Development and validation of classification criteria for idiopathic inflammatory myopathies (IIM)

Abstract

In patients with idiopathic inflammatory myopathies (IIM), there is a clear need for improved treatment due to the persisting impaired muscle function in most patients treated with the current regimens of high-dose corticosteroids and immunosuppressive drugs. Recently the International Myositis Assessment and Clinical Studies Group (IMACS), a multinational and multidisciplinary group, developed consensus on outcome measures and proposed definitions of improvement to be used in clinical trials for adults and children. A significant and fundamental problem in clinical studies, however, is the limitation of diagnostic criteria for inflammatory myopathies (Bohan and Peter, 1975) as they are considered too inclusive and may allow patients with some forms of muscle dystrophy to be included in a group of inflammatory myopathies. These criteria also misclassify patients with inclusion body myositis (IBM), and some variables are not specified or operationally defined. Because evolving concepts in pathogenesis have altered our thinking about myositis, and since new diagnostic tools including MRI and myositis-specific autoantibodies have been recently developed, it is now timely to develop and validate new myositis classification criteria.

The aim of this project is to develop and validate classification criteria for idiopathic inflammatory myopathies (IIM) and major subgroups of the IIM in adults and children for clinical research, especially clinical trials, and to document the reliability of these new criteria.

Methods: A multidisciplinary and multinational collaborative project including clinical scientists from neurology, rheumatology, paediatric rheumatology, dermatology, pathology and epidemiology will be mounted. We will establish a commitment from the major professional organizations which represent the specialists who see patients with inflammatory muscle disease, to review, vote, and if in agreement with the work, to endorse the criteria. In addition, we will also seek support for the project, including the support of representatives to the 2 meetings, the analyses and the costs of the meetings. These include organizations in the myositis field: EULAR, ACR, American Academy of Neurology (AAN), and Academy of Dermatology. A steering committee (n= 8-10) will prepare background materials, case forms consisting of candidate classification criteria and the blinded analyses of data. A Working Committee (n=20-25) and additional experts will collect data retrospectively from patients with inflammatory myopathies and comparator groups. The performance characteristics (sensitivity and specificity and predictive value) of single criterion and combinations of criteria will be explored with multivariate analyses, including logistic regression, CART, and Random Forests Classification, to maximize discrimination between cases and comparator conditions. The results will be summarized and presented at a second working committee meeting. At this meeting the final criteria will be determined after consensus has been reached. The next step will be have them reviewed by sponsoring organizations and, if approved, receive official endorsement. The International Myositis Assessment and Clinical Studies Group (IMACS), European Neuromuscular Centre (ENMC), the Muscle Study Group (MSG) and paediatric rheumatology networks (PRINTO, CARRA and the PRES network for juvenile dermatomyositis) will be invited as reviewers during the process. All sponsoring organizations that ratify the criteria will have their names in the developed international classification criteria of myositis.

Importance: Improved classification criteria for poly- and dermatomyositis are important for clinical trials to test new drugs. Improved classification criteria will also be very important in the work to understand disease mechanisms and to develop new targeted therapies.

1. Aims
A combined effort to address both adult-onset and childhood-onset myositis

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

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.

To test the reliability of these new criteria.

2. Background
Scientific advances in immunology and molecular biology over recent years have led to increased knowledge of disease mechanisms and to the development of new and more specific biologic therapies for patients with chronic inflammatory diseases. In patients with chronic idiopathic inflammatory myopathies, myositis, there is a clear need for improved treatment due to the persisting impaired muscle function in most patients treated with the current regimens of high-dose glucocorticoids and immunosuppressive drugs such as methotrexate or azathioprine. Currently recommended treatment is mainly based on uncontrolled studies and case reports; few controlled trials have been conducted in patients with myositis. A significant barrier to the conduct of studies has been the lack of standardized validated outcome measures. The International Myositis Assessment and Clinical Studies Group (IMACS), a multinational and multidisciplinary group was established to standardize the conduct and reporting of clinical studies in myositis. The IMACS has over 100 international members from adult rheumatology, neurology, pathology, dermatology and paediatric rheumatology communities (see https://dir-apps.niehs.nih.gov/imacs/). IMACS has developed consensus on outcome measures and proposed definitions of improvement to be used in clinical trials for adults and children with PM and DM (Miller et al 2001, Rider et al 2004).

