

MUSCULAR DYSTROPHY COOPERATIVE RESEARCH CENTERS

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National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
(<http://www.niams.nih.gov/>)

National Institute of Child Health and Human Development (NICHD)
(<http://www.nichd.nih.gov/>)

National Institute of Neurological Disorders and Stroke (NINDS)
(<http://www.ninds.nih.gov/>)

LETTER OF INTENT RECEIPT DATE: January 15, 2003

APPLICATION RECEIPT DATE: February 24, 2003

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PURPOSE OF THIS RFA

The purpose of this Request for Applications (RFA) is to establish Muscular Dystrophy Cooperative Research Centers (MDCRCs), in order to increase basic and clinical research on all forms of muscular dystrophy. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Child Health and Human Development (NICHD) invite applications for MDCRCs that promote side-by-side basic, translational, and clinical research; provide resources that can be used by the national

muscle biology and neuromuscular research communities; and provide training and advice about muscle diseases for researchers and physicians who provide initial diagnosis and treatment, including rehabilitation, care for cognitive and behavioral concerns, and therapy for other system complications. Taken together, the centers will constitute a cohesive program, the MDCRC Program, operating under guidelines for NIH cooperative agreements.

The primary goal of this initiative is to establish research centers, each of which will bring together expertise, infrastructure and resources focused on major questions about muscular dystrophy. Centers should use innovative research designs and state-of-the-art technologies. Achieving high levels of expertise and resources may require multi-institutional consortia. Centers are expected to provide an environment and core resources that will enhance collaborations of established basic, clinical, and behavioral science investigators to study muscular dystrophy research questions. Further, the environment should promote cross-disciplinary research training. Each center should develop in accordance with available expertise, interests, and resources, but should also be responsive to national needs related to muscular dystrophy. Although the types of activities that should be included are indicated in these guidelines, specific approaches to accomplish them are left to applicants.

In addition to the self-contained activities of individual centers, the MDCRCs will collaborate with other centers, overseen by a Steering Committee involving representation from each center and from NIH. The centers will be funded through NIH Cooperative Agreements with the goal of maximizing collaborative utilization of the unique resources in infrastructure, expertise, and clinical recruitment that will be created.

Investigators interested in applying for support of muscular dystrophy research using mechanisms other than this RFA should see NIH PAS01-041, "Therapeutic and Pathogenic Approaches for the Muscular Dystrophies" at http://www.niams.nih.gov/rtac/funding/grants/pa/pas_01_041.pdf.

RESEARCH OBJECTIVES

Background and Rationale

Muscular dystrophies collectively have a high impact on health, affecting tens of thousands of people in the United States alone. The diseases are characterized by progressive weakness and wasting of muscles. Many cases of muscular dystrophy represent new occurrences of disease, where there is no prior family history. Though research has recently revealed much about genetic defects associated with many forms of muscular dystrophy, treatment for the diseases has not changed significantly. There is a need to learn more about pathogenesis of the diseases and improve early detection and screening, diagnosis, treatment, and prevention.

Duchenne muscular dystrophy (DMD) is most common, affecting approximately one in 3,500 male births. This X-linked disease is characterized by muscle necrosis and

regeneration. The regenerative process cannot maintain normal muscle tissue and mass, resulting in progressive muscle fiber loss and considerable elevations in serum creatine kinase. Affected boys usually must use wheelchairs by age 12, with death often occurring in the third decade from cardiac or respiratory problems. The genetic defect leads to missing or abnormal dystrophin, an important structural protein unknown until the gene was discovered. A milder variant, Becker muscular dystrophy (BMD), is caused by different defects in the DMD gene, that produce truncated but partially functional dystrophin. NINDS, NIAMS and the NIH Office of Rare Diseases sponsored a workshop on Therapeutic Approaches for Duchenne Muscular Dystrophy (DMD), May 15-16, 2000, in Bethesda, MD. The goals of this workshop were to address key questions in improving treatments for DMD and identify areas of needed scientific knowledge, impediments, and critical next steps to promote effective therapy. A summary of the workshop may be found at:

http://www.ninds.nih.gov/news_and_events/dmdmtngsummary.htm.

Myotonic dystrophy (DM) is the most common form of adult onset muscular dystrophy. It is dominantly inherited and characterized by muscle hyperexcitability (myotonia), progressive myopathy, cataracts, defects of cardiac conduction, neuropsychiatric impairment, and other developmental and degenerative manifestations. Myotonic dystrophy is one of the growing number of triplet repeat disorders; it is associated with a CTG expansion in an untranslated region of 19q13.3. Larger numbers of repeats are found in more severely affected individuals, and the number of repeats tends to increase from generation to generation, thus explaining earlier age of onset and increased symptoms in subsequent generations (anticipation). Recently a second form of the disease, Myotonic Dystrophy 2 (DM2), has been shown to be due to a defect on chromosome 3. DM2 appears to be caused by an expanded CCTG repeat, rather than the CTG repeat in DM1. Manifestations of both forms of the disease are similar, though initial weakness is usually in different muscles. One hypothesis for the pathogenesis of DM is that copies of the expanded region interfere with normal expression of unrelated proteins.

Facioscapulohumeral (FSH) muscular dystrophy is an autosomal dominant form that initially affects muscles of the face, scapula (shoulder blades), and upper arms. Symptoms may develop in early childhood and are usually noticeable in the teenage years. A progressive skeletal muscle weakness usually develops in other areas of the body as well; often the weakness is asymmetrical. Life expectancy is normal, but some affected individuals become severely disabled, and some families have an associated hearing loss. Nearly all cases are associated with a distal 4q35 deletion. Because there are no known genes in this region, a novel position effect has been postulated to explain the disease phenotype. NIAMS, NINDS, and the NIH Office of Rare Diseases sponsored a Conference on the Cause and Treatment of Facioscapulohumeral Muscular Dystrophy, held on May 8-9, 2000, in Bethesda, MD. A summary of this meeting may be found at http://www.niams.nih.gov/ne/reports/sci_wrk/2000/fshdexsummary.htm.

The limb-girdle muscular dystrophies (LGMD) are genetically heterogeneous, with both dominant and recessive forms reported. All limb-girdle muscular dystrophies show a

similar distribution of muscle weakness, affecting both upper arms and legs. The recessive LGMDs are more frequent than the dominant forms, and usually have a childhood or teen-age onset. The dominant LGMDs usually show an adult onset. In addition to muscle weakness, the creatine kinase (CK) values are elevated in affected individuals, usually 4-10 times the normal laboratory values. Four of the recessive forms have been associated with defects in genes coding for the sarcoglycan complex, which, along with dystrophin, helps anchor muscles to the extracellular matrix. More devastating mutations in these same genes can cause severe childhood autosomal-recessive muscular dystrophy (SCARMD).

Emery-Dreifuss muscular dystrophy (EMD) is a sex-linked form characterized by wasting of shoulder, upper arm, and shin muscles. Joint deformities are common. It also inflicts serious cardiac problems that can result in premature and sudden death. Cardiac involvement may also cause premature death in female carriers. The responsible sex-linked gene has been located (Xq28), and it has been found to code for a previously unknown protein, called emerin, associated with the muscle membrane. Emerin is normally found in both skeletal and heart muscle. Different mutations of this gene may result in the absence of emerin and thus the disease. A few cases have been found in which emerin is normal, suggesting genetic heterogeneity.

