

PROGRAM CONTACT: **SUMMARY STATEMENT** **Release Date:** 12/07/2010
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Application Number: 1 R01 HD069039-01

Principal Investigators (Listed Alphabetically):
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Applicant Organization: MICHIGAN PUBLIC HEALTH INSTITUTE

Review Group: ZHD1 MRG-C (19)
 National Institute of Child Health and Human Development Special Emphasis
 Panel
 Natural History

Meeting Date: 11/02/2010 *RFA/PA:* HD10-019
Council: JAN 2011 *PCC:* IDD -TU
Requested Start: 04/01/2011

Project Title: Inborn Errors of Metabolism Collaborative: Defining the Natural History of Inborn

SRG Action: Impact/Priority Score: 20

Human Subjects: 30-Human subjects involved - Certified, no SRG concerns

Animal Subjects: 10-No live vertebrate animals involved for competing appl.

Gender: 1A-Both genders, scientifically acceptable

Minority: 1A-Minorities and non-minorities, scientifically acceptable

Children: 1A-Both Children and Adults, scientifically acceptable

Clinical Research - not NIH-defined Phase III Trial

Project Year	Direct Costs Requested	Estimated Total Cost
1	741,920	999,801
2	742,156	1,000,119
3	741,987	999,891
4	742,222	1,000,208
5	742,054	999,981
TOTAL	3,710,339	5,000,000

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

RESUME AND SUMMARY OF DISCUSSION: This application, submitted in response to RFA-HD-10-019, entitled "Natural History of Disorders Identifiable by Newborn Screening", proposes to collect data that capture the clinical progress of persons affected with 27 metabolic conditions identified by newborn screening. This application represents a comprehensive attempt to monitor outcomes from expanded newborn screening. The investigators have already been successfully working together through the HRSA established Region IV Genetics Collaborative, presenting preliminary data for piloting infants identified as having medium chain acyl CoA dehydrogenase (MCAD) deficiency as well as the collection and analysis of data on 233 subjects with 19 inborn errors of metabolism. The likelihood of success is therefore very high. Nevertheless, there are some reservations of possible shortage of staff at clinical sites to screen the large number of disorders included in the study. Overall, the application has considerable merit and it is recommended for further consideration as requested with high enthusiasm.

DESCRIPTION (Provided by Applicant): Newborn blood spot screening is undertaken with the primary assumption that early diagnosis and treatment is a good investment of public resources, both for the individuals tested and for society. Although some effects of improved outcomes seem self-evident, for most newborn-screened disorders there is no comprehensive, long-term assessment of outcomes for children identified by screening. To verify the effectiveness of early identification, intervention, and treatment, longitudinal assessment of outcomes is essential. A better understanding of the natural histories of rare metabolic disorders and the effectiveness of current treatments is necessary to provide optimum care and promote the best possible outcomes for children with these conditions.

The Inborn Errors of Metabolism Collaborative (IBEMC), consisting of 13 clinics from 10 states, will collect longitudinal data that capture the clinical progress of persons affected with conditions identified by newborn screening, focusing on inborn errors of metabolism. Data will be used to better define the natural histories and understand the effect of treatment interventions. The database will allow for: 1. Investigation of the relationship among NBS values, genotype, and early manifestations as well as complications of inborn errors of metabolism; 2. Evaluation of the impact of early identification and intervention on metabolic conditions; 3. Informed decision making about optimal public health investment in NBS; 4. Clarification of the previously undefined natural history of very rare metabolic conditions; and 5. Identification of current nutritional and therapeutic interventions for children with metabolic conditions and evaluation of their effectiveness.

The IBEMC will build on the work of the HRSA-funded Region 4 Genetics Collaborative and be developed in collaboration with other national efforts, including the Newborn Screening Translational Research Network. The project will establish innovative practices to engage clinicians in a culture of collaboration, provide incentives to ensure collection of both intake and interval data, as well as offer supports that encourage data analysis. These efforts will result in investigations that provide a foundation for clinical trial design and improved treatment for children with inborn errors of metabolism.

