MGNet V1.0
07 Sep 2022

MYASTHENIA GRAVIS ACTIVITIES OF DAILY LIVING (MG-ADL)

Instructions

Introduction

The MG-ADL was designed to assess the severity of 8 MG symptoms (2 ocular, 3 oropharyngeal, 1 respiratory and 2 extremity). These symptoms were selected based on their anticipated impact on activities of daily living. Although originally designed as an instrument to be administered by a trained technician, consensus among experts is that the MG-ADL, as a patient reported outcome measure (PROM), should be self-reported by the patient.

Procedures for Administration

The patient should be provided with the MG-ADL form that includes instructions for self-completion. The patient with MG should complete the MG-ADL without evaluator input or guidance. Similarly, no family members or other visit attendees should provide input to the patient on how to answer the items.

Evaluator Review

The evaluator should review the MG-ADL once the patient has completed the form.

- If an MG-ADL item is not completed by the patient, inquire whether the omission was intentional or not. If omitted in error, then ask the patient to complete.
- If a patient asks for clarification about a question, please simply remind the patient to answer questions based on the severity of their MG-related symptoms. Do not help the patient to tease apart relative contributions from MG and non-MG causes.
- If a patient makes a mark on the boundary line between two scores or marks two scores, ask the patient to clearly select only one score. If the patient cannot decide between two scores, record the higher score.

MGNet V1.0
07 Sep 2022

MG Activities of Daily Living (MG-ADL)

This form includes 8 questions about the severity of your MG-related symptoms.

For each item, read the instruction first. Then choose the one answer that best describes your average functioning over the last 7 days. You may have had good days and bad days, but select the answer that best describes how you felt on average.

Please answer all questions by circling the response that best describes your MG-related symptoms. Do not leave any blank.

Please keep in mind the following as you complete the form:

- Do not try to imagine how severe your symptoms might be if you were not taking your MG medication. Score each item based on how you feel given that you are taking your current MG medications.
- If you are in doubt about how to answer a question, choose the option that is most appropriate for you most of the time over the last 7 days.
- Sometimes it can be difficult to determine whether a particular symptom is related to MG or to some other condition. When responding, please use your best judgement and try to consider only symptoms related to your MG. Exclude symptoms arising from any other illness you might have.

1. **Talking**
   Choose the one answer that best describes your average functioning over the last 7 days.

   Read all the options before choosing an answer. Do not leave this item blank.

0	1	2	3
Normal ◯	Intermittent slurring or nasal speech ◯	Constant slurring or nasal, but can be understood ◯	Difficult to understand speech ◯

- This question mentions slurring and nasal speech. However, it is really asking about any change in speech that you think is related to MG. If you have had any MG related speech disturbance, indicate how much it has impacted your speech (intermittent, constant, or makes your speech difficult to understand).

2. Chewing

Choose the one answer that best describes your average functioning over the last 7 days.

Read all the options before choosing an answer. Do not leave this item blank.

0	1	2	3
Normal ○	Fatigue with solid food ○	Fatigue with soft food ○	Gastric tube ○

- This question asks about fatigue while chewing food.
- You may have made changes to the consistency of your food to avoid jaw fatigue while chewing. If you avoid solid food because of chewing fatigue, but you can chew soft food, then score as 1.
- If you changed the way that you cut food in order to avoid fatigue while chewing (for example, cutting into smaller bites) or it takes longer to finish a meal, then score as 1.
- A gastric tube is any feeding tube used to provide nutrition into the stomach (e.g., inserted through the nose or through the skin)

3. **Swallowing**
   Choose the one answer that best describes your average functioning over the last 7 days.
   Read all the options before choosing an answer. Do not leave this item blank.

0	1	2	3
Normal ◯	Rare episode of choking ◯	Frequent choking necessitating changes in diet ◯	Gastric tube ◯

- If you choke on saliva occasionally, score as 1.
- If you have changed the consistency of foods you eat because of choking, score as a 2. You should score as a 2 even if the choking episodes have resolved since you changed your food consistency.
- A gastric tube is any feeding tube used to provide nutrition into the stomach (e.g., inserted through the nose or through the skin)

4. **Breathing**
   Choose the one answer that best describes your average functioning over the last 7 days.
   Read all the options before choosing an answer. Do not leave this item blank.

0	1	2	3
Normal ○	Shortness of breath with exertion ○	Shortness of breath at rest ○	Ventilator dependence ○

- This question asks about shortness of breath or feeling “winded” due to MG.
- Exertion could mean physical activity or exercise, such as walking. It could also include everyday activities such as getting dressed or eating.
- Shortness of breath at rest means that you feel winded even if not physically active at all. Examples include just lying down, talking, or eating.
- Ventilator dependence means any need for a ventilator, including noninvasive ventilation (e.g., BiPAP), even if only during the night. But do not count ventilator at night for another reason (e.g. CPAP for sleep apnea). Remember, these questions are asking about the severity of MG-related symptoms.