Congenital muscular dystrophy (CMD) is a heterogeneous group of severe autosomal-recessive neuromuscular diseases with early clinical onsets. Manifestations of CMD are evident at birth or in the first few months of life and consist of muscle weakness and hypotonia, delayed motor milestones, severe and early contractures, and, often, joint deformities. Some forms of CMD are associated with central nervous system (CNS) malformations. Some cases of CMD have been attributed to the absence of merosin, a component of laminin. Laminin is the extracellular component of the complex that, together with dystrophin and associated glycoproteins, anchors the muscle cell. The same gene is responsible for one of the animal models of muscular dystrophy, the dy/dy mouse.

Despite advances in knowledge about the genetic defects of these diseases, the life expectancy and quality of life for children and adults with muscular dystrophy have not improved significantly. Recent workshops identified the need for shared research resources and increased collaborative studies, since individual researchers may not have the resources to perform critical research in these areas.

In May 2002, NIAMS, NINDS, and NICHD brought together a Muscular Dystrophy Research Task Force to identify ways to increase the level of understanding of muscular dystrophies and improve diagnosis and treatment approaches. A summary of the first meeting of the Task Force is available at: http://www.niams.nih.gov/ne/reports/sci_wrk/2002/mdmeet.htm. Among other suggestions, the Task Force recommended support for research centers to promote the exchange of ideas and information between basic and clinical investigators. Such centers should have a broad approach including components in training and plans to move new knowledge to a clinical setting.

Objectives and Scope

NIAMS, NINDS, and NICHD seek to establish multidisciplinary Muscular Dystrophy Cooperative Research Centers (MDCRCs) to serve as focal points for collaboration and expansion of research and training on muscular dystrophy. Each MDCRC is to support an integrated basic and clinical research program focused on improving knowledge and treatment of muscular dystrophy. The close interaction between basic researchers and clinicians will accelerate the translation of fundamental advances to the clinic and the utilization of patient materials for basic research.

Collectively and in cooperation with NIH, the centers will be part of a national MDCRC Program. The Steering Committee that is described below is to help coordinate this program. For example, collaborative activities between funded MDCRCs, which may include full or pilot research projects, will be developed and monitored by the Steering Committee. In addition, collaborations may be developed with other federally funded projects related to muscular dystrophy, such as the National Registry for Myotonic Dystrophy and Facioscapulohumeral Dystrophy (see <http://www.niams.nih.gov/hi/registry/registry.htm#dystrophy>) or recent initiatives from the CDC. This does not preclude applicants from including such collaborations within proposed research projects.

The MDCRCs are to emphasize new ideas, novel approaches, and state-of-the-art technology to increase understanding of the basic mechanisms of disease pathogenesis and facilitate translation of that knowledge to design and evaluate clinical interventions to prevent or treat muscular dystrophy. Muscular dystrophy research requires multidisciplinary approaches, based on expertise in muscle biology, genetics, imaging, muscle plasticity, exercise science and physical therapy, nutrition, molecular biology, neuroscience, rehabilitation medicine, epidemiology, clinical trials, bioengineering, electrophysiology, psychology, and behavioral sciences. Health care providers include neurologists, rheumatologists, cardiologists, orthopedists, pediatricians, medical geneticists, physiatrists, and rehabilitation practitioners, as well as nurses and primary care practitioners. Applicants are encouraged to include researchers representing a broad range of approaches, including, as appropriate, skilled investigators who have been involved in areas other than muscular dystrophy.

Centers should encourage specialized training of personnel in cross disciplinary approaches. It is expected that the centers will be planned so as to facilitate the inclusion of trainees sponsored through separate mechanisms. MDCRCs are to maximize the resources, technologies, investigators, disciplines, and concepts that will build a foundation for basic, applied and clinical research. Likewise, these centers should promote education of diverse health care trainees in the diagnosis, treatment and prevention of the muscular dystrophies and their complications, and should model the utilization of multi-disciplinary management teams.

Applicants are encouraged to use innovative and novel approaches to studying and treating disease. Examples that illustrate possible areas of research are presented below.

They are intended only to provide a broad direction for research and should be considered illustrative and not restrictive. General examples of scientific topics are:

- o study pathogenic mechanisms leading from gene defects to muscular dystrophy phenotypes;
- o clarify the role of inflammatory changes that accompany tissue degeneration; e.g., explore the relationship between inflammatory cells, muscle cell death, and blood vessels;
- o clarify relationships between genotype and natural history of disease;
- o develop improved outcome measures and methods to monitor changes due to treatment or disease progression;
- o study the involvement of apoptotic cell death in the process of muscle fiber degeneration;
- o develop methods and procedures, such as enhanced imaging that will provide for better monitoring of disease processes;
- o examine genetic heterogeneity, and search for additional candidate genes;
- o examine genotype/phenotype correlations within and between families;
- o determine if the dystrophin-glycoprotein complex has both a mechanical and signaling role;
- o study properties of muscle cells derived from affected tissue;
- o determine basis of differential involvement of muscles, reflected by the regional pattern of disease;
- o pursue the development and sharing of appropriate animal models for muscular dystrophies;
- o explore further development of new types of therapy, including gene transfer and gene correction;
- o pursue the development of improved pharmacological therapeutic approaches, and determine mechanisms of action;
- o improve techniques for possible gene transfer therapies, by optimizing the expression cassette, improving the design of viral vectors, clarifying and managing immunologic consequences, and optimizing gene delivery in terms of tissue targeting and efficiency of transfecting cells;

- o expand studies on alternative (non-viral) approaches that target either the utrophin gene or the endogenous dystrophin gene;
- o expand the use of muscle stem cells for possible therapy, through clarifying their origin and developmental state;
- o improve conditions for culturing and expanding cell populations;
- o determine if stem cells can be delivered through the circulatory system efficiently and effectively;
- o improve therapeutic value of protein expression from transplanted myoblasts;
- o promote bioengineering and other innovative research into rehabilitation of patients with muscular dystrophies;
- o expand research into the pathogenesis of non-muscle system associated with muscular dystrophies; and
- o encourage research into the psychosocial, emotional, behavioral and cognitive aspects of muscular dystrophy, including mental health concerns of affected persons and families.

ORGANIZATION OF MUSCULAR DYSTROPHY COOPERATIVE RESEARCH CENTERS

Each MDCRC will include at least one basic research project and one clinical research project, with a minimum of three individual, but interrelated, research projects. At least one project should be collaborative or discussed in terms of its ability to be expanded through collaborations. There will be an Administrative Core and at least one Scientific Research Resource Core that will serve as a resource for the national muscular dystrophy research effort. Research projects should have high scientific merit and clear research objectives, and be organized around a central theme related to muscular dystrophy. Research projects should have mutually supportive interactions between basic scientists and clinical investigators.

NIH defines human clinical research as: (1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or a colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies. (2) Epidemiologic and behavioral studies. (3) Outcomes research and health services research.

