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POSITION PAPER

Expert consensus recommendations for improving and standardising the assessment of patients with generalised myasthenia gravis

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Abstract

Background: Regular and consistent disease assessment could provide a clearer picture of burden in generalised myasthenia gravis (gMG) and improve patient care; however, the use of assessment tools in practice lacks standardisation. This modified Delphi approach was taken to review current evidence on assessment tool use in gMG and develop expert-derived consensus recommendations for good practice.

Methods: A European expert panel of 15 experienced gMG neurologists contributed to development of this consensus, four of whom formed a lead Sub-committee. The PICO (Population, Intervention, Control, Outcomes) framework was used to define six clinical questions on gMG assessment tools, a systematic literature review was conducted, and evidence-based statements were developed. According to a modified Delphi voting process, consensus was reached when ≥70% of the experts rated agreement with a statement as ≥8 on a scale of 1–10.

Results: Eighteen expert- and evidence-based consensus statements based on six themes were developed. Key recommendations include: consistent use of the Myasthenia Gravis Activities of Daily Living score (MG-ADL) across clinical settings, followed by a simple question (e.g., Patient Acceptable Symptom State [PASS]) or scale to determine patient satisfaction in clinical practice; use of a Quantitative Myasthenia Gravis [QMG] or quality of life [QoL] assessment when the MG-ADL indicates disease worsening; and consideration of symptom state to determine the timing and frequency of recommended assessments. Expert panel consensus was reached on all 18 statements after two voting rounds.

Conclusions: This process provided evidence- and expert consensus-based recommendations for the use of objective and subjective assessment tools across gMG research and care to improve management and outcomes for patients.

KEYWORDS
ADL, consensus, Delphi study, generalised, myasthenia gravis, myasthenia gravis, patient care, QoL

Sub-committee members are listed in the Acknowledgements.

INTRODUCTION

Generalised myasthenia gravis (gMG) is a rare and chronic, immunoglobulin G (IgG)-mediated, neuromuscular autoimmune disease, which causes debilitating and potentially life-threatening muscle weakness [1, 2]. Most patients with myasthenia gravis (MG) first present with ocular symptoms only; however, approximately 80% will have gMG within 2 years of initial disease onset [2]. gMG is classified by degree of muscle weakness, which, along with other symptoms of the disease, may vary greatly among individuals and fluctuate over time [1–6]. This variation in symptoms, combined with infrequent and isolated evaluations, means accurate tracking of symptom state and full comprehension of disease burden is difficult [4–6]. The impact of gMG on patient's lives can therefore be underappreciated [4–6].

In addition, the impact of gMG on key areas of patient health and health-related quality of life (HRQoL) is profound, increasing substantially with increased disease severity [3]. Many patients also continue to experience substantial disease burden while on treatment, and poor HRQoL may persist even if gMG is considered to be well managed [4, 5]. Nonetheless, current measures of impairment have the potential to provide a good score-based measure of the impact of symptoms and treatment on HRQoL in patients, if used consistently [5, 6].

Several scores are currently used to assess the severity of disease in patients with gMG; however, there is no standardisation of assessment approach regarding which scores to use, and when to use them. Existing scores have mostly been developed based on expert opinion of relevant impairments and, therefore, may measure different aspects of the disease [5, 6]. Also, current measures of impairment may not fully reflect the impact of symptoms or adverse events (AEs) from treatment on HRQoL over time, which hampers a holistic understanding of patients' disease burden [5–7]. Therefore, there is a need to standardise assessment approaches in clinical practice to fully understand gMG disease burden and ensure continuity of patient management.

There is also a need to standardise endpoints in clinical trials, where a variety of validated measures of disease severity are currently used [8]. The Myasthenia Gravis Foundation of America (MGFA) classification—although not an outcome measure—has long been used to identify specific subsets of patients for clinical trials and is recommended in this setting, facilitating meaningful comparison of data from trials [9, 10]. While the Quantitative Myasthenia Gravis (QMG) has been recommended to objectively evaluate treatment efficacy [9, 10], there is a current shift in clinical assessment towards tools measuring quality of life (QoL) and patient-reported outcomes [10]. Standardising these endpoints has become increasingly important, particularly as novel assessment scores and treatments have been developed for gMG in the last few decades [11, 12]. Standardisation would ensure physicians have robust clinical evidence and are able to compare different treatment options tested in different trials or through real-world evidence.

Summary points

- Recognising the broad impact of gMG beyond the disease itself reinforces the need for a holistic approach to disease management, from assessment through to follow-up and ongoing care.
- The MG-ADL is a reliable patient-reported scale that can be used at various stages of a patient's gMG disease journey to give a good indication of gMG improvement or worsening and can be followed by other assessments when further evaluation is warranted [18].
- The PASS should follow the MG-ADL to determine patient satisfaction with symptom state and treatment; however, as a simple tool, it can also be used at various other stages of the patient's gMG disease journey.
- Fluctuations in MG-ADL scores can swiftly highlight the need for a QMG or QoL assessment.
- Both the MG-ADL and QMG are validated scores used in clinical trials and observational studies to measure gMG symptoms and response to treatment; however, use of other disease assessment tools should follow when further assessment of HRQoL impact is required [8, 23].
- The Sub-committee recommend careful attention to ocular subscores in assessments such as the MG-ADL and raising questions about changes in vision during consultations to help build a clear picture of disease burden.
- The Sub-committee could not make any recommendations on absolute thresholds for a MCID in assessment tools at this current time, or on how to decide upon retreatment or treatment escalation—understanding of patient- and disease-specific factors should inform treatment decisions and further studies are needed to determine thresholds for a MCID from the perspectives of physicians, patients and caregivers, and to understand whether achieving a MCID in assessment scores translates to satisfaction with scores and symptom control.
- Timing and frequency of gMG assessments should be consistent and reflect the patient's symptom state such that individuals with fluctuating symptoms have more frequent assessment than patients with stable disease.

An expert panel, comprising neurologists experienced in the management of gMG, was convened to review the current evidence about use of patient assessment tools in gMG, propose expert-derived guidance for good practice, and develop a consensus to standardise and improve assessment procedures across Europe, ultimately improving outcomes for patients. Paediatric patients were not specifically considered and the recommendations relate to adults with MG.