5. **Impairment of ability to brush teeth or comb hair**
   Choose the one answer that best describes your average functioning over the last 7 days.
   Read all the options before choosing an answer. Do not leave this item blank.

0	1	2	3
None ○	Extra effort, but no rest periods needed ○	Rest periods needed ○	Cannot do one of these functions ○

- This question asks about difficult you might have brushing your teeth or combing your hair. When answering this question, please also consider other activities that require you to elevate your arms/shoulders such as washing or blow-drying your hair.
- If you have made modifications or any type of adaptation (e.g. rest your elbows on table) for these activities, score as at least 1.

6. **Impairment of ability to arise from a chair**
   Choose the one answer that best describes your average functioning over the last 7 days.
   Read all the options before choosing an answer. Do not leave this item blank.

0	1	2	3
None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance
○	○	○	○

- This question asks about difficulties you may have getting up from a chair. Do not consider other activities such as climbing stairs.
- The severity grades refer to the difficulty when getting up from a chair (mild, moderate, severe).
- Remember to focus only on whether you need to use your arms because of your MG.
- If the only reason you have trouble getting from a chair is not related to MG (e.g., back pain), score as 0.

7. Double vision

Choose the one answer that best describes your average functioning over the last 7 days.

Read all the options before choosing an answer. Do not leave this item blank.

0	1	2	3
None	Occurs, but not daily	Daily, but not constant	Constant
○	○	○	○

- If you are blind in one eye, then score that you do not have double vision.
- If you wear a patch, wear prism glasses, use a cloudy glasses/contact lens, or squint sometimes to prevent double vision, then score as 1.
- If you wear a patch, wear prism glasses, or use a cloudy glasses/contact lens all the time to prevent double vision, then score as 2.
- If you have had double vision in the past 7 days, but it does not go away when you cover either eye, then score as 0.

8. **Eyelid droop**
   Choose the one answer that best describes your average functioning over the last 7 days.
   Read all the options before choosing an answer. Do not leave this item blank.

0	1	2	3
None ○	Occurs, but not daily ○	Daily, but not constant ○	Constant ○

- This is about how *<u>you</u>* feel about drooping eyelids. Do not score eyelid drooping that you are not aware of. For example, do not score eyelid drooping of which you are unaware, but someone else has noticed it and brought it to your attention.

Participant ID: _____

Visit ID: _____ **Date of Evaluation: _____**

MG-ADL Score Summary and Total Score

Enter the score selected by the participant

Item	Score (0, 1, 2, or 3)
1. Talking	
2. Chewing	
3. Swallowing	
4. Breathing	
5. Impairment of ability to brush teeth or comb hair	
6. Impairment of ability to arise from a chair	
7. Double vision	
8. Eyelid droop	
TOTAL SCORE (Sum of items 1-8)	

Evaluator Signature: _____ Date: _____

MYASTHENIA GRAVIS QUALITY OF LIFE-15 REVISED (MG-QOL15R)

Instructions

Introduction

The MG-QOL15r is a 15-item quality of life scale designed to assess important aspects of the patient's experience related to MG. The MG-QOL15r is a validated modification of the MG-QOL15 and scores each of 15 items 0-2 (max score 30), while the MG-QOL15 scores items 0-4 (max score 60). In addition, the wording of some items was modified in the MG-QOL15r compared to the MG-QOL15.

The MG-QOL15r component items were chosen to reflect physical, psychological, and social domains of patient well-being. The scale was developed as a patient reported outcome measure and the consensus among experts is that the MG-QOL15r should be self-reported by the patient.

Procedures for Administration

The patient should be provided with the MG-QOL15r form that includes instructions for self-completion. Remind the patient to answer items based on the impact MG has had their quality of life over the past 4 weeks. The patient with MG should complete the MG-QOL15r without evaluator input or guidance. Similarly, no family members or other visit attendees should provide input to the patient on how to answer the items.

Evaluator Review

The evaluator should review the MG-QOL15r once the patient has completed the form.

- If any MG-QOL15r item is not completed by the patient, inquire whether the omission was intentional or not. If omitted in error, then ask the patient to complete.
- If a patient asks for clarification about a question, please simply remind the patient to answer questions based on the impact of their MG-related symptoms. Do not help the patient to tease apart relative contributions from MG and non-MG causes.
- If a patient makes a mark on the boundary line between two scores or marks two scores, ask the patient to clearly select only one score.

MGNet V1.0
07 Sep 2022

Revised Myasthenia Gravis Quality of Life-15 (MG-QOL15r)

This form includes 15 questions related to how your quality of life is affected by MG-related symptoms.

