International Myositis Classification Criteria Project (IMCCP) Workshop

Held on November 11, 2005

MEETING SUMMARY

This document summarizes a meeting of available members of the Steering and Working Committees of the International Myositis Classification Criteria Project who met on Friday November 11, 2005 from 8:30 AM to 3:30 PM at the Washington Dulles Airport Marriott Hotel, Dulles, Virginia (attendees listed in **Appendix 1)**. The purpose of the meeting was to define approaches and variables to be collected in a retrospective study to develop new classification criteria for the idiopathic inflammatory myopathies and their subgroups.

In prior meetings, it was decided that this project is needed because of the lack of reliable information on sensitivity and specificity of all current criteria sets, because of the many different unvalidated criteria now being used, and due to the availability of novel technologies and approaches today that offer new opportunities to revise our thinking and definitions of myositis. For those who are members of the International Myositis Assessment and Clinical Studies Group (IMACS) and who wish to view all the documents and slides presented at the IMCCP Planning Meeting in 2004, see https://dir-apps.niehs.nih.gov/imacs/index.cfm?action=home.meetings.

It was decided that a combined interdisciplinary effort addressing both adult-onset and childhood-onset myositis would be ideal and that there should be two primary **goals** for the project:

I. Criteria should be developed for use by basic and clinical researchers that distinguish the idiopathic inflammatory myopathies (IIM) from other major mimicking conditions with high sensitivity and specificity; and

II. Criteria should be developed for use by basic and clinical researchers that separate the major subgroups of the IIM from each other with high sensitivity and specificity.

1. Introduction – Ingrid Lundberg, Chair of the Project, summarized the developments that led to the current meeting emphasizing the growing split among different specialities in terms of how the idiopathic inflammatory myopathies and their major subgroups are viewed and defined and how this could lead to great difficulties in future meta-analyses and attempts to correlate findings from one trial or study to another. She discussed the activities of the first Steering Committee held in November 2004 that lead to this meeting. She also described current interest and joint funding by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) to support these efforts to develop criteria that would be recognized by these and possibly other groups.

2. Matthew Liang reviewed his background from previous work on development or revision of criteria in other disorders and the general processes that would be followed during the meeting and then led the Nominal Group Technique throughout the sessions.

3. Fred Miller reviewed the organization and conduct of the pilot study which retrospectively collected data from 50 variables on 34 subjects with myositis and 14 subjects without myositis in order to assess the availability and feasibility of collection of certain of these variables (see **Appendix 2**). He then introduced the Nominal Group Technique and its advantages and how it was going to be used at this meeting.

4. Variables were considered by Nominal Group Technique in the following categories:

A. Clinical Muscle Variables
B. Skin Variables

C. Other Clinical Variables
D. Laboratory Variables
E. Muscle Biopsy Variables

A common approach was used for each category: first, Tony Lachenbruch reviewed his statistical analyses of the variables from the pilot study. Then Matt Liang, Ingrid Lundberg, Fred Miller or Lisa Rider led the group in repeated round-robin fashion asking for possible additional useful variables. Finally each member was given the opportunity to mark a set number of proposed variables that should be eliminated from the list for a variety of reasons including:

a. They were likely to often be missing in the retrospective medical record review
b. They were difficult to define
c. They were redundant
d. They were too rarely endorsed
e. They were non-discriminatory
f. They were costly to obtain, either financially or due to inconvenience, or
g. They were likely to differ in various ethnic populations

The proposed variable list obtained by this process, and including those variables from prior proposed and published criteria, needed to assess their sensitivity and specificity, is listed in **Appendix 3**.

5. Fred Miller presented the subgroups proposed by the Steering Committee to include within the umbrella rubric of idiopathic inflammatory myopathies and those diagnostic groups to include as non-idiopathic inflammatory myopathies. Attendees added to the list of potential myositis subgroups and non-myositis diagnoses. Following the meeting, however, the number of myositis subgroups was restricted due to sample size considerations for the study (**see G7 in Appendix 3**).