METHODS

Convening the Collegium and Sub-committee

A European Collegium, or expert panel—consisting of 21 experienced gMG neurologists from eight European countries (Belgium, Denmark, France, Germany, Italy, Poland, Spain and the UK)—was formed to review the current evidence about use of patient assessment tools in gMG. The Collegium was first convened in October 2021 at a face-to-face meeting in Zurich (organised and funded by argenx SE, Belgium), where the need for a standardised approach to patient assessment in gMG was discussed. Four of the experts formed a Sub-committee to lead this consensus study and a further 11 contributed to the development of the recommendations (Appendix, Table A1).

Setting the clinical questions

The Sub-committee identified six key areas where improvement and standardisation in the assessment of adult patients with gMG could improve outcomes: assessment of disease burden, assessment of depression, anxiety and fatigue, domains not currently assessed by tools, assessment of clinically meaningful thresholds, assessment of treatment-related burden, and assessments supporting treatment decisions.

The following six clinical questions were defined using the Patient, Interventions, Comparator and Outcome (PICO) [13] framework:

1. What are the optimal tools/combination of tools, and optimal frequency, for understanding gMG disease burden in (a) clinical practice, (b) a clinical trial/research setting and (c) a telemedicine setting?
2. What are the general principles/recommendations for incorporating depression, anxiety and fatigue scales in patient assessment?
3. Are there any patient assessment domains (i.e., outcomes or symptoms) that should be captured to assess disease status, but are currently not included in any existing gMG patient assessment tools?
4. What are the thresholds for minimally important/clinically meaningful differences in assessment scores in gMG within clinical practice?
5. How should treatment-related burden be assessed in patients with gMG in clinical practice?
6. How do current gMG assessments support decisions around retreatment or escalation of treatment, and which tools can optimally inform treatment decisions?

Literature search and development of evidence-based statements

Search terms and strings were created to interrogate the questions developed using the PICO framework (Appendix, Table A2) and systematic literature searches, based on Medical Subject Headings (MeSH) terms, were conducted under the supervision of the Sub-committee (Figure 1). Trained medical writers performed the literature search: two writers independently performed the systematic review using the search strings, and a third writer independently adjudicated any discrepancies. The writers assessed the level of evidence for each question using the Oxford Centre for Evidence-based Medicine (OCEM) criteria, and presented these to the Sub-committee in a report which summarised the literature review results and highlighted key findings for each question, study limitations and knowledge gaps. The Sub-committee were provided with full access to all the results and a review meeting was held during which they discussed the evidence alongside their own expert opinions and clinical experience to direct development of draft consensus statements. These were refined by the authors in a follow-up review meeting, prior to being sent for voting.

For each publication, the following information was extracted where applicable into a standardised form: assessment tool/method used or questions asked; the domains captured by the tool (daily living, social, psychological, general symptom satisfaction); patient and physician satisfaction with the tool (i.e., how well it reflects the patient burden); correlation between patient and physician assessment of disease burden; information on practical application of the tool; how anxiety, depression and fatigue were assessed in patients with gMG (e.g., specific scales or general questions from their physician); the extent to which assessment of depression, anxiety or fatigue was captured by the scale/tool; if the tool required physician or patient assessment; outcomes not captured by current tools; whether the tool was used in a clinical trial or clinical practice setting; minimally important/clinically meaningful differences for the tool used; whether the assessment tool/method/questions capture treatment-related burden; and how the tool was used to indicate a need for retreatment/change of treatment. The terms “scales” and “scores” were used synonymously for the measurement tools mentioned, although the term “scores” was more commonly used.

Voting process

Voting on the evidence-based statements was conducted using a modified Delphi consensus voting process. Using Microsoft Forms online, individuals in the Collegium assigned an agreement score between 1 (lowest) and 10 (highest) to each consensus statement in the modified Delphi survey. Each participant was blinded to other votes during the voting process to exclude bias. Consensus was reached when ≥70% of the Collegium gave a statement a rating of 8 or higher, with a rating of 7 or below considered disagreement. Respondents were encouraged to provide rationale if they disagreed with a statement, but this was not mandatory. All authors were provided with full access to all the results and associated commentary following each voting round.