Each MDCRC will have a Center Director (the Center Principal Investigator) who will make scientific and administrative decisions relating to the center, will oversee identification and selection of key personnel, and will be responsible for allocation and monitoring of MDCRC funds. The Center Director will work closely with a Co-Director. It is recommended that the Director and Co-Director separately provide leadership in basic and clinical research. The Director and Co-Director should have a demonstrated capability to organize, administer and direct the center. It is expected that the Director and Co-Director will have a substantial investment in the center and be its scientific leaders. Thus, each should have a minimum total time commitment (including core and project activities) of 20% to the MDCRC. Direction and decisions for each center will be undertaken with the advice of its own executive committee and Scientific Advisory Committee, as described below.

Each center will have a team of appropriate investigators. Involvement of several departments and disciplines will broaden the scientific basis of muscular dystrophy research. Collaborations among different institutions are encouraged, if scientifically appropriate. To make an application competitive for support, there should be substantial and appropriate infrastructure and departmental and institutional support set in place that will allow the proposed center to accomplish the goals of the MDCRC Program.

MDCRC support is not intended to be a substitute for individual grant support. It is, therefore, expected that project and core leaders will have independent, peer-reviewed research support. It is desirable for MDCRC-supported research to complement other funded research related to muscular dystrophy taking place at the applicant institution, including activities supported by R01, P01, and other mechanisms. It is anticipated that resources and projects that are in place with funding from sources other than the MDCRC Program will synergistically interact with MDCRC infrastructure, cores, and projects. The application should explain how MDCRC support would facilitate the development and progress of related projects that may not be an integral component of the MDCRC itself.

o Administrative Core

The successful operation of each MDCRC will require the integration of the activities of several projects and cores, as well effective organization of the efforts of scientific and professional personnel from a variety of disciplines and subspecialties. This requires substantial effort by the principal investigator and the presence of an administrative structure to organize the flow of information, distribution of effort, allocation of resources, and to implement other necessary administrative functions. This will require an administrative core or its equivalent. The administrative requirements of each MDCRC will necessitate the assistance of an administrator with business management expertise. It is important that such an individual be identified and directly involved with the fiscal and administrative aspects of the MDCRC application and award. It is expected that the MDCRC administrative structure will facilitate the following:

- 1) coordination and integration of MDCRC components and activities;

- 2) planning and review of the utilization of funds;
- 3) provide support and advice for the MDCRC Director and Co-Director in his/her oversight of the activities of the center;
- 4) interact with the scientific and lay communities to develop relevant goals for the MDCRC within the immediate environment of the Center;
- 5) interact with other MDCRCs and the Centers' NIH Science Officers to develop trans-MDCRC research activities. The Science Officer is the NIH representative who implements the NIH aspects of the Cooperative Agreement in each Center;
- 6) promote the use of the core facilities among researchers within the parent institution and among investigators in other institutions. Information on the activities and opportunities present at the MDCRC should be made available to as broad a community as possible, through websites or other appropriate mechanisms.

o Scientific Research Resource Core(s)

The Scientific Research Resource Cores are to serve as resources for the national muscular dystrophy research effort in addition to supporting research within the MDCRC. Sharing of unique and powerful research tools is expected to foster collaborations across departments or schools at a single institution, as well as among investigators at several institutions. They should be designed to attract researchers and foster interactive approaches to questions relevant to muscular dystrophy. The MDCRC will show how scientific research resource cores will develop to provide research resources for investigators not affiliated with the center.

Examples of scientific cores include, but are not limited to: medical imaging (fMRI, PET, MRS, optical imaging), statistics and research design (clinical trial design, database management, patient registries, epidemiology), special animal facilities (primate centers, transgenic/knockout technology), bioengineering/biomechanics (gait analysis, tissue engineering, biomaterials), or molecular biology (genetic screening, gene discovery, bioinformatics). Resources could include development and sharing of model organisms for muscular dystrophies, bioinformatics and computational services for information relevant to muscle disease, DNA chips and similar devices for microarray analysis of gene expression, improved imaging of healthy and diseased muscle, and high-throughput mass spectrometric analysis. Please refer to the summaries of NIH sponsored meetings on muscular dystrophy for further examples and discussions of resources:

http://www.niams.nih.gov/ne/reports/sci_wrk/2002/mdmeet.htm;

http://www.ninds.nih.gov/news_and_events/dmdmtngsummary.htm;

http://www.niams.nih.gov/ne/reports/sci_wrk/2000/fshdexsummary.htm.

o Executive Committee

In order to assist the Center Director and Co-Director in making scientific and administrative decisions, each center will establish an executive committee, composed of the Center Director, Co-Director, project leaders, core directors, and the administrator. The executive committee should be encouraged to seek outside advice and consultation, both from within the institution and from other institutions, in its monitoring and development of the scientific content and direction of the program.

o Scientific Advisory Committee (SAC)

Each MDCRC will also establish a SAC consisting of scientists from outside of the institution or consortium to advise the Director and Co-Director regarding the activities of the Center. The inclusion of public members is encouraged. Final appointment of SAC members will require NIH approval. This committee will be used to evaluate the programs of the Center, research progress, the effectiveness of communications within the Center, and any other activities for which outside expertise is required or desirable. The committee should meet at least annually and the NIH Science Officer for that Center and the Program Officer for the MDCRC Program should be invited to attend each meeting as observers. The SAC will prepare an annual report including recommendations to assist the Center. Copies of the SAC's report will go to the Director, Co-Director, the appropriate NIH Science Officer, and to the Program Officer.

o Genetics Data Sharing in the MDCRC Program

NIH has a strong interest in the sharing of data and other resources produced through its funding, and has long-standing policies in this area (for the most recent statement, see the NIH Grants Policy Statement, page II-62, "Unique Research Resources," published in October 1998, related to the distribution of unique research resources produced with DHHS funding (<http://grants.nih.gov/grants/policy/nihgps/>)).

More specific policies have been promulgated from time to time to address the needs of particular areas of research. For example, NIH has worked with journals and databases to encourage the rapid placement of unpublished DNA sequence data and crystallographic coordinates into public databases. The National Human Genome Research Institute has a policy that all genomic data, whether published or not, should be shared as rapidly as possible and placed in the public domain (http://www.nhgri.nih.gov/Grant_info/Funding/Statements/RFA/new_data_release.html). For grantees engaged in large-scale sequencing, the policy specifies data release within 24 hours of generation (<http://www.genome.gov/page.cfm?pageID=10000910>).

Each application for MDCRC support must include a plan for the sharing of genetic materials and data. This plan will be evaluated during the peer review of the application. This sharing plan should address the issues raised in the following paragraphs. The timeline for sharing of genetic data will be compatible with the timeline for sharing of other types of data as described under 6. Public Domain of Data (below).

MECHANISM OF SUPPORT

This RFA will use the National Institutes of Health (NIH) specialized cooperative research center (U54) award mechanism, in which the Principal Investigator retains the primary responsibility and dominant role for planning, directing, and executing the proposed project, with NIH staff being substantively involved as a partner with the Principal Investigator, as described under the section "Cooperative Agreement Terms and Conditions of Award." Applicants should request five years of support. It is anticipated that competitive renewal applications for a second 5-year period will be allowed.