Need and Relevance - Limitations of myositis classification criteria.
A significant and fundamental problem in clinical studies is the classification criteria for inflammatory myopathies. Three different criteria have been proposed (Bohan & Peter 1975, Tanimoto 1995, Hoogendijk 2004) but the criteria of Bohan and Peter are the most often used in clinical studies. Several limitations of these criteria are recognised. Some criterion are not specified or operationally defined, for example, the biopsy criterion is considered too inclusive and may allow patients with some forms of muscle dystrophy to be included in a group of inflammatory myopathies. These criteria also misclassify patients with inclusion body myositis (IBM), which was not known when these criteria were proposed, as having PM.

Since the 1980s, a variety of discoveries could impact the subsetting of myositis. The biology of muscle in PM/DM has advanced with careful immunohistochemical characterization (Engel & Arahata 1986) (Dalakas 1991). Magnetic resonance imaging (MRI), can now visualize muscle inflammation and myositis-specific autoantibodies could be helpful for diagnostic purposes but are not included in the Bohan and Peter criteria (Love et al 1991).

Other criteria for inflammatory myopathies have been put forward. Engel and Arahata proposed immuno-histopathology based criteria (Engel & Arahata 1986). The Tanimoto criteria added arthritis, systemic inflammatory signs, muscle pain and tenderness to the Bohan

and Peter criteria, to also distinguish myositis patients from other myopathies and neuropathies (Tanimoto et al 1995). The American Academy of Dermatology has published recommendations for diagnostic evaluation of the skin manifestations in DM (Drake et al 1996). For IBM, classification criteria have been developed and because this phenotype is unresponsive to immunosuppressive treatment, patients with IBM should be regarded as a separate entity in clinical trials (Griggs et al 1995). The Bohan and Peter criteria have also been used for children with myositis. A group of paediatric rheumatologists has started to revise the criteria for this group (PreS network for juvenile dermatomyositis).

At the European Neuromuscular Centre (ENMC) workshop on trial design in adult idiopathic inflammatory myopathies in 2003 (Hoogendijk et al 2004) more extensive muscle biopsy findings were added to the criteria and two new subsets of inflammatory myopathies were proposed:
a) Non-specific myositis (in patients with non-specific perimysial/perivascular infiltrates, but without biopsy features diagnostic of PM or DM), and
b) Immune-mediated necrotizing myopathy (characterized by absence of inflammatory infiltrate) (Hoogendijk et al 2004).
The ENMC participants recommended revision of the current criteria to exclude other diseases, to include information relevant to understanding underlying pathogenesis and to facilitate the comparison of studies.

In summary, there is a consensus to revise the classification criteria for PM and DM. Furthermore, most workers in the field believe that this should be a collaborative effort between specialists in neurology, rheumatology, paediatric rheumatology, dermatology, pathology and epidemiology and that it should be international to ensure greatest acceptance.

Research Plan
We think it important to involve scientists from a variety of fields including adult and paediatric specialists in rheumatology, neurology, dermatology, clinical epidemiology and statistics in the project. They should also represent expertise from Europe and the U.S. A. A clinical epidemiologist with experience in classification criteria, but who is neutral in the myositis research field, will be the facilitator.

We will use methods and processes that have been successfully employed in criteria development with planned inputs from a gradually increasing circle of international stakeholders and experts to promote consensus and "buy-in". A Steering Committee (n=8-10 internationally recognized experts in the field), a Working Committee (n=20-25 additional experts) and a larger number of invited reviewers (reference group) will be involved.

A mandate and sponsorship from the American College of Rheumatology (ACR), EULAR, American Academy of Neurology (AAN), the American Academy of Dermatology, the Muscle Study Group (MSG), IMACS, the ENMC and the paediatric networks CARRA, PRINTO and PreS network for juvenile dermatomyositis will be secured.

The Steering Committee will prepare background materials and evidence - tables for the Working Committee and analyse the blinded data. The Steering Committee includes a representative of the ACR Subcommittee on Classification and Response Criteria and one from the ECSICIT committee (Standing Committee on International Clinical Studies Including Clinical Trials) of EULAR.