RELEVANCE: As a sufficient number of cases are entered for the rarer disorders, research will provide evidence as to the efficacy of early diagnosis and treatment. If research does not support the assumption on which NBS is based, *i.e.*, early diagnosis and treatment are good investments of public resources, both for the individuals tested and for society, the NBS public health paradigm may change. It is possible that the increase in knowledge about the natural history of IBEM will lead to a change in how conditions are added to the NBS panel and that the conditions currently in the panel may be reviewed and revised.

CRITIQUE NOTE: The sections that follow are the essentially unedited, verbatim comments of the reviewers assigned to this application. They are provided to illustrate the range of opinions expressed. The application was discussed and scored by all reviewers present. The attached commentaries may not necessarily reflect the position of the reviewers at the close of group discussion, nor the final

majority opinion of the group. The Resume and Summary of Discussion, however, is the authoritative representation of the final outcome of group discussion.

CRITIQUE 1:

Significance: 1
Investigators: 2
Innovation: 1
Approach: 2
Environment: 1

Overall Impact: Strengths

- This application proposes to use data from the Inborn Errors of Metabolism Collaborative (IBEMC), made up of 13 clinics from 10 states, building on a collaboration funded by HRSA to the Region IV Genetics Collaborative. The investigators state that all sites have received IRB approval and have begun collecting data. They present some preliminary data on infants identified as having medium chain acyl CoA dehydrogenase (MCAD) deficiency on newborn screening. Likelihood of success is high, given that these investigators have already been successfully working together and collecting data.
- The investigators plan to collect data on 27 metabolic conditions (excluding PKU and urea cycle disorders). They have already collected data on 233 subjects with 19 conditions. It is estimated that, by the end of the five-year period, information on 2,146 cases with metabolic disorders will be entered into the database. Given the broad range of disorders included in the study and numbers of cases estimated to be collected, ample data will be available for analysis.
- The investigators have put together a plan to share data with investigators inside and outside the collaborative. This will increase the likelihood that the data will be used, and it is likely that multiple publications will result from this effort.
- Overall, this project has a high likelihood of having a sustained powerful impact on the field.

Weaknesses

- No major weaknesses noted.

1. Significance: Strengths

- This project addresses an important problem in the field. As the investigators note, decisions about the current panel of metabolic disorders included in expanded newborn screening were based on expert opinion, for the most part, without a strong evidence base. This project will describe the natural histories of children identified with these disorders, and will evaluate whether factors that predict the severity of disease can be identified (e.g., initial levels on newborn screening, genotype, etc.).
- The investigators note that the expected data could have a significant impact on treatment and management of these disorders, as well as in how decisions might be made about newborn screening for disorders in the future. When parents consent to be included in the database, they are also asked if they are willing to be contacted for future studies. Thus, the database will serve as a source of patients that could be included in clinical trials of future interventions.

Weaknesses

- No major weaknesses noted.

2. Investigators:

Strengths

- Drs. Cynthia Cameron and Susan Berry are well-suited to this project. Most of the co-investigators are established with a strong track record of accomplishments that have advanced the field.
- Dr. Cynthia Cameron is currently Director for the Region 4 Genetics Collaborative. It appears that she has been effective in this position. She is working closely with Dr. Susan Berry, a well-recognized expert in metabolic disorders and newborn screening.
- Other investigators are also appropriate.
- The investigators note that statistical expertise will be available to clinically-oriented investigators, so that lack of this expertise will not limit the types of projects that can be done.

Weaknesses

- No publications are listed on Dr. Cameron's biosketch; however, her skills appear to be in project coordination, and she has put together a strong team with metabolic expertise and ample experience with publication.