Use of the Cooperative Agreement Mechanism

The use of a cooperative agreement mechanism for this RFA is intended to enhance coordination among MDCRCs in order to increase the impact of the MDCRC Program on the public health issues of muscular dystrophy. The U54 mechanism implements a process of NIH coordination, guidance, and ongoing evaluation. For example, it will permit NIH participation in a process of standardizing diagnostic and other tools across the MDCRCs in collaboration with the Center Directors and investigators. It will permit awardee and NIH participation in the Steering Committee (described below) that will make decisions about collaborative studies that will use the resources of multiple centers, thus exceeding the capabilities present in any one center.

FUNDS AVAILABLE

NIAMS, NINDS, and NICHD intend to commit approximately \$4,500,000 in FY 2003 to fund 2 to 3 new grants in response to this RFA. An applicant must request a project period of 5 years. The direct costs requested cannot exceed \$1,000,000 each year (exclusive of facilities and administrative costs of subcontracts with collaborating organizations). Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. Although the financial plans of NIAMS, NINDS, and NICHD provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications. It is anticipated that this RFA will be reissued in 2004 for funding in FY 2005.

ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your institution has any of the following characteristics:

- o For-profit or non-profit organizations
- o Public or private institutions, such as universities, colleges, hospitals, and laboratories
- o Units of State and local governments
- o Eligible agencies of the Federal government
- o Domestic

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

SPECIAL REQUIREMENTS

Note: The Following website has been established as an information resource for this RFA: http://www.niams.nih.gov/rtac/funding/grants/muscular_dystrophy_coop.htm.

To be funded, an MDCRC must include at least three highly meritorious scientific projects approved for five years. One of these must have the MDCRC Director as the principal investigator, and the highly meritorious projects must include one that is basic research and one that is clinical research. At least one project should be collaborative or discussed in terms of its ability to be expanded through collaborations. There should be an Administrative Core and at least one Scientific Research Resource Core that will serve as a resource for the national muscular dystrophy research effort.

The Director, Co-Director, and all project and core PIs should be prepared to devote at least 20 percent effort to the MDCRC.

The Administrative Core Budget should include 5 percent of the total budget (up to \$50,000 per year) for Travel and Collaborative Activities developed through the Steering Committee and for Travel, including travel by the Director and Co-Director to an annual one-day meeting with NIH staff in Bethesda, Maryland.

MDCRCs must commit to cooperate fully and to share data concerning patients, control subjects and specimen resources within the MDCRC Program, and with the broad scientific community, as specified by NIH.

COOPERATIVE AGREEMENT TERMS AND CONDITIONS OF AWARD

As part of the U54 Cooperative Center Grant process, the following Terms and Conditions of Award and details of the arbitration procedures pertaining to the scope and nature of the interaction between the NIH staff and the participating awardees will be incorporated into the Notice of Grant Award and provided to the Principal Investigator and the institutional official at the time of award. These procedures will be in addition to the customary programmatic and financial negotiations that occur in the administration of grants.

Cooperative agreements are assistance mechanisms subject to the same administrative requirements as grants. The special Terms and Conditions of Award are in addition to, and not in lieu of, otherwise applicable OMB administrative guidelines, HHS Grant Administration Regulations at 45 CFR Part 74 and 92, and other HHS, PHS, and NIH grant administration policies and procedures. Cooperative Agreements are subject to the

administrative requirements outlined in pertinent OMB, HHS, PHS, and NIH guidelines, with particular emphasis on HHS regulations at 42 CFR Part 52 and 45 CFR Part 74. Facilities and Administrative Cost (indirect cost) award procedures will apply to cooperative agreement awards in the same manner as for grants.

The administrative and funding instrument used for this program is a Cooperative Agreement (U54), an "assistance" mechanism (rather than an "acquisition" mechanism) in which substantial NIH scientific and/or programmatic involvement with the awardee is anticipated during performance of the activity. Under the cooperative agreement, the NIH purpose is to support and/or stimulate the recipient's activity by involvement in and otherwise working jointly with the award recipient in a partner role, but it is not to assume direction, prime responsibility, or a dominant role in the activity. Consistent with this concept, the dominant role and prime responsibility for the activity resides with the awardee(s) for the project as a whole, although specific tasks and activities in carrying out the studies will be shared among the awardees and an NIH Science Officer.

Failure of the awardees to meet the performance requirements, including these special terms and conditions of award, or significant changes in level of performance, may result in a reduction of budget, withholding of support, suspension and/or termination of the awards.

1. Awardee Rights and Responsibilities

Awardees have primary authorities and responsibilities to define objectives and approaches, and to plan, conduct, analyze, and publish results, interpretations, and conclusions of their studies. The primary responsibilities of the awardees are to:

- o Define the research objectives
- o Design the necessary research protocols
- o Conduct specific studies
- o Analyze and interpret research data
- o Propose protocol modifications as required
- o Establish a Scientific Advisory Committee to the Center
- o Provide information to the NIH Science Officer and NIH Program Officer concerning progress
- o Interact with the Food and Drug Administration (FDA) concerning clinical investigations, when appropriate

- o Maintain career development opportunities to encourage new investigators to work in the field of muscular dystrophy research
- o Serve on the MDCRC Steering Committee
- o Participate in MDCRC collaborative activities approved by the Steering Committee
- o Agree to sharing of data and biological materials in accordance with approved sharing plans
- o Agree to participate in any centralized data facility that may be established according to Steering Committee policies
- o Abide by all scientific, practical and policy decisions of the Steering Committee

Awardees will retain custody of and primary rights to their data and intellectual property developed under the award, subject to current government policies regarding rights of access as consistent with current HHS, PHS, and NIH policies and subject to the terms and conditions of this RFA. All research publications shall be submitted to NIH for administrative and policy review prior to submission for publication. This review shall not be for the purpose of scientific oversight, but rather to ensure that NIH policies and/or representations that may imply NIH endorsement of clinical or research standards are not proposed. These reviews may not unreasonably delay submission for publication.

2. NIH Responsibilities

NIH Science Officers:

NIH Science Officers will be NIH program staff that will have substantial scientific involvement during the conduct of this activity, through technical assistance, advice, and coordination above and beyond normal program stewardship for grants. Each Center will have a designated NIH Science Officer, and a given individual may be the NIH Science Officer for more than one Center. The NIH Science Officers will be selected by the NIAMS, NINDS, and NICHD. The degree of involvement by the NIH Science Officers will include the following:

- o Assist in coordinating collaborative research efforts that involve multiple centers and avoiding unwarranted duplication of effort across centers;
- o Review and comment on critical stages in the research program before subsequent stages are implemented;
- o Assist in the interaction between the awardee and the FDA, when appropriate;
- o Assist in the interaction between the awardee and investigators of other institutions, as well as between the awardee and potential commercial sponsors;

- o Retain the option of recommending termination of studies if technical performance falls below acceptable standards, or when specific lines of research cannot be effectively pursued in a timely manner;
- o Retain the option to recommend additional research endeavors within the constraints of the approved research and negotiated budget;
- o Serve on the MDCRC Steering Committee.