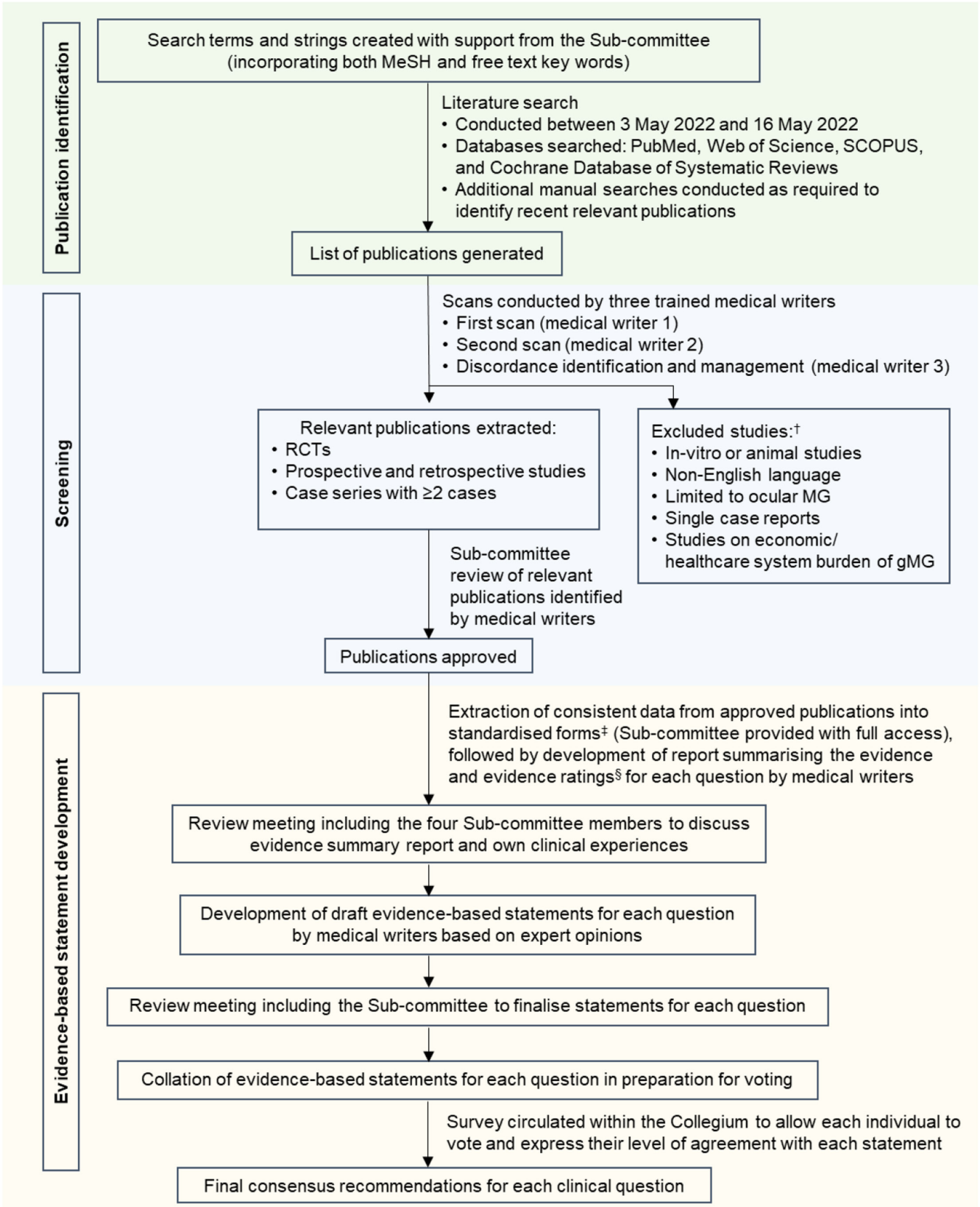

FIGURE 1 Overview of the literature search and evidence-based statement development process. Representation of the publication identification and screening processes and evidence-based statement development. gMG, generalised myasthenia gravis; MeSH, Medical Subject Headings; MG, myasthenia gravis; RCT, randomised clinical trial. †Studies that did not include tools or scores assessing gMG symptoms or disease burden, studies not reporting patient assessment domains or that did not refer to a minimally/clinically important difference in assessment scores were excluded from questions 1, 3 and 4 respectively. ‡ Standardised forms were created to capture information consistently and systematically from relevant publications. §Evidence was rated according to the Oxford Centre for Evidence-based Medicine (OCEM) criteria (https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009).

If consensus was not reached, the statements were discussed and amended by the Sub-committee and voting took place again. If consensus was not reached after a second voting round, the statement was further discussed and amended by the Sub-committee and then a final voting round took place. If no consensus was reached after the third voting round, a lack of agreement would be recorded. This multi-round modified Delphi approach was chosen based on prior work establishing its superiority to Delphi methodology [14], its applicability to the disease setting [15], and its suitability for enabling contribution from the entire expert panel.

RESULTS

The modified Delphi approach generated 18 consensus statements, across the six clinical questions, which were sent to the 21 members of the Collegium for voting. In round one of voting (open for 4 weeks), consensus was reached for 16 of the 18 statements, with responses from 15 members. Six members did not respond to the voting for reasons not disclosed. During the second round of voting (open for 5 weeks), consensus was reached on the two amended statements, with responses from the same 15 members who voted in round one. Detailed results for each question are discussed below.

Assessment of disease burden

Over 1500 articles related to gMG disease burden were screened, with 17 additional articles found through manual searches. Of these, 165 were included in data extraction to support the development of consensus statements on the optimal tools for understanding the disease burden of gMG and how frequently they should be utilised (Appendix, Figure A3). The algorithms for disease burden assessment in clinical practice, clinical trials and telemedicine, based on these consensus statements, are summarised in Figure 2. Here, 'optimal' was defined as how accurately the assessment outcome reflects the real state of disease as assessed by the patient and physician, and includes objective as well as subjective measures of disease.

In clinical practice

Based on clinical evidence and expert opinion, the group derived four statements to help guide optimal tool use and frequency to aid understanding of gMG disease burden in clinical practice (Table 1).

Objective and subjective measures of gMG disease burden are widely used in clinical practice and generally incorporate physical and HRQoL domains, such as in the Myasthenia Gravis Activities of Daily Living score (MG-ADL), QMG and the Revised Myasthenia Gravis Quality of Life 15-item score (MG-QoL-15r) [3, 16, 17]. The