For each item, please read the question, and then choose the one answer that best describes the average impact of your MG on your quality of life over the past 4 weeks. You may have had good days and bad days. Please select the answer that best describes how you felt on average.

Please answer all questions by circling the response that best describes your MG-related symptoms. Do not leave any item blank. If an item does not seem to apply to you, score as 0.

Please keep in mind the following as you complete the form:

- Score each item based on how you feel given that you are taking your current MG medications. Do not try to imagine how severe your symptoms might be if you were not taking your MG medication.
- You may be in doubt about how to answer a question. If this happens, choose the option that is most appropriate for you most of the time over the past 4 weeks.
- Sometimes it can be difficult to determine whether a particular symptom is related to MG or to some other condition. When responding, please use your best judgement and try to consider only symptoms related to your MG. Exclude symptoms arising from any other illness you might have.
- Complete the form without input or guidance from family members or other attendees.

Participant ID: _____

Visit ID: _____ **Date of Evaluation:** _____

MG-QOL15r Scale

Please indicate how true each statement has been (over the past 4 weeks).	**Not at all 0**	**Somewhat 1**	**Very much 2**
1. I am frustrated by my MG			
2. I have trouble with my eyes because of my MG (e.g. double vision)			
3. I have trouble eating because of MG			
4. I have limited my social activity because of my MG			
5. My MG limits my ability to enjoy hobbies and fun activities			
6. I have trouble meeting the needs of my family because of my MG			
7. I have to make plans around my MG			
8. I am bothered by limitations in performing my work (include work at home) because of my MG			
9. I have difficulty speaking due to MG			
10. I have lost some personal independence because of my MG (e.g. driving, shopping, running errands)			
11. I am depressed about my MG			
12. I have trouble walking due to MG			
13. I have trouble getting around public places because of my MG			
14. I feel overwhelmed by my MG			
15. I have trouble performing my personal grooming needs due to MG			

Evaluator Signature: _____ **Date:** _____

Total MG-QOL15r score

Quantitative Myasthenia Gravis-Revised Score

Date: 07 SEP 2022

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.

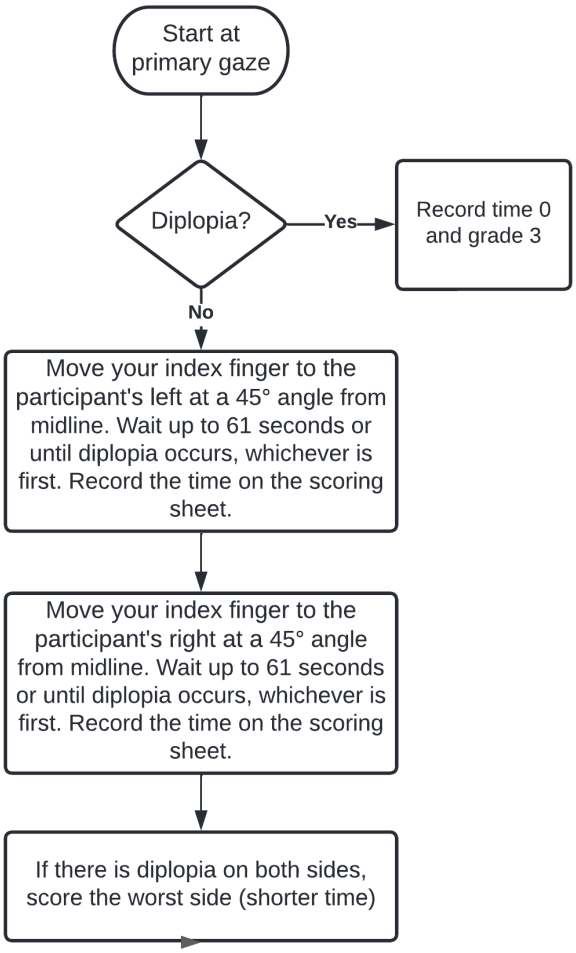
10. The QMG-R may be performed by any trained and certified evaluator to allow the most flexibility for study teams.