NIH Program Officer:

NIAMS, NINDS, and NICHD will jointly appoint a Program Officer who will have program oversight responsibilities for each Center and for the entire MDCRC Program. This individual will not be a Science Officer. The Program Officer will:

- o Exercise the normal stewardship responsibilities of an NIH Program Officer
- o Carry out continuous review of all activities to ensure objectives are being met
- o Have the option to recommend withholding support to a participating institution if technical performance requirements are not met
- o Will not be a member of the MDCRC Steering Committee

3. Data Safety and Monitoring Board

NIH will facilitate establishing a Data Safety and Monitoring Board (see http://www.niams.nih.gov/rtac/clinical/safe_monitoring_plan.htm).

4. Collaborative Responsibilities/Steering Committee

Overall coordination of the MDCRC Program, consistent with the stated intent of the RFA, will be done by a Steering Committee consisting of the Principal Investigators of each MDCRC, NIH Science Officers, a public member, and a bioethicist. An NIH grants management representative will serve as liaison to the Steering Committee. Each Center Director (or designee) and Science Officer will have one vote. Center membership on the Steering Committee becomes effective upon issuance of the Notice of Grant Award. The Steering Committee may establish additional bylaws, subcommittees, or workgroups for specific tasks. Science Officers may not chair any committee or subcommittee. The Steering Committee meetings will be convened at least once yearly. The purpose of these meetings is to share scientific information, assess scientific progress, identify new research opportunities, and discuss strategy and potential avenues of collaborations such as with industry, private foundations and/or NIH intramural scientists, establish priorities that will accelerate the translation of preclinical findings into clinical applications, reallocate resources and conduct the business of the cooperative research program. Decisions will be made by a majority vote of a quorum, with an attempt for consensus

when possible. A quorum is the presence of a majority of the Center Directors and at least one Science Officer. The Steering Committee can convene through telephone conferences or in person. Outside consultants/experts may be asked to participate in these discussions as nonvoting advisors. Collaborative projects among the MDCRCs will require Steering Committee approval. It is expected that new collaborative programs will not replace the projects originally proposed in applications for MDCRC support, but will be supported by the funds set aside in the Administrative Core budget for this purpose. The Steering Committee may also be used to endorse research instruments that will be used across multiple centers.

Steering Committee members will abide by all scientific, practical, and policy decisions of the Steering Committee. Any Center Director who considers a Steering Committee decision unacceptable may appeal by following the arbitration procedure described below.

5. Arbitration Process

When agreement between an awardee and NIH staff or between awardees cannot be reached on scientific/programmatic issues that may arise after the award is made, an arbitration panel will be formed. The arbitration panel will consist of one person selected by the Directors of the Centers, one person selected by the NIH, and a third person selected by both NIH staff and the Directors. The decision of the arbitration panel, by majority vote, will be binding. The special arbitration procedure in no way affects the right of an awardee to appeal any adverse action in accordance with PHS Regulations at 42 CFR Part 50, Subpart D, and HHS Grant Administration Regulations at 45 CFR Part 74, section 304, and HHS Regulations at 45 Parts 16 and 75.

6. Public Domain of Data

The data from this cooperative agreement will first be available to be analyzed and interpreted by the collaborators in the project. However, since the creation of the data set is funded through public monies and because the data set will constitute a national scientific resource for the research community, the awardees will make data of all types available to the larger research community no more than 24 months from the date after which the final waves of data for a particular project have been collected and cleaned. More rapid sharing of data is encouraged.

7. Scientific Advisory Board

The Steering Committee will recommend a Scientific Advisory Board (SAB) of independent experts in the research areas represented among the centers. The SAB will be appointed by and report to NIH (namely NIAMS, NINDS, and NICHD). It will advise the Steering Committee on the scientific aspects of MDCRC activities, including providing review of collaborative studies that will need to be approved by the Steering Committee before being implemented. The SAB will participate in the annual meeting of the Steering Committee and be consulted as necessary. There should be at least seven

members of SAB, at least one a public member. There may be overlap between the SAB and the NIH Muscular Dystrophy Research Task Force (see http://www.niams.nih.gov/ne/reports/sci_wrk/2002/mdmeet.htm).

8. Progress Reviews

Progress of the MDCRC will be reviewed annually by the NIH Program Officer at the time each continuation application is considered for funding to assure that satisfactory progress is being made in achieving the project objectives and that each site is following the procedures recommended and approved by the Steering Committee. During the first year of funding, and during subsequent years, if deemed necessary by the Program Officer, reviews will be more frequent. Human subject enrollment should be reported every six months. Should problems arise in the conduct of the Center, the NIH Program Officer may require that the awardee submit quarterly reports on progress and fiscal matters. By acceptance of this award, the awardee agrees to abide by decisions and policies of the Steering Committee and the other terms and conditions listed above or referenced in the Notice of Grant Award.

WHERE TO SEND INQUIRIES

We encourage inquiries concerning this RFA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

o Direct your questions about scientific/research issues to:

Richard W. Lymn, Ph.D.
Chief, Muscle Biology Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
One Democracy Plaza
6701 Democracy Blvd., Suite 800
Bethesda, MD 20892-4872
Telephone: (301) 594-5128
FAX: (301) 480-4543
Email: LymnR@mail.nih.gov

James W. Hanson, M.D.
Chief, Mental Retardation and Developmental Disabilities Branch
Center for Research for Mothers and Children
National Institute of Child Health and Human Development
6100 Executive Blvd., Room 4B09 MSC 7510
Bethesda, MD 20892-7510
Telephone: (301) 496-1383
FAX: (301) 496-3791
Email: hansonj@mail.nih.gov

Giovanna M. Spinella, M.D.
Neurogenetics and Development Program
National Institute of Neurological Disorders and Stroke
6001 Executive Blvd. Rm. 2132
Rockville, MD 20892-9527
Telephone: (301) 496-5745
FAX: (301) 401-1501
Email: gs41b@nih.gov

o Direct your questions about peer review issues to:

Alan Willard, Ph.D.
Chief, Scientific Review Branch,
National Institute of Neurological Disorders and Stroke
6001 Executive Blvd. Rm. 3208
Rockville, MD 20892
Telephone: (301) 496-5390
FAX: (301) 402-0182
Email: aw135y@nih.gov

o Direct your questions about financial or grants management matters to:

Melinda Nelson
Grants Management Officer
National Institute of Arthritis and Musculoskeletal and Skin Diseases
One Democracy Plaza
6701 Democracy Blvd. Suite 800
Bethesda, MD 20892-4872
Telephone: (301) 594-3535
FAX: (301) 480-5450
Email: nelsonm@mail.nih.gov

Christopher Myers
Grants Management Officer
National Institute of Child Health and Human Development
Building 6100E/Room 8A17
6100 Executive Blvd. MSC 7510
Bethesda, MD 20892-7510
Email: cm143g@nih.gov