6. Tony Lachenbruch gave a brief presentation of the general issues to consider in defining cases and variables and listed some power analyses for our consideration of the number of cases to study. These questions included: How many variables should we collect? In which way should we choose patients and over what period of time? Subsequent discussions by members of the Steering Committee resolved that 750 IIM cases (divided as evenly as possible among the IIM subgroups below) and 500 non-IIM comparators (divided as evenly as possible among the non-IIM diagnostic groups below) should be initially studied, with a first request for 5-10 cases of IIM and 5-10 cases of non-IIM from each participant. Following the collection of data on these initial cases (by either a paper form or by an Excel database), an assessment of these data will be made to determine the number and types of additional cases that may be needed to achieve adequate power to complete the study. The criteria for choosing subjects for the study, in order of priority, should be:

i. The subject has been diagnosed for at least 6 months to allow for an adequate assessment of response to corticosteroid or other immunosuppressive therapy
ii. The physician is certain of the diagnosis – only cases with known idiopathic inflammatory myopathy or, as comparators, known non-IIM cases (but in which myositis was considered in the initial differential diagnosis) are chosen
iii. The most complete data are available - >60% of all variables present
iv. The most recent cases are chosen first – these would likely result in more consistent evaluations and therapy

7. Ingrid Lundberg then led the group in discussing the overall work plan for the meeting and timeline for the project, in hopes that it could be completed in the next two years:

Oct. 2004 – First planning meeting held at NIH
Sept. 2005 – Pilot project performed on 50 variables
Early 2006 – Variables and project plans finalized, including glossary of the variables
Late 2006 – Complete data collection of initial 1250 pts

Late 2006 – Complete analyses of initial data to determine needs for additional data collection
Mid 2007 – Complete all data collection
Late 2007 – Completion of all data analyses
Late 2007 – Experts determine final proposed criteria and possible future plans

8. Ingrid Lundberg and Matthew Liang closed the meeting by defining some other aspects of the process for the development of these criteria and future plans.

a. The next step was to summarize the meeting and preliminary variable list with definitions of the variables and distribute this by email to the larger number of experts interested in this project, but who could not all attend this meeting, for their comments and suggestions. Members of the working and steering committees represent many collaborative study groups and are encouraged to involve their respective groups in the project.

b. A concern was raised that the participants in this project should represent different specialties with a balance among disciplines and it is particularly important that neurology is balanced with rheumatology. Furthermore, the participants recruited so far represent North America, Mexico, Europe and Australia, but additional representatives from Asia and South America are particularly needed. The participants of the meeting were asked to nominate other experts to be invited for the future work. A list of participants that have accepted to participate in this project as well as nominated experts to be contacted is attached as a separate file. This larger group would be invited to join the International Myositis Classification Criteria Project, to vote on variables to define the final list, and then contribute cases to the study. It is to be emphasized that many of the current participants represent larger collaborative study groups, including IMACS, ENMC, Muscle Study Group, European JDM Network, PRINTO and CARRA. It is intended to engage a broad participation in the medical record review from each of these and other collaborative groups. As a consequence of the workshop we have also extended the Steering committee with one dermatologist and two neurologists.

c. The process should include the development of an extensive glossary with standardized nomenclature as the variables are finalized.

d. Different approaches to analyze the data were discussed including heuristic methods, major and minor criteria lists, probable and definite criteria, classification and regression tree (CART) approaches, regression methods, random forests classification – or, if funds permit, a combination of these could be used.

e. It may be useful to define a pathology subcommittee of at least 3 members to blindly review muscle biopsies and record findings using a specified format.

f. Other as yet unresolved issues that will eventually need to be addressed include: possible training to enhance consistency in use of terms and collection of data elements; possible subcommittees for MRI, autoantibodies, biopsies and immunohistochemistry studies, if funding for these projects is obtained; how to handle missing data (EMG, biopsies etc.); how to address international ethics issues (possibly use a central Institutional Review Board (IRB) in the U.S. and ethics exemptions when possible for retrospective anonymized chart reviews); which of multiple statistical approaches are best; data collection and validation methods; approval or acceptance of the developed criteria by neurology, dermatology and other academies and groups.

