

Myasthenia Gravis: Recommendations for Clinical Research Standards

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The need for universally accepted classifications, grading systems, and methods of analysis for patients undergoing therapy for MG is widely recognized and is particularly needed for therapeutic research trials. The Medical Scientific Advisory Board (MSAB) of the Myasthenia Gravis Foundation of America (MGFA) formed a Task Force in May 1997 to address these issues. Initially, the Task Force planned to develop classifications and outcome measures pertaining only to standardizing thymectomy trials. However, it quickly became apparent that their efforts should apply to all therapeutic trials for MG, and thus the scope of the mission was expanded.

During the development of these recommendations, the Task Force faced numerous dilemmas for which no universally satisfactory solution was available. Dilemmas were defined as "situations that require one to choose between two equally balanced alternatives or predicaments that seemingly defy satisfactory solutions." The Task Force members agreed at the outset, however, that their primary goal was to develop a uniform set of classifications to be used in the comparative analysis of the various therapeutic interventions for MG. With this as the primary goal, a consensus was gradually developed. In developing a consensus, at least two meetings were held each year during a 3-year period. Between meetings there was exchange of all proposals by electronic and surface mail, consultation with national and international experts in the field, critical analysis of all proposals, and many revisions. All conflicts (both minor and major) were resolved by vote. Virtually all issues were eventually approved unanimously; a few received a plurality of six.

This report presents the work of the Task Force and proposes classification systems and definitions of re-

sponse to therapy designed to achieve more uniformity in recording and reporting clinical trials and outcomes research. Although designed primarily for research purposes, we think physicians may find some of the recommendations useful in the clinical management of patients with MG.

MGFA Clinical Classification

This classification (Table 1) is designed to identify subgroups of patients with MG who share distinct clinical features or severity of disease that may indicate different prognoses or responses to therapy. It should not be used to measure outcome. It defers quantitative assessment of muscle weakness to the more precise Quantitative MG Score for Disease Severity, defers response to therapy to the MGFA Postintervention Status and the Quantitative MG Score, and defers the status of medication to the Therapy Status classification.

The fluctuating extent and severity of MG, and the variable predominance of the muscle groups involved, makes it extremely difficult to classify these patients. Most existing classifications are modifications of Osserman's [1], separating patients with purely ocular involvement from those with generalized weakness, and further separating those with mild, moderate, or severe generalized weakness. Osserman classifications have included categories based on the course of the disease, such as "acute fulminating" and "late severe," and at times also included categories for muscle atrophy and childhood onset. Experienced clinicians have devised other classifications to monitor response to treatment, some based on the degree of disability or age at onset, and others that include quantitative measurements of specific muscle function, such as arm abduction time and vital capacity.

In general, these classifications use subjective assessments and lack quantification. What one physician may regard as "mild," another might regard as "moderate" or "severe." Furthermore, some experienced clinicians believe that oropharyngeal involvement is more dangerous, and perhaps different than limb weakness, and thus should be identified by the classification system. Some

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Table 1. MGFA Clinical Classification

Class I	Any ocular muscle weakness May have weakness of eye closure All other muscle strength is normal
Class II	Mild weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity
IIa	Predominantly affecting limb, axial muscles, or both May also have lesser involvement of oropharyngeal muscles
IIb	Predominantly affecting oropharyngeal, respiratory muscles, or both May also have lesser or equal involvement of limb, axial muscles, or both
Class III	Moderate weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity
IIIa	Predominantly affecting limb, axial muscles, or both May also have lesser involvement of oropharyngeal muscles
IIIb	Predominantly affecting oropharyngeal, respiratory muscles, or both May also have lesser or equal involvement of limb, axial muscles, or both
Class IV	Severe weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity
IVa	Predominantly affecting limb and/or axial muscles May also have lesser involvement of oropharyngeal muscles
IVb	Predominantly affecting oropharyngeal, respiratory muscles, or both May also have lesser or equal involvement of limb, axial muscles, or both
Class V	Defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

feel that "crisis" (respiratory insufficiency necessitating intubation and assisted ventilation) is the result of coincidental infection or other stress in susceptible patients, whereas others regard crisis as defining the ultimate in disease severity.