Sheila Simmons
Grants Management Officer
National Institute of Neurological Disorders and Stroke
6001 Executive Blvd. Rm. 3250
Rockville, MD 20892
Telephone: (301) 496-9231

FAX: (301) 402-0219

Email: simmonss@ninds.nih.gov

LETTER OF INTENT

Prospective applicants are asked to submit a letter of intent that includes the following information:

- o Descriptive title of the proposed research
- o Name, address, and telephone number of the Principal Investigator
- o Names of other key personnel
- o Participating institutions
- o Number and title of this RFA

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows NIH staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent by the date listed at the beginning of this document. The letter of intent should be sent to:

Richard W. Lymn, Ph.D.
Chief, Muscle Biology Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
One Democracy Plaza
6701 Democracy Blvd., Suite 800
Bethesda, MD 20892-4872
Telephone: (301) 594-5128
FAX: (301) 480-4543
Email: LymnR@mail.nih.gov

PRE-APPLICATION MEETING

The NIAMS, NINDS, and NICHD anticipate holding a pre-application meeting in January 2003, through a teleconference to which all interested prospective applicants are invited. Program and review staff will make presentations that explain their goals and objectives for the Muscular Dystrophy Cooperative Research Centers and answer questions from the attendees. Prospective applicants are urged to monitor the NIH Guide Notice for the date and time of the meeting at

<http://grants.nih.gov/grants/guide/index.html>.

Additionally, consult the following website, established as an information resource for this RFA: http://www.niams.nih.gov/rtac/funding/grants/muscular_dystrophy_coop.htm

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at <http://grants.nih.gov/grants/funding/phs398/phs398.html> in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

SPECIFIC INSTRUCTIONS FOR PREPARING AN APPLICATION

Use form PHS 398 (<http://grants.nih.gov/grants/funding/phs398/phs398.html>). Each budget unit (project or core) should be written in the style and within the page limitation described in the PHS 398 instruction kit. To aid in the review of these applications, the applicant should assemble the component units following the format described below. Additional instructions for preparing an MDCRC grant application and sample formats are available at the following URL link: http://www.niams.nih.gov/rtac/funding/grants/muscular_dystrophy_coop.htm.

Please note that each part of the application should be complete in itself, as different reviewers may review different parts.

SECTION I - GENERAL INFORMATION FOR THE ENTIRE APPLICATION

A. FACE PAGE

This is Form Page 1 of the application; number succeeding pages consecutively.

Complete all items on the face page as directed. In the title block, item 1, put "MUSCULAR DYSTROPHY COOPERATIVE RESEARCH CENTER." Mark item 2 "yes" and write in the RFA code AR03-001, as listed in the NIH Guide to Grants and Contracts, and "MUSCULAR DYSTROPHY COOPERATIVE RESEARCH CENTERS" for the title.

B. DESCRIPTION, PERFORMANCE SITES, AND KEY PERSONNEL

On Form Page 2, describe briefly the proposed program indicating the goals and objectives of the research projects and identify the purposes of the proposed cores. Do not exceed the space allowed. List key scientific and technical personnel participating in the Center. Use continuation pages as necessary, numbering consecutively.

C. TABLE OF CONTENTS

Adapt this page from Form PHS 398 and write a Table of Contents appropriate for the MDCRC grant application, following these instructions. This is paginated to follow the list of Key Personnel. Do not use letters (e.g., 4a, 4b, 4c, etc.). The Table of Contents should list all projects and cores for which funding is sought. Each project and core should be listed by the title and Principal Investigator. Specifically list the locations of

the checklist and the various requested supporting documents, e.g., animal and human subject assurances, and bibliographies.

D. BUDGET ESTIMATES

To aid in the review of your application, it is suggested that the forms found as pages 4 and 5 in PHS Form 398 be used for all budgets. Justify and document all costs for current and future years throughout. Prepare a series of composite Budget Tables for the Center as requested below.

1. Composite Budget

The direct costs requested cannot exceed \$1,000,000 each year (exclusive of facilities and administrative costs of subcontracts with collaborating organizations). The Administrative Core Budget should include 5 percent of the total budget (up to \$50,000 per year) for Travel and Collaborative Activities developed through the Steering Committee.

a. Use Form Page 4, "DETAILED BUDGET FOR INITIAL BUDGET PERIOD," of the PHS 398 to present the total direct cost budget for all requested support for the first year. For each category, such as "PERSONNEL," "EQUIPMENT," etc., list the amount requested for each research project and for each core unit.

If consortium arrangements have been made involving other institutions or organizations, include total costs (direct and F&A) associated with such third party participation in the "CONSORTIUM/CONTRACTUAL COSTS" category. Costs for purchased services should be itemized under "OTHER EXPENSES."

b. Use Form Page 5, "BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD," of the PHS 398 to prepare a budget, by category, that provides direct cost totals for each year of requested support.

E. BIOGRAPHICAL SKETCHES

Biographical sketches are required for all key scientific and technical personnel participating in the research projects and core units as listed on Form Page 2.

Beginning with the Center Director and Co-Director, and following in alphabetical order, submit biographical sketches as described in the "Instructions for Form PHS- 398," using Form Page 6.

G. ENVIRONMENT AND RESOURCES

Complete the "RESOURCES" section on Form Page 8 of the PHS 398 for the overall Center. Briefly describe the features of the institutional environment that are or would be relevant to the effective implementation of the proposed program. As appropriate,

describe available resources, such as clinical and laboratory facilities, participating and affiliated units, patient populations, geographical distribution of space and personnel, and consultative resources. Include information on the support and commitment of the parent institution for the Center. Use continuation pages as needed. Include any supporting letters from the Institution.

H. CENTER LEADERSHIP

The emphasis in this section should be on the qualification of the MDCRC leadership. Describe the qualifications of the MDCRC Director to lead the program, and that of the Co-Director to assist.

I. INTRODUCTORY OVERVIEW OF THE CENTER (10-page limit)

Provide an overview of the entire proposed Center describing the research central theme and goals. Describe how the overall Center can achieve its major objectives. Explain the proposed contribution of each of the projects in achieving the objectives of the Center. Furthermore, the administrative arrangements and support necessary to effect the research should be carefully described in the application. Shared resources should be described. In addition, provide detailed information on collaborations, recruitment, facilities and resources.

1. Purpose and Objectives of the Center. Discuss the philosophy and objectives of the Center and general plans for the proposed grant period. Discuss the composite research program, highlighting its central theme. List by title and investigator the component research projects and core units, showing the interrelationship between the research projects and the core units and their relationship to the central theme. Describe relevant history leading up to the Center application.

2. Administration, Organization, and Operation of the Center. Include information on the support and commitment of the parent institution for the Center, the authority of the Director, the use of advisory committees, and the method of determining core access and space assignment. Describe an organizational framework and provide an organizational chart.

3. Assurances and Collaborative Agreements. Any arrangements for collaborative and cooperative endeavors or subcontracting should be highlighted. Letters of Intent to Collaborate and Letters of Agreement from consultants should be referenced here and included at the end of the appropriate research project or core unit.

