MG-ACTIVITIES OF DAILY LIVING (ADL)[1]

Focus	MG specific symptoms and impact on daily activities
Patient or clinician centric	Patient
Administration	Clinician administered vs patient self-reported[2]
# items	8
Equipment needed	None
Item scoring	0 (normal) to 3 (severe); max score=24
Domains evaluated	• Ocular • Bulbar • Respiratory • Limb
Time to complete	5 minutes
Clinically meaningful change	2 points[3]
Psychometric properties	• Test-retest reliability: acceptable[3] • Responsiveness: excellent[3,4] • Content validity: good, measures appropriate domains for MG patients • Construct validity, correlation with other MG outcome measures: good. Good correlation with QMG, MG-C, MG-QOL15[1,3,5,6,4,7] • Limitations: floor effect[5]
Virtual visit use	No validation studies, but currently used in this setting
Translations/validations	• Arabic[8] • Italian[9] • Korean[2] • Polish[10] • Turkish[11]
Key test instructions	• The time duration over which the patient is asked to assess their symptom burden is past 7 days • Patients should only consider symptoms attributed to MG, not other medical conditions
Other information	• Common primary endpoint in phase 2/3 clinical trials[12,13] • Minimal symptom expression defined as MG-ADL score of 0 or 1 is being used as a trial endpoint[14] • More sensitive to clinical change than QMG[6] • PASS threshold is 2[15]
Areas contributing to lack of standardization	• Clinician administered vs patient self-report • Should a script be used to assess each item? • Can caregiver be involved in assessment? • Time duration over which patients are asked to assess their symptom burden is past 7 days • Administration in clinic vs telemedicine setting • How to minimize the influence of non-MG related factors on responses?

Abbreviations: MG-C: myasthenia gravis composite scale, MG-QOL15: myasthenia gravis Quality of Life-15 score, PASS: patient-acceptable symptom state; QMG: quantitative myasthenia gravis score

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Quantitative MG Score (QMG)

Focus	Evaluation of Strength and Fatigable weakness geared towards MG (including ocular muscles)
Patient or clinician centric	Clinician[1]
Administration	Clinician/Evaluator Administered[1]
# items	13[2]
Equipment needed	Spirometer (with Mouth Pieces), Stopwatch, Cups and water, Dynamometer, Goniometer
Item scoring	None (0), Mild (1), Moderate (2), Severe (3) Severity is graded by time (for positional tests), percentage (FVC), Kg (hand grip), subjective strength (eyelid closure)
Domains evaluated	• Ocular (ocular movements, ptosis, eyelid closure) • Bulbar (swallowing, dysarthria) • Limb/axial (arm strength, leg strength, grip, neck flexion) • Respiratory (FVC)
Time to complete	~20-30 minutes
Clinically meaningful change	≥2 points for QMG 0-16, and ≥3 points for QMG >16 per Katzberg et al[3] ≥2.3 per Bedlack et al.[4,5] 2.6 per Barohn et al.[2] Note that per Barnett et al[6], at an individual level, **minimum detectable change** (4.3) may be higher than **minimum clinically meaningful change**, suggesting that minor changes at an individual level may be due to measurement error.
Psychometric properties	• Test-retest reliability: Adequate[6] • Inter-rater reliability: High[7,2] • Responsiveness: Excellent[4] • Content validity: Relevant – measures frequently affected domains in MG • Construct validity, correlation with other MG outcome measures: Good, correlates well with MG-QOL15, MGFA Class, MG-MMT, MG-ADL, MG impairment index[8,9,7,10-13] • Limitations: - Criticized for its items not being weighted for clinical relevance.[9,1] - In the MMF study (muscle study group), QMG was less sensitive to changes than MMT and ADL at weeks 12 and 36[10] - By contrast, correlation analysis of MG-ADL and QMG in the MGTX study demonstrated that MG-ADL was more susceptible to floor effect than QMG[14] - Unclear if the scoring of the timed items in the test were determined arbitrarily - Analysis of prospective study of IVIG in MG suggested a significant floor effect in swallowing, speech, vital capacity and grip strength (and, therefore, did not differentiate well between subjects)[8]
Virtual visit use	Not possible unless modified
Translations/validations	• Portugese[15] • Translation is less relevant than other outcome measures since items are administered by clinicians. MAPI Research trust makes the instructions available in Czech, Dutch (Holland), German, Hungarian, Italian, Japanese, Portuguese, Russian, Serbian, Spanish (Spain and US versions), Turkish, Korean, Polish
Key test instructions	• Available by MAPI in writing. A video version is also available but difficult to access. Latest written version of the instructions are dated August 6, 2017