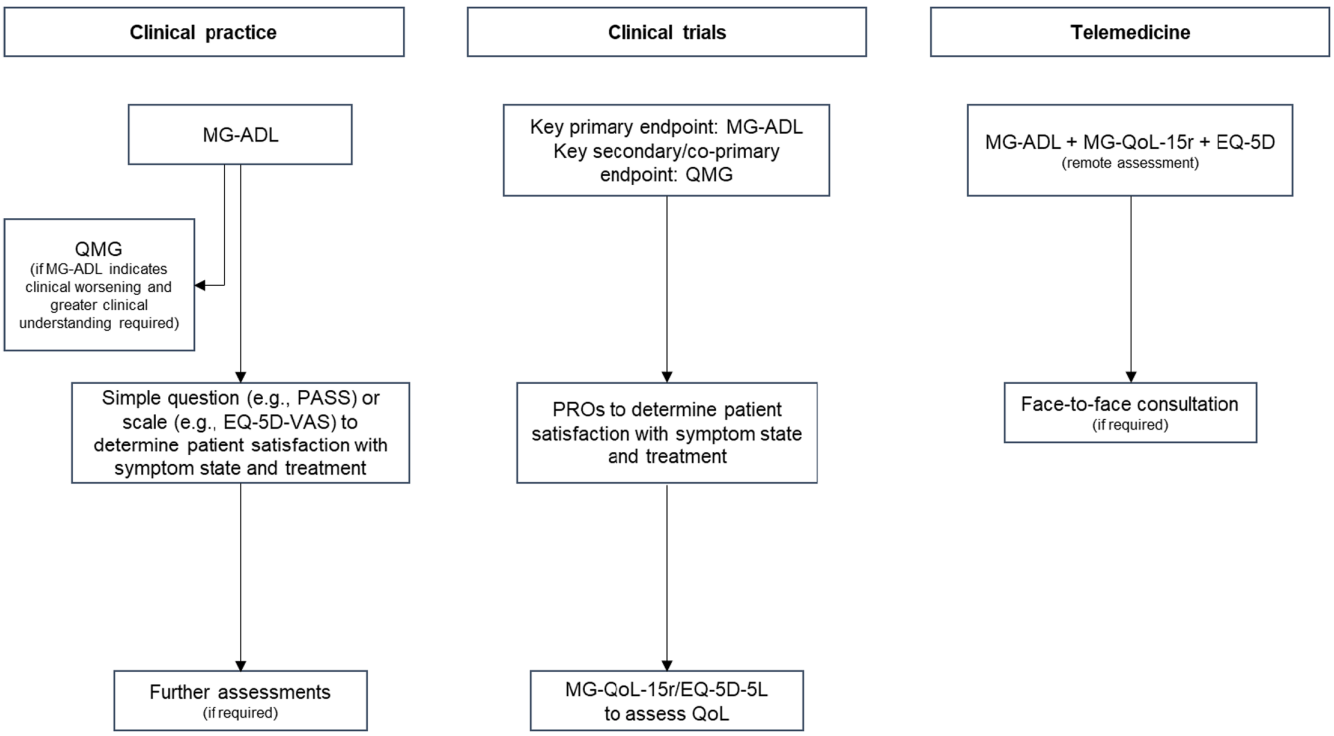

FIGURE 2 Algorithms for disease burden assessment based on consensus recommendations. Recommended approaches for optimal assessment tool use in clinical practice, clinical trials and telemedicine to support understanding of gMG disease burden. EQ-5D, EuroQoL five dimensions; EQ-5D 5 level version, EQ-5D 3 level version; MG-ADL, Myasthenia Gravis Activities of Daily Living score; MG-QoL-15r, Revised Myasthenia Gravis Quality of Life 15-item score; QMG, Quantitative Myasthenia Gravis score; QoL, quality of life; PASS, Patient Acceptable Symptom State; PRO, patient-reported outcome; VAS, visual analogue scale.

TABLE 1 Consensus statements on the assessment of disease burden in clinical practice, clinical research and telemedicine.

Statement	Evidence level and grade	Consensus, % (*n*)
Clinical practice		
Consistent use of the MG-ADL scale should be applied in clinical practice to understand gMG disease burden; if the MG-ADL indicates worsening gMG, the QMG scale can be used to provide greater clinical understanding and support onward decisions.	1a[a]	93.3 (14/15)
	Grade A	
A patient scale, such as the PASS or EQ-5D-VAS, should follow the MG-ADL in clinical practice to determine patient satisfaction with symptom state and treatment and to determine the need for further assessments.	2b	66.7[b] (10/15)
	Grade B	
Revision: It is advised that an additional scale should follow the MG-ADL in clinical practice to determine patient satisfaction with symptom state and treatment; the MG-QoL-15r, PASS or EQ-5D-VAS can be used effectively in this setting.	2b	93.3[c]
	Grade B	(14/15)
In clinical practice, should patients be dissatisfied with their symptom state or treatment, additional outcomes should be explored, such as quality of life, psychological/emotional burden or fatigue, with appropriate assessments.	5	100 (15/15)
	Grade D	
Timing of gMG assessments should reflect the patient's symptom state (i.e., less frequent for stable vs fluctuating symptoms) and guidance for continuing, stopping retreatment or repeating treatment, should be based on clinical evaluation.	5	100 (15/15)
	Grade D	
Clinical research		
The MG-ADL is recommended as the primary endpoint in clinical trials, with the QMG as a co-primary or key secondary endpoint.	1a	93.3 (14/15)
	Grade A	
PROs are recommended to be included for the assessment of patient satisfaction with symptom state and treatment in the clinical trial setting.	1a	93.3 (14/15)
	Grade A	
The MG-QoL-15r or EQ-5D-5L may be used to measure quality of life in clinical trial settings.	2b	100 (15/15)
	Grade B	
Telemedicine		
In telemedicine settings, MG-ADL should be used to assess disease severity and combined with EQ-5D and MG-QoL-15r to assess QoL; the combined results can determine the need and urgency for a face-to-face consultation.	2b[a]	93.3 (14/15)
	Grade B	
Timing of gMG assessments should reflect the patient's symptom state (i.e., less frequent for stable vs fluctuating symptoms) and guidance for continuing, stopping retreatment or repeating treatment should be based on clinical evaluation.	5	100 (15/15)

Abbreviations: EQ-5D, EuroQoL five dimensions; EQ-5D-5L, five-level EuroQoL five dimensions; gMG, generalised myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living score; MG-QoL-15r, revised Myasthenia Gravis Quality of Life 15-item score; QMG, Quantitative Myasthenia Gravis score; QoL, quality of life; PASS, Patient Acceptable Symptom State; PRO, patient reported outcome; VAS, visual analogue scale.

[a]Evidence was from patients with MG, and not gMG specifically.

[b]Consensus not reached after first round of voting; statement was revised.

[c]Consensus reached after revision and second round of voting.

MG-ADL is used in the routine clinical management of gMG, where a two-point improvement since the last patient visit indicates clinical improvement [18]. Of benefit, the MG-ADL is an MG-specific questionnaire that can be self-administered or recorded by the physician, and evidence shows that the MG-ADL is a reliable assessment, independent of whether it is used as a self-administered tool by the patient or recorded by a physician [19]. The MG-ADL provides a good balance between disease evaluation and administration time (approximately 2–3 min) [18], and its consistent use is recommended by the Sub-committee.

The QMG is a more comprehensive measure of disease symptoms than the MG-ADL. In routine practice, however, the Sub-committee

TABLE 2 Consensus statements on the assessment of depression, anxiety and fatigue.

Statement	Evidence level and grade	Consensus, % (*n*)
No specific scales are validated for measuring depression, anxiety and fatigue in the context of gMG at the current time. However, fatigue and fatigability may be measured effectively using the FSS, MFI-20 or CFQ 11; and depression and anxiety may be measured effectively using the PHQ, HADS or MDI.	2b Grade B	80 (12/15)
Comorbidity assessment should include the relevant multidisciplinary team member, such as a psychiatrist for anxiety or depression.	5 Grade D	86.7 (13/15)

Abbreviations: CFQ 11, Chalder Fatigue Scale; FSS, Fatigue Severity Scale; gMG, generalised myasthenia gravis; HADS, Hospital Anxiety and Depression Scale; MDI, Multiscale Depression Inventory; MFI-20, Multidimensional Fatigue Inventory-20; PHQ, Patient Health Questionnaire.

agreed that the QMG takes approximately 30 min to complete, depending on disease severity, and requires specific equipment [20], which makes it difficult to apply to every patient at all stages of treatment. As such the recommendation is if MG-ADL indicates worsening, the QMG score can be used to provide greater clinical understanding and support onward decisions. In addition, the QMG could be used at therapeutic switch to create a baseline for the new treatment and allow physicians to measure clinical response.

