Two Phase Request for Proposals: Population-based US Prevalence of Mutations for Myotonic Dystrophy Types DM1 & DM2.

Phase One: Development and validation of screening methodology (Issued)
Phase Two: Implementation of Population-based US Screen (Anticipated issue date: 4-1-16)

Solicitation Name: 2015-PDMPhase1-MDF
Contracting Office Address:

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Contracting Officer: Sharon Hesterlee, Ph.D, Research Director, MDF
Place of Performance: United States or Canada
Date Issued: April 28th, 2015
Proposals Due: July, 1, 2015, 5:00 PM PDT
Notification of Selection: September 20, 2015
Period of Award: October 1, 2015 – March 1, 2016
Anticipated Overall Award: $50,000 Each
Number of Phase I Awards: Two

Synopsis:

The Myotonic Dystrophy Foundation (MDF) is pleased to announce the availability of funding under the first of a two phase request for proposals to conduct a population-based prevalence study in the United States of genetic mutations and pre-mutations[1] responsible for myotonic dystrophy (DM) types 1 and 2 (DM1 and DM2).

MDF, based in San Francisco, CA, is the world's largest patient organization focused solely on myotonic dystrophy (abbreviated as DM after its Latin name *dystrophia myotonica*). In addition to comprehensive patient support and advocacy work, the Foundation focuses on improving quality of life for those with the disease and advancing the basic and clinical science searching for a cure for DM. MDF partners with, and complements the work of, the National Institutes of Health (NIH), the Centers for

Disease Control and Prevention, and other governmental, advocacy, academic, and philanthropic organizations.

Diagnosed rates of prevalence for DM range 0.46 to 210/100,000 in different European populations; specific US prevalence information is lacking. Given that the diagnostic odyssey for the disease may last 7 years for DM1 and 14 years for DM2[1], it is possible that the mutation load in the population is significantly higher than the diagnosed prevalence. Accurate information regarding how many people, in the US have DM1 and DM2 mutations, or are at risk of repeat expansion, will improve service provision, basic research, drug development and policymaking related to DM.

The first phase of this RFP will provide funding to develop and validate a cost-effective screening methodology capable of estimating the prevalence of DM1 and DM2 mutations and pre-mutations in the general US population.

Based on the results from Phase 1 funding, the Foundation anticipates issuing a second phase of this RFP on April 1, 2016 will provide funds sufficient to implement a screen in a group representative of the general population, for example via newborn bloodspots, or via banked blood from other ongoing studies as appropriate, with the statistical power to extrapolate to the whole US population with a 95% confidence interval no more than +/- 25% of the prevalence estimate. Although applicants applying for Phase 2 funding will be required to demonstrate that they can use valid laboratory methods to perform the proposed work, they need not have been funded in Phase 1 of this RFP in order to successfully apply for Phase 2 funding.

Phase One: Development and validation of screening methodology.

Study Requirements:

- Develop and validate a screening methodology that can be used to estimate the prevalence of DM1 and DM2 mutations and pre-mutations in the general US population in a statistically appropriate number of blinded samples using a secondary method such as southern blot and/or haplotype analysis.

For the purpose of this application the following definitions[2] will apply:

Normal: 5-34 repeats

Premutation: 35-50 repeats

Potential Symptomatic or Symptomatic: >51 repeats

Rationale:

Myotonic dystrophy is a highly variable genetic disorder, affecting multiple organ systems, including the eye, brain, and endocrine, gastrointestinal, reproductive and cardiopulmonary systems, in addition to both smooth and skeletal muscle. Impacts are

understood to be less severe in DM2 than in DM1, and significantly more severe in the congenital- and juvenile-onset phenotypes.

Estimates of the prevalence of diagnosed DM1 reported in the research literature vary widely, from 0.5-18.1 per 100,000 in specific population groups, almost all of which are in Europe.[3] The prevalence of diagnosed DM in the general US population is not known. Although a general prevalence of 1/8000 is often quoted either for DM1 or DM1 and DM2 combined, the source is often not referenced and the accuracy of this estimate is in question.

Beyond diagnosed cases, the prevalence of the expanded repeats for DM1 and DM2 in in the general US population is also not known. One study has examined DM1 and DM2 mutations in the general Finnish population and found the DM2 mutation represented at a higher than predicted rate based on diagnosed cases[4.]

Studies in other repeat expansion diseases have also found higher-than-predicted rates of the expansion in the population. For example, a recent UK population-based study of the c9orf72 mutation linked to ALS and frontotemporal dementia determined that the carrier rate for the expanded repeat was significantly higher than anticipated and also that the repeat expansion was associated with other neurological disorders such as Huntington's, a fact not previously appreciated[5].

An accurate understanding of the epidemiology of DM, both diagnosed and undiagnosed, is a fundamental building block for efforts to improve treatment resources and develop a cure for DM. The ability to speak confidently about the true burden of disease will enhance the credibility of advocates when they speak with policy makers about treatments and research towards a cure. An understanding of whether certain population groups have higher prevalence will guide resource allocation and targeting of outreach efforts for treatment. An accurate understanding of the potential "market" for pharmaceutical products for treatment of DM will help make it easier to attract investment and research by pharmaceutical companies.