Other information	• The need for equipment, need for proper training and duration of the evaluation makes QMG less desirable for day-to-day clinic use. (Note: a Thai group published a modified QMG Score, removing speech, vital capacity (replaced by peak flow) and dynamometry, demonstrating a correlation coefficient of 0.96, N=45)[16] • Very commonly used in clinical trials. Was recommended to be included in ALL clinical trials by original MGFA task force but not in the updated version in 2012.[1] Tested in most clinical trials. • A pediatric version does not exist
Areas contributing to lack of standardization	• Difficult to access instructions (especially video) • Should the scoring of the right vs. left hand be modified as "dominant vs. non-dominant hand"? (the test may differentially score a right vs. left-handed individual with equal strength) • Glasses are removed in ocular tests but not contact lenses (what if a participant reports blurry vision without glasses)? • Per instructions, ptosis is considered present only when the eyelid is at the mid-pupil level. How is milder ptosis vs. no ptosis are differentiated? • Difficult to assess eye closure strength (mild vs. moderate) • What is incomplete eye closure? Should the sclera be visible or incomplete burial of eyelids is considered incomplete closure? • Should we be still using the Knudson 83 as the normative data? • A mask is listed as an option in the scoring sheet of the VC but not mentioned in the instructions. Relevant given the possible poor seal of the mouthpiece in patients with oral weakness. • Should the patients with baseline NON-MG related limitations be scored "as is"? e.g. if a patient has difficulty with shoulder abduction due to rotator cuff tear, is that item ignored or should we score the shoulder abduction as whatever we time, regardless of the etiology?

Abbreviations: FVC: forced vital capacity; MG-ADL: myasthenia gravis activities of daily living scale MG-C: myasthenia gravis composite scale, MG-QOL15: myasthenia gravis Quality of Life-15 score, MG-MMT: myasthenia gravis manual muscle test; QMG: quantitative myasthenia gravis score

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Myasthenia Gravis Composite Scale (MGC)[1]

Focus	MG specific symptoms and examination findings
Patient or clinician centric	Both
Administration	A derived measure based on MG-ADL (patient reported), QMG and MMT (clinician determined).
# items	10
Equipment needed	Stopwatch
Items scoring	**Weighted score**: normal = 0, severe = 2-9 (*domain dependent*) Maximum score: 50

Domains evaluated	• Ocular (*ptosis, eye closure strength*)
	• Bulbar (*talking, chewing, swallowing*)
	• Respiratory (*neck flexion strength, breathing*)
	• Limb strength
	  • Upper (*shoulder abduction*)
	  • Lower (*hip flexion*)

Time to complete	5 minutes
Clinically meaningful change	3-point change[2,3]; Minimal detectable change: 4.3-point change[4]

Psychometric properties	• Test-retest reliability: excellent[2]
	• Responsiveness: good differentiation between moderate and severe disease[1,5]
	• Content validity: good
	• Construct validity
	  • Despite the weighting, "the score can be summated to estimate an overall disease severity score".[6]
	  • Assigned weighted scoring is clinically (weights assigned by field experts) and ?statistically (Rasch analysis) appropriate[1,4,6]
	  • Correlation with other MG outcome measures: stronger correlation with MG-ADL than MG-QOL15[2]; strong correlation with MG-ADL and MG-QOL15 following TPE[7]
	• Limitations: floor effect for patients in remission (expected)[5,6]

Virtual visit use	Not applicable at this point. Ongoing study to develop and validate a virtual version (MGCv).
Translations/ validations	• Czech[8] • Brazilian-Portugese[9] • Spanish[10] • Japanese – translated; no published validation study • Germany, Denmark, Norway – use English version (personal communications to Dr. James Howard from respective experts).
Key test instructions	<u>Patient symptom domains (*bulbar and breathing above*) – MG-ADL derived:</u> • Time frame in clinical trials: 7 days; clinical practice: ? <u>Evaluator assessed domains (*ocular, neck flexion, limb strength*) – QMG/MMT derived:</u> • Last pyridostigmine dose at least 10 or 12 hours prior; • Patient comfortably seated, back unsupported (neck flexion: tested seated or supine?); • Ptosis definition: upper eyelid touches the pupil (QMG Manual)[11] vs covers half the pupil (recent clinical trials); • Weakness grading: mild = 25%, moderate = 50%, severe = 75%.
Other information	• Contains both longitudinal (physician-assessed) as well as period information (patient reported; typically 7-day period average).