3. Innovation:

Strengths

- This project builds on efforts of the HRSA-funded Region 4 Collaborative. This will mean that the investigators will be able to start collecting data shortly after funding begins (*e.g.*, IRB approval has already been obtained, database is already up and running, etc.)
- The investigators note some key questions in the area of metabolic disorders and provide preliminary data to answer one of these questions.
- They plan to share their database with investigators inside and outside their collaborative. Issues regarding data sharing appear to have already been considered.

Weaknesses

- No major weaknesses noted.

4. Approach:

Strengths

- This application builds on work of a collaborative group that has already shown to be successful. Infrastructure, IRB approval, etc. are already in place. Funds from NIH would be used to improve data collection (*i.e.*, improve likelihood of prompt data entry by funding study coordinators in each site). By working together collaboratively, the investigators estimate that they will have collected data on 2,146 cases. Although these numbers are for 27 metabolic disorders and the distribution is not specified, this should provide sufficient numbers for analyses of several disorders.
- Population to be studied is "any individuals ascertained by newborn blood spot screening or clinical presentation as having an inborn error of metabolism" – this will potentially increase number of cases by extending to those diagnosed symptomatically.
- The investigators will use DocSite, a flexible and secure database that has a number of features that allow confidential pooling of data.
- The investigators specifically address how they will coordinate efforts with the Newborn Screening Translational Research Network (by meeting twice a year with study investigators, including one meeting in conjunction with NBSTRN).

- The application has included a timeline (benchmarks) and anticipated challenges (including proposed solutions).

Weaknesses

- It would be helpful to know the number of cases that are estimated to accrue for some of the more common metabolic disorders.
- In addition, it would be helpful to know how estimates of numbers of cases were calculated.

5. Environment: Strengths

- The scientific environment will contribute to the probability of success. The plan for a project that is a collaborative group increases the likelihood of collecting sufficient numbers for meaningful analysis.
- Institutional support at the different sites appears appropriate. The primary need at each site is for a metabolic clinic and for computer support.

Weaknesses

- No major weaknesses noted.

Protections for Human Subjects:

Acceptable risks and/or adequate protections

- Appropriate plans are in place for protection of human subjects. Just one comment – it is stated in the application that all 13 sites have received IRB approval, yet the date for the University of Pittsburgh is listed as pending.

Data and Safety Monitoring Plan:

Not applicable (no clinical trials)

- Clinical Trials are not part of this project, although the investigators mention the possibility of doing a clinical trial in the future looking at different doses of carnitine supplementation in MCAD -- if this is done, a Data and Safety Monitoring Plan may need to be developed.

Inclusion of Women, Minorities and Children:

G1A - Both genders, acceptable

M1A - Minority and non-minority, acceptable

C1A - Children and adults, acceptable

- This study proposes a long-term outcome registry for patients with inborn errors of metabolism. Potential subjects are any individuals ascertained by newborn blood spot screening or clinical presentation as having one of the study conditions. Because ascertainment will be based on university screened disorders, there will be no subpopulation selectively included or excluded. Children will be specifically included as they are the most frequently ascertained subjects with inborn errors of metabolism. Age range includes newborns through adulthood.

Vertebrate Animals:

Not applicable (no vertebrate animals)

Biohazards:

Not applicable (no biohazards)

Budget and Period of Support:

Recommend as requested

- Budget and requested period of support are justified and reasonable.

Resource Sharing Plans:

Acceptable

CRITIQUE 2:

Significance: 2

Investigators: 2

Innovation: 2

Approach: 2

Environment: 2

Overall Impact:

This application represents the first attempt to comprehensively monitor outcomes from expanded newborn screening. The investigators would enhance the knowledge of natural history for a number of very rare disorders of metabolism, from among fatty acid oxidation disorders, organic acidemias, and amino acidopathies, and they could provide new information regarding successful interventions for individual rare disorders of metabolism, eventually providing evidence to support therapeutic regimens and practices used to treat these disorders. Metabolic specialists from centers in Region 4 Genetics Collaborative almost completely represented among the investigators, and Dr. Berry has published experience with the survey to be used, having designed it and published data on outcomes in patients with MCAD deficiency collected with this tool.