The Working Committee will have the role of investigators of the study and will collect clinical data. They will include diverse representation with experts in the fields of rheumatology, neurology, paediatric rheumatology and neurology, dermatology, neuropathology and epidemiology. European and American experts and a representative from the patient organisation, The Myositis Association (TMA) will be invited.

The reviewers will be identified through the IMACS, ENMC, MSG networks as well as from the paediatric networks: PreS network for juvenile dermatomyositis, PRINTO and CARRA. These are large networks that can easily recruit participants to collect clinical data and help disseminate the proposed criteria. Since it is essential that revised criteria be validated to distinguish myositis patients from subjects with other connective tissue disorders and neuromuscular diseases that may be mistaken for myositis, some of which are uncommon or rare, multiple sites will need to identify comparator patients with these disorders.

3. Development of candidate criteria (Face and content validity)

In 2004 a Steering Committee with eight experts from rheumatology, neurology, paediatric rheumatology and epidemiology was formed and formulated a process for development of the criteria. The experts represent America and Europe and both genders.

- The primary aim of the project is to develop classification criteria for idiopathic inflammatory myopathies (IIM) and criteria that separate the major subgroups of the IIM from each other with high sensitivity and specificity.

This will be performed through a retrospective study. The focus is the idiopathic inflammatory myopathies in adults and children. This includes the myositis syndromes, including inclusion body myositis, polymyositis, dermatomyositis, non-specific myositis, necrotizing myopathies, overlap myositis and cancer-associated myositis as well as juvenile forms of idiopathic inflammatory myopathies.

A list of variables to be included in the criteria will be defined. This will be defined by experts in the field of muscle diseases and will be decided after consensus has been reached at the first meeting of the experts in the Steering and Working Committees.

The Steering committee has scrutinized previous criteria presented above as well as inclusion criteria that have been used in published controlled clinical trials of PM and DM. A complete set of potential variables from all previous published and recently proposed criteria was collected, adding up to a total of 188 variables. These variables include: clinical signs and symptoms, such as the detailed pattern of muscle weakness, pain, cutaneous and other organ manifestations; muscle enzymes; EMG data; detailed muscle biopsy data; MRI information; autoantibodies; initial clinical diagnosis; treatment and treatment responses. Each Steering committee member was asked to identify the 10 most clinically sensible, important, easy to measure and reliable variables for discriminating between the inflammatory myopathies and other conditions which could be confused with myositis and that were likely to be retrieved from patient records.

This smaller list of 50 variables will be further assessed for the feasibility to retrieve information for these variables from 30 patient records in a pilot study to be conducted by steering committee members. Comments on the list of variables to collect will also be solicited from experts in the IMACS, MSG, ENMC, CARRA, PRINTO networks and the PreS network for juvenile dermatomyositis.

Variables will be defined and explained, by members of the Steering Committee, in a glossary and have a short name, and a long name. Value labels (male/female, yes/no, etc.) will be generated for all variables.
Examples of domains and variables: The Demographic domain will contain date of birth, gender (0 if male, 1 if female), race (white, black, Asian, etc.) among others. The History domain will contain date of diagnosis, family history, concomitant diseases (Systemic sclerosis, SLE, RA, etc). The Physical Findings domain will include the presence or absence of weakness of specific muscle groups, skin rashes, etc. The Laboratory domain will include serum levels of CK, LD, presence and method of detection of autoantibodies (ANA, ENA, muscle specific autoantibodies) muscle biopsy data, etc.

Variables which are not likely to be retrievable, imprecise in measurement, or unreliable will be excluded, as well as variables which are not likely to be obtained because they are difficult to measure, or require technology which is not widely available or are not clinically sensible to use. Some of the listed clinical variables have been tested for inter-rater reliability in our previous studies through the IMACS network (Rider LG et al 2003). Skin variables (e.g. Gottron's papules and heliotrope rash) have been tested by some of the members of this application and data from those tests can be used in this project to assure reliability. Muscle biopsies will be evaluated by a muscle – biopsy committee, please see below. The myositis specific autoantibodies will be tested in one center with expertise in these autoantibody tests, on cases where serum samples are available. Through the previous IMACS studies we have gained great experience on how these types of clinical and laboratory studies can be effectively performed in multi-center settings.

