Gravis-Revised Score

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Version 1.0

Developed by the MGNet Clinical Trial Outcome Measure Working Group

EQUIPMENT LIST

1. Stopwatch with lap timer function
2. Spirometer
3. Printer
4. Mouthpieces
5. Nose clips
6. Measuring cup
7. Grip Dynamometer – The same dynamometer should be used by all sites throughout a given study.
8. Metronome device/app at a rate of 1 count per second
9. Eye patch (may be used during the ptosis assessment for participants with prominent vertical misalignment of the eyes)

QUANTITATIVE MYASTHENIA GRAVIS-REVISED (QMG-R)

General Instructions

1. Pyridostigmine should be held for at least 12-hours; extended-release formulations should be held for at least 24-hours prior to QMG-R. The time and amount of the last dose taken should be clearly recorded.

2. Tests should be performed in the order listed in this manual, with the possible exception of the forced vital capacity (FVC). If you must perform the FVC out of order than what is listed on the case report form, then that order must be adhered to throughout the study.

3. Calibrate the respiratory equipment on the day of the test, as needed and per manufacturers' instructions, before beginning the test. Place the calibration record in a folder in an accessible place, if applicable. If multiple study visits are conducted on the same day, the equipment only needs to be calibrated once on that day.

4. For all measurements, record actual numbers (raw score) as well as the grade, i.e., if it takes 30 seconds before a participant sees double, record the 30 seconds and the grade of 1.

5. At the bottom of the scoring case report form, add up the score for each item to calculate the Total QMG-R Score.

6. Please do not leave items unscored.

7. Throughout the test, encourage the participant to optimize their performance

8. Refer to this guide below for detailed instructions.

9. The QMG-R is appropriate for patients twelve years of age, or older.

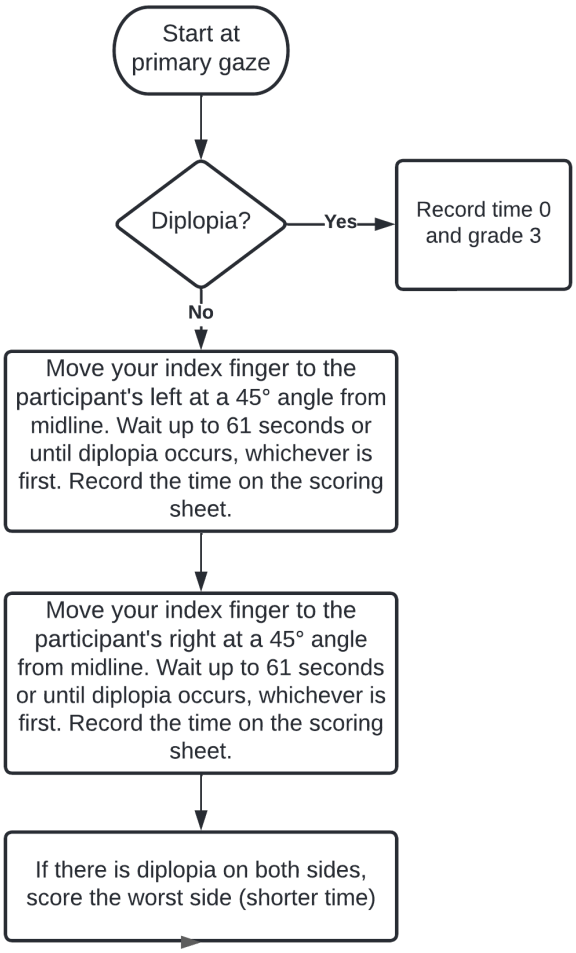
10. The QMG-R may be performed by any trained and certified evaluator to allow the most flexibility for study teams.

1. **DOUBLE VISION (Diplopia):**
   Participant position: Sitting approximately 3 feet (1 meter) from the examiner. Eyeglasses should be off unless the participant cannot see an index finger held up by the examiner. Contacts can remain in. If the participant has head drop, you may have someone hold the head up to complete this test.

   Examiner position: Sitting in front of the participant, hold up one of your index fingers vertically at eye level.

   Detailed instructions:
   - Instructions to the participant are provided based on their performance according to the algorithm shown in **Figure 1**. The evaluation starts with the participant's eyes in the primary position of gaze (i.e., looking straight ahead).
   - Give the following instructions as needed according to the algorithm:
     1. *"Look straight ahead and focus on my finger. Do you have double vision?"*
     2. *"Without turning your head, follow my finger to the left and let me know if you see double as soon as it occurs. You will look in this direction for up to ~1 minute or until you see double."*
     3. *"Without turning your head, follow my finger to the right and let me know if you see double as soon as it occurs. You will look in this direction for up to ~1 minute or until you see double."*

Figure 1. Algorithm for assessment of diplopia



Additional considerations**:**

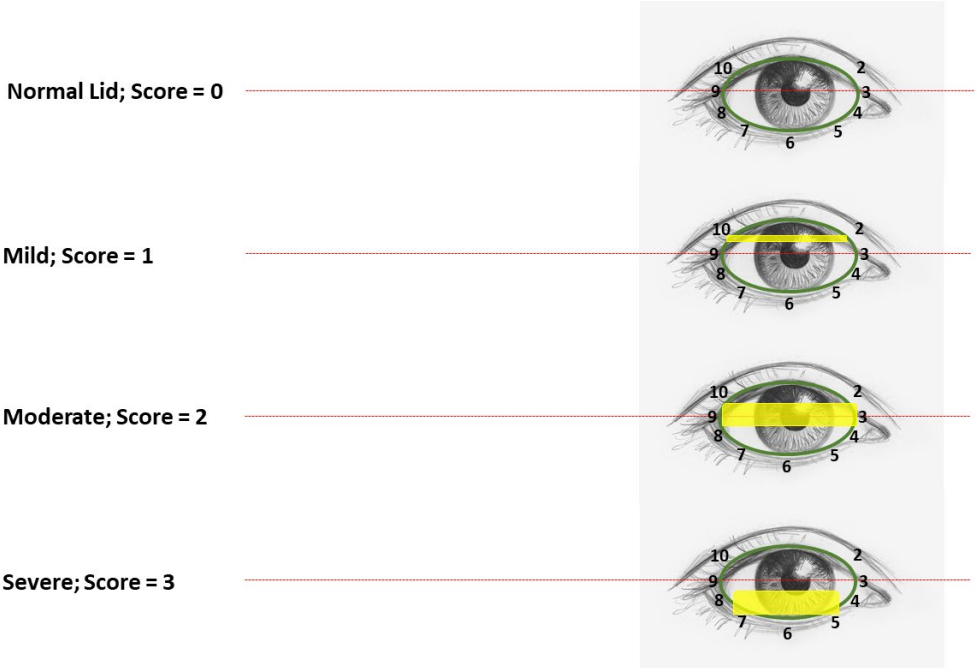
- When diplopia occurs, cover one eye and ensure that diplopia is BINOCULAR. Monocular double vision should be scored as “0 None.”
- Diplopia occurring in primary gaze or immediately upon left or right gaze should be scored as a “3 Severe.” If there is diplopia on primary gaze, indicate this by using the check box on the case report form.
- Diplopia should be scored ONLY if the participant sees “double”.
    - Blurry vision should NOT be considered diplopia for this test.
- In certain situations, participants may have myasthenic ocular weakness without diplopia. Examples include blindness in one or both eyes, chronic ocular weakness with central nervous system compensation, and complete ophthalmoparesis (no eye movements). In this setting where the participant does not report diplopia, score this item as “0 None.” However, if there is obvious misalignment of the eyes, indicate this on the case report form.

2. **PTOSIS (UPWARD GAZE):**
   Participant position: Sitting with feet supported, approximately 3 feet (1 meter) from the examiner. Eyeglasses should be off. Contacts can remain in. If the participant has a head drop, you may have someone hold the head up to complete this test.

   Examiner position: Sitting in front of the participant at approximately eye level.

   Detailed instructions:

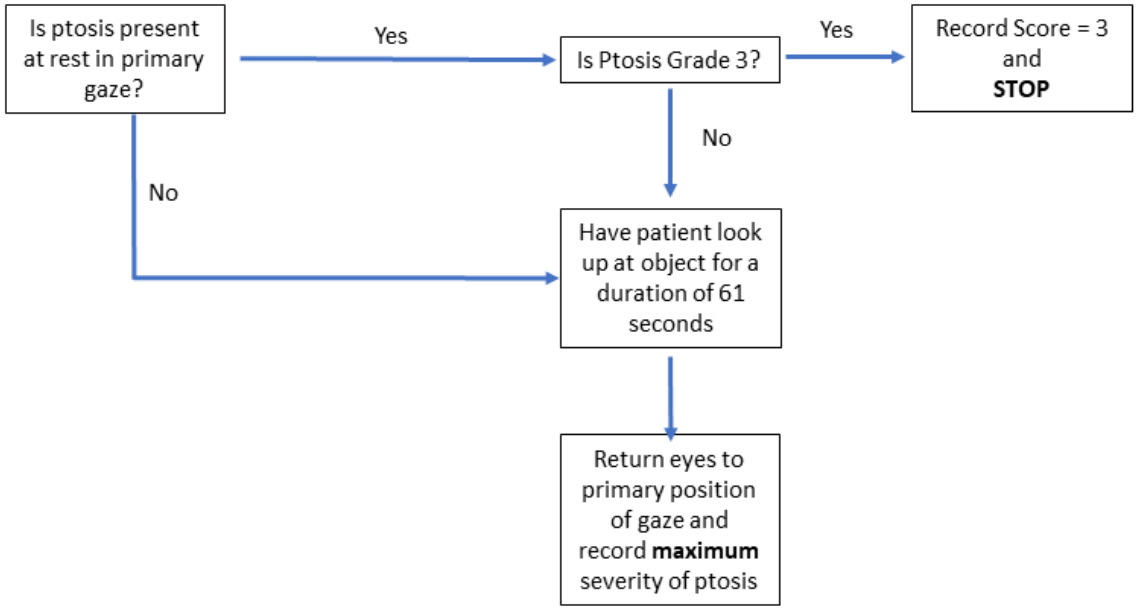
   - **Figure 2. Grading of ptosis.** Only the upper eyelid is assessed for ptosis. The horizontal red line indicates the middle of the pupil. The yellow shaded boxes indicate the possible range of eyelid positions corresponding to each severity grade. For mild ptosis there can be an exception based on asymmetry in the upper eyelid position. In this case, there is drooping of the eyelid that does not meet the criteria for mild ptosis as shown in the figure (upper lid does not fall within the shaded area), but the eyelid asymmetry is considered abnormal for the specific participant. The drooping eyelid should be scored as "1 Mild." Thus, it is critically important to perform a side-to-side comparison of eyelid positioning. Evaluators will need to judge whether preexisting factors could account for any eyelid asymmetry (i.e., asymmetry not related to MG weakness), which should not be scored.



   - Following the algorithm in **Figure 3**, evaluate the participant for ptosis, indicate the maximum amount of ptosis on the case report form, and score as

instructed. To perform upgaze, have the participant look at your finger or a flashlight elevated approximately 45^0 from primary gaze.

Figure 3. Algorithm for assessment of ptosis



- Give the following instructions as needed according to the algorithm:
    1. *"Look straight ahead. Make sure that your forehead is relaxed."*
    2. *"Now, look up at my finger. You will look up at my finger for ~1 minute."*
    3. At the end of ~1 minute, instruct the patient: *"Look straight ahead again, making sure your forehead remains relaxed."*

<u>Additional considerations</u>**:**

- The forehead must be relaxed.
    - Be wary of frontalis muscle "peaking," whereby the patient uses excessive frontalis muscle contraction to open the eyelid (i.e., overcome upper lid ptosis).
- Excessive upper eyelid skin tissue may push the lid lower (termed senile ptosis).
    - Carefully lift the upper lid tissue out of the way but not to the degree to alter its true position.
- If there is a prominent vertical misalignment of the eyes at any visit, test each eye independently, with patching of the untested eye.

- If the participant is unable to look up, have the patient attempt to do so and look for contraction of the frontalis muscle to verify participant effort. Grade any ptosis according to the scoring system.
- Watch for squinting, which may produce apparent ptosis. If squinting is observed, ask the participant to relax the muscles around the eye as much as possible while still looking up (sometimes touching the muscle that you want them to relax will help). Apparent ptosis related to squinting should not be scored.
    - This may be recognized by an elevation of the participant's lower eyelid in the region of 5-7 o'clock on the face of a clock.

3. **FACIAL MUSCLES:**

Participant position: Sitting with feet supported. Eyeglasses should be off. Contacts can remain in. However, be aware that contact lenses may pop out or displace in the eye with forceful eye closure. Ask the participant if they would prefer to keep their contact lenses or remove them. If the participant has a head drop, you may have someone hold the head up to complete this test.

Detailed instructions:

- Instruct the participant: *"Squeeze your eyes shut. Do not allow me to open the eyelid."*
- Attempt to pry the eyes open using both your thumbs.
- Assign the appropriate grade.

Additional considerations:

- Complete eye closure means eyelashes must be buried.
- You may encourage the participant to shut their eyes as hard as they can.
- If there is an asymmetry in eye closure weakness, record the grade of the weaker eye.

4. **SWALLOWING:**

Participant position: Sitting with feet supported.

Detailed instructions:

- Pour 4 ounces (120ml, 8 tablespoons) of water (no ice) into a cup. The water should be at room temperature.
- Instruct the participant: *"Drink the water as quickly as you think is safe. There should be no prolonged pauses between swallows."*
    - It will take about 5-7 swallows to drink all the water.

- Listen for throat clearing or coughing for up to 30 seconds, as delayed cough or throat clearing may occur, and record the appropriate score.

Additional considerations**:**

- If a participant is suspected of having a significant swallowing issue, they should first take a small sip to see how it is handled. If there is immediate severe coughing/choking, the complete test should not be performed, and the highest score recorded.

5. SPEECH:

Participant position: Sitting with feet supported.

Detailed instructions:

- Set up the audible metronome/app to ensure a standardized counting rate of 1 per second.
- Instruct the participant:
    1. *"For this item, you will count out loud from 1 to 50 at a rate of 1 number per second. You will hear a repeating sound that will ensure you count at the correct speed. I will demonstrate the repeating tone now so you can hear the counting rate and know what to expect."*
        - At this point, start the metronome/app so the participant can hear the tone. Then move on to the next instruction.
    2. *"Now, we will start the test. OK, begin."*
        - Start the metronome/app at this point.
- Record the number when you notice a nasal quality or slurring of the speech.
- If there is no dysarthria or nasal quality, record "None at 50" on the score sheet.

Additional considerations**:**

- Some participants might have a nasal quality to their speech with certain sounds. With MG, the nasal tone will not go away with the following number and will worsen as they continue the count.

6. RIGHT & LEFT ARM OUTSTRETCHED:

Participant position: Sitting in a chair with feet on the floor. When the test begins, the participant should sit forward, away from the back of the chair. The back of the chair must be against a wall. Use a goniometer at the shoulder joint. Place a piece of tape on the wall to mark where the location of the participant's hand when the shoulder joint is at a 90° angle in abduction with the elbows extended. Repeat the same process to mark the spot where the hand would fall when the shoulder is at 80° abduction. Support the participant's arm before the test to

prevent fatigue. Test both arms at the same time. To start the test, the arms should be fully extended at the elbow and out to the side (abducted) at a 90° angle.

Note: If the arms cannot be abducted to a 90° angle due to mechanical issues, an angle of a minimum 80^0 is acceptable as a starting position. In such a situation, mark the start position and a secondary position that is 10° below the start position.

Detailed instructions:

- Instruct the participant:
    1. *"Hold both arms straight out to the side with your elbows extended. Do not lean back against the chair. We will continue the test for up to 4 minutes."*
        - You may illustrate the arm position if the participant displays any difficulty understanding what is needed.
    2. *"Keep the arms out for as long as possible. If one arm tires more than the other, you may lower that arm but keep the other arm up."*
- Time both arms simultaneously. Stop the test if both arms drop 10^0 or more below the start position (i.e., your marked 80^0 tape line). If one arm drops before the other, make a note of that time and continue the test on the stronger arm.
- Throughout the test, encourage the participant to keep their arms up.
- Record the time on both sides and assign the appropriate grade for each arm.

Additional considerations**:**

- It is not uncommon that the arms will start to droop. If either or both arms start to droop, ask the participant to lift them back up. They should be able to maintain this position for longer than 2 seconds. If, after one reminder, the arm drops 10^0 or more as determined by the rater, stop the test.
- If the arm/arms start to droop immediately after starting the test, stop the test with that arm/arms. If they drop only one arm, they can continue with the other arm.
- If the participant cannot achieve at least 80^0 abduction due to MG related weakness, then score as severe.
- If one arm cannot be maintained in abduction at 80^0 or better due to a NON-myasthenia gravis related problem (such as shoulder injury, arm fracture, etc.), do not score the affected arm; instead, use the score from the unaffected arm to grade the affected arm. Indicate the specific reason the test could not be performed on the case report form.

- Watch for and try to prevent compensatory movements by the participant throughout the test. Compensatory movements include:
    - Leaning back against the chair.
    - Bending the elbow.
    - Drifting the arm forward (away from the wall) to use other muscles of abduction.
    - If one arm has fallen, participants may also tilt the trunk to make the remaining arm appear horizontal.

7. FORCED VITAL CAPACITY (FVC):

Participant position: Sitting on a chair with feet on the floor. They may lean against the back of the chair.

Detailed instructions:

- Set up the spirometer according to manufacturer instructions.
- Instruct the participant:
    1. *"I am testing total lung capacity. I am going to ask you to take a deep breath in. At the same time, I will place nose clips on your nose. After you take your deep breath in, place the mouthpiece in your mouth and blow out as hard and as fast as you can. Keep blowing until I tell you to stop."*
    2. *"We will repeat the test 3 to 5 times. There will be a 1-minute rest period between trials."*
- Throughout the test, encourage the participant to optimize performance.
- Perform a minimum of 3 trials, resting one minute between each trial. If 3 adequate trials are completed without any quality issues, stop.
- If there is a quality issue (e.g., incomplete seal around the mouthpiece, poor effort, etc.), up to 5 trials may be performed.
- Record the volume (in liters) and percent predicted for each trial. The volume should be recorded to one decimal point. Percent predicted should be recorded as a whole number (no decimal points).
- The trial with the **best** percent predicted and volume will be scored.
- Score appropriately on the QMG-R case report form.

Additional considerations**:**

- For clinical trials or any longitudinal study, the same spirometer and mouthpiece should be used throughout the study.
- Follow the instructions of the specific spirometer selected for the trial.
- The mouthpiece should be inserted into the mouth, not just put up to the participant's lips.
- A hard oval mouthpiece is preferred over a round mouthpiece.

- Historically, the QMG has relied on the Knudsen 83 normative data, which are based on age, sex, and height.
- There may be value in updating to more recent norms (e.g., GLI, NHANES III), but this decision should be made at the outset and maintained throughout the study. If norms other than Knudsen 83 are used, then study data may not be fully compatible with historical data.
- For adult clinical trials, or any longitudinal study, height should be measured at the initial visit, and then the same height should be used for calculating % predicted FVC at all future visits. For studies in children height may need to be assessed at multiple visits.
- The use of a face mask is recommended for participants who cannot maintain the mouthpiece due to oral weakness. The decision to use or not use a face mask should be made at the first study visit, and the same approach for testing FVC should be used for all subsequent study visits (i.e., if a face mask is used once, it should continue to be used at all future visits).
- Slow vital capacity may also be used in future clinical trials. If slow vital capacity is chosen, it must be used in all study visits at all sites. If slow vital capacity is performed, then the instructions above (*After you take your deep breath in, place the mouthpiece in your mouth and blow out as hard and as fast as you can*) should be replaced with "(*After you take your deep breath in, place the mouthpiece in your mouth and breathe out normally*)".

8. DOMINANT & NON-DOMINANT HAND GRIP:

Participant position: Seated with knees and hips at 90^0 and feet flat on the floor. The arm should rest by the side of the body, and the elbow flexed at 90^0. The forearm should be in mid-position between pronation and supination.

Detailed instructions:

- For the Jamar dynamometer (for other instruments, follow manufacturer/instrument guidance): At the first visit, introduce grip settings 2 and 3 to the subject by having them lightly squeeze the dynamometer at each setting. Ask the subject which setting feels more comfortable/natural. You may explore other settings with the participants to find the most comfortable setting. Make note of which setting the subject prefers and use this same setting throughout the duration of the study. The same setting should be used for both sides. Otherwise, follow instructions for the specific dynamometer selected for the trial.
- Place the dynamometer in the testing hand with the dial facing toward the examiner; instruct the subject to squeeze with his or her hand as hard as possible. Prevent subjects from pronating the forearm or flexing the wrist to an extreme.

- Document handedness on the QMG case report form. If the patient indicates they are ambidextrous, ask the participant "Which hand do you think is your dominant hand?" and use this response as their dominant hand.
- Support the testing arm under the forearm and under the grip device if needed.
- Perform three trials for each hand. Rest 1 minute between trials for each hand. While resting one hand, test the other side.
- Reset the dynamometer to "0" prior to each trial.
- Instruct the participant:
    1. *"I am testing grip strength. I need for you to squeeze as hard as you can. Nothing will move, but the instrument is measuring how hard you are squeezing."*
    2. *"We will perform 3 trials with each hand, resting at least 1 minute between each trial."*
- Record the raw value (in kg) from each trial on the case report form.
- Score appropriately using the best raw value.

Additional considerations**:**

- If a subject cannot perform the assessment due to MG weakness, score the worst value ("0" Severe).
- If a subject cannot perform the assessment due to a reason other than weakness (e.g., injury), do not score the affected arm. Instead, use the score from the unaffected arm to grade the affected arm. Indicate the specific reason the test could not be performed on the case report form.

9. HEAD LIFT:

Participant position: Supine, with a pillow under their knees for comfort if desired. You may retain a pillow under their head while providing instructions and demonstration, but the pillow should be removed prior to the start of the test.

Detailed instructions:

- Note the starting position of the participants head (usually on the examination table).
- Passively move the participants head to the maximal degree of neck flexion that is possible.
- Instruct the participant:
    1. *"Hold you head in this position for as long as you can. Do not let your head drop. Keep your shoulders on the bed. The test will last up to 2 minutes."*
- Start the timer as soon as you remove your hand from the participant's head.

- Keep a hand under their head, but not touching, so it will not hit the bed if the head drops.
- Throughout the test, encourage the participant to keep their head up.
- Stop the timer when the participant's head returns to the starting position.

Additional considerations**:**

- Some participants may have limitations in neck flexion/extension that need to be accounted for. Some participants may not be able to extend their neck to the point where the head touches the table or flex their neck to the point where the chin touches their chest. Thus, **for each participant it is important to identify the appropriate starting position and point of maximal flexion**.

10. RIGHT AND LEFT LEG OUTSTRETCHED:

Participant position: Supine with a pillow under their head. For this test, you may place a pillow under their knees for comfort while explaining the test. Remove the pillow under the leg being tested prior to testing.

Detailed instructions:

- Ideally, the leg should be completely extended at the knee. A slight bend is acceptable if the patient cannot fully extend due to limited mobility.
- Lift the leg to a 45° angle (or mechanical range); use a goniometer to check the 45° angle.
- Ideally, the test is performed with the bed next to a wall to mark the 45^0 starting point and the point of a 10^0 excursion from 45^0 (similar to instructions for outstretched arms).
- Instruct the participant:
    1. *"With your knee as straight as possible, hold your leg up for as long as you can. You will hold your leg up for a maximum of 100 seconds."*
- Throughout the test, encourage the participant to keep their leg up.
- When the test is started, place your hand at the 10^0 excursion mark. If the leg starts to droop, ask the participant to lift it back up. They should be able to maintain this position for longer than 2 seconds. If, after one reminder, the leg drops 10^0 or more as determined by the rater, stop the test and record the time.
- If measuring a 10^0 excursion on the wall is not possible, place your hand 3 inches (~8cm) below the starting point. If the heel touches your hand at this position, stop the test and record the time.
- Repeat the test on the other leg. Remember to repeat the verbal instruction.

Additional considerations**:**

- If one leg cannot be maintained at 45^0 due to a NON-myasthenia gravis related problem (such as back or hip injury), do not score the affected leg and use the score from the unaffected leg to grade the affected leg. Indicate the specific reason the test could not be performed on the case report form.
- Watch for and try to prevent compensatory movements by the participant throughout the test. Compensatory movements include:
    - Placing hands under their hip
    - Rotating the leg
    - Ab/adducting the leg
    - Bending the knee