The protocol summary should outline the research plan according to factors the IRB and the ORA consider essential for review. The protocol summary should be prepared according to the following outline. If your research involves social and behavioral research, use the Social/Behavioral Science (SBS) protocol summary.

Please note "N/A" or "not applicable" under any section that does not apply to the proposed research – **do not leave any section blank**.

INTRODUCTION & OBJECTIVES

1. **Background:**

The idiopathic inflammatory myopathies ((IIM)s are a heterogeneous group of disorders characterized by limb girdle muscle weakness and inflammation with or without cutaneous inflammatory disease. IIM include polymyositis (PM), inclusion body myositis (IBM), dermatomyositis (DM) and juvenile DM, each of which is considered a distinct clinicopathologic entity.

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, or 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 corticosteroids 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 but that has been developed during the last years through a collaborative myositis network called the International Myositis Assessment and Clinical Studies Group (IMACS).

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 recognized. 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 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.

Deleted: 4 NOVEMBER 2007

A group of paediatric rheumatologists has started to revise the criteria for this group (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 IIMs. Furthermore, most workers in the field believe that this should be a collaborative effort of specialists in neurology, rheumatology, paediatric, dermatology, pathology and epidemiology and that it should be international to insure greatest acceptance.

2. **Study objectives:**

To develop and validate classification criteria for idiopathic inflammatory myopathies (IIM) and major subgroups of the IIM in adults and children for basic and clinical research, especially clinical trials, and to document the reliability of these new criteria. To test the reliability of these new criteria.
This will be accomplished through a multi-center, international, multi-disciplinary study known as the International Myositis Classification Criteria Project (IMCCP). Each participating center in the IMCCP is asked to perform a retrospective chart review of patients at their center with the IIM and with mimicking conditions. Each center is being asked to contribute 10 -15 IIM patients and 10 - 15 patients with mimicking conditions (in which myositis was a consideration in the diagnosis of the patient or the patient has a condition that might be considered in the differential diagnosis of myositis). Following a first round of data collection, an additional 10 - 15 IIM patients and 10 – 15 with mimicking conditions may be requested from each participating center. If enrollment goals are not achieved, participating sites will be re-contacted to see if they can enroll additional patients (with a maximum of 60 per site). The total number includes 1000 myositis patients (4 major subgroups of PM, DM, IBM and Juvenile DM, and then other miscellaneous subgroups) and 1000 comparator patients (700 adults and 300 pediatric) without myositis

3. **Location: (if applicable)**
This is a multi-center retrospective chart review. Study patients will be identified from the clinical practices of the Departments of Dermatology, Rheumatology or Neurology at the Hospital of the xxxxxxxx

STUDY DESIGN

4. **Research design & methodology**:
The design of this study is a retrospective chart review of IIM patients identified by CPT codes. There are no experimental therapies used in this protocol as it is strictly observational. In addition, no patients are excluded from the study because of particular medications they are taking. No additional laboratory work will be performed. Patients with greater than 30% missing variables on chart review may be contacted for additional information. Verbal informed consent and HIPAA consent will be obtained. Subjects with charts that contain

Deleted: 4 NOVEMBER 2007

greater than or equal to 70% completeness will not be contacted and HIPAA authorization will be waived. Subjects with additional records at other physicians who agree to participate in our study will be mailed a medical records release form to be filled out and signed permitting the Department of xxxxxxxx to obtain more extensive medical records.

5. **Duration**
The subjects will be identified by CPT codes and the review is expected to be completed in 6-12 months from initiation. However there may be further prospective sampling based upon the results obtained.
Once a list is generated from CPT codes, a systematic review of charts from the Departments of xxxxx will commence. Data requested by the IMCCP that is not contained within the charts will be obtained through patient contact via telephone or by medical records from another physician.

SUBJECT SELECTION & WITHDRAWAL

6. **Inclusion & exclusion criteria**
Inclusion: i. The subject has been diagnosed for at least 6 months
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 patients in whom most complete data are available
iv. The most recent cases are chosen first – these would likely result in more consistent evaluations and therapy.

Patients with IIM may include adult or juvenile-onset DM, or PM, IBM, and immune-mediated necrotizing myopathy. DM patients may include amyopathic and hypomyopathic DM. Patients without myositis, but with a mimicking condition may include, but not be limited, to the following conditions:

- □ Non-inflammatory inclusion body myopathy
- □ Dystrophy, specify diagnosis
- □ Metabolic myopathy
- □ Mitochondrial myopathy
- □ Drug or toxin associated myopathy
- □ Infectious myopathy
- □ Endocrine myopathy
- □ Motor neuron diseases
- □ Other neuromuscular disease
- □ Other rheumatic disease
- □ Other dermatologic disease

Deleted: 4 NOVEMBER 2007

Exclusion: Patients without myositis, in which myositis was not considered in the differential diagnosis. Patients with uncertain diagnoses. Patients with a large degree of missing information resulting in a very incomplete data collection form for the study.

7. **Vulnerable populations**

Since there is no intervention taking place in this study, vulnerable populations with a diagnosis of IIM are not excluded from this study unless further information is required that the patient is not able to render or consent is required for medical record release and the patient is not capable of consenting. Pediatric patients are included, but the risk of participation is minimal.

8. **Subject accrual**

To obtain the needed data from 2000 subjects for this study, each center will initially be asked to contribute 10 – 15 subjects with myositis and an equal number of comparator subjects. Preliminary statistical analyses will be conducted after the completion of the first phase of this study and if needed each contributing physician will be asked to contribute up to 10 15 additional subjects with myositis and an equal number of additional comparator subjects. If enrollment goals are not achieved, participating sites may be re-contacted to see if they can enroll additional patients (with a maximum of 60 per site).
We expect a maximum of 60 charts to be reviewed in each center. Since there may be as many as 2000 subjects, obtaining a HIPAA authorization waiver for subjects with greater than 70% chart completion is imperative to decrease extraneous phone calls.

9. **Subject recruitment & screening**

Subjects will be identified by CPT code diagnoses in the clinics of the Departments of Dermatology, Rheumatology, Neurology or Pediatrics. Charts will be reviewed for information contained in the IMCCP data collection form. Missing variables will be obtained through patient contact via telephone. Subjects with missing variables will also be approached for permission to obtain medical records from other health care providers. No referrals from physician offices, clinics, programs, advertisements or brochures will be involved and there will be no handouts, brochures, flyers and advertisements.
All physicians and health care professionals in the Departments of Dermatology, Rheumatology, Neurology and Pediatrics will be notified of this study and will have the opportunity to affect the manner in which their patients are invited to participate. If a physician does not want a particular patient contacted, we will exclude that subject from the study. Direct recruitment by a researcher who has not taken care of the patient may occur by telephone when additional information is required for the data collection form.
Additional subjects will only be recruited if they are seen in clinic during the study period and their charts are referred for inclusion into this study. Otherwise, all subjects will be identified by CPT codes before study initiation.

10. **Data and/or specimens**

a.) Data: The data collection form is attached to this protocol. Demographic, clinical muscle variables, skin variables, family history, onset of symptoms, other clinical variables, muscle biopsy results, laboratory results, EMG, EKG, and MRI results are among the data that will be collected. HIPAA identifiers (Name, MRN, age, elements of date) will only be used to cross-reference patients between the Departments of Dermatology, Rheumatology or Neurology so that patients are not included twice in this study. Name and phone numbers will be used to contact patients for additional information. Data will be collected on the data collection form, then entered into a website base proforma, Survey Monkey, to establish a preliminary database for the study. Linkage to identifying information at each individual study site will be destroyed after the coordinating center obtains a download of the database from Survey Monkey and performs checks for out of range or missing values. The identifying information will be destroyed upon

Deleted: 4 NOVEMBER 2007

resolution of queries from the coordinating center and upon completion of the study data, so that the same patient is not contributed twice during the study.

b.) Specimens: No additional specimens will be collected.

c.) Genetic testing: There will be no genetic testing.

INVESTIGATIONAL AGENT

11. **Drugs/devices: (if applicable)**

No drugs or devices are being tested in this study.

STUDY PROCEDURES

12. **Procedures:**

No procedures or interventions will take place in this study.

STATISTICAL PLAN

13. **Sample size determination:**

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

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.

14. **Statistical methods**:

Since this is a multicenter initiative, the raw data will be compiled by the steering committee and analyzed as aggregate data without any patient identifiers. The sensitivity and specificity of the proposed individual variables and combinations of variables to form new criteria will be tested in 150 patients in a given subgroup of myositis and 500 comparator patients.

CART or Random Forests will be used to develop multiple rules and determine which variables are regularly selected. Another approach will be to randomly select a subset of cases and comparators (e.g. 50%), develop criteria sets on the subset and apply them to the remainder and to repeat this 5 to 10 times to confirm the most sensitive and specific criteria. These will be selected at random and is the derivation set of subjects. The ability

Deleted: 4 NOVEMBER 2007

of the criteria to distinguish between inflammatory myopathies from comparator groups will be tested (construct validity and convergent and divergent validity). The variables will also be tested in subsets of inflammatory myopathies to assess their ability to distinguish between subsets within the inflammatory myopathies. The new study criteria will be assessed in comparison with the Bohan and Peter criteria for myositis, which are the most often used criteria and will thus be the "gold standard" against which the new criteria will be compared for sensitivity and specificity and positive and negative predictive value. New criteria will also be tested against other published criteria of Tanimoto 1995 and Hoogendijk 2004. The ability of the new criteria to distinguish between inflammatory myopathies from comparator groups will be tested. The database will be managed by Dr. Ingrid Lundberg and her associates at the Karolinska Institutet in Stockholm, Sweden. The statistical analysis will be performed by Dr. Peter Lachenbruch, Oregon State University, Corvallis, OR 97330.

SAFETY & ADVERSE EVENTS

15. **Potential risks:**
There is very low risk associated with this study. Patients may be at psychological risk regarding breach of confidentiality (of PHI). It is very unlikely that a breach of confidentiality will occur, but this is always possible. Subjects are also at risk of misunderstanding the purpose of the study and expecting a positive diagnostic or health benefit from participation.

The alternative for this study is not to participate. There is no real risk in this except perhaps guilt of knowing they are not contributing to the advancement of scientific knowledge.

16. **Potential benefits:**
This study offers the possibility of developing standardized, validated criteria for diagnosis and classification of patients with all forms of myositis. It is the hope that criteria will emerge for various myositis subsets that will enable a standardized approach across disciplines and throughout the world for all research studies and therapeutic trials.

17. **Protection of subjects:**
Subject with greater than 70% data collection variables complete will be waived of HIPAA authorization as no direct identifiers will be used after initial cross-referencing between the departments of Dermatology, Rheumatology and Neurology. Subjects with less than 70% data collection variables complete will be protected by obtaining verbal informed and HIPAA consent via telephone and by consenting to release of medical records through written documentation when necessary.

18. **Confidentiality & specimen/data storage**:
a.) Data will be stored on password protected computers and on data collection sheets that will remain at the laboratory of Dr xxxxxxxx
b.) After data collection is complete, personal identifiers will be removed before submission to the IMCCP.
c.) Data will be submitted to the IMCCP using Survey Monkey (http://www.surveymonkey.com/).
d.) Separate databases will be used for information containing protected health information with links to known identifiers kept in a separate, secure password-protected location. Linking data sets will be destroyed at the end of the study and no secondary use of the data will be attempted after study end without subsequent IRB approval.

19. **Data safety & monitoring: (if applicable)**
a.) Stopping rules, unblinding, or subject withdrawal criteria do not apply.

Deleted: 4 NOVEMBER 2007

20. **Risk/benefit ratio:**
    a.) There is minimal risk of harm anticipated in the proposed research as only a fraction of the study population will be contacted regarding this study. Further, no physical or psychological examinations or tests are needed. Thus, the benefit of this study to the individual subjects and society far exceed the potential risks.

ETHICAL CONSIDERATIONS

21. **Informed consent procedures:**
    a.) Patients with less than 70% of data collection variables contained within their chart will be contacted by telephone and informed consent and HIPAA authorization will be obtained verbally by xxxxxxxxx sub-investigator.
    b.) Written consent will be given by patients that consent to the study and require additional medical records released. If adult subjects are not competent to consent on their own behalf, their health care proxy will be contacted for consent or the subject will be excluded from the study. Competency will be assessed by prior medical records.
22. **Request for waived informed consent:**
    (1) Since this is a retrospective data collection without any intervention taking place, the research involves no more than minimal risk to the subjects. Since the most intrusive aspect of this study is either a telephone survey or a request for medical record release, a waiver of written informed consent seems reasonable given the sample size. Further, verbal informed consent and HIPAA authorization will be obtained for contacted subjects.
    (2) The waiver or alteration will not adversely affect the rights *and* welfare of the subjects as those that are contacted will receive verbal consent. Since there is little data linking the subject and the research in this study, a written consent document may bear more risk and potential harm resulting from a breach of confidentiality than a verbal consent for contacted patients and a HIPAA waiver for patients with greater than 70% complete data collection variables on chart review.
    (3) Given the potential sample size of this retrospective data analysis, practically, it would be difficult for the research to be carried out without the waiver for subjects with complete (>70%) records.
    (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

STUDY FINANCES

23. **Compensation to subjects for participation:**
    a.) There will be no compensation of cash payments, free hospitalization, medication, clinical testing, etc. given to patients in this study.

24. **Conflict of interest**
    a.) **No conflict of interest** exists for the principal investigator or any member of the study staff.

PUBLICATION PLAN

25. **Publication plan:**
There is intent to publish and present this research.

Deleted: 4 NOVEMBER 2007