
Phase One: Development and validation of screening methodology (Issued)
Phase Two: Implementation of Population-Based US Screen (Issued 4 April 2016)

Solicitation Name: 2015-PDM Phase2
Contracting Office Address:

    Myotonic Dystrophy Foundation
    1004A O'Reilly Avenue
    San Francisco, CA 94129, USA
    E-mail: elizabeth.habeeb-louks@myotonic.org
    Phone: 415-800-7777

Contracting Officer: John Porter, Ph.D, Interim Chief Science Officer, MDF
Place of Performance: does not have to be UK or US
Date Issued: 4 April 2016
Proposals Due: 1 September 2016, 5:00 PM PDT
Notification of Selection: 15 December 2016
Period of Award: 1 January 2017 – 31 December 2017
Anticipated Overall Award: Up to $500,000
Number of Phase II Awards: One

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

The Wyck Foundation, based in the UK, focuses on funding grants that accelerate drug development and research discovery for myotonic dystrophy, as well as discrete advocacy projects. 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).
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 RFA provided 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.

This phase II RFA 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 RFA in order to successfully apply for Phase 2 funding.

**Phase Two: Population-based Screen**

**Background:**

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.\(^2\) 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 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\(^3\).

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\(^4\).
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.

**Study Requirements:**

The proposed study must address two goals:

- Substantively improve knowledge about the true population prevalence of DM1 and DM2 mutations in the US as a whole.
- Enhance experience with techniques to rapidly screen large numbers of tissue samples for DM1 and DM2 mutations and pre-mutations.

Applicants must clearly explain in their proposal how their proposed study will address these goals.

Applicants will be expected to screen tissues from a large sample of individuals that is representative of the US population as a whole or from which an estimate can be extrapolated for the US population as a whole. Newborn bloodspots from an entire state are one example of such a sample of tissues. While the racial and ethnic makeup and sex distribution of newborns in each state may differ, a national prevalence estimate can be generated by summing the prevalence of DM mutations in each demographic group weighted according to the national distribution of race, ethnicity and sex.

Screening of tissues from patients with health conditions that are associated with DM, and therefore likely to yield higher numbers of positive screens than a general population sample, may also be acceptable, as long as any major biases in the representativeness of the sample can be controlled for and a valid national estimate can be derived. Tissues from a consecutive series of patients with early cataracts may be one example of such a population sample. Although some bias may be introduced into this sample by the fact that only those patients who seek health care would be represented in the sample, the condition is so disabling that it seems likely that most patients would have sought care. Again, weighting by demographic and perhaps other variables could be employed to generate a national estimate.
Both DM1 and DM2 mutations and premutations must be screened for.

The sample of tissues screened must be sufficiently large to generate estimates with a 95% confidence interval that is no more than +/- 25% of the prevalence estimate itself.

Investigators must report the number of screens that are normal, have a pre-mutation or have a mutation that is potentially symptomatic, according to the following definitions:

- Normal: 5-34 repeats
- Pre-mutation: 35-50 repeats
- Potential Symptomatic or Symptomatic: >51 repeats

Investigators must also generate a prevalence estimate for these three health states for the US population as a whole, using a credible methodology. If appropriate, investigators may present estimates generated using a range of credible assumptions, rather than just a single estimate.

**Eligibility**

Proposals are welcome from academic institutions and/or biotechnology or pharmaceutical companies. Collaborative projects are encouraged.

- Applicants or teams of applicants must have access to the knowledge, resources and skills necessary to carry out the proposed research
- Submitting PIs and Co-PIs must:
  - Be a professional or faculty member at an appropriate educational, medical or research institution, or company and be qualified to conduct and supervise a program of original research;
  - Have both administrative and financial responsibility for the grant;
  - Have access to organizational resources necessary to conduct the proposed research project; and
  - Hold a Doctor of Medicine, Doctor of Philosophy, Doctor of Science or equivalent degree.

Applicants from academic institutions or companies outside the US are permitted.

**Submission Process and Requirements**

Proposals cannot exceed 10 pages in length, and must be submitted in 11-point font. Proposals should be submitted via email to MDF Grants Manager Elizabeth Habeeb-Louks (elizabeth.habeeb-louks@myotonic.org) no later than 1 September, 2016 5pm Pacific time.

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

1. Brief lay abstract, no more than four sentences
2. Technical abstract of no more than two paragraphs
3. 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

4. Strategy for obtaining biological samples, if needed, with supporting documentation as appropriate demonstrating availability/access to samples

5. Description of plan for implementing the screening methodology for a whole population screen, including estimated sample size needed, cost and timeline.

6. If the application involves a collaboration, description of the rationale for, and logistics of the collaboration, including contributions of all parties, plan for communication and sharing of equipment and/or team members;

7. Figures (may be embedded in text or included at the end)

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

8. References

9. Detailed budget in spreadsheet or table format (see “Other Requirements” for instructions on dividing the budget between collaborators)

10. Accompanying budget description and justification (1000 words or less)

11. Description of facility(ies) and equipment, if any, that will be used for the project (one paragraph)

12. Very brief: Names, degrees, training/qualifications, experience, role in project and percent effort for team members from both groups in the collaboration (may be submitted as a table)

13. CVs of all participating team members;

14. Letters from collaborators and/or in support of the application

15. Face page provided by MDF for this RFA (see attached)

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 reviewed by an ad hoc committee of subject matter experts, including those with expertise in diagnostic and screening methods, epidemiology and statistics.

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 and budget, 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 and results. Investigators are also strongly encouraged to publish their results in a peer-reviewed journal.

Questions regarding this RFA may be directed to John Porter, Chief Science Officer, Myotonic Dystrophy Foundation, at john.porter@myotonic.org, or via phone at.

References