No one has comprehensively monitored outcomes for this number of disorders detected by expanded newborn screening. The number of data elements to be monitored is exhaustive, yet each one can be justified. The Region 4 Collaborative has a long-term follow-up workgroup in place that has already begun tracking outcomes of infants detected by newborn screening. The 13 clinics in 10 states that will participate will follow a high percentage of infants with disorders of metabolism detected by MS/MS.

DocSite is encrypted for protection of health information collected during the study, protecting participants' confidentiality, and informed consent will be obtained. Given the established productivity and use of the survey in the Region 4 Collaborative, the weaknesses are limited to those inherent to this type of research: the inability to truly comprehensively collect data, and the inability to enroll every potential participant in the region.

1. Significance:

Strengths

- This is the first attempt to comprehensively monitor outcomes from expanded newborn screening.
- It would expand knowledge of natural history for a number of very rare disorders of metabolism, from among fatty acid oxidation disorders, organic acidemias, and amino acidopathies.
- The study could provide new information regarding successful interventions for individual rare disorders of metabolism, eventually providing evidence to support therapeutic regimens and practices used to treat these disorders.
- It would demonstrate the effectiveness and limitations of expanded newborn screening by attempting to comprehensively monitor outcomes of infants with disorders of metabolism detected by MS/MS.

Weaknesses

- Complete ascertainment for the region will not be possible, because some patients will be followed at centers or clinics not involved in this study.

2. Investigators: Strengths

- Metabolic specialists from centers in Region 4 almost completely represented among the investigative team.
- Dr. Cynthia Cameron is Director of Region 4 Genetics Collaborative.
- Dr. Susan Berry has published experience with the survey to be used, having designed it and published data on outcomes in patients with MCAD deficiency collected with this tool.

Weaknesses

- Adding the metabolic specialists at centers not included here should be a goal.

3. Innovation: Strengths

- No one has comprehensively monitored outcomes for this number of disorders detected by expanded newborn screening.
- The number of data elements to be monitored is exhaustive, yet each one can be justified.
- The sampling of data from all these disorders will stratify them with regard to value from screening and intervention, and determine whether some disorders need not be screened for.
- Systematic data collection will reveal effectiveness of clinical practices, and explore effective clinical practices, eventually providing evidence-based protocols.
- Potentially useful prognostic information might be gained from newborn screening information, if long-term outcomes are studied in a systematic manner as planned.

Weaknesses

- Data entry will be incomplete, regardless of the efforts made to be comprehensive.

4. Approach: Strengths

- The Region 4 Genetics Collaborative has a long-term follow-up work group in place that has already begun tracking outcomes of infants detected by newborn screening.
- The 13 clinics in 10 states that will participate will follow a high percentage of infants with disorders of metabolism detected by MS/MS.
- DocSite is encrypted for protection of health information collected during the study as well as protecting participants' confidentiality.
- IRB approval is obtained in the form of written consent for subjects.
- Additional information collected on patients with disorders of metabolism ascertained prior to expanded newborn screening will reveal the benefit of newborn screening.
- Data elements are comprehensive and selected by the collaborative group of metabolic specialists in Region 4.
- DocSite offers clinic based data collection, facilitating the entry of data, and potentially synchronizing the conduct of the study with routine clinic procedures.

- The survey is organized such that data will be entered in a logical manner that seems coordinated with a clinic note that would be written for each participant.

Weaknesses

- The number of participants might not meet benchmarks due to unforeseen issues with enrollment.

5. Environment:

Strengths

- The Region 4 metabolic clinics are state-of-the-art centers for the care of patients with metabolic disorders.
- The collaborative group represents many of the largest metabolic clinics in the region.
- These clinics are the main providers of care for patients with metabolic disorders in the region.