	• Sensitivity and specificity of 3-point change is higher with initial MGC score of 7 or more (100% and 81% respectively) compared to initial MGC of 5 or more (94.6% and 80% respectively)[2] • PASS threshold is: ≤3[12]
Areas contributing to lack of standardization	• Definition of ptosis used for grading • Positions in which weakness is scored, particularly for neck and hip flexion • Lack of individual level correlative studies with other established outcome measures (e.g., MG-ADL, QMG)

Abbreviations: MG-ADL: myasthenia gravis activities of daily living; MMT: myasthenia manual muscle testing; MG-QOL: myasthenia gravis quality of life 15 score; QMG: quantitative myasthenia gravis score; PASS: patient-acceptable symptom state; TPE: therapeutic plasma exchange

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Revised Myasthenia Gravis Quality of Life (MG-QOL15r)[1]

Focus	Impact of MG on physical, psychological and social domains of well-being
Patient or clinician centric	Patient
Administration	Patient self-report or clinician/evaluator administered
# items	15
Equipment needed	None
Item scoring	0 (Not at all), 1 (somewhat), 2 (Very much); max score=30 vs MG-QOL15: 0 (Not at all), 1 (A little bit), 2 (Somewhat), 3 (Quite a bit), 4 (Very much); max score=60
Domains evaluated	• Mobility[2] • Symptoms • General Contentment • Emotional Well-being
Time to complete	Less than 10 minutes[3]

Clinically meaningful change	• Not clearly defined
	  ○ Scores varied by 4 points or less in 94% in test-retest reliability study for MG-QOL15[4]
	  ○ Patient-acceptable symptom state for MG-QOL15 is ≤8[5]

Psychometric properties	• Internal Consistency: excellent[2] • Test-retest reliability: excellent (coefficient 98.6%)[4] • Responsiveness: good (-3 points: 82% sensitivity, 67% specificity)[4] • Content validity: good, measures appropriate domains for MG patients • Construct validity, correlation with other MG outcome measures: Good correlation with QMG, MG-MMT, MG-ADL[2,4] • Limitations: Above properties studied in MG-QOL15
Virtual visit use	No validation studies, but currently used in this setting
Translations/validations (all MG-QOL15, except last bullet)	• Japanese[6] • Brazilian Portuguese[7] • Persian[8] • Turkish[9] • French[10] • Italian[11] • Polish[12] • Dutch[13] • Chinese[14] • Malay, Thai, Indonesian, Hindi, Marathi[1] • Patients from Japan, Iran, France and China were included in MG-QOL15r validation study[1]
Key test instructions	• The time duration over which the patient is asked to assess their symptom burden is “past 4 weeks” in MG-QOL15 and “past few weeks” in MG-QOL15r
Other information	• Common secondary endpoint in phase 2/3 clinical trials, MG-QOL15[15,16] MG-QOL15r[17] • MG-QOL15r was revised from MG-QOL15 by reducing response categories from 5 to 3, “driving” item was reworded to “loss of independence”, “including work at home” was added to work/occupation item, “double vision” was added in vision item[1] • MG-QOL15r showed better clinimetric properties compared to MG-QOL15, thus recommended for use[1]
Areas contributing to lack of standardization	• Clinician administered vs patient self-report • Time duration over which the patient is asked to assess their symptom burden is not precise (past few weeks) and different with MG-QOL15 (past four weeks)

Abbreviations: MG-ADL: myasthenia gravis activities of daily living scale; MG-C: myasthenia gravis composite scale, MG-QOL15: myasthenia gravis Quality of Life-15 score, MG-QOL15r: revised Myasthenia Gravis Quality of Life-15 score; QMG: quantitative myasthenia gravis score