In addition, a better understanding of the "mutation load" in the US population, including both mutation and pre-mutation for DM1 and DM2, will lay the groundwork for determining the true penetrance of these mutations (including the influence of modifiers) and for studies designed to investigate the rate of conversion from pre-mutation to mutation.

Until recently the diagnosis of DM was based on identifying a complex set of clinical signs and symptoms, many of which are not specific for DM. However, the recent development of a laboratory test for the genetic mutations associated with the disease raises the potential for wide scale, population-based screening of the general population and establish an accurate prevalence of the disease in the US population. Although this test has been used for patients with clinical symptoms of DM, its use for wide-scale screening has not been evaluated.

Eligibility

Proposals are welcome from academic institutions, government agencies and/or multidisciplinary teams encompassing several organizations. Submitting organizations or teams must meet the following requirements:

- Organizations or teams must have access to the knowledge, resources and skills necessary to carry out the proposed research, including access to samples from a large enough population;

- Phase I proposals that are incomplete or in excess of the maximum budget limit will be excluded from the process, unless external funds are available to support the proposed budget; and
- The study organization or team must confirm that the funds awarded will only be used to execute the DM prevalence study; indirect costs and overhead charges will not be funded or allowed through this study award.

Submission Process and Requirements

Proposals cannot exceed 10 pages in length, and must be submitted in 12 point font. Proposals must be submitted via email to elizabeth.habeeb-louks@myotonic.org by July, 1, 2015, 5 PM Pacific time.

The proposal must include the following (within 10 pages):

- Names, degrees, training, qualifications, experience, role in project and percentage effort for team members
- Documentation of study team members' prior experience in the administration and management of epidemiological prevalence studies and in laboratory analysis appropriate for the proposed study methodology, along with related research published by team members
- Brief abstract of research upon which the study proposal is based, with references
- Detailed description of proposed screening rationale and methodology, including any examples of the use of the methodology in other disease areas or preliminary data from its use in myotonic dystrophy; include assumptions, validation strategy and relevant citations
- Strategy for obtaining relevant tissue, if needed, with supporting documentation as appropriate demonstrating availability/access to tissue samples
- Description of plan for implementing the screening methodology for a whole population screen, including estimated sample size needed and cost (work beyond the scope of this RFP, but please describe, briefly, how this might be accomplished in the future)
- Description of facility(ies) that will be used to develop and test screening methodology
- Description of in-kind institutional contributions that will be provided if selected for award
- Cover sheet provided by MDF for this RFP (see attached)

In addition, (not included in the 10 page count) proposals must include:

- Detailed budget in spreadsheet or table format
- Accompanying budget description and justification
- CVs of all participating team members

Review and Selection Process

All proposals must be received by the submission deadline and in compliance with the eligibility criteria provided above. Eligible proposals will be peer-reviewed by two committees of subject matter experts: one focused on laboratory methods and one focused on epidemiology.

Proposals will be evaluated based on the following criteria:

- Addresses the research question as outlined in the Specific Study Requirements section above
- Ability to complete the project including adequacy of resources available, reasonableness of timelines, qualifications of identified study team members and scientific rigor and validity of proposed methods
- Potential for wide dissemination and use of study results, including specific plans for scholarly publications, public presentations and white papers
- Appropriateness of project budget to project scope
- Qualifications of team leadership/principal investigator including previous history of work in the area, successful completion of previous funded projects, research awards and publications

Other Conditions of Award

- Funded researchers must receive approval from their institution's review board (IRB) for any work involving human subjects before grant funds will be released.
- All study institutions and project work must be HIPAA compliant as applicable.
- Upon study completion, funded study teams must produce a report for MDF that includes an executive summary and a detailed description of the screening methodology. Investigators are also strongly encouraged to publish their results in a peer-reviewed journal.

Questions regarding this RFP may be directed to Sharon Hesterlee, research director, Myotonic Dystrophy Foundation, at sharon.hesterlee@mytonic.org, or via phone at 520-444-4462.

References

1.Hilbert JE, Ashizawa T, Day JW, *et al*. Diagnostic odyssey of patients with myotonic dystrophy. *J Neurol* 2013; **260:** 2497-504.

2 Kamsteeg E-J, Kress W, Catalli C, *et al*. Best practice guidelines and recommendations on the molecular diagnosis of myotonic dystrophy types 1 and 2. *Eur J Hum Genet* 2012; **20:** 1203-8.

3.Theadom A, Rodrigues M, Roxburgh R, *et a*l. Prevalence of muscular dystrophies: a systematic literature review. *Neuroepidemiology* 2014; **43**: 259-68.

4. Suominen T, Bachinski LL, Auvinen S, *et al*. Population frequency of myotonic dystrophy: higher than expected frequency of myotonic dystrophy type 2 (DM2) mutation in Finland. *Eur J Hum Genet* 2011; **19**: 776-82.

5 .Beck J, Poulter M, Hensman D *et al*. Large C9orf72 Hexanucleotide Repeat Expansions Are Seen in Multiple Neurodegenerative Syndromes and Are More Frequent Than Expected in the UK Population. *Am J Hum Genet*. 2013; **7**: 345-53.