Weaknesses

- Additional centers could be added to be more comprehensive.

Protections for Human Subjects:

Acceptable risks and/or adequate protections

- Appropriate care is taken to safeguard the protection of human subjects.

Data and Safety Monitoring Plan:

Not applicable (no clinical trials)

Inclusion of Women, Minorities and Children:

G1A - Both genders, acceptable

M1A - Minority and non-minority, acceptable

C1A - Children and adults, acceptable

- Appropriate inclusion of women, minorities, and children.

Vertebrate Animals

Not applicable (no vertebrate animals)

Biohazards:

Not applicable (no biohazards)

Budget and Period of Support:

Recommend as requested

Resource Sharing Plans:

Acceptable

CRITIQUE 3:

Significance: 2

Investigators: 2

Innovation: 3

Approach: 2

Environment: 2

**Overall Impact:
Strengths**

- This program will collect and analyze important, much needed data regarding diagnosis, optimal treatment, and natural history of the major disorders identified by newborn screening.

Weaknesses

- Plan may be overly ambitious in view of the shortages of staff at clinical sites and the large number of disorders chosen for inclusion in the initial studies.

**1. Significance:
Strengths**

- The proposed study undertakes the most extensive effort to date to characterize the clinical features, diagnosis, treatment, and natural history of disorders detected by contemporary newborn screening programs. Current knowledge is deficient in many of these areas.

Weaknesses

- Effort devoted to collecting and analyzing data, preparing care plans, etc. for the rare disorders in this very ambitious project should not be allowed to compromise progress with the more frequent disorders.

**2. Investigators:
Strengths**

- Strong leadership is apparent.
- Co-investigators are well qualified by training and experience.

Weaknesses

- None apparent

**3. Innovation:
Strengths**

- This program is the largest to date in regard to the scope and detail with which inherited metabolic disorders detected by newborn screening will be analyzed.

Weaknesses

- Not particularly innovative at the outset. The originality will come from the investigator-initiated research projects and clinical trials that are expected to be developed to use these data, but success in these has yet to be demonstrated.

**4. Approach:
Strengths**

- Detailed protocols for collection of each disorder at the initial encounter and in subsequent visits are well designed and already in use.
- The use of the DocSite registry with data entry from the various clinical sites is a strength of the application.

Weaknesses

- Shortage of staff and support thereof may limit acquisition and entry of data in the clinical sites.

**5. Environment:
Strengths**

- All of the major sites and the clinical sites are involved in patient care and clinical investigation of inherited metabolic disorders identified by newborn screening.

Weaknesses

- Essentially all of the sites to which newborn screens are referred are short of staff.

Protections for Human Subjects:

Acceptable risks and/or adequate protections

- All participating programs undergo IRB review in the home institution.

Data and Safety Monitoring Plan:

Not applicable (no clinical trials)

Inclusion of Women, Minorities and Children:

G1A - Both genders, acceptable

M1A - Minority and non-minority, acceptable

C1A - Children and adults, acceptable

- Initial contacts will be with newborns and infants regardless of sex, race, ethnic origin, etc. Follow-up studies will involve older children and adults. Family studies will involve adults.

Vertebrate Animals:

Not applicable (no vertebrate animals)

Biohazards:

Not applicable (no biohazards)

Budget and Period of Support:

Recommend as requested

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW ADMINISTRATOR TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume): Acceptable

INCLUSION OF WOMEN PLAN (Resume): Acceptable

INCLUSION OF MINORITIES PLAN (Resume): Acceptable

INCLUSION OF CHILDREN PLAN (Resume): Acceptable

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-10-080 at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-080.html>.

The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

**National Institute of Child Health and Human Development Special Emphasis Panel
EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD HEALTH & HUMAN DEVELOPMENT
Natural History
ZHD1 MRG-C (19)
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Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.