Appendix 1 - Steering and Working Committee Members of the International Myositis Classification Criteria Project who attended the Workshop held on November 11, 2005.

NAME	EMAIL ADDRESS
WORKING COMMITTEE MEMBERS	
VINAY CHAUDHRY	VCHAUDH@JHMI.EDU
LISA CHRISTOPHER	LCHRIST4@JHMI.EDU
MARY CRONIN	MCRONIN@MCW.EDU
KATALIN DANKO	DANKO@IIIBEL.DOTE.HU
BRIAN FELDMAN	BRIAN.FELDMAN@SICKKIDS.CA
IGNACIO GARCIA DE LA TORRE	IGDLT@AOL.COM
GERALD HENGSTMANN	G.HENGSTMAN@NEURO.UMCN.NL
RENATO MANTEGAZZA	RMANTEGAZZA@ISTITUTO-BESTA.IT
CHET ODDIS	ODDIS@DOM.PITT.EDU
PAUL PLOTZ	PLOTZP@ARB.NIAMS.NIH.GOV
ANGELO RAVELLI	ANGELORAVELLI@OSPEDALE-GASLINI.GE.IT
MICHAEL ROSE	M.R.ROSE@KCL.AC.UK
IRA TARGOFF	IRA-TARGOFF@OUHSC.EDU
JIRI VENCOVSKY	VENC@REVMA.CZ
VICTORIA WERTH	WERTH@MAIL.MED.UPENN.EDU
ROBERT WORTMANN	ROBERT-WORTMANN@OUHSC.EDU
STEERING COMMITTEE MEMBERS	
ANTHONY AMATO	AAMATO@PARTNERS.ORG
PETER LACHENBRUCH	LACHENBRUCHPA@AOL.COM
MATTHEW LIANG	MLIANG@PARTNERS.ORG
INGRID LUNDBERG (CHAIR)	INGRID.LUNDBERG@KI.SE
FRED MILLER	MILLERF@MAIL.NIH.GOV
CLARISSA PILKINGTON	C.PILKINGTON@BTCONNECT.COM; C.PILKINGTON@ICH.UCL.AC.UK
LISA RIDER	RIDERL@MAIL.NIH.GOV
OBSERVER FROM THE MYOSITIS ASSOCIATION	
THERESA CURRY	THERESA@MYOSITIS.ORG

Appendix 2. Pilot study on 50 variables from 34 subjects with myositis and 14 subjects without myositis to assess variable availability from retrospective chart review.