The Task Force discussed these issues at length, and the members think that a uniform classification is necessary if meaningful comparison of data is to be achieved. The Task Force sees no alternative but to accept the inherent imprecision of a clinical classification, and it recommends that the MGFA Clinical Classification be used to supplement or to replace the classifications now in use. It also recommends that the most severely affected muscles be employed to define the patient's Class and that the "maximum severity" designation be used to identify the most severe pretreatment clinical classification status. The "maximum severity" designation may be made historically and is employed as a point of reference. The maximum severity remains the point of reference

thereafter, with any worsening of the MG being reflected in the postintervention status determination.

The Quantitative MG Score for Disease Severity

A quantitative MG scoring system (QMG Score) is essential in the objective evaluation of therapy for MG. This scoring system is based on quantitative testing of sentinel muscle groups. The QMG Score should be used in conjunction with the Clinical Classification and the Postintervention Status. It does not replace the clinical evaluation of the patient and should not be used to compare severity between patients. To assess the effect of treatment, the QMG Score should be determined before beginning the treatment under study and at appropriate intervals thereafter. As with all patient evaluations, the time of the examination in relation to therapy, and the presence of factors that may alter the clinical course, should be recorded.

The Task Force recommends that a QMG Score be used in all prospective studies of therapy for MG. The specific scoring system recommended (Table 2) [2] is a modification of earlier systems developed for this purpose [3-6]. Its interexaminer reliability has been confirmed. A manual and a demonstration video of this system are available from the MGFA [7].

The Task Force encourages proposals to improve and validate this quantitative scoring system and specifically recommends that studies be performed to determine the value of "weighting" certain subscores of the QMG score (oropharyngeal and respiratory muscle weakness, for example). As it now stands, a patient can have an improved total score but be incapacitated by poor strength in one or two areas. The evaluation and addition of other objective means of testing muscle strength is also recommended. This includes the use of a hand-held dynamometer, the time taken to swallow a fixed volume of liquid [8], oral muscle function assessment [9], the measurement of respiratory muscles forces [10], and objective functional tests in children.

MGFA Therapy Status

The MGFA Therapy Status (Table 3) defines the treatment regimen of the patient at a given time and is most useful when used with the MGFA Postintervention Status. The Therapy Status, at any point in time, is defined by using a single designation or a combination of the designations. In addition, the duration of this status, the current doses of all pertinent medications, and the schedule of plasma exchanges and IV immunoglobulin (Ig) should be recorded.

MGFA Postintervention Status

The Postintervention Status (Table 4) is designed to assess the clinical state of MG patients at any time after institution of treatment for MG. Use of this classification requires that specific forms of therapy be recorded separately in the Therapy Status section.

Table 2. Quantitative MG Score for Disease Severity

Test Item	None	Mild	Moderate	Severe	Score
Grade	0	1	2	3	
Double vision on lateral gaze right or left (circle one), seconds	61	11-60	1-10	Spontaneous	
Ptosis (upward gaze), seconds	61	11-60	1-10	Spontaneous	
Facial muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete	
Swallowing 4 oz water (½ cup)	Normal	Minimal coughing or throat clearing	Severe coughing/choking or nasal regurgitation	Cannot swallow (test not attempted)	
Speech after counting aloud from 1 to 50 (onset of dysarthria)	None at 50	Dysarthria at 30-49	Dysarthria at 10-29	Dysarthria at 9	
Right arm outstretched (90 degrees sitting), seconds	240	90-239	10-89	0-9	
Left arm outstretched (90 degrees sitting), seconds	240	90-239	10-89	0-9	
Vital capacity, % predicted	≥ 80	65-79	50-64	<50	
Rt-hand grip, kgW					
Men	≥ 45	15-44	5-14	0-4	
Women	≥ 30	10-29	5-9	0-4	
Lt-hand grip, kgW					
Men	≥ 35	15-34	5-14	0-4	
Women	≥ 25	10-24	5-9	0-4	
Head lifted (45 degrees supine), seconds	120	30-119	1-29	0	
Right leg outstretched (45 degrees supine), seconds	100	31-99	1-30	0	
Left leg outstretched (45 degrees supine), seconds	100	31-99	1-30	0	
Total QMG score (range, 0-39) _____					

The criteria defining the Postintervention Status require that the patient be examined by someone skilled in the evaluation of neuromuscular disease. 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. What constitutes a sustained

substantial change in medication should also be defined specifically in each study protocol. Composite analysis ("bundling") of postintervention categories is discouraged because it circumvents the goal of response-specific analysis. However, if composite analysis is employed, the individual categories should also be analyzed. Pending further study, it is recommended that treatment and strength be stable for at least 3 months as a baseline before beginning prospective studies. If the patient has attained CSR, PR, or MM status, the change in status should be indicated as well.