To develop consensus on the list of variables, the Delphi method will be used before the first meeting of the Steering Committee and the Working Committee. This will reduce the number of variables that will need to be discussed at the meeting. At the first meeting the participants will decide on the final variables. A modified nominal group technique will be used to facilitate consensus.

The criteria will be imputed to discriminate redundant or overlapping variables.
To avoid redundancy, we will examine Spearman correlations for continuous variables and contingency tables for categorical variables and drop those variables that are highly correlated/associated with each other. For contingency tables – as a first cut, we will use the chi-square or the contingency coefficient which is a direct function of chi-square.

4. Validation

A. Variables

The list of variables that has been developed and proposed by experts, as described above under 3. "Development of candidate criteria (Face and content validity)" will be tested in patients with inflammatory myopathies as well as in other cases that could be confused with myositis.

B. Data collection

Acquiring data: Data will be collected retrospectively by members of the Steering Committee, Working Committee and from experts who are recruited from the networks involved in the project. As there is no gold standard for definition of myositis, each case will be defined according to the expert submitting the case, who will list the variables that were used for the diagnostic decision for each case. We will ask that only cases with definitive

diagnoses be submitted for this study. Cases will be assembled to cover the entire spectrum of diseases under consideration as well as the countries and referral patterns. Cases and control conditions will have their clinical data recorded from patient records on standardized case forms.
a. Cases will include adult and juvenile cases and will attempt to cover the spectrum of disease severity. This will be ensured by involving clinicians from different disciplines; neurology, rheumatology, dermatology and paediatric rheumatology. Cases from secondary and tertiary referral centers will be included and from different countries in Europe, the US, Canada, Latin America and Australia.
b. Comparator conditions which are commonly confused with idiopathic inflammatory myopathies and cause a differential diagnostic problem will be assembled. These conditions are:
-Non-inflammatory inclusion body myopathies
-Limb-girdle dystrophies
-Fascioscapulohumeral (FSH) dystrophy
-Drug/toxin associated myopathies (particularly associated with statin use)
-Metabolic myopathies
-Mitochondrial myopathies
-Endocrine myopathies
-Rheumatic conditions; Systemic lupus erythematosus, Polymyalgia Rheumatica, and Scleroderma
-Dermatologic conditions: discoid lupus erythematosus

Myositis cases and comparators that have the most complete data and are also most secure in their diagnoses (from the referring expert) will be candidates for inclusion in the study. There are two main groups, (1) patients presenting with weakness as a primary complaint and (2) patients presenting with rash or systemic features as a primary complaint. For the first group we will mainly include patients with muscle biopsies that include both myositis patients and comparator conditions. For the second group, patients who have skin rash and most of the other variables present will be included but a muscle biopsy may not be required
The minimum number and types of allowable missing variables for cases will be defined by the Working Committee at the first meeting. This will limit the problem of missing data.

Each center will be asked to commit to submit data on 10 – 15 patients with definite diagnoses of DM, PM or IBM and at least 10 – 15 additional cases that are not "myositis" but have a definite diagnosis in the comparator list above. If the number of cases collected in the first phase are inadequate in one or more diagnoses (see below), a second phase of a directed collection of additional 10- 15 cases with definite specific diagnoses will be made. If enrollment goals are not achieved, participating sites could be re-contacted to see if they can enroll additional patients with a ceiling of 60 per site.

Sample size calculations:
We will request 200 patients per subgroup for a total of 1000 myositis patients (4 major subgroups of PM, DM, IBM and Juvenile DM, and then other miscellaneous subgroups) and then 1000 comparator patients (700 adults and 300 pediatric) without myositis. We assume that certain of these patients or comparators will not be evaluable for certain classification criteria (for example, ones that involve biopsies, autoantibody testing, and certain imaging data) due to missing data.

Based upon the expected enrollment of 150 evaluable patients in each of the 4 major subgroups of myositis (PM, DM, JDM and IBM), and the expected enrollment of 500 evaluable comparators (300 adults and 200 pediatric), the following power calculations support this level of enrollment:

Null Hypothesis: P1=P2 Alternative Hypothesis: P1<>P2. Continuity Correction Used.

Power	N1 Alpha	N2 Beta	Allocation Ratio	P1	P2	Odds Ratio
0.98279	600 0.05000	500 0.01721	0.833	0.75000	0.85000	1.889
0.97234	150 0.05000	300 0.02766	2.000	0.75000	0.90000	3.000
0.94547	150 0.05000	200 0.05453	1.333	0.75000	0.90000	3.000

Where N1 is a number of the total group or subgroup of myositis patients and N2 is the sample size of the total or subgroup of comparator patients and P1 and P2 are either sensitivity or specificity for the myositis groups vs. the comparators. The Odds Ratio is P2/(1-P2)/(P1/(1-P1)). The beta is the type 2 error and is 1-power.

C. Data quality assurance and management.
The data will be entered into a web-based survey (Survey Monkey) or by manually into a paper questionnaire. Thereafter the data will be entered into a standardized database at the site Karolinska Institutet in Stockholm, Sweden, by a research assistant. We will create a template for each data domain: demographic, physical exam, labs. There will always be an anonymized linking case study number. The case study number will be the link that is used to merge any data files, and must be included in all domain files. The case study number will consist of a 3 digit center number followed by a 3 digit subject number.

Edit/Fix step: The web-based survey has some editing checks. Furthermore, the recorded spreadsheets after being forwarded to the data management center will be subject to some simple editing checks: data will be assessed for within allowable range impossible values (e.g., age >150, etc). Any discrepancies need to be resolved by the center where the data was acquired. Test step: This includes simple editing tests and consistency checks. After merging data from datasheets, we will check to see if they are consistent e.g. patient does not change sex etc.

D. Muscle biopsy data
A pathology committee of 3 members will be appointed by the Steering Committee when the project has been funded. These 3 myopathologists will read each available biopsy individually in a blinded fashion using a standard scoring form. For quantitative variables (i.e., degree of inflammation, etc.) the 3 readings will be averaged and for dichotomous variables (i.e., presence of rimmed vacuoles within myocytes) only those biopsies where 2 of the 3 pathologists agreed will be scored as positive. The biopsy findings will be compared between the inflammatory myopathies, comparator groups, and subsets of inflammatory myopathies.

An international muscle biopsy standardization study for juvenile myositis cases was initiated in 2004 under the lead of Dr. Lucy Wedderburn, London, UK, and she has agreed to advise us, using her experience from this group, in the evaluation of muscle biopsies in this study.

E. Construct validity

The new study criteria will be assessed in comparison with the Bohan and Peter criteria for myositis, which are the most frequently used criteria and will thus be the "gold standard" against which the new criteria will be compared for sensitivity and specificity. New criteria will also be tested against other published criteria of Tanimoto 1995 and Hoogendijk 2004. The ability of the new criterion to distinguish between inflammatory myopathies from comparator groups will be tested as well as the subgroups of myositis, polymyositis dermatomyositis, inclusion body myositis and juvenile dermatomyositis. Sensitivity, specificity, and predictive value of the potential new classification criteria schema will compared to those of Bohan and Peter and other published criteria (gold standards).

F. Statistical analyses

Dr Peter Lachenbruch, statisticiam Oregon, State University, will be responsible for the statistical analyses of the study.

Analytical approaches will include descriptive statistics (means, standard deviations, percentiles (10, 25, 50, 75, 90)) for the measured variables and for derived variables. We will examine differences across disease groups as a preliminary means of constructing various indices, and to study differences in already defined indices – e.g., number of key symptoms present in each disease group. Many combinations of variables can be generated to establish "criteria" but selecting some combinations will be needed. An additional option is to use CART, which will permit us to develop non-linear rules to classify subjects into IM or other. Random Forest Classification analysis will also be used to determine combinations of variables that best separate cases from other diagnoses, and the relative importance of these variables in this discrimination (http://www.stat.berkeley.edu/users/breiman/RandomForests/). Sensitivity and specificity will be computed for all criteria. The Predictive value of a negative or a positive outcome depends on the prevalence of the condition and the sensitivity and specificity. We will compute these for a variety of prevalence values.

We can calculate candidates for diagnostic measures in many ways. Factor analysis will be used to obtain a weighted combination of variables – this could be simplified by omitting variables with low weights, and rounding the weights to "nice" numbers. A second option would be to determine weighted sums of variables that best separate the IM from the other diseases. Techniques for this include logistic regression and discriminant analysis. Random Forest Classification analysis would be a very novel and practical approach. A third option is to solicit experts for appropriate candidates for such measures. This can lead to many options that depend on how much change is observed, what level of a variable is needed, etc.