Category	Variable	IIM % (N) present	IIM %(N) missing	Not IIM %(N) present	Not IIM %(N) missing	Sensitivity%	Specificity%
Clinical Muscle	1M Weakness, Prox UE	97 (33)	0	71 (10)	0	97	29
	2M Wrist or FF weakness	56 (19)	6 (2)	2 (15)	1 (7)	56	79
	3M Wrist/FF > shoulder abduct	18 (6)	9 (3)	7 (1)	14 (2)	18	79
	4M Weakness, Prox LE	97 (33)	0	50 (7)	0	97	50
	5M Hip abductor weakness	88 (30)	6 (2)	43 (6)	7 (1)	88	50
	6M Weakness distal LE	41 (14)	0	21 (3)	14 (2)	41	64
	7M Knee extensor weaker than hip	18 (6)	6 (2)	7 (1)	14 (2)	18	79
	8M Neck flexor weakness	85 (29)	0	43 (6)	0	85	57
	9M Neck extensor weakness	21 (7)	21 (7)	7 (1)	21 (3)	21	71
	10M Symmetric weakness	85 (29)	0	57 (8)	7 (1)	85	36
	11M Muscle pain at rest	32 (11)	18 (6)	29 (4)	0	32	71
	12M Muscle tenderness	35 (12)	9 (3)	7 (1)	7 (1)	35	86
	13M Muscle atrophy distal forearms	18 (6)	3 (1)	0	0	18	100
	14M Thigh atrophy	32 (11)	3 (1)	0	0	32	100
Clinical Skin	1S Heliotrope	38 (13)	0	0	0	38	100
	2S Gottron's papules	44 (15)	0	14 (2 DM sine)	0	44	86
	3S Erythema extensor surfaces	35 (12)	0	29 (4)	0	35	71
	4S V-sign	21 (7)	0	7 (1)	0	21	93
	5S Shawl sign	24 (8)	0	0	0	24	100
	6S Calcification	9 (3)	3 (1)	0	0	9	100
	7S. Periungual eryth, petech, telan, cutic over	41 (14)	0	7 (1)	0	41	93
	8S Raynaud's	18 (6)	3 (1)	29 (4)	0	18	71
Clinical Other	1O Family history AD	26 (9)	9 (3)	28 (4)	0	26	71
	2O Acute onset	71 (24)	3 (1)	43 (6)	0	71	57
	3O Arthritis	47 (16)	0	43 (6)	0	47	57
	4O Polyarthralgia	44 (15)	0	50 (7)	0	44	50
	5O Sjogren's syndrome	3 (1)	0	7 (1)	0	3	93
	6O Systemic sclerosis	0	0	7 (1)	0	0	93
	7O MCTD	0	0	0	0	0	0
	8O Rheumatoid arthritis	0	3 (1)	43 (6)	0	0	57
	9O SLE	3 (1)	0	29 (4)	0	3	71
	10O Autoimmune thyroid disease	12 (4)	18 (6)	7 (1)	42 (6)	12	50
	11O Objective improvement strength p corticoid	79 (27)	6 (2)	43 (6)	43 (6)	79	14
	12O No improvement strength p corticoid	3 (1)	35 (12)	14 (2)	43 (6)	3	43

Appendix 2 (cont.). Pilot study on 50 variables from 34 subjects with myositis and 14 subjects without myositis to assess variable availability from retrospective chart review.

Category	Variable	IIM % (N) present	IIM % (N) missing	Not IIM %(N) present	Not IIM %(N) missing	Sensitivity %	Specificity %
Laboratory	1L EMG c/w IIM	59 (20)	32 (11)	14 (2)	79 (11)	59	7
	2L CK elevated	76 (26)	15 (5)	36 (5)	14 (2)	76	50
	3L LD elevated	53 (18)	38 (13)	7 (1)	43 (6)	53	50
	4L AST/SGOT elevated	65 (22)	24 (8)	29 (4)	29 (4)	65	43
	5L ALT/SGPT elevated	59 (20)	15 (5)	29 (4)	14 (2)	59	57
	6L Aldolase elevated	15 (5)	82 (28)	7 (1)	64 (9)	15	29
	7L ANA +	62 (21)	12 (4)	50 (7)	14 (2)	62	36
	8L Anti-Jo-1 autoantibody +	21 (7)	21 (7)	0	29 (4)	21	71
	9L STIR/T2 MRI c/w inflammation	62 (21)	26 (9)	21 (3)	50 (7)	62	29
Muscle Bx	1B Inflammation & degen/regen on H&E	34 (25)	15 (5)	14 (2)	57 (8)	34	29
	2B MHC I ag present on muscle fibers	21 (7)	76 (26)	0	92 (13)	21	7
	3B Non-necrotic fibers surr/invaded by MNC	44 (15)	15 (5)	7 (1)	57 (8)	44	36
	4B Endomysial MNC infiltrates	65 (22)	15 (5)	21 (3)	57 (8)	65	21
	6B Perimysial MNC infiltrates	18 (6)	35 (12)	7 (1)	57 (8)	18	36
	7B Perifascicular atrophy	21 (7)	15 (5)	0	57 (8)	21	43
	8B Rimmed vacuoles	12 (4)	32 (11)	0	57 (8)	12	43

Appendix 3

Development of Classification Criteria for the Idiopathic Inflammatory Myopathies and their Major Subgroups

Proposed Data Collection Form and Preliminary Variable List for Comment

Variables in italics are from prior proposed criteria and are needed to assess their sensitivity and specificity