A patient-centred approach is important in gMG treatment. Following assessment with MG-ADL, the use of a simple question such as the Patient Acceptable Symptom State (PASS) [21] or a scale (e.g., Revised Myasthenia Gravis Quality of Life 15-item score [MG-QoL-15r] or EuroQoL five dimensions visual analogue scale [EQ-5D-VAS]) [3, 16, 22] to determine patient satisfaction with symptom state and treatment can be used effectively in this setting. We recommend that if the patient is dissatisfied with their symptom state and treatment, additional outcomes should be explored, such as psychological/emotional burden or fatigue, with appropriate assessments.

There is limited consensus in the literature regarding the optimal frequency at which gMG assessment tools should be used. We recommend that timing of gMG assessments reflect the patient's symptom state such that individuals with fluctuating symptoms have more frequent assessment than patients with stable symptoms.

In clinical trials

Three statements were derived for the optimal use of tools in clinical trials (Table 1). The patient-reported MG-ADL measure is often used as a primary endpoint in studies exploring clinical outcomes of gMG treatments, and is frequently complemented by physician assessment with QMG [8, 23]. The consensus recommendation is to use MG-ADL as a primary endpoint with QMG, either as a key secondary or co-primary endpoint, as currently implemented in many ongoing clinical trials.

Patient-reported outcomes (PROs) are an increasingly recognised and important part of understanding the effectiveness of interventions and, as such, are recognised in the consensus statements. For QoL measurements, the MG-QoL-15r (revised Myasthenia Gravis Quality of Life 15-item score) or EQ-5D-5L (five-level EuroQoL five dimensions) can be used [3, 16]. The MG-QoL-15r is specific for MG and the EQ-5D-5L is a generic instrument consisting of a descriptive system and visual analogue scale (EQ-VAS) [3]. Both tools broadly capture HRQoL, but do not fully capture psychological or emotional burden, or fatigue. Fatigue and fatigability scales are seldom used in studies exploring clinical outcomes of treatments and, as such, we were unable to make specific recommendations on these scales.

In telemedicine

Two statements were derived for the optimal use of tools in the telemedicine setting (Table 1). Both objective and subjective measures of gMG disease burden may be captured by patients remotely [24–26]. Online questionnaires and surveys, such as the MG-ADL, MG-QoL-15r and 36-Item Short Form Health Survey (SF-36), incorporate measures of fatigue, physical symptoms and HRQoL [3, 24, 27], with MG-QoL-15r scores obtained by telephone demonstrating consistency with those obtained in the clinic [28]. Patients are also able to perform negative inspiratory force measurement tests at home, which can give a good indication of respiratory strength and function [29].

It was recommended by consensus that in telemedicine settings the MG-ADL should be used to assess disease severity and combined with EQ-5D or MG-QoL-15r to assess QoL; the results can determine the need for face-to-face consultation. Prior studies have established the MG-ADL as a useful tool in telemedicine for MG [30, 31]. Similar to clinical practice, there is limited guidance on optimal frequency of gMG assessment tools in telemedicine according to the literature and, as such, these consensus recommendations centre around the patient's symptom state.

Assessment of depression, anxiety and fatigue

A total of 203 articles were screened relating to fatigue, depression and anxiety scales, with 10 additional articles found through manual searches. In total, 58 of these were included in data extraction; two consensus statements were produced for understanding fatigue, depression and anxiety in patient assessments (Table 2).

Fatigue severity in MG is typically assessed using standardised questionnaires. The Myasthenia Gravis Fatigue Scale (MGFS) was developed as a MG-specific tool; however, it is not consistently used in clinical practice [32]. There is a range of non-specific tools used in the MG field for assessing fatigue, with the Chalder Fatigue Scale (CFQ 11), Multidimensional Fatigue Inventory-20 (MFI-20), Fatigue Severity Scale (FSS) and Fatigue Impact Scale (FIS) among the most common [32].

Evidence from the literature suggest that the FSS and FIS are frequently used to assess the psychological burden of fatigue in patients with MG and are reliable and validated tools, able to discern meaningful clinical aspects of fatigue in MG [32, 33]. A pilot study using the modified FIS to capture the effects of physical therapy and psychology on fatigue management found it to be a useful outcome scale and easy to apply in a research setting [34]. The MFI-20 is a self-reported composite assessment tool consisting of five fatigue domains (general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue) [24]; this tool is multidimensional and can discern between general and physical fatigue, providing a more granular assessment of fatigue compared with FSS that may be more appropriate for clinical research.

Validated assessments for depression and anxiety include Hamilton rating scales, Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS), Multiscale Depression Inventory (MDI) and the SF-36 [32, 35–38]. Few studies report using depression and anxiety scales that patients can use on their own, such as the Centre for Epidemiologic Studies Depression Scale, Self-rating Depression Scale (SDS), Self-rating Anxiety Scale (SAS), and Patient Health Questionnaire (PHQ) [39, 40]. Physicians may find it beneficial to use tools such as the PHQ, which can be completed in less than 3 min [40]. Depression is often associated with fatigue, which can be attributed to an overlap in symptomatology, such as physical fatigue; the HADS excludes physical symptoms and could therefore be useful to overcome this overlap [41]. Both depression/anxiety and fatigue assessments are frequently accompanied by MG-specific assessments (e.g., MG-ADL) to assess disease severity, with positive correlations being demonstrated between fatigue assessments and the MG-ADL [37, 41, 42].

The expert group acknowledged that anxiety and depression could sit outside the medical area of expertise of many gMG-treating physicians and, as such, including an appropriate multidisciplinary team (MDT) member in these assessments would be recommended.

Domains not currently assessed by tools

From the literature search, 65 articles were screened regarding domains not assessed by current tools, with 10 additional articles found through manual searches. Of these, 20 articles were included in data extraction. Three statements reached consensus regarding assessment domains that are not adequately captured by current tools (Table 3).

Currently, widely used and validated assessment tools do not consider the psychosocial impact of gMG on patients, their families and caregivers. The psychological impact of some physical symptoms on patients with gMG, such as ptosis, which can have a profound impact on patients' confidence and self-image [43], was not fully recognised in the included literature or in clinical practice, based on the collective experience of the Sub-committee. Emotional factors may also impact the course of the disease, with higher levels of stress potentially linked to higher MG relapse rates [44].

The Sub-committee agreed there is also a need for a greater understanding of the impact of MG on employment, social life, family members, and any changes on how the roles of family members are perceived by partners, children and friends. In a cross-sectional, multicentre study of 917 Japanese patients with MG, 115 patients (47.1%) experienced a reduction in their total income of more than 50%, 185 (27.2%) were unemployed and 449 (49.0%) reported reduced social positivity and activity [45]. Productivity losses have also been reported among caregivers, with 15.6% needing to cut down their working hours, and 20.8% needing to give up paid employment due to caregiving responsibilities related to MG [46].

Ocular symptoms pose a considerable burden to patients with gMG, as they impact daily activities and QoL [6], which may impair their ability to drive or maintain employment. However, in our clinical experience, full evaluation of ocular symptoms can be time consuming and require specialisation such that obtaining full ocular-specific symptom scores may not be feasible for every patient. Instead, we recommended that ocular item subscores of gMG assessments should be reviewed with careful attention to evaluate specific ocular symptoms in patients.

Assessment thresholds

Only 10 articles were identified and screened that related to thresholds for minimally important or clinically meaningful differences in assessment scores in clinical practice, with no additional articles found through manual searches. Of these, nine articles were included in data extraction and led to the development of two consensus statements for assessing minimally important/clinically meaningful differences in assessment scores (Table 4).

The minimal clinically important difference (MCID), the smallest change in a measure that is meaningful for patients, is necessary for interpretation of change scores [47]. However, there

TABLE 3 Consensus statements on domains not currently assessed by tools.

Statement	Evidence level and grade	Consensus, % (*n*)
There is a need for physician- and patient-administered assessment tools to better understand the practical, psychosocial impact of gMG and its treatment on patients, their families and caregivers.	5 Grade D	100 (15/15)
Although current evidence does not support the use of a specific scale over others to assess fatigability, measures such as the MFI-20 and CFQ 11 scales should be used more consistently to assess the burden and impact of this important symptom in patients with gMG.	2b[a] Grade B	73.3 (11/15)
It is important to ensure full evaluation of ocular symptoms in patients with gMG with the use of ocular-specific symptom scores and scales as they may not be fully assessed by generalised assessment tools.	5 Grade D	66.7[b] (10/15)
Revision: Ocular item subscores of gMG assessments should be reviewed with careful attention to evaluate specific ocular symptoms in patients.	5 Grade D	93.3[c] (14/15)

Abbreviations: CFQ 11, Chalder Fatigue Scale; gMG, generalised myasthenia gravis; MFI-20, Multidimensional Fatigue Inventory-20.

[a]Evidence was from patients with MG, and not gMG specifically.

[b]Consensus not reached after first round of voting; statement was revised.

[c]Consensus reached after revision and second round of voting.

TABLE 4 Consensus statements on assessment thresholds.

Statement	Evidence level and grade	Consensus, % (*n*)
At the current time it is not possible to make recommendations on absolute thresholds for minimally important and clinically meaningful differences in gMG scores as these are heavily dependent on the patient's experience and should be considered relative to baseline assessment scores.	5 Grade D	100 (15/15)
Use of a patient satisfaction scale, such as the PASS or a symptom satisfaction questionnaire, can give an indication of whether changes in symptom state as assessed by a clinician, with a scale such as the MG-ADL, correspond to meaningful changes from the patient's perspective.	2b Grade B	86.7 (13/15)

Abbreviations: gMG, generalised myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living score; PASS, Patient Acceptable Symptom State.

is limited evidence on absolute thresholds for MCID in gMG assessment scores and, as such, the Sub-committee could not reach consensus to form recommendations at this time. There are few studies reporting minimal clinically important differences for outcome measures; a two-point improvement in MG-ADL or a three-point improvement in QMG was used in the ADAPT study [11], while in the CHAMPION study, the MCID was considered to be a five-point improvement in QMG [12]. However, PASS or MCID may help to inform disease state in patients with MG, with thresholds for acceptable symptom state (PASS-positive status)

using QMG, MG-ADL and MG-QoL-15 reported as ≤7, 2 and 8 points, respectively [21].

In research settings, minimal symptom expression (MSE), defined as an MG-ADL total score of 0–1 or MG-QoL-15 total score of 0–3, is a strong, clinically meaningful endpoint [48]. In recent trials of newer gMG treatments, such as the CHAMPION and REGAIN clinical trials, MCID was primarily measured by a three-point change in the MG-ADL score, while in the ADAPT trial an MSE of 0–1 was used [8, 11, 12]. Of note, patients may fail to achieve these endpoints but still achieve significant reductions in MG-ADL or QMG scores that are clinically meaningful. As such, absolute changes should be considered alongside the MSE or MCID threshold [48]. There remain discrepancies between physician- and patient-assessed scores as clinically meaningful improvements in one do not necessarily align to improvements in the other, and this should be explored.

Assessment of treatment-related burden

From the literature search, 301 articles for the assessment of treatment-related burden in clinical practice were screened, with five additional articles found through manual searches. In total, 19 articles were included in data extraction, with the Sub-committee reaching consensus on one statement regarding the assessment of treatment-related burden in clinical practice (Table 5).

Several studies report on the lived experience of patients with MG and the short- and long-term toxicities associated with treatment [49–52], and identify patient anxiety and frustration around treatment and treatment inertia due to potential treatment-related adverse events (TRAEs) [53]. However, there are currently no scales that measure TRAEs, such as cholinergic effects from acetylcholinesterase inhibitors, or AEs associated with steroid therapy or steroid withdrawal. Nor are there any scales to enable differentiation of TRAEs from gMG-related symptoms (e.g., cholinergic muscle spasms vs gMG-attributable muscular dysfunction). Despite the lack of scales measuring TRAEs, we recommend that proactive and routine AE assessment and recording can ensure detailed understanding of treatment safety and help facilitate treatment decisions.

Assessments supporting treatment decisions

A total of 413 articles were screened, with no additional articles found through manual searches, and 31 were included in data extraction. One consensus statement was developed to inform decisions around retreatment and treatment escalation (Table 6).

Important considerations with respect to retreatment or treatment escalation include but are not limited to: clinical assessment, with a score such as the MG-ADL; change in symptom score; comorbidities and health beyond gMG; adverse events; changes in steroid use/dose; and patient satisfaction [15, 54, 55]. Based on the consensus recommendation, validated gMG assessments, such as the MG-ADL and QMG scores, may be used to assess disease severity and monitor treatment response; however, scores must not be used in isolation and the patient's experience must be taken into consideration when using these gMG assessments to inform treatment decisions.

DISCUSSION

The impact of gMG on patients' lives is profound and goes beyond the disease state itself [56–58]. Indeed, comorbidities, treatment-related burden and poor psychological wellbeing can have serious implications for patients' employment, social interactions and family life, and the burden on caregivers and family members is becoming increasingly apparent [56–58]. We recognised the broad impact of gMG, resulting from the variety of symptoms observed and the fluctuation in symptoms over time, and, in developing these consensus statement, have reinforced the need for a holistic approach to disease management, from assessment through to follow-up and ongoing care.

TABLE 5 Consensus statements on assessment of treatment-related burden.

Statement	Evidence level and grade	Consensus, % (*n*)
There are currently no appropriate scales to measure the adverse event, psychological or practical burden associated with gMG treatment, or to differentiate treatment-related adverse events from gMG-related symptoms; however, treatment-related adverse event burden can be assessed through longitudinal measurement of objective parameters, such as frequency, and the use of toxicity indices in conjunction with MG-specific assessments of MG burden.	2b[a] Grade B	80 (12/15)

Abbreviations: gMG, generalised myasthenia gravis; MG, myasthenia gravis.

[a]Evidence was from patients with MG, and not gMG specifically.

TABLE 6 Consensus statement to inform treatment decisions.

Statement	Evidence level and grade	Consensus, % (*n*)
Multiple disease, patient and treatment-related factors, including the patient's preferences, need to be considered when defining treatment goals and making therapeutic decisions in gMG; therefore, a general recommendation on how to decide upon retreatment or treatment escalation is not appropriate.	5 Grade D	86.7 (13/15)

Abbreviations: gMG, generalised myasthenia gravis.

PROs may help provide an accurate representation of relevant impairments and their impact on patients' HRQoL over long periods of time. As a result, we strongly advised that the MG-ADL is used consistently across all clinical settings. The MG-ADL is a reliable outcome measure that can be used at various stages of a patient's journey with gMG to give a good indication of gMG improvement or worsening [18], and can be followed by other assessments when further evaluation is warranted. Additionally, the frequency of MG-ADL use can be at the physician's discretion or based on clinical judgement.

Since the MG-ADL can be accurately recorded by the patient, it has applications in telemedicine [18, 19], which is becoming increasingly important given the recent global COVID-19 pandemic. Although there has been no formal validation of the MG-ADL in telemedicine for MG, recent work has come close to validating the MG-ADL in this setting; in this study, only a suitable digital device (e.g., smartphone, tablet) was needed to capture MG-ADL scores and complete formal validation [19]. If digitalised, training could be provided to enable patients to complete the assessment on their smartphone, which they would be able to do more regularly (e.g., on a weekly basis). As a simple tool, the PASS could also be completed remotely following the MG-ADL to determine patient satisfaction with symptom state and treatment; however, it can also be used at various other stages of a patient's journey with gMG [23]. Despite the QMG being a more comprehensive and subjective measure of disease severity, the MG-ADL is quicker to perform and can be performed remotely [17, 18], swiftly highlighting the need for the QMG or a QoL assessment.

Both the MG-ADL and QMG are validated outcomes used in clinical trials and observational studies and, as regulatory authorities are recommending that PROs are evaluated, the MG-ADL is becoming more popular as a primary outcome measure [8, 11, 12, 23]. Since most ongoing Phase III clinical trials use the MG-ADL as a primary endpoint [8], we agreed that this score is useful for allowing trial results to be put into perspective against real-world data. It is important to note that the MG-ADL and QMG do not cover all patient assessment domains and may not provide a complete picture of disease burden; we therefore recommended that use of these measures should be followed with other disease assessment tools, when required. A recent consensus study noted a lack of standardisation in the performance of outcome measures in gMG, including the MG-ADL and QMG, which could confound certain results from such assessments [59]. The study recommended some changes to outcome measure instructions—for example, instructing patients not to leave any items blank when completing the MG-ADL assessment—to help improve standardisation, with some modifications to specific instruments [59]. The recommendations from this study would require further assessment for validation and broader implementation.

The use of PASS or other similar assessments, such as the single simple question or EQ-5D VAS [22, 60], can give an indication of whether changes in symptom state assessed by a clinician, with a score such as the MG-ADL, correspond to meaningful changes from the patient's perspective and may help to improve the correlation between patient and physician assessment of gMG disease burden. The PASS can be formulated specifically for a patient with MG, and measures holistic satisfaction with the MG condition based on a dichotomous "yes" or "no" response, for example: "Considering all the ways you are affected by myasthenia, if you had to stay in your current state for the next months, would you say that your current disease state status is satisfactory?" [4, 60]. Based on further discussion, the Sub-committee agreed that it is important for the patient and physician to understand if any dissatisfaction is due to the disease, the treatment or another factor. With the PASS, the Sub-committee agreed it is also important to consider appropriate language translation and personal interpretation of the question when understanding the patient's response.

Measures of HRQoL can be useful in quantifying the impact of MG on patients' lives and MG-QoL scores in particular can allow clinicians to follow groups of individuals over time, such as may be required in clinical research. The MG-QoL-15 is a shorter version of the MG-QoL-60 and has been demonstrated to correlate as highly as the MG-QoL-60 to disease-specific scores such as the MG-ADL, QMG and MGC, despite fewer questions [5]. As such, the MG-QoL-15 is widely used in the clinic, and has been translated and modified for use in multiple languages [22]. The modified version (MG-QoL-15r) is also frequently used and has demonstrated better psychometric properties than the original version [22].

It is worth noting that MCIDs are yet to be established for the MG-QoL-15r [12]. More generally, we could not make any recommendations on absolute thresholds for a MCID in assessment tools at this current time, particularly because endpoints and associated MCIDs in clinical trials vary [61, 62]. The appropriate threshold for

a MCID can also differ between physician and patient perspectives. Indeed, individual changes from baseline, which do not necessarily meet a preset threshold, might still reflect an important change for the patient. Future studies should therefore incorporate perspectives of physicians, patients and caregivers to enable meaningful differences—in domains such as the psychological burden of gMG, symptom improvement, responsiveness to specific treatments, and the steroid-sparing effect of new treatments—to be defined. This will consequently enable thresholds for a MCID to be clearly determined.

We noted that the assessment and management of psychological and emotional burden in patients with gMG is an important entity of care that potentially sits outside the medical area of expertise of gMG-treating physicians. There is an array of useful and validated non-MG specific assessment tools that should be used to examine psychological aspects of gMG [35–40]. Many can be self-administered (e.g., PHQ and HADS) [40] and therefore used in a telemedicine setting, but they may not fully capture the impact of mood disorders on patients and the psychological impact of certain physical symptoms, such as ptosis. As such, the Sub-committee agreed it may be necessary for a member of the MDT with appropriate expertise, such as a psychiatrist or specialist nurse, to be involved in psychological assessments and subsequent clinical decisions.

For measures of fatigue and fatigability, it is important to consider that, unlike depression/anxiety scales, it might be useful for novel MG-specific scales to be developed and validated. Fatigue can be measured independently from muscle weakness and is an important symptom of worsening HRQoL [37]. Furthermore, fatigability can result in disability if it causes patients to take longer to complete tasks, thus limiting activities of daily living [6]. Although the MGFS has shown high test–retest reliability, measures of fatigue and fatigability that have been specifically validated in MG are sparse and not consistently used in clinical practice or trial settings [32]. Most studies include patient-reported questionnaires that assess clinically relevant fatigue with a known cut-off point; however, there is minimal insight on which questionnaire is most appropriate to assess fatigue in gMG. While current evidence does not support the use of a specific scale over others, we agreed that measures such as the MFI-20, FSS and CFQ 11 could be used more consistently to assess the burden and impact of this important symptom in patients with gMG. Although the MFI-20 provides a more detailed assessment of fatigue than the FSS, which may be useful, further evidence for the use of these scales is needed. We acknowledge that the PROMIS fatigue tool is an outcome measure being used in some ongoing and recently completed trials in MG [62, 63]; however, to answer the PICO question defined, this particular search was performed to explore the measures of fatigue being used in routine patient assessment as opposed to MG clinical trials. Physicians may also find it more practical to use scales that are patient-reported or self-administered.

Ocular symptoms of gMG can be highly impactful, negatively affecting patients in ways not fully recognised in the literature or clinical practice [43]. We noted that changes in ocular symptoms may not be captured with sufficient accuracy by current scores. This is also the case for limb weakness assessment, which may not accurately capture distal hand weakness. We therefore recommended careful attention to ocular subscores in assessments such as the MG-ADL and raising questions about changes in vision during consultations to help build a clear picture of disease burden. If ocular symptoms are severe, referral to an orthoptist or neuro-ophthalmologist should also be considered.

With the emergence of novel therapies for MG in recent years, clinical trials including patients with MG should use endpoints consistently to ensure comparability between study drugs and reference values. Available evidence for new immunomodulatory therapies demonstrates clinically meaningful benefits for patients, including improvements in HRQoL with efgartigimod [64], reductions in exacerbations, hospitalisations and rescue therapy with eculizumab [65], and improvements in symptoms with ravulizumab [66]. With these new observations, similar data for other gMG treatments are needed to allow physicians to compare treatment burden and outcomes across agents. Studies assessing treatment burden were mainly associated with older, broadly immunosuppressive therapies and acetylcholinesterase inhibitors; there was a general lack of information on the burden associated with newer therapies, possibly because of the relative novelty of some emerging drug classes. Nevertheless, the Sub-committee highlighted the need for data on longitudinal assessment of treatment burden and burden associated with newer therapies, ideally comparing them with older, more established therapies in the gMG treatment paradigm.

Although a general recommendation on how to decide upon retreatment or treatment escalation is not appropriate, the Sub-committee agreed that understanding properties of the treatment—speed of response, for example—overall disease burden, and variability in patient scores at different times of the day is important for determining the timing of assessments in clinical practice. It is important to consider how possible variations in assessment timing may affect results and, consequently, treatment decisions. The most appropriate process for assessing outcomes should be determined and any treatment change can then be evaluated based on observations made about timing.

CONCLUSIONS

In summary, the Sub-committee was able to reach a consensus on all 18 statements explored and concluded that it is critical to consistently incorporate subjective and objective measures of gMG severity and disease burden across the continuum of care to improve outcomes for patients. This consensus provides recommendations for the use of assessment tools at multiple stages of the patient journey with gMG. Based on their expert clinical experience, the Sub-committee agreed that frequency and timing of gMG assessments should reflect the patient's symptom state and that a holistic approach should be adopted to address the broad impact of gMG beyond the disease state itself.

AUTHOR CONTRIBUTIONS

Andreas Meisel: Conceptualization; data curation; methodology; investigation; writing – review and editing; visualization; supervision. **Francesco Saccà:** Conceptualization; data curation; methodology; investigation; supervision; visualization; writing – review and editing. **Jennifer Spillane:** Conceptualization; data curation; investigation; methodology; supervision; visualization; writing – review and editing. **John Vissing:** Conceptualization; data curation; investigation; methodology; visualization; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors confirm that there are no conflicts of interest in connection with this article and provide the following statement of disclosures for transparency.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

DISCLOSURES

Professor Meisel is an advisor, consultant, investigator and/or speaker and has received grants (paid to institution) and honoraria from Alexion, argenx, Axunio, Grifols, Hormosan, Janssen, Merck, Octapharma and UCB. He serves as chairman of the medical advisory board of the German Myasthenia Gravis Society. Professor Saccà received public speaking honoraria from Alexion, argenx, Biogen, Mylan, Novartis, Roche, Sanofi and Teva; he also received compensation for advisory boards or consultation fees from Alexion, Almirall, argenx, Avexis, Biogen, Forward Pharma, Lexeo Therapeutics, Merk, Novartis, Novatek, Reata, Roche, Sanofi and Takeda; he is principle investigator in clinical trials for Alexion (argenx); Immunovant (Novartis) and Prilenia (Sanofi) (ORCID: 0000–0002–1323-631). Dr Spillane has received compensation for advisory boards and travel compensation from argenx and UCB and has received public speaking honoraria for argenx (ORCID: 0000–0002–9339-0938). Professor Vissing has acted as advisory board consultant or speaker for Amicus Therapeutics, argenx BVBA, Arvinas, Atamyo Therapeutics, Biogen, Dyne Therapeutics, Fulcrum Therapeutics, Horizon Therapeutics, Lupin, ML Biopharma, Novartis Pharma AG, Regeneron, Roche, Sanofi Genzyme, Sarepta Therapeutics, UCB Biopharma SPRL and Zogenix, and received research grants, travel support and/or speaker fees from Alexion, AstraZeneca Rare Disease; Edgewise Therapeutics; Fulcrum Therapeutics; Sanofi Genzyme; and UCB Biopharma SPRL (ORCID: 0000–0001–6144-8544).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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