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**:**

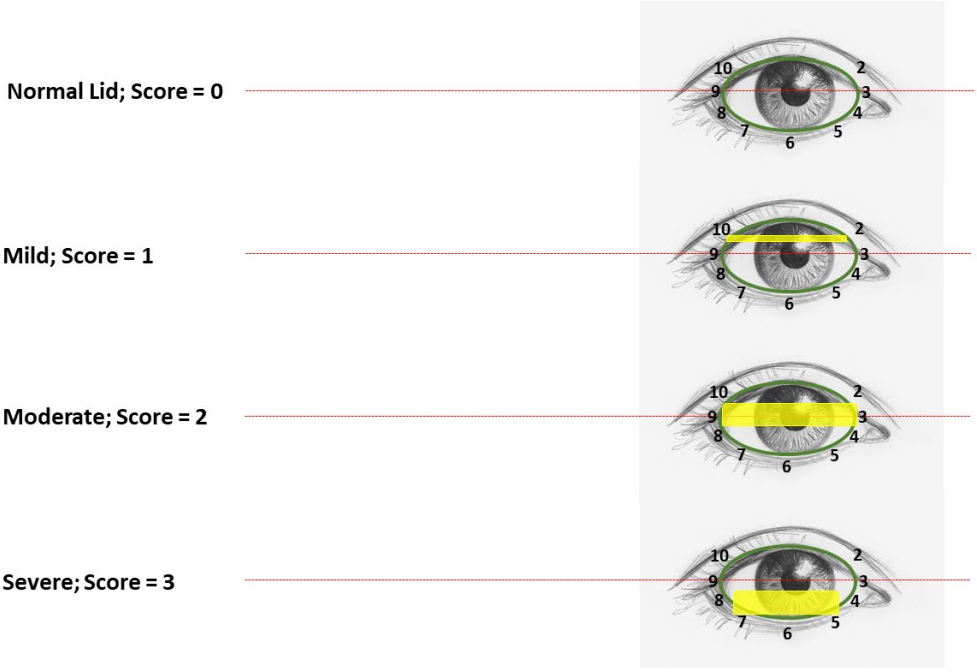
- When diplopia occurs, cover one eye and ensure that diplopia is BINOCULAR. Monocular double vision should be scored as “0 None.”
- Diplopia occurring in primary gaze or immediately upon left or right gaze should be scored as a “3 Severe.” If there is diplopia on primary gaze, indicate this by using 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:

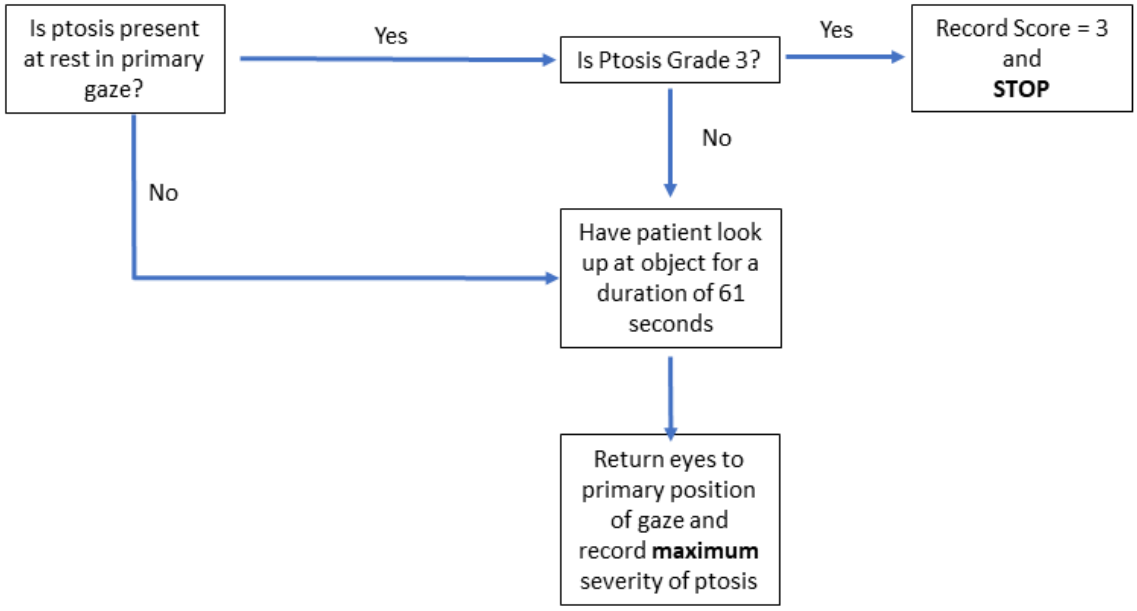
   - **Figure 2. Grading of ptosis.** Only the upper eyelid is assessed for ptosis. The horizontal red line indicates the middle of the pupil. The yellow shaded boxes indicate the possible range of eyelid positions corresponding to each severity grade. For mild ptosis there can be an exception based on 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**:**

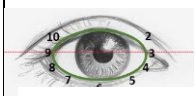
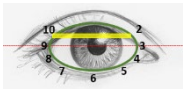
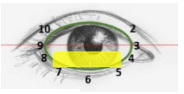
- If one leg cannot be maintained at 45^0 due to a NON-myasthenia gravis related problem (such as back or hip injury), do not score the affected leg and use the score from the unaffected leg to grade the affected leg. Indicate the specific reason the test could not be performed on the case report form.
- 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