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MG-IMPAIRMENT INDEX (MGII)[1]

Focus	MG-specific impairments
Patient or clinician centric	Patient
Administration	Patient self-report (22 items) and clinical examination (6 items)[1]
# items	28
Equipment needed	Watch with seconds or smartphone or stopwatch
Item scoring	• Total score ranges from 0 (no impairments) to 84 (worst possible) • Ocular and Generalized sub-scores
Domains evaluated	• Ocular • Bulbar • Respiratory • Limb
Time to complete	10 minutes
Clinically meaningful change	≥6 points in total score, for individuals[2]
Psychometric properties	• Test-retest reliability: excellent[1] • Responsiveness: excellent (cohort study)[2] • Content validity: measure developed with patient input, based on dedicated qualitative study[1,3] • Construct validity: met pre-defined hypotheses of correlations with disease-specific measures: (MGC, QMG, MG-ADL, MG-QOL15) and generic measures. Good discriminatory validity (i.e. ocular vs generalized)[1] • Limitations: no RCT data; longer to complete than MGC and ADL
Virtual visit use	Currently used in this setting (questionnaire), paper under review
Translations/validations	• Dutch[4] • Under way: Spanish, French, Italian, Chinese
Key test instructions	• Recall time for questionnaire is 2 weeks • Patients should only consider symptoms attributed to MG, not other medical conditions
Other information	• Less floor effect than MG-ADL and MGC [1,4] • Responsive in pure ocular MG, but small cohort, needs more data[2] • Patient-acceptable symptom state (PASS) threshold is ≤10[5]
Areas contributing to lack of standardization	• Administration in clinic vs telemedicine setting • Electronic format vs phone interview for virtual clinic • Instructions for dealing with ≥2 responses marked by patients, and to deal with missing scores

Abbreviations: QMG: quantitative myasthenia gravis score; MGC: myasthenia gravis composite scale, MG-QOL15: myasthenia gravis Quality of Life-15 score

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MGFA Postintervention Status (PIS)[1]

Focus	Clinical state after initiation of treatment
Patient or clinician centric	Clinician
Administration	Clinician skilled in evaluation of neuromuscular disease
# items	8 major categories; Minimal Manifestations has 4 sub-choices
Equipment needed	None
Item scoring	N/A, qualitative
Domains evaluated	N/A, global impression
Time to complete	Less than 5 min
Clinically meaningful change	Qualitative scale, so undefined
Psychometric properties	• Test-retest reliability: N/A • Responsiveness: N/A • Content validity: good from perspective of individual clinical evaluator • Construct validity, correlation with other MG outcome measures: • Limitations: variable/unclear definitions limit usefulness
Virtual visit use	No validation studies, can probably be used
Translations/validations	None published
Key test instructions	Clinicians determine which category patient falls into based on symptoms and MG therapy
Other information	• PROMISE-MG comparative effectiveness study and clinical trials identified several areas contributing to lack of standardization • Used as an exploratory outcome measure in some trials.[2,3] • International consensus guidance for management of MG includes treatment goal of "MGFA PIS classification MM or better, with no more than grade 1 Common Terminology Criteria for Adverse Events (CTCAE) medication side effects".[4]

Areas contributing to lack of standardization	• Unclear if PIS should be determined based on other outcome measures (i.e. QMG), or be used an independent metric.
	  ○ Original description states "criteria for change in the patient's status should be defined in each study protocol based on quantitative assessment of strength in pertinent or sentinel muscles."
	  ○ If based on other metrics, which one(s), and what quantitative change in other metrics is considered significant?[5]
	• Should PIS be assigned as compared to 1) prior to initiation of any therapy, 2) last assessment, 3) worst ever state, 4) prior to initiation of therapy under evaluation in clinical trial?
	• Definitions are not intuitive, require referencing by evaluator, and are subject to disagreement among investigators. Some definitions encompass others, which lead to inconsistencies.
	• Is subclassification of the MM status really necessary and/or significant?

Abbreviations: MGFA-PIS: Myasthenia Gravis Foundation of America Postintervention Status; MM: Minimal Manifestations, QMG: quantitative myasthenia gravis score

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