In reviewing patients please use the following criteria for selecting cases for submission:

i. The subject has been diagnosed for at least 6 months to allow for an adequate assessment of response to corticosteroid or other immunosuppressive therapy
ii. The physician is certain of the diagnosis – only cases with known idiopathic inflammatory myopathy or, as comparators, known non-IIM cases (but in which myositis was considered in the initial differential diagnosis) are chosen
iii. The most complete data are available - >60% of all variables present
iv. The most recent cases are chosen first – these would likely result in more consistent evaluations and therapy

GENERAL INFORMATION

G0. IRB or Ethic's Committee approval identifier and date of approval:

G1. Clinician submitting case:

G2. Case identifier/number:

G3. Gender: □ Female
□ Male

G4. Age at onset: (of first symptom assumed to be related to the disease

G5. Age at diagnosis

G6. Ethnicity: □ Of European descent

□ Of African descent

□ Of Asian descent

□ Of Native American descent

□ Of Pacific Island descent

□ Of Mixed descent

□ Unknown

G7. Study diagnosis and onset (adult onset = age >17) according to the clinician (check only one diagnosis):

Idiopathic Inflammatory Myopathy (IIM), adults or children:

Myositis Onset: adult □ or childhood □

□ Polymyositis

□ Dermatomyositis

□ Inclusion body myositis

□ Non-specific myositis

□ Immune-mediated necrotizing myopathy

NOT Idiopathic Inflammatory Myopathy (Not IIM), adults or children, but in which the diagnosis of idiopathic myositis was considered in the differential diagnosis:

Disease Onset: adult □ or childhood □

□ Non-inflammatory inclusion body myopathy

□ Dystrophy, specify diagnosis

□ Metabolic myopathy, specify diagnosis

□ Mitochondrial myopathy, specify diagnosis

□ Drug or toxin associated myopathy, specify diagnosis

□ Infectious myopathy, specify diagnosis

□ Endocrine myopathy, specify diagnosis

□ Other Neuromuscular disease, specify diagnosis

□ Other Rheumatic disease, specify diagnosis

□ Other Dermatologic disease, specify diagnosis

G8. Basis for study diagnosis (check and explain in detail all supporting reasons):

□ Muscle weakness

□ Muscle biopsy abnormalities

□ Elevated muscle enzymes

□ EMG abnormalities

□ Rashes

□ Other, specify

G9. Clinician's additional comments on the case:

G10. Other diagnoses in this case:

□ Hypothyroidism
□ Hyperthyroidism
□ Type I diabetes
□ Rheumatoid arthritis
□ Juvenile Rheumatoid arthritis

□ Systemic lupus erythematosus
□ Systemic sclerosis
□ Multiple sclerosis
□ Other, specify

	Present	**Absent**	**Not available**	**Comments**
Clinical Muscle Variables				
1M. Objective symmetric weakness, usually progressive, of the proximal upper extremities				
2M, Objective shoulder abductor weakness				
3M. Objective elbow flexor weakness				
4M. Objective elbow extensor weakness				
5M. Wrist and finger flexors are weaker than shoulder abductors				
6M. Wrist flexors are weaker than wrist extensors				
7M. Objective finger flexor weakness				
8M. Objective symmetric weakness, usually progressive, of the proximal lower extremities				
9M. Objective hip flexor weakness				
10M. Objective hip abductor weakness				
11M. Objective knee extensor weakness				
12M. Knee extensors are as weak or weaker than hip girdle muscles				
13M. Objective muscle weakness of distal lower extremities				
14M. Objective axial weakness				
15M. Objective neck flexor weakness				
16M. Neck flexors are weaker than neck extensors				
17M. Proximal muscles are weaker than distal muscles				