J. PROGRESS REPORT/PRELIMINARY DATA PERTAINING TO THE WHOLE CENTER (5-page limit)

This section should be used to present, in condensed form, previously published and/or preliminary data that are relevant to proposed center activities and research projects that will be unique to the center and will involve collaboration across projects and/or cores

within the center. Since individual projects, and preliminary data relevant to them, will be described in the following section, only those collaborative activities/projects that bear directly on the proposed center activities should be summarized here. For ongoing projects or existing cores, list relevant publications published or accepted for publication during the past five-years. The list of publications does not count against the page limit.

SECTION II. PROPOSALS FOR INDIVIDUAL PROJECTS AND CORES

A. PROJECTS: Identify each project by an Arabic numeral (1, 2, 3, etc.) and a title. For each component research project, a full description is to be provided following the format and page limits presented in Form PHS 398. Begin the presentation of each component research project on a separate cover page. The description of each project must be complete in itself, as different reviewers may review different projects. Each research project will receive a priority score. At least one project should be collaborative or discussed in terms of its ability to be expanded through collaborations.

For each project, include the following information using Form PHS 398:

1. Face Page. Do not use Form 398 face page; instead, use plain paper, and include the following information:
 - a. Project Title
 - b. Project Principal Investigator, degree, title, location
 - c. Other investigators, consultants, and collaborators, degrees, titles (Associate Professor, Postdoctoral Fellow, student).
2. Description, Performance Site(s) and Personnel (use Form Page 2 of PHS 398)
3. Budget (use the budget pages from Form PHS 398)
 - a. First year (use Form Page 4 of PHS 398 for each)
 - b. Total project period (use Form Page 5 of PHS 398 for each)

Consortium Budgets (if applicable) should be presented as described in Item 1 (Composite Budget), including a budget for the entire proposed project period. Total Direct and F&A costs of sub-awardees are to be shown under "CONSORTIUM/CONTRACTUAL COSTS" on individual research project or core budgets and a detailed consortium budget is to be inserted following the appropriate research project or core budgets.

Budget Justifications: Describe the specific functions of key scientific and technical personnel, consultants, collaborators, and support staff. For all years, explain and justify any unusual items such as major equipment or alterations and renovations. For future years of support requested, justify any significant increases in any category over the first 12-month budget period. Identify such significant increases with asterisks against the appropriate amounts.

4. Resources and Environment (use the relevant pages from Form PHS 398)
5. Research Project Plan (Do not exceed 25 pages for Sections a-d)

Start with an Introductory remark addressing: (i) whether and how it is a clinical project; and (ii) its relevance to the overall theme of the Center. Then address the following:

- a. Specific Aims
- b. Background and Significance
- c. Preliminary Studies
- d. Research Design and Methods. In addition to usual contents of this section, describe the research project's use of core unit services, including need for the services, and the advantages and cost effectiveness of core unit usage for the project.
- e. Human Subjects. For research involving human subjects, this section must address: Protection of Human Subjects; the inclusion of women, minorities and their subgroups, and children as research subjects; and Data and Safety Monitoring Plan as provided in the instructions for PHS 398.
- f. Vertebrate Animals
- g. Literature Cited
- h. Consortium/Contractual Agreements: including pertinent letters of assurance and intent.
- i. Consultants: including pertinent letters of assurance and intent.

B. CORES: Identify each proposed core unit by a letter (A, B, C..., core A being the Administrative Core and Core B will be a Scientific Research Resource Core) and a title (Administrative, Molecular/Cellular...). For each core, a full description is to be provided following the format and page limits presented in Form PHS 398. Begin the presentation of each core on a separate cover page. The description of each core must be complete in itself, as different reviewers may review different cores, without cross-referencing. Each core will be rated using an adjectival descriptor, such as outstanding, excellent, or poor.

A core is a shared central laboratory or clinical research facility, service, or resource. A core may be a unit designed just for the MDCRC projects or may be an institutional core unit. However, funds may only be requested for MDCRC use, and the core must serve a minimum of two projects within the MDCRC, with no project dominating use of the core. Each core is directed by a faculty investigator (the Core Director) with substantial expertise related to the core. Applicants should document and describe briefly the

projects that will depend upon resources provided by the cores (clinical cores, in particular).

Scientific Research Resource Cores should be able to support research for projects by researchers not in the MDCRC. Two important and related considerations are (1) the degree to which currently funded investigators within or outside the center will use and benefit from core resources and (2) the degree to which the resources will promote new and/or expanded muscular dystrophy research efforts locally, regionally or nationally. The core principal investigator should devote at least 20 percent effort to the core.

For each core, include the following information using Form PHS 398:

1. Face Page. Do not use Form 398 face page; instead, use plain paper, and include the following information:
 - a. Core Title
 - b. Core Director, degree, title, location
 - c. Other investigators, consultants, and collaborators, degrees, titles (Associate Professor, Postdoctoral Fellow, student).
2. Description, Performance Site(s) and Personnel (use Form Page 2 of PHS 398)
3. Budget (use the budget pages from Form PHS 398)
4. Resources and Environment (use the relevant pages from Form PHS 398)
5. Research Plan. This part also should be presented using the headings a-i, as described for Projects above, taking care that the following ADDITIONAL points are addressed in appropriate sections:

For Research cores:

- a. a decision-making process for use of the core unit
- b. plans for quality control
- c. a summary table for the first year of the proposed grant showing the quantitative use (percent) of the core unit by the component research projects
- d. cost effectiveness
- e. cost recovery, if any

For Scientific Research Resource Cores, also discuss:

- f. suitability as a resource for the national muscular dystrophy research effort
- g. plans for access by researchers outside the MDCRC
- h. plans for setting priorities of access and use

For the Administrative core, the following additional points should be addressed in the "Research Plan" Section:

- a. the authority of the Director
- b. advisory committees
- c. an organizational framework and organizational chart
- d. a contingency plan in case the Center director is unable to perform his responsibilities
- e. services that will be provided

The Administrative Core Budget should include 5 percent of the total budget (up to \$50,000 per year) for Travel and Collaborative Activities developed through the Steering Committee.

SECTION III - CHECKLIST - As required in Form PHS 398

SECTION IV - APPENDIX

Include materials as appropriate (see PHS 398). All appendix material must be clearly marked with the name of Center Director and the appropriate project or core. Separate copies of appendix material should be supplied for each core or project to which it is applicable.

USING THE RFA LABEL: The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: <http://grants.nih.gov/grants/funding/phs398/label-bk.pdf>.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the Checklist, and three signed, photocopies, in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

At the time of submission, two additional copies of the application, including all appendix material, must be sent to:

Richard W. Lymn, Ph.D.
Chief, Muscle Biology Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
One Democracy Plaza
6701 Democracy Blvd., Suite 800
Bethesda, MD 20892-4872
[Bethesda, MD 20817 (for express/courier service)]

APPLICATION PROCESSING: Applications must be received by the application receipt date listed in the heading of this RFA. If an application is received after that date, it will be returned to the applicant without review.

The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an Introduction addressing the previous critique.

PEER REVIEW PROCESS

Applicants should keep in mind that the written application is the basis for the merit review. Site visits are not anticipated. Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the NIH program staff. Incomplete and/or non-responsive applications will be returned to the applicant without further consideration.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by NIH in accordance with the review criteria stated below. As part of the initial merit review, all applications will:

- o Receive a written critique
- o Undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed and assigned a priority score
- o Receive a second level review by the National Advisory Councils for NIAMS, NINDS, and NICHD.

REVIEW CRITERIA

The criteria to be used in the evaluation of grant applications are listed below.

The Centers must include three or more individual research projects, which reflect hypothesis-driven research, plus shared research resources (cores). The application must represent more than an interesting collection of projects. It is critical that there is evidence of the potential for a meaningful center with a real theme and identity.

A. RESEARCH PROJECTS

Reviewers will evaluate each research project using the criteria listed below and assign a priority score. Each criterion will be addressed and considered by the reviewers in assigning the overall score for project merit:

(1) SIGNIFICANCE: Does your study address an important problem? If the aims of your application are achieved, how do they advance scientific knowledge? What will be the effect of these studies on the concepts or methods that drive this field?

(2) APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Do you acknowledge potential problem areas and consider alternative tactics?

(3) INNOVATION: Does your project employ novel concepts, approaches or methods? Are the aims original and innovative? Does your project challenge existing paradigms or develop new methodologies or technologies?

(4) INVESTIGATOR: Are you appropriately trained and well suited to carry out this work? Is the work proposed appropriate to your experience level as the principal investigator and to that of other researchers (if any)?

(5) ENVIRONMENT: Does the scientific environment in which your work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

B. SHARED RESOURCES (CORES)

Each core will be evaluated and assigned an adjectival descriptor.

1. Adequacy of the justification for each specialized resource relative to its essential need for the conduct of MDCRC research and MDCRC collaborative projects.
2. Adequacy of qualifications and performance (if applicable) of managers of resources to conduct high quality, reliable resource operations.
3. Appropriateness of the requested budgets to conduct each resource operation.
4. Adequacy of plans for oversight of resources and the prioritization of work.

SCIENTIFIC RESEARCH RESOURCE CORES

In addition to the above, the following criteria will be addressed:

5. Value as a national resource for research on muscular dystrophy.
6. Accessibility to researchers not a part of the MDCRC.
7. The quality of the system to set priorities for access and use as a shared resource.

C. ADDITIONAL REVIEW CRITERIA SPECIFIC TO MDCRC PROGRAM

Listed below are additional review criteria to be used in the evaluation of MDCRC applications; these criteria will be applied to applications by evaluating preliminary work to organize the center, history of muscular dystrophy research by the applicants, and plans for implementation of the proposed program.

Applicants should clearly demonstrate the ways in which the MDCRC would contribute to the growth of local research programs, support ongoing projects, cooperate with other MDCRCs in collaborative research, and attract both senior and new investigators to muscular dystrophy.

It is anticipated that inclusion of a 'weak' or 'nonessential' project in the application will reflect poorly on the overall program. In addition, NIH retains the right to delete individual projects when making final funding decisions regarding MDCRC applications, for example, those that score below the current R01 funding level. It will be mandatory for each successful application to include at least three fundable research projects. At least one of the fundable projects must be clinical research as defined above.

Specific Review Criteria:

Each project will receive a priority score. This score reflects not only the feasibility of the project and adequacy of the experimental design, but also the design of the project to advance both the theme of the MDCRC and the interaction between basic research and clinical investigation.

1. How the proposed MDCRC combines basic and clinical research into the scientific goals and research theme;
2. Scientific merit of each proposed project.
3. Scientific merit of combining the component parts into an MDCRC;
4. Technical merit and justification of each core unit; will each core enhance collaborative and/or interdisciplinary research within the MDCRC and the wider research community?
5. Competence of the investigators to accomplish the proposed research goals, their commitment, and the time they will devote to the research program;
6. Adequacy of facilities to implement the goals of the MDCRC Program and perform the proposed research, including laboratory and clinical facilities, instrumentation, and data management systems, when needed;
7. Adequacy of plans for interaction among investigators, the integration of the various projects and core units, and potential for interaction with scientists from other departments and components;

8. Qualifications, experience and commitment of the MDCRC Director and his/her ability to devote time and effort to provide effective leadership; evidence for the scientific and organizational vision;

9. Scientific and administrative structure, including internal and external procedures for monitoring and evaluating the proposed research and for providing ongoing quality control and scientific review;

10. Effectiveness of the proposed center in meeting the purpose of the RFA, namely, does it promote side-by-side basic, translational, and clinical research; provide resources that can be used by the national muscle biology research community; and provide training and advice about muscle diseases for researchers and physicians who provide initial diagnosis and treatment? What are the potentials for collaborations with other MDCRCs and investigators?

11. Management capabilities for the Center that include fiscal administration, procurement, property and personnel management, planning, and budgeting;

12. Institutional commitment to the program, and the appropriateness of resources and policies for the administration of an MDCRC, including faculty positions for muscular dystrophy research.

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, your application will also be reviewed with respect to the following:

o PROTECTIONS: The adequacy of the proposed protection for humans, animals, or the environment, to the extent they may be adversely affected by the project proposed in the application.

o INCLUSION: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria included in the section on Federal Citations, below).

RECEIPT AND REVIEW SCHEDULE

Letter of Intent Receipt Date: January 15, 2003
Application Receipt Date: February 24, 2003
Scientific Review Date: May/June 2003
Advisory Council Date: September 2003
Earliest Date of Award: September 2003

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

- o Scientific merit (as determined by peer review)
- o Availability of funds
- o Programmatic priorities, including balance between muscular dystrophy research and scientific resource areas.

REQUIRED FEDERAL CITATIONS

MONITORING PLAN AND DATA SAFETY AND MONITORING BOARD: Research components involving Phase I and II clinical trials must include provisions for assessment of patient eligibility and status, rigorous data management, quality assurance, and auditing procedures. In addition, it is NIH policy that all clinical trials require data and safety monitoring, with the method and degree of monitoring being commensurate with the risks (NIH Policy for Data Safety and Monitoring, NIH Guide for Grants and Contracts, June 12, 1998: <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>).

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH: It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the AMENDMENT "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001

(<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html>);

a complete copy of the updated Guidelines are available at

http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

. The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS:

The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at

<http://grants.nih.gov/grants/funding/children/children.htm>.

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT

PARTICIPANTS: NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. You will find this policy announcement in the NIH Guide for Grants and Contracts Announcement, dated June 5, 2000, at

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html>.

HUMAN EMBRYONIC STEM CELLS (hESC): Criteria for federal funding of research on hESCs can be found at http://grants.nih.gov/grants/stem_cells.htm and at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html>. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see <http://escr.nih.gov>). It is the responsibility of the applicant to provide the official NIH identifier(s) for the hESC line(s) to be used in the proposed research. Applications that do not provide this information will be returned without review.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF

INFORMATION ACT: The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this RFA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

URLS IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at <http://www.health.gov/healthypeople>.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance Nos. 93.846 (NIAMS), 93.853 (NINDS), and 93.865 (NICHD) and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies described at <http://grants.nih.gov/grants/policy/policy.htm> and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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