Participant ID: _____ **Dominant Hand: Right** ◯ **Left** ◯

Visit ID: _____ **Date of Evaluation:** _____

QMG Revised Form

Date/Time of last cholinesterase inhibitor:_____ ☐ **Last dose was an extended release formulation**

Test Item	Raw Value		None	Mild	Moderate	Severe	SCORE
			0	1	2	3	
Double vision *Document time in sec. for both sides. Score worst side.*	**R**	**L**	≥61 *Check box if obvious ocular misalignment but no diplopia* ☐	11-60	1-10	Spontaneous *Check box if diplopia in primary gaze* ☐	
Ptosis *Document severity for both sides according to scoring in pictures. Score worst side.*	**R**	**L**	 ***Refer to manual for details of grading mild ptosis***				
Eyelid Closure			Normal	Complete, weak, some resistance	Complete, without resistance	Incomplete	
Swallowing			Normal	Minimal coughing or throat clearing	Severe Coughing/ choking or nasal regurgitation	Cannot swallow 120ml (test not completed)	
Speech	**Record the number at onset of dysarthria:**		None at 50	Dysarthria/ nasal speech at 30-49	Dysarthria/ nasal speech at 10-29	Dysarthria/ nasal speech at 0-9	
Right arm outstretched *Check if not testable due to non-MG cause** ☐	**Time (s):**		240	90-239	10-89	0-9	
Left arm outstretched *Check if not testable due to non-MG cause** ☐	**Time (s):**		240	90-239	10-89	0-9	
Vital Capacity ◯ **Forced** ◯ **Slow**	**Trial #**	**Volume (L):**	**% Predicted:**	≥80%	65-79%	50-64%	<50%	
	1						
	2						
	3						
	4						
	5						

Evaluator Signature: _____ Date: _____ (CRF V1.0 07Sep2022)

Participant ID: _____ **Dominant Hand: Right ◯ Left ◯**

Visit ID: _____ **Date of Evaluation: _____**

Test Item	Raw Value	None	Mild	Moderate	Severe	SCORE
		0	**1**	**2**	**3**	
Dominant hand grip: *Check if not testable due to non-MG cause** ☐	**Trial:** **1** **2** **3** Best Value (kg):	>45 (M) >30 (F)	15-44 (M) 10-29 (F)	5-14 (M) 5-9 (F)	0-4 (M) 0-4 (F)	
Non-Dominant hand grip: Check if not testable due to non-MG cause* ☐	**Trial:** **1** **2** **3** Best Value (kg):	>35 (M) >25 (F)	15-34 (M) 10-24 (F)	5-14 (M) 5-9 (F)	0-4 (M) 0-4 (F)	
Head Lift	**Time (s):**	120	30-119	1-29	0	
Right hip flexion Check if not testable due to non-MG cause* ☐	**Time (s):**	100	31-99	1-30	0	
Left hip flexion Check if not testable due to non-MG cause* ☐	**Time (s):**	100	31-99	1-30	0	
					TOTAL SCORE	

** Please describe the specific cause if an arm or a leg were not tested due to a non-MG-related cause:*

Evaluator Signature: _____ Date: _____ (CRF V1.0 07Sep2022)

MYASTHENIA GRAVIS COMPOSITE SCALE

Introduction

The Myasthenia Gravis Composite scale (MGC) was designed to incorporate both patient-reported and examiner-determined items that could be administered within a relatively short time, about 5 minutes. All items are adopted from other validated scales.

The patient reported items (talking, chewing, swallowing, breathing) are derived from the Myasthenia Gravis Activities of Daily Living (MG-ADL) profile without modification. Although originally designed as an instrument to be administered by a trained examiner, growing consensus amongst experts is that the MG-ADL Score, as a patient reported outcome measure (PROM), could be self-reported by the patient after proper instruction (see separate instructions for administration of the MG-ADL).

The examiner-determined items (double vision, eye closure, neck flexion/extension, shoulder abduction, hip flexion) are derived from the Quantitative Myasthenia Gravis-Revised (QMG-R) and Myasthenia Gravis Manual Muscle Testing (MG-MMT) instruments with some modifications. The ptosis item is derived from the Quantitative Myasthenia Gravis (QMG) (note that the ptosis item in the original QMG measures time to onset of ptosis, whereas the QMG-R measures maximum severity of ptosis). Maximum time for onset of diplopia and ptosis are reduced from >60 seconds in the QMG-R to 45 seconds in the MGC for both symptoms; this was done after construct validity testing showed that <1% of ocular score times occurred between 46 and 60 seconds.[1] Eye closure weakness was specifically defined (normal; can be forced open with effort; can be forced open easily; unable to keeps eyes closed) instead of the MG-MMT use of four categories. Neck flexion, shoulder abduction and hip flexion muscle strength is scored based on the modified Medical Research Council (MRC) grading (see below for details).[1]

Unlike the above scales, the MGC uses a weighted scoring system so that item scores do not all carry equal weight. Despite the weighting, the score can be summated to estimate an overall disease severity score. The maximum score is 50, and a 3-point change in the summated score is considered clinically meaningful.[2]

General procedures for administration

- **Patient reported items:**
  - In most instances, participants will have completed the MG-ADL profile prior to the MGC and item scoring can directly be imported from this into the MGC. In instances where the MG-ADL has not been performed, the identical instructions from the MG-ADL should be used to inform participants on how to score these items.
  - Refer to the MG-ADL instructions for details on administration of the patient reported items of the MGC.

- **Examiner determined items:**
  - Pyridostigmine needs to be held for at least 12 hours prior to these assessments, whereas long-acting (extended release) formulations should be held for at least 24 hours. The time and amount of the last dose taken should be recorded.
  - If the QMG-R assessment has already been performed, the item score for diplopia can be calculated from the QMG-R, provided the exact time for diplopia onset is recorded. Importantly, the maximum duration and item score cut-offs are not the same between the QMG-R and MGC (Table).

Table. Duration of assessment for QMG and MGC

	QMG	MGC
Diplopia	0-61s	0-45s

  - If the QMG-R has not been performed, please refer to the instructions for testing diplopia in the QMG-R manual. The instructions for performing this assessment in the MGC and QMG-R are the same, only the scoring is different. Make sure to record the time to onset.
  - Instructions for performing ptosis, eye closure, neck flexion/extension, shoulder abduction, and hip flexion as part of the MGC are included in the detailed instructions that follow.

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ITEM-SPECIFIC MYASTHENIA GRAVIS COMPOSITE SCALE INSTRUCTIONS

1. Ptosis, upward gaze

The participant should be 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. The examiner should sit in front of the participant at approximately eye level.

Give the following instruction:
"Look straight ahead. Make sure that your forehead is relaxed."
If the participant has ptosis where the upper eyelid drops down midway through the pupil looking straight ahead, stop the test and record a time of 0.

If there is no ptosis or insufficient ptosis (i.e., upper lid does not cross midway through the pupil) while looking straight ahead, give the next instruction:
"When I ask, look up at the ceiling without moving your head. Keep looking up until I tell you to relax. You will look up for up to 45 seconds."

If the participant has ptosis instantaneously when looking up to the ceiling (again, upper eyelid drops down midway through the pupil), stop the test and record a time of 0. If not, start the timer. Stop the test if the upper eyelid drops down midway through the pupil or after 45 seconds. Record the time at which ptosis developed or the test was stopped.

Additional Considerations:

- You may ask the participant to look up your finger rather than the ceiling (some participants prefer to have a specific target to look at).
- If the subject cannot move their eyes, they should be given a time of 0.

2. Double vision on lateral gaze, left or right

Transfer **time** from QMG-R scale, and score based on MGC cut-offs.
If QMG-R has not been performed, or time not documented, then refer to the separate QMG-R instructions.

3. Eye closure

Patient positioning and examiner instructions for the MGC eye closure and QMG-R facial muscles assessments are the same.

If the QMG-R has been performed, assess eye closure according to the MGC specific grading (normal (0); can be forced open with effort (0); can be forced open easily (1); or unable to keeps eyes closed (2)).

If the QMG-R has not been performed, refer to the QMG instructions for facial muscles assessment and assess eye closure according to the MGC specific grading.

4. **Talking**

   Transfer response from MG-ADL.

   If MG-ADL has not been performed, then refer to the separate MG-ADL instructions.

5. **Chewing**

   Transfer response from MG-ADL.

   If MG-ADL has not been performed, then refer to the separate MG-ADL instructions.

6. **Swallowing**

   Transfer response from MG-ADL.

   If MG-ADL has not been performed, then refer to the separate MG-ADL instructions.

7. **Breathing**

   Transfer response from MG-ADL.

   If MG-ADL has not been performed, then refer to the separate MG-ADL instructions.