Isolated weakness of eyelid closure was thought not to be a sign of active disease and therefore was not considered an exclusionary criteria from CSR or PR status. In contrast, patients receiving cholinesterase inhibitors are excluded from PR and MM-1 status because these medications mask myasthenic symptoms.

Grouping by Age, Sex, Race, and Geography

The sex, race, age at onset, and geographic distribution of patients may be important variables in assessing response to treatment of MG [11, 12]. Accordingly, these variables

Table 3. MGFA MG Therapy Status

NT	No therapy
SPT	Status post-thymectomy (record type of resection)
CH	Cholinesterase inhibitors
PR	Prednisone
IM	Immunosuppression therapy other than prednisone (define)
PE(a)	Plasma exchange therapy, acute (for exacerbations or preoperatively)
PE(c)	Plasma exchange therapy, chronic (used on a regular basis)
IG(a)	IVIg therapy, acute (for exacerbations or preoperatively)
IG(c)	IVIg therapy, chronic (used on a regular basis)
OT	Other forms of therapy (define)

Table 4. MGFA Postintervention Status

Complete Stable Remission (CSR)	The patient has had no symptoms or signs of MG for at least 1 year and has received no therapy for MG during that time. There is no weakness of any muscle on careful examination by someone skilled in the evaluation of neuromuscular disease. Isolated weakness of eyelid closure is accepted.
Pharmacologic Remission (PR)	The same criteria as for CSR except that the patient continues to take some form of therapy for MG. Patients taking cholinesterase inhibitors are excluded from this category because their use suggests the presence of weakness.
Minimal Manifestations (MM)	The patient has no symptoms of functional limitations from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of CSR or PR do have weakness that is only detectable by careful examination.
MM-0	The patient has received no MG treatment for at least 1 year.
MM-1	The patient continues to receive some form of immunosuppression but no cholinesterase inhibitors or other symptomatic therapy.
MM-2	The patient has received only low-dose cholinesterase inhibitors (< 120 mg pyridostigmine/day) for at least 1 year.
MM-3	The patient has received cholinesterase inhibitors or other symptomatic therapy and some form of immunosuppression during the past year.
Change in Status	
Improved (I)	A substantial decrease in pretreatment clinical manifestations or a sustained substantial reduction in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific decrease in QMG score.
Unchanged (U)	No substantial change in pretreatment clinical manifestations or reduction in MG medications as defined in the protocol. In prospective studies, this should be defined in terms of a maximum change in QMG score.
Worse (W)	A substantial increase in pretreatment clinical manifestations or a substantial increase in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific increase in QMG score.
Exacerbation (E)	Patients who have fulfilled criteria of CSR, PR, or MM but subsequently developed clinical findings greater than permitted by these criteria.
Died of MG (D of MG)	Patients who died of MG, of complications of MG therapy, or within 30 days after thymectomy. List the cause (see Morbidity and Mortality table).

should be identified in all studies and their effect on response to treatment should be evaluated.

At this time, definitions of the age limits of childhood, adolescence, or onset of puberty have not been universally accepted or applied [11, 13]. Appropriate age subdivision in children needs to be defined for universal use. Until such time as these age groups can be agreed on, it is recommended that age grouping occur by decade (ie, up to 10 years, 11 to 20 years, 21 to 30 years, etc).

Thymic Pathology

There are no comprehensive guidelines for the evaluation of the nonthymomatous thymus removed from patients with MG. Incomplete and variable sampling techniques [14] and the lack of comprehensive diagnostic guidelines may account for the conflicting reports regarding the relationship between the histologic changes in the thymus and the response to thymectomy.

To determine the prognostic and therapeutic importance of pathologic changes in the thymus removed during thymectomy, uniform criteria for specimen management, sampling techniques, criteria for the diagnosis of hyperplasia and involution, characterization of immunocytochemical changes, and other determinants need to be defined and standardized [12, 15, 16].

The histologic classification and grading of thymic neoplasms, including the identification of noninvasive

and invasive thymomas, other neoplasms of the thymus, and their relation to MG results, also need to be standardized [15, 17-24]. Patients with thymoma undergoing thymectomy for MG should be analyzed separately from those without thymoma, because combining these patient cohorts has made it difficult to determine whether the presence of a thymoma, even when noninvasive, alters the prognosis.

The Task Force recommends that the multiple issues involved be addressed with the development of guidelines for the evaluation of the nonthymomatous thymus in MG and a universally acceptable single classification of thymic neoplasms.

MGFA Thymectomy Classification

Multiple techniques are described for removal of the thymus in MG. The debate regarding which technique is preferable is not resolved. Although, classically, "total thymectomy" is considered the goal of surgery, it has not been demonstrated unequivocally that this is necessary, nor is it clear that all the resectional techniques do achieve this goal.

To resolve the issues regarding the choice of thymectomy technique and whether there is a relationship between the resectional technique employed and the rate of remission and improvement, the type of thymic resection used needs to be defined in as objective terms as

Table 5. Thymectomy Classification

T-1	Transcervical Thymectomy
	(a)-Basic
	(b)-Extended
T-2	Videoscopic Thymectomy
	(a)-"Classic"
	(b)-"VATET"
T-3	Transsternal Thymectomy
	(a)-Standard
	(b)-Extended
T-4	Transcervical & Transsternal Thymectomy

possible. In addition, multiple resectional techniques should not be reported as a single cohort.

The Thymectomy Classification (Table 5) is based on published reports. The techniques are grouped according to the primary approach (transcervical, videoscopic, transsternal, or combinations) and are described briefly. Referenced reports are recommended for details. Because, within each category, there may be variations in the extent of the resection from surgeon to surgeon, the extent of the resec-

tion for each patient cohort must be recorded. In all prospective studies it is recommended that detailed descriptions of the operative technique be supplied, accompanied by drawings and photographs of typical specimens. Ideally, a video of the technique should also be available.

At this time, two types of transcervical thymectomy are performed. The "Basic" resection employs an intracapsular extraction of the mediastinal thymus via a cervical incision and is limited to the removal of the central cervical-mediastinal lobes (Figure 1, A and B). No other tissue is removed in either the neck or the mediastinum [25, 26]. The original "Extended" resection employs a special manubrial retractor for improved exposure of the mediastinum. The mediastinal dissection is extracapsular and includes resection of the visible mediastinal thymus and fat. Sharp dissection may or may not be performed on the pericardium. The neck exploration and dissection varies in extent and may or may not be limited to exploration and removal of the cervical-mediastinal extensions [27, 28]. Variations include the addition of a partial median sternotomy [29] and the associated use of mediastinoscopy [30].

A number of variations in videoscopic technique are

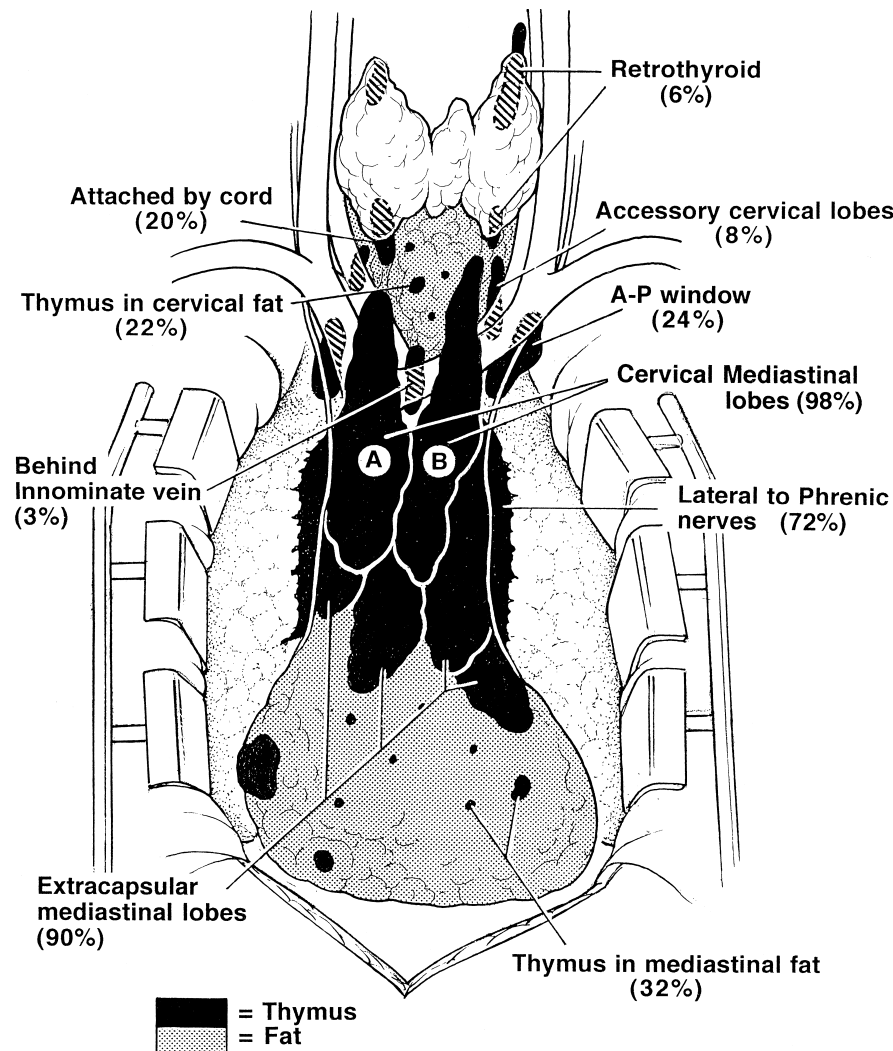


Fig 1. Anatomy of the thymus. This illustration represents what is now generally accepted as the surgical anatomy of the thymus [41]. The frequencies (percent occurrence) of the variations are noted. Black = thymus; gray = fat that may contain islands of thymus and microscopic thymus. A-P window = aorto-pulmonary window. Source: Neurology 1997;48(suppl 5):S52-S63.

being developed to assist in the performance of a thymectomy. The "Classic" video-assisted thoracic surgery (VATS) technique employs unilateral videoscopic exposure of the mediastinum (right or left) with removal of the grossly identifiable thymus and variable amounts of anterior mediastinal fat. The cervical extensions of the thymus are usually removed from below [31, 32]. The Video-assisted Thoracoscopic Extended Thymectomy (VATET) employs bilateral thoracoscopic exposure of the mediastinum for improved visualization of both sides of the mediastinum. Extensive removal of the mediastinal thymus and perithymic fat is described, the thymus and fat being removed separately. A cervical incision is performed with removal of the cervical thymic lobes and pretracheal fat [33].

There are several variations to the Transsternal Thymectomy approach. The "Standard" technique was originally designed to remove the well-defined central cervical-mediastinal lobes. At this time, although a complete or partial [34-36] sternotomy may be performed, the resection is more extensive than originally described, with removal of all visible mediastinal thymus. Mediastinal fat, varying in extent, may or may not be removed. The cervical extensions of the thymus are removed from below, with or without some adjacent cervical fat. Variations of this technique include a video-assisted technique using a complete median sternotomy via a limited lower sternal transverse skin incision [37]. The "Extended" [38] procedure is also known as Aggressive Transsternal Thymectomy [39] and Transsternal Radical Thymectomy [40]. These resections remove the entire mediastinal thymus and most of the mediastinal perithymic fat. They vary somewhat in extent in the mediastinum and may or may not include all tissue removed by the T-4 techniques. The cervical extensions are removed from below, with or without additional tissue, but without a formal neck dissection.

The combined transcervical and transsternal thymectomy procedures are known as Transcervical-Transsternal Maximum Thymectomy [41] and Extended Cervical-Mediastinal Thymectomy [42]. These resections routinely use wide exposure in the neck and a complete median sternotomy with en bloc removal of all tissue in the neck and mediastinum that may contain gross or microscopic thymus anatomically. The resections include removal of both sheets of mediastinal pleura and sharp dissection of the pericardium. A similar procedure, although a less extensive resection in the neck and mediastinum, has been described by Lennquist and associates [43].

It is recommended that the thymectomy classification, with modifiers as necessary, be employed when reporting the results of thymectomy for MG.

MGFA Morbidity and Mortality Classification

During the evaluation of therapeutic options, in addition to the determination of the remission and improvement status, quality of life and cost-benefit assessments should be performed [44]. This requires the analysis of, among other things, the number and duration of hospitalizations and intensive care unit stays, and complications related directly to each form of therapy (Table 6).

Table 6. MGFA Morbidity and Mortality

Hospitalizations
Number per year (average since onset Rx and number in the last year)
Days per year (average since onset Rx and number in the last year)
Intensive care stays
Number per year (average since onset of Rx and number in the last year)
Days per year (average since onset Rx and number in the last year)
Ventilatory support
Pre-Rx or During Rx
Duration in place (days)
Tracheostomy
Pre-Rx or During Rx
Duration in place (days)
Infections
Pulmonary
"Line"
Other
Therapy-specific Complication (name of drug and complication)
Death (list cause, relation to therapy, and indicate whether therapy related. Include all deaths occurring during a hospitalization.)
Operative/postoperative
Length of surgery (hours/minutes)
Intraoperative complications
Hospital stay (days)
Intensive care stay (days)
Ventilatory support (days)
Infection (location, type, and severity)
Transfusions (number)
Nerve injury (phrenic/recurrent/intercostal—temporary/permanent)
Persistent pain (severity, duration, and therapy)
Chylothorax (severity and duration)
Death (occurring within 30 days of surgery, even if the patient has been discharged, and occurring after 30 days when clearly related to the surgical procedure. Deaths within 90 days of surgery should also be recorded).

Formal Clinical Trial and Outcomes Research

A prospective, randomized clinical trial remains the preferred method to evaluate therapy (Class I evidence in the American Academy of Neurology [AAN] nomenclature) [45]. When a randomized trial does not appear feasible, a prospective risk-adjusted outcome analysis of nonrandomly assigned treatment (Class II evidence in the AAN nomenclature) is recommended [46]. In prospective studies, in addition to the use of the classification, definitions, grading systems, and methods of analysis recommended herein, the CONSORT guidelines [47, 48] are recommended.

"Survival" instruments, which are used in the analysis of remissions, are fundamental in the comparative analysis of therapeutic programs for MG. Although different levels of clinical improvement should be evaluated in the analysis of all forms of therapy, Complete Stable Remis-

sion remains the primary focus of the analysis, at least in the assessment of thymectomy.

Quality-of-life instruments should also be employed because therapy for MG is usually not innocuous and frequently does not produce a completely stable remission. Quality-of-life measures evaluate the impact of intermediate levels of clinical improvement and morbidity of therapy, and complement information provided by remission and clinical improvement analysis. Although a functional status instrument assessing activities of daily living has been developed for MG [49], there are no disease-specific quality-of-life instruments for MG at this time. The Task Force recommends that these be developed. The steps necessary to accomplish this have been defined [50].

An Outcomes Analysis guideline and an accompanying diagram defining their interrelationships were developed to provide background information on the available analytic techniques [44]. Experts in the field of biostatistics and outcomes analysis should be consulted in the design of all studies, and in the collection and evaluation of the data.

Data Bank

Multi-institutional studies utilizing the data bank concept and fulfilling the requirements discussed next are recommended. This method of study should be particularly useful and practical for multiple institutions to compare the relative value of the many therapies, including various thymectomy techniques.

For a data bank program to be successful, it must be developed appropriately and monitored rigorously. Computer-based patient records, including the "human language" component [51], are required. Definitions, classifications, and standardized forms must be agreed on and used. Standardization of numeric grading for all important variables is required. Mechanisms must be in place to review all the clinical records and to monitor the quality of the database, including validation for completeness and accuracy through a rigid auditing process. The monitoring requirement involves a major commitment by the sponsoring institutions, professionals, and staffs. Mechanisms to defray costs would need to be developed.

Amendments

The MSAB of the MGFA has established a Standing Committee for review of the Clinical Research Standards. The goal of any proposed amendment is to improve the guidelines based on demonstrable errors in the existing guidelines, development of new data, and common sense. The Review Committee will review recommendations from national and international neurologic organizations and centers, journal editorial boards, neurologists, immunologists, surgeons, biostatisticians, nurses, respiratory therapists, and others working in the field of MG. The Review Committee will also serve as a clearinghouse for questions, as they arise, concerning the application of the Clinical Research Standards.

Please submit questions and proposals in writing to Chairperson, Clinical Research Standards Review Committee, Medical Scientific Advisory Board, Myasthenia

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INVITED COMMENTARY

Will Rogers once commented that "Everyone talks a lot about the weather, but no one does anything about it!" The same might be said perhaps about those of us involved in the care of patients with myasthenia gravis. We remain somewhat frustrated at our inability to more precisely understand this baffling disease. This is due in part to our lack of uniformity in categorizing the various manifestations and severity of our patients' disease both prior to and following the available medical and surgical interventions.

A major step has been taken to "do something about it" with the formation of the Myasthenia Gravis Task Force. This multi-specialty group of knowledgeable clinicians, after innumerable discussions and consultations with colleagues, and after many months of gestation, have

given birth to a comprehensive set of Recommendations for Clinical Research Standards. The delivery of this much needed set of guidelines has been the result of a lengthy and at times painful labor. It is hoped that we will all welcome this new arrival, congratulate its parents, and cooperate in "doing something" about advancing our knowledge and capabilities in caring for our patients with myasthenia.

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