Final classification criteria

The final classification criteria will be validated using bootstrapping methods to validate the top few criteria (or the top one). This could be done with a large initial data set.

Manuscript will be prepared. Additional external expert opinion will be sought. Revisions made accordingly with the consent and advice of the entire committee and the report will be

submitted to all stakeholder organizations for review and hopefully formal endorsement. After this voting the work will be submitted for publication.

5. Project organization in detail
Project director
1. Ingrid E. Lundberg, professor in rheumatology, Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden

Steering Committee
- Ingrid E. Lundberg, professor in rheumatology, Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden
- Matthew Liang, MD, MPH, Rheumatologist, Epidemiologist, Harvard Medical School, Brigham and Women´s Hospital, Facilitator of the project.
- Frederick W. Miller, M.D., Ph.D. Chief, Environmental Autoimmunity Group, National Institute of Environmental Health Sciences, National Institutes of Health, Bethesda, MD, U.S.A.
- Anthony A. Amato, M.D., Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston MA, U.S.A.
- Lisa G. Rider, M.D. Deputy Chief, Environmental Autoimmunity Group, NIEHS, National Institutes of Health, Bethesda, MD , U.S.A, (Pediatric rheumatologist).
- Clarissa Pilkington, Paediatric Rheumatologist, MBBS, Consultant in Adolescent and Pediatric Rheumatology, Department of Rheumatology, Great Ormond Street Hospital, London
- Peter A. Lachenbruch, PhD, statistician, Oregon State University
- Marianne de Visser, MD, Professor, Academic Medical Centre, Dept. of Neurology, Amsterdam, The Netherlands
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- Victoria P Werth, M.D, Professor of Dermatology and Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA
- Gerald JD Hengstman, MD, PhD, Neuromuscular Centre Nijmegen, Department of Neurology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
- Richard Finkel, MD, Department of Neurology, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA

An American College of Rheumatology Representative, Jas Singh, Minnesota University
A Representative of EULAR will be invited to the next meeting

Working Committee
25-30 experts including rheumatologists, neurologists, dermatologist, neuropathologist, from Europe and the US will be invited. A preliminary list of experts is presented in Appendix 1.
Representative from the Myositis Association

A reference group
Reviewers will be invited from IMACS and other networks such as ENMC, MSG and the paediatric networks; PRINTO, the PreS network for juvenile dermatomyositis and CARRA.

6. Dissemination of the recommendations
Post the endorsed classification criteria on websites of ACR, EULAR and other organizations. Secure review by sponsoring organizations and if approved, official endorsement.

All sponsoring organizations will have their names in the developed classification criteria of myositis.
Abstracts to the EULAR, ACR and AAN scientific meetings.
Final manuscript publication
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Implementation of the recommendations
This will be done through the already existing networks the IMACS, ENMC, MSG, and PRINTO, PreS network for juvenile dermatomyositis and CARRA and by using these criteria in clinical trials.

Relevance for ACR and EULAR
This will be a multidisciplinary project involving all of the key players within this scientific field and the big collaborative study groups, both for adults and juvenile myositis. It will also be a first effort between the two major organisations ACR and EULAR to develop classification criteria, and we are working to involve the major neurology organisations as well to get wide acceptance for the criteria.

Timelines and milestones
During 2005 we defined a preliminary list of variables to be tested in a pilot study during fall 2005. We achieved support from the ACR and EULAR.

In November 2005 we had the first meeting with the Working Committee. A list of variables for revised criteria was defined to be sent out to the reference group for further comments.

In 2006 the list of variables was defined after comments from the Reference group. A glossary was made.

In 2007 Institutional Review Board. Forms are being prepared and will be sent out to participants. Clinical data will be collected.

2008. Clinical data will be collected. Statistical analyses will be performed. Revised criteria will be proposed. The proposed criteria will be sent to reviewers in the reference groups.

2009: a second meeting with the Working Committee will be organized to agree upon the criteria.

2009: Manuscript will be written. Seek ratification by EULAR, ACR, ENMC, MSG and AAN. The name of the new criteria will be determined.

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