8. **Neck flexion or extension**

   The participant should be positioned supine for testing neck flexion, and prone for testing neck extension. If the participant is unable to lie in these positions, the reason(s) should be clearly documented on the case report form. The alternative position is seated. Arms should be at the participant's sides. You may place a pillow under the patient's knees for comfort. While you are giving the instructions and demonstration, you may keep a pillow under their head, but this should be removed prior to the start of the testing. Grade strength using the modified Medical Research Council (MRC) grading system,* and the weaker of neck flexion vs. extension is used to score item:

- Mild weakness = MRC grade 4+
- Moderate weakness = MRC grade 4 to 4-
- Severe weakness = MRC grade 3 or less

9. Shoulder abduction

The participant should be sitting upright, feet planted on ground, and without back support. The arms should be abducted to 90 degrees and elbows should be flexed. Shoulder abduction should be tested bilaterally at the same time by putting downward pressure on upper arms above the elbows. If testing cannot be performed on one side (e.g., rotator cuff injury), assume the same score as the contralateral side. Document the reason for the inability to test the side. If there is asymmetry in the weakness, the weaker side should be recorded. Grade strength using the modified MRC grading system:*

- Mild weakness = MRC grade 4+
- Moderate weakness = MRC grade 4 to 4-
- Severe weakness = MRC grade 3 or less

10. Hip flexion

Hip flexion testing should be performed with the participant in the supine position and with the knee flexed at 90 degrees. Testing is performed unilaterally by exerting resistance just proximal to the knee. If testing cannot be performed in the recommended position, the reason for this should be clearly documented (e.g., orthopnea). The alternative position is seated. In the seated position, testing is also performed unilaterally. Whichever position (supine or seated) is used at baseline, should ideally be used throughout the study. Ask the patient to raise their knee and then the examiner applies downward pressure on the thigh just proximal to the knee. Document the testing position on the case report form. If testing cannot be performed on one side (e.g., back pain), assume the same score as the contralateral side. Document the reason for the inability to test the side. If there is asymmetry in the weakness, the weaker side should be recorded. Grade strength using the modified MRC grading system:*

- Mild weakness = MRC grade 4+
- Moderate weakness = MRC grade 4 to 4-
- Severe weakness = MRC grade 3 or less

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Once all responses have been recorded, the item scores can be added to obtain the total score.

REFERENCES:

1. Medical Research Council. Aids to the examination of the peripheral nervous system. London, England: The White Rose Press; 1976; Memordanum No. 45. ISBN 0 11 450033 9.
2. Burns TM, Conaway M, Sanders DB. The MG Composite: A valid and reliable outcome measure for myasthenia gravis. *Neurology*. 2010;74:1434-1440. doi:10.1212/WNL.0b013e3181dc1b1e

***** Modified MRC grades:

4+: muscle can be moved against gravity and strong resistance

4: muscle can be moved against gravity and moderate resistance

4-: muscle can be moved against gravity and slight resistance

3: muscle can be moved fully against gravity

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Participant ID: _____

Visit ID: _____ **Date of Evaluation: _____**

MG Composite Scale

Ptosis, upward gaze (physician examination)	>45 seconds = **0** ◯	11-45 seconds = **1** ◯	1-10 seconds = **2** ◯	Immediate = **3** ◯
Double vision on lateral gaze, left or right (physician examination)	>45 seconds = **0** ◯	11-45 seconds = **1** ◯	1-10 seconds = **3** ◯	Immediate = **4** ◯
Eye closure (physician examination)	Normal = **0** ◯	Mild weakness (can be forced open with effort) = **0** ◯	Moderate weakness (can be forced open easily) = **1** ◯	Severe weakness (unable to keep eyes closed) = **2** ◯
Talking (patient history)	Normal = **0** ◯	Intermittent slurring or nasal speech = **2** ◯	Constant slurring or nasal but can be understood = **4** ◯	Difficult to understand speech = **6** ◯
Chewing (patient history)	Normal = **0** ◯	Fatigue with solid food = **2** ◯	Fatigue with soft food = **4** ◯	Gastric tube = **6** ◯
Swallowing (patient history)	Normal = **0** ◯	Rare episode of choking = **2** ◯	Frequent choking necessitating changes in diet = **5** ◯	Gastric tube = **6** ◯
Breathing (thought to be caused by MG)	Normal = **0** ◯	Shortness of breath with exertion = **2** ◯	Shortness of breath at rest = **4** ◯	Ventilator dependence = **9** ◯
Neck flexion or extension (weakest) (physician examination)*	Normal = **0** ◯	Mild weakness = **1** ◯	Moderate weakness = **3** ◯	Severe weakness = **4** ◯
Shoulder abduction (physician examination)*	Normal = **0** ◯	Mild weakness = **2** ◯	Moderate weakness = **4** ◯	Severe weakness = **5** ◯
Hip flexion (physician examination)*	Normal = **0** ◯	Mild weakness = **2** ◯	Moderate weakness = **4** ◯	Severe weakness = **5** ◯
			TOTAL SCORE (Sum of items 1-10)	

Evaluator Signature: _____ Date: _____

*Modified MRC:

- Mild weakness = MRC grade 4+ (muscle can be moved against gravity and strong resistance)
- Moderate weakness = MRC grade 4 to 4- (muscle can be moved against gravity and slight/moderate resistance)
- Severe weakness = MRC grade 3 or less (muscle can be moved fully against gravity or less)

Myasthenia Gravis Impairment Index (MGII)

Administration Manual - MGNet Clinical Trial Outcome Measure Working Group

Introduction:

The MGII is a measure of disease severity based on the signs and symptoms of myasthenia gravis. It was developed using a patient-centered approach, and followingcurrent guidelines for outcome measure development, incorporated patient input throughout the different development phases.

The MGII has 22 patient reported items, administered as a questionnaire, and 6 examination items, performed by a rater. Scores are presented in a sum of all items for a total score, but also as an ocular and a generalized sub-score.

MGII Questionnaire, Administration Instructions:

The patient should be provided with the MGII questionnaire form that includes instructions for self-completion. The patient should complete the MGII without evaluator input or guidance. Similarly, no family members or other visit attendeesshould provide input to the patient on how to answer the items.

Evaluator Review:
The evaluator should review the MGII questionnaire once the patient has completed the form.

• If any MGII questionnaire item is not completed by the patient, inquire whether the omission was intentional or not. If omitted in error, then ask the patient to complete.

• If a patient asks for clarification about a question, please simply remind the patient to answer questions based on the impact of their MG-related symptoms. Do not help the patient to tease apart relative contributions from MG and non-MG causes.

Scoring instructions are detailed in page 4.

MGII- Examination Instructions

- Pyridostigmine needs to be held for at least 12 hours prior to these assessments, whereas long-acting (extended release) formulations should be held for at least 24 hours. The time and amount of the last dose taken should be recorded.
- If the QMG-R assessment has already been performed, the item scores for arm, leg and neck endurance can be calculated from the QMG-R, provided exact endurance times are recorded. Importantly, item score cut-offs are not the same between the QMG-R and MGII.
- If the QMG-R has not been performed, please refer to the instructions for testing arm, leg and neck endurance in the QMG-R manual. The instructions for performing these assessments in the MGII and QMG-R are the same, only the scoring is different. Make sure to record the endurance time.

1. Diplopia:

Ask the patient to follow your finger in all primary directions (up, down, right and left). Ask the patient if they have diplopia in any direction, including in primary gaze. Record the number of gaze directions where diplopia is present. This is not a fatigability test, so no need to hold gaze once patient has reported on presence or absence of diplopia.

A patient with monocular vision will score 0 in this item. A patient with severe restriction of extraocular movements will score 0 if they do not report diplopia.

2. Ptosis:

Ask the patient to hold their gaze upwards, for up to 60 seconds, and record the time to develop ptosis (in seconds). A patient with clear ptosis at baseline (i.e. lid touching the pupil) will score 2 points in this item, and no sustained upgaze test is needed.

3. Lower Facial Strength:

Ask the patient to blow air into their cheeks and hold it against resistance. You can provide cues such as “like blowing a balloon”.

4. Arm Endurance:

Transfer endurance **time** from QMGS-R. Record the time for the **best** performing arm (right or leg) on the MGII scoring sheet. Note that the scoring ranges are different for the QMGS-R and the MGII.

If QMGS-R has not been performed, then refer to the separate QMGS-R instructions.

5. Leg Endurance:

Transfer endurance **time** from QMGS-R. Record the time for the **best** performing leg (right or leg) on the MGII scoring sheet. Note that the scoring ranges are different for the QMGS-R and the MGII.

If QMGS-R has not been performed, then refer to the separate QMGS-R instructions.

6. Neck Endurance:

Transfer endurance time from QMGS-R. Note that the scoring ranges are different for the QMGS and the MGII.

If QMGS-R has not been performed, then refer to the separate QMGS-R instructions.

MGII- Scoring Instructions

- The MGII can be summarized as a total score and also as 2 sub-scores, reflecting an Ocular and a Generalized domain.

- The total score is the raw sum of all the items, including the clinical examination (E) and the patient-reported (PR) questionnaire.

- The ocular score is calculated by summing 8 items reflecting ocular impairments.These items are: PR items 1 to 6 and examination items 1 and 2.

- The generalized score is calculated by adding PR items 7 to 22 and examination items 3 to 6.

- The scoring sheet provided can be used for manually calculating sub-scores and can help visualize how items are summed. For larger datasets, we can provide an R script for calculating the sum-scores and imputing missing data.

Missing Data:

- If 2 boxes are marked, count the response indicating more severity. If a mark is placed outside of a box, count the response closer to the mark. If the mark is in the middle of two boxes, count the response indicating higher severity.

- For missing answers, impute the average score for the other items in the same domain or region (ocular or generalized).

Important: We consider the total sum-score reliable when there are ≤3 items missing (<10% missing responses). On the validation and responsiveness studies (n>200), less than 5% of patients had more than 3 missing items, so this scenario is infrequent.