18M. Muscle pain at rest				
19M. Muscle tenderness				
20M. Muscle atrophy of distal forearms				
21M. Muscle atrophy of thighs				
22M. Scapular winging				
23M. Involuntary muscle movement				
	Present	**Absent**	**Not available**	**Comments**
Skin Variables				
1S. Heliotrope rash				
2S. Gottron´s papules				
3S. Gottron's sign				
4S. Erythema of the neck (V-sign)				
5S. Erythema of the back of neck and shoulders (Shawl sign)				
6S. Periorbital edema				
7S. Linear extensor erythema				
8S. Cutaneous, fascial or muscular calcification				
9S. Periungual erythema or nailfold capillary abnormality				
10S. Cuticular overgrowth				
11S. Mechanic's hands				
12S. Facial erythema				
	Present	**Absent**	**Not available**	**Comments**
Other Clinical Variables				
1O. Family history of autoimmune disease				
2O. Family history of muscle disease				
3O. Subacute onset (weeks to several months) of symptoms				
4O. History of episodic weakness associated with exercise or fasting				
5O. Arthritis				
6O. Polyarthralgia				
7O. Unexplained Fevers				
8O. Interstitial lung disease				
9O. Peripheral neuropathy				
10O. Dysphagia or esophageal dysmotility				
11O. Objective improvement in strength after corticosteroid therapy				
12O. Objective improvement in strength after other immunosuppressive therapy				

	Present	Absent	Not available	Comments
Muscle Biopsy Variables				
1B. Necrosis of type I and type II muscle fibers, phagocytosis, degeneration/regeneration of myofibers with variation in myofiber size, endomysial, perimysial, perivascular or interstitial mononuclear cells (MNCs)				
2B. Perifascicular atrophy				
3B. Non-necrotic fibers surrounded and invaded by MNCs				
4B. MHC Class I antigen present on scattered muscle fibers				
5B. Endomysial inflammatory cells surrounding, but not invading, myofibers				
6B. Endomysial CD8+ cells surrounding myofibers with MHC Class I expression on myofibers				
7B. Vacuolated muscle fibers				
8B. Intracellular amyloid deposits or 15-18 nm tubulofilaments by electron microscopy (EM)				
9B. Many necrotic muscle fibers as the predominant feature. Inflammatory cells are sparse; perimysial infiltrate is not evident.				
10B. Rimmed vacuoles, ragged red fibers, or cytochrome oxidase-negative fibers that would suggest inclusion body myositis (IBM)				
11B. Membrane attach complex (MAC) depositions on small blood vessels, or reduced capillary density, or tubuloreticular inclusions in endothelial cells on electron microscopy, or MHC-1 expression of perifascicular fibers				
12B. Endomysial mononuclear cell infiltrates				
13B. Perivascular mononuclear cell infiltrates				
14B. Perimysial mononuclear cell infiltrates				
15B. Fatty replacement of muscle				
16B. Glycogen or fat vacuoles				

Laboratory Variables				
	Value	**Normal range**		**Comments**
1L. Serum creatine kinase (CK) activity				
2L. Serum lactate dehydrogenase (LDH) activity				
3L. Serum aspartate aminotransferase (ASAT/AST/SGOT) activity				
4L. Serum alanine aminotransferase (ALAT/ALT/SGPT) activity				
5L. Serum Aldolase activity				
6L. Erythrocyte sedimentation rate (ESR)				
7L. C-reactive protein (CRP)				
	Value	**Normal range (method)**		**Comments**
8L. Anti-Jo-1 autoantibodies				
9L. Other myositis-specific autoantibody				
10L. Anti-nuclear autoantibodies (ANA)				
11L. Other autoantibodies				
a. Ribonucleoprotein (RNP)				
b. La				
c. Ro				
d. Smith (Sm)				
	Present	**Absent**	**Not available**	**Comments**
12L. Electromyogram (EMG) - Increased insertional and spontaneous activity in the form of fibrillation potentials, positive sharp waves, or complex repetitive discharges				
13L. EMG - Morphometric analysis reveals the presence of short duration, small amplitude, polyphasic MUAPs				
14L. Electrocardiogram (EKG) abnormalities consistent with myositis				
14L. Muscle inflammation on STIR or T2-weighted magnetic resonance imaging (MRI)				
15L. Muscle abnormalities on T1-weighted MRI scanning consistent with myositis				

Other features important in making the diagnosis not listed above – please specify: