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Priority 1: Laboratory Quality Improvement

Purpose

The purpose of the project is to:

- Achieve uniformity of testing panel by MS/MS to maximize detection of affected newborns within the region and nation
- To improve overall analytical performance
- To set and sustain lowest achievable rates of false positive results

In 2004, the newborn screening programs of all seven Region 4 states (IL, IN, KY, MI, MN, OH, and WI) agreed to participate in a project aimed to improve the analytical quality of newborn screening by tandem mass spectrometry (MS/MS). The rationale to expand participation beyond Region 4 relates to the reality of dealing with rare conditions. Greater participation in this project implies larger sets of data available for calculation and progressive definition of the disease and cutoff ranges. The minimum target was to include at least 50 cases of each condition included in the HRSA/ACMG panel (primary and secondary targets), a number that is simply impossible to obtain at any single testing site for the vast majority of conditions.

Since 2004, the grant has resulted in the following:

- Active participation has expanded substantially beyond the boundaries of the region and even of the US, to include a total of 45 US states from all seven regions and 74 international participants from 35 countries.
- A total of 7,436 true positive cases (as March, 18, 2009). One objective of the project is to obtain data of markers and ratios measured by MS/MS in a significant number of cases (N=50 or greater) for each condition included in the HRSA/ACMG uniform panel, and related secondary targets. To date, this objective has been reached for 24 conditions, 16 primary and 8 secondary targets, respectively.
- A culture of data sharing and open communication, constructive inter-laboratory comparison, and ready exchange of methods, reagents, and specimens has developed among participants.
- The Region 4 website (<http://region4genetics.org>) includes standard operating procedures, data collection tools, and a growing number of project tools and reports.

In this grant cycle the project has entered a new phase with the custom creation and successful deployment on November 10 2008 of a dedicated computer program (Region 4 Stork or R4S) capable of (1) supporting a web-based, password protected environment where participants enter their own data; (2) generating customized reports on demand; and (3) adding new conditions and markers

R4S was rolled out during the November 2008 face-to-face meeting of Priority 1 participants in San Antonio with over 60 participants from eight countries in attendance.

Needs Assessment

To date, the ACMG uniform panel has been implemented to cover 98% of US annual births. As such, expansion has become a much lesser priority, but there is an even greater need to focus on quality improvement. This project is recognized as the primary driver behind the adoption of evidence-based, objective performance metrics.

Ongoing needs of this project will be identified by the National MS/MS Advisory Board (established fall 2007). For a description of the Advisory Group see page 38). In the past year, the National Advisory Board has identified the following issues that need to be address future growth of the project:

- A biostatistician needs to be available to consult with the project on statistical methods and data analysis
- CEUs need to be made available to professionals attending the training course offered six times per year at Mayo
- Training sessions could be more beneficial if held at sites in other regions, in addition to Mayo
- Consideration needs to be given to creating an online training course for laboratorians who are unable to travel
- Linkages with other national data collection projects need to be maintained
- Infrastructure needs to be sufficient to support the current size of the project and potential growth

Goals and Objectives

Goal 1: Develop and implement clinically validated cut-off values

Obj 1: Collection (N=50 or greater) of informative markers and ratios measured by MS/MS for the detection of the conditions included in the HRSA/ACMG uniform panel, and related secondary targets (time frame: 2007-2012);

Obj 2: Definition of CUTOFF RANGES for informative markers and ratios measured by MS/MS for the detection of the conditions included in the HRSA/ACMG uniform panel, and related secondary targets (time frame: 2007-2012);

Obj 3: Development and implementation in screening practice of clinically validated post-analytical interpretive tools and algorithms based on the disease ranges for the biochemical segregation of conditions with particularly challenging biochemical phenotypes (VLCAD deficiency, urea cycle defects) (2007-2009)

Goal 2: Training courses at Mayo in small groups (one week, 10 people or less)

Obj 1: Improve post-analytical skills and competence with website and project tools of attendees (2007-2012);

Obj 2: Foster personal interactions and exchanges of information between programs, including international ones, which had limited contacts before getting involved in this project (2007-2012)

Goal 3: Development of customized software to manage NBS data

Obj 1: Hiring of dedicated data entry FTE for timely communication with a fast growing number of participants in more than 100 sites worldwide (2007-2009);

Obj 2: Custom creation of a software to deliver all functions of the project (data entry, processing, reporting) (2007-2012)

Goal 4: Collection, compilation and monitoring of performance metrics

Obj 1: Data collection and anonimized inter-laboratory comparison of performance metrics (detection rate, false positive rate, and positive predictive value (2007-2012);

Obj 2: Analytical development, clinical validation and implementation of 2nd tier tests for the reduction of the false positive rate of selected conditions.

Goal 5: Round robin sample exchange

Obj 1: Inter-laboratory exchange of true positive specimens with quantitative comparison of results (known submitter, anonimized recipient);

Obj 2: Achievement of the following targets: a) 100% agreement of diagnosis; b) 90% of primary analyte(s) values within 20% of submitter's corresponding values; c) 100% active participation from all states within Region 4 ; and d) Increase participation to include at least 3 states outside of Region 4 each year

Methodology

Goal 1: Development and implement clinically validated cut-off values and post-analytical tools

R4S is a custom-designed and -coded application for the collection and reporting of MS/MS newborn screening data. The system is a web-based application that implements a three-tier client-server architecture model. The client or presentation tier is the user interface, which can be accessed using any internet-connected computer's web-browser. The R4S software is compatible with Internet Explorer 6+ and Firefox 2+ (as well as other Mozilla-based browsers such as Safari, Opera and Netscape). The application, logic or business tier is located on a web server, housed by MPHI, and implementing Microsoft Internet Information Server (IIS) version 6. The application code is written in ASP and C# for Microsoft .NET version 2.0. Winnovative HTML to PDF and dotnetCharting software packages are utilized by the web software for pdf and chart generation respectively. The data tier, located on a database server, also housed by MPHI, uses Microsoft SQL Server 2005 with custom-written T-SQL stored procedures.

Over the last five years, this project has evolved to an organized, web-based data collection system with a computer program designed specific to the needs of the project. National and international participants are provided with a user ID and password to gain access to a secure section of the Region 4 website (www.region4genetics.org). Once logged in, authorized participants have access to folders unique to their state for data submission and comparison tools and to common folders inclusive of project tools and reports. The PI of the project, Mayo personnel involved in programming, and senior MPHI personnel have administrative privileges and can access all folders. Participants contribute the following data:

- Complete set of data (amino acids, acylcarnitines) of confirmed true positive cases
- Percentiles (%iles) of all markers in the respective normal population

- Cutoff values
- Performance metrics (period, volume, detection rate, false positive rate, positive predictive value)

These databases include:

- True positive data (7,436 cases as March 19, 2008, 328,708 data points; same date applies to totals listed below)
- Cutoff data (3,556 data points)
- %iles of normal population (>15,138 data points)

Each database is set to automatically perform basic calculation of descriptive statistics, particularly the calculation of pre-defined percentiles. These values (and the number of data points used to calculate them) are automatically linked to a tool called the “Score card”

This file offers a comparison between the distribution of values for each analyte and ratio in the normal population, the spread of cutoff values, and the %iles of the disease range (collection of data points of a given analyte or ratio in confirmed cases).

The main deliverable of the collaborative project is the definition of evidence-based, clinically driven CUTOFF TARGET RANGES for all analytes detected by MS/MS, and calculated ratios. The cutoff target range could be either above (HIGH) or below (LOW) the range of the normal population:

- The HIGH target range is defined as the interval between the cumulative 99%ile of the normal population and the lowest 5%ile of disease ranges, if the analyte is informative for multiple conditions.
- The LOW target range is defined as the interval between the highest 99%ile of disease ranges, if the analyte is informative for multiple conditions, and the 1%ile of the normal population.

When the degree of overlap between normal population and disease range makes it inapplicable to use the rules stated above, one or both limits are modified to give priority to the disease range. In such instances, the value is shown with a black background. To provide a more visual comparison between the three groups, the same data are accessible in a variety of formats: visual score cards (individual percentiles and cutoffs compared to disease ranges), plots by target range (collective percentile and cutoff ranges compared to disease ranges) and others. Each group (normal population, cut-offs, and individual conditions, as applicable) are shown as a box encompassing the range between the 10%ile and the 90%ile of values included in the database. The vertical lines extend to the 1%ile (below) and 99%ile (above), respectively.

During the first cycle of the grant (2004-2007), the most pressing priority was to engage as many participants as possible. The rationale to expand participation beyond the boundaries of Region 4 relates to the reality of dealing with rare conditions, and our primary goal to collect data of at least 50 cases affected with each one the conditions included in the HRSA/ACMG recommendations.

To date, 16 of the 20 primary targets listed in the uniform panel have reached, and in some cases greatly exceeded (MCAD: N=1,435), the initial goal of 50 cases, 8 of the 22 secondary targets have reached the target as well. This has been possible only because of the expansion of the project beyond the regional boundaries: beside all 7 states in region 4, 18 participants have contributed more than 100 cases. The benefits of a broad participation are not limited to data collection, but also include fostering a culture of data sharing and open communication, constructive inter-laboratory comparison, and ready exchange of methods, reagents, and specimens among participants.

As anticipated in the first cycle of the grant, the collection of multiple cases with the same condition allows the clinical validation and implementation into routine practice of interpretive post-analytical tools. These tools are directed to the resolution of the most challenging findings encountered in the interpretation of MS/MS results. Improved result interpretation is expected to enhance overall performance, the ultimate goal of this project. Initially, we have focused this effort on the biochemical characterization of carriers in conditions known to have an abnormal biochemical phenotype in heterozygote individuals as well as false negative outcomes [10-13].

Goal 2: Training course at Mayo in small groups

2008 Training Schedule					
Feb 9-13	Apr 27- May 1	Jun 22-26	Sep 14-18	October 12-16	December 7-11

The application process for attendance at one of the sessions consists of three components:

1. Completion of the Application form;
2. Formal commitment from the leadership of the program of employment stating that funds are available to cover travel and lodging expenses;
3. Evidence of good standing of the laboratory with regard to submission of all data related to the collaborative project (true positive cases, %iles of normal population, updated cutoff values, and performance metrics).

The small group training course at Mayo has proved to be very beneficial to project participants and lab staff. Because of the overwhelming support for this project by those who have participated, Region 4 requested and received approval for use of carry forward funds to support the participation of seven additional participants this FY (one participant from each Region 4 state).

There is no competitive selection involved. Following submission of an application by a member of an active participant's program, all requests from eligible individuals are accommodated to the best of the ability of the Mayo staff.

A total of 89 individuals have either attended or registered for 2009, 61 national and 28 international, respectively. The curriculum is a combination of formal lectures, hands-on training in the laboratory, and review of daily batches of newborn screening and 2nd tier test results.

Goal 3: Collection, compilation and monitoring of performance metrics, with definition of targets of acceptable performance

We have improved the rate of participation in the inter-laboratory comparison of three key performance metrics: detection rate (prevalence; collective and for individual condition), false positive rate, and positive predictive value [14].

The detection rate of a newborn screening program is expressed as the number of neonates that on average needs to be tested to detect one affected patient. Published data relative to the outcome of MS/MS screening are sparse, and often widely variable. Until an even greater uniformity of testing is accomplished, the collective detection rate is likely to represent the least informative of available metrics, so we anticipate the need to express the detection rate separately for each condition. This process will be implemented by generating program-specific reports annually. The prevalence figures will be compared and monitored, with feedback provided to the group as well as to individual participants. The false positive rate of a newborn screening program is expressed here as the proportion of positive tests in subjects proven by follow up evaluation not to have one of the conditions targeted by a given screening program. For the purpose of objective comparison, we believe that all cases requiring follow-up testing beyond the analysis of the initial blood spot should be included in the determination of the false positive rate over a defined period of time, with the exception of specimens considered unsatisfactory because they were collected at less than 24 hours of age. The positive predictive value of a test is the probability that the patient has the disease when restricted to those patients who test positive. This metric is less dependent of the extent of the panel of conditions, and should not be arbitrarily restricted to subsets of cases. These metrics, of course, have been applied to newborn screening for decades, but apparently they have been kept local, restricted to own longitudinal assessment (variations over time in a single lab), with limited interest to seek inter-laboratory comparison as an objective mean to define what constitutes an acceptable, or at least average, performance. Currently, the targets we considered indicative of adequate performance are as follows:

- 1) Detection rate <1:3,000 births
- 2) False positive rate <0.3%
- 3) Positive predictive value >20%.

Goal 4: Continuing clinical validation of 2nd tier tests

Additional participants have embraced the strategy to reduce their false positive rate by the implementation of 2nd tier tests, which are defined as reflex tests performed on the same dried blood spot used for the primary screening, without additional patient contact. The trigger to perform the 2nd tier test could be a result in the range of values corresponding to the overlap between normal (unaffected) population and true positives, or an intrinsic poor specificity of the primary screening (for example, 17-OH progesterone measured by fluoroimmuno assays). Most of the analytical development and clinical validation of these tests has been performed in the Biochemical Genetics Laboratory at Mayo [15-19], however both on site testing and outsourcing are available to all participants. To date, the participation of other states is as follows:

- 1) Steroid profiling for CAH (5 states)
- 2) Succinylacetone for TYR-1 (9 states)

3) Methylmalonic acid/Homocysteine for disorders of propionate metabolism, Homocystinuria, and re-methylation disorders (13 states)

In addition, 13 states have requested informal second opinions of unusual amino acids and acylcarnitine results

Goal 5: Round robin sample exchange

The validation of the process behind the definition of cutoff ranges is based on objective comparison of diverse data obtained by different laboratories. In addition to the comparison (and assessment of variability) of %iles values in the normal population, we have sought the implementation of a sample exchange initiative, a process where the same specimen is analyzed by the laboratory where the initial diagnosis was made (submitter) and another participant (recipient) chosen in alphabetical round robin order. For example, if Illinois has 6 samples to distribute, the first will go to Indiana, second will go to Kentucky, third will go to Michigan, 4th will go to Minnesota, 5th will go to Ohio, and 6th will go to Wisconsin. Both laboratories submit a copy of their results to Dr. Stephanie Mayfield (KY) and her associates, who compile a summary file where the identity of the recipient is not disclosed. Results are posted quarterly on the Region 4 Collaborative website, sample exchange folder in the password protected section under Newborn screening by MS/MS.

The results are posted showing the submitter, the submitter diagnosis and informative results, and the recipient's diagnosis and values.

During the upcoming year, the administration of the Sample Exchange will be transferred to Mayo. Software will be developed to integrate the sample exchange with R4S.

Collaboration and Coordination

One of the important outcomes of the first four years of this project is the ongoing communication among lab personnel in Region 4. This was brought about through monthly conference calls and face-to-face meetings, which provided a venue for participants to get to know each other. Region 4 participants now use each other as resources and call and email each other on a regular basis with questions and/or problems (personal communication, Nancy Breen, Indiana NBS lab).

National MS/MS Advisory Board

In January 2008, the National MS/MS Advisory Board was created. The Board consists of 12 invited members (see Organizational Chart, attachment 6) and the HRSA Liaison. Membership consists of one representative from each Regional Collaborative, and national representatives with expertise needed to ensure that as the project moves forward, it meets the needs of laboratory personnel and links appropriately with other national data collection efforts. The charge to the group is as follows:

- Be an advocate of the project
- Provide direction on how to maximize participant benefits
- Recommend means to improve participation and timely data submission

- Provide feedback on project progress reports, requirements for active participation, and exclusion
- Advise on the design of the web-based software under development
- Provide guidance for interaction and collaboration of Region 4 MS/MS working group with other regional collaborative projects and national entities (APHL, CDC, NCC, NNSGRC)

The Board held its first meeting via conference call on February 5, 2008. A second conference call was held in June 2008 and the group met face-to-face November 2, 2008 in San Antonio. In 2009, the Board had a first conference call on February 24. The input of the group has been invaluable in charting the course for the continued expansion of the project. If funds are available, the following activities to address recommendations made by Advisory Board members will be implemented in the coming year.

- A 0.2% FTE biostatistician will be employed through Mayo to consult with the project leader on statistical methods and data analysis
- The project will work with the Association of Public Health Laboratories to provide CEUs to training participants
- A 1 ½ day off-site training will be piloted in collaboration with one of the other Regional Collaboratives.
- The creation of an online training course will be explored.
- Dr. Rinaldo will continue to participate in the National Coordinating Center's Data Workgroup and the Advisory Committee to the Newborns Screening Translational Research Network in order to maintain linkages with other national data collection projects
- Additional staff is needed in order to support the growth of the project. David McHugh, currently acting as the data management assistant will become the formal project coordinator and a new assistant will be added to the project team. The effort of Neil Maffitt, software programmer, will be increased.

Resolution of challenges

There were many challenges at the beginning of the project, mostly driven by a diffuse skepticism (inside and outside Region 4) that comparison and harmonization could be achieved in a constructive and collegial manner. Furthermore, there were substantial concerns about confidentiality, especially when the collection of data was driven by a private, non public health entity. To date, the situation has improved dramatically, with a pervasive impression of voluntary desire to actively participate. The critical role of the program director (Cynthia Cameron, PhD) as facilitator of the face-to-face meetings and conference calls cannot be overstated, as she has been able to diffuse tension between participants and at the same time stand firm and curtail inappropriate behaviors. Difficult situations were also addressed in a very effective way by the Regional advisory group which provided mediation and sound advice on how to reach resolution of conflicts. With the advent of the National MS/MS Advisory Board, the Region 4 Advisory Group is no longer meeting on a regular basis. The National Advisory Board now considers challenges and provides suggestions on how to resolve those challenges.

Administration and Organization

For a description of how the Region 4 Genetics Collaborative is administered and organized see base grant narrative pg. 21 and Organizational chart, attachment 6.

Staffing

Piero Rinaldo, MD, PhD, project PI, provides scientific direction for this project. Dr. Rinaldo promotes participation in the project, both nationally and internationally; shares his expertise on MS/MS and the project and analyzes the data and identifies issues for discussion; selects the format and content for monthly updates; and trains visiting lab personnel.

David McHugh,

TBA, data manager, updates project databases, cutoff range plots and other tools, prepares and circulates monthly updates; creates user-friendly tools to display project data.

Neil Maffitt, software programmer is responsible for developing R4S and sample exchange software.

Cynthia Cameron, PhD, Region 4 Director, facilitates conference calls and face-to-face meetings of the working group and the National MS/MS Advisory Board.

Patricia Losey, MPHI Systems Reform is responsible for meeting logistics.

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Priority 2: Inborn Errors of Metabolism Information System (IBEM-IS)

Purpose

In the absence of protocols based on clinical evidence, clinicians caring for children with very rare disorders are faced with challenging treatment decisions. Practitioners often determine how they will treat children with inborn errors of metabolism based on how their mentor approached treatment, what they have read in a manual or text, and what they have learned from their own clinical experience. With only a handful of children diagnosed with inborn errors of metabolism each year in any given state, the lack of controlled studies and evidence based standards is not surprising.

The purpose of this project is to develop and implement a comprehensive Inborn Errors of Metabolism Information System (IBEM-IS). It is anticipated that the IBEM-IS will result in evidence-based care protocols for children with metabolic disorders and improved health outcomes.

Needs Assessment

All seven Region 4 Collaborative states¹ screen newborns using MS/MS to identify a number of rare, serious IBEM. Newborn screening by MS/MS, first implemented by States in 1998, is gradually being added to newborn bloodspot screening programs across the nation. In Region 4, approximately 740,000 babies are screened per year by MS/MS, resulting in an estimated 265 cases confirmed with a metabolic disorder each year (assuming an incidence of approximately 1:2800 for all IBEM combined).

While long-term follow-up is critical for monitoring health outcomes and evaluating the effectiveness of newborn screening, standards of clinical care for MCADD and most other screened conditions have never been subjected to evidence-based study. More information about outcomes for these disorders is essential to a better understanding of the natural history of the conditions and development of best practice models for treatment.

Over time, disease registries will build the foundation for evidence-based medical practice and care for rare disorders ascertained through newborn screening because they will provide data to support treatment decisions based on larger cohorts of affected children than can be seen by an individual practitioner or specialty center. With the collaboration of multiple states over time, disease registries will have the power to provide a foundation for evidence-based medical practice and care for rare disorders ascertained through newborn screening.

Goals and Objectives (See Priority 2: IBEM-IS Work Plan, Attachment 7)

Project Goal: Improve health outcomes of children with metabolic disorders

Objectives

1. Implement the IBEM-IS

¹ Illinois, Indiana, Kentucky, Michigan, Minnesota, Ohio, and Wisconsin,

2. Refine research and intellectual questions that can be explored employing the data in the disease registry (time frame: 2007-2012).
3. Expand the scope of Inborn Errors of Metabolism Registry – both the spectrum of IBEM encompassed in the registry and the power of the data for each condition by adding other regions to the project (time frame: 2007-2012).
4. Integrate the IBEM Registry with other electronic systems, creating an IBEM Information System (time frame 2009-2012).
5. Evaluate project progress (time frame 2008-2012).

Methodology:

Region 4 Priority 2 Workgroup began with the development of a web-based registry for Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD). The MCADD registry has been expanded to include fatty acid oxidation disorders, organic acidemias, and aminoacidopathies found by tandem mass spectrometry (MS/MS). This expanded system is known as the Inborn Errors of Metabolism Information System (IBEM-IS).

The IBEM-IS is designed to be dynamic, collecting information about both initial diagnosis and key data elements necessary to monitor long-term clinical health outcomes to support ongoing development and evaluation of treatment protocols for this rare disorder, using a HIPAA-compliant web-based product. This web-based system is designed to document and share relevant demographic, laboratory, clinical, educational, developmental, and other aspects of long-term follow-up care for individuals with inborn errors of metabolism who have never before had the opportunity to participate in structured disease registries that have the capacity to generate high quality longitudinal data about their conditions.

Region 4 includes thirty-three metabolic clinicians representing 17 pediatric metabolic centers actively involved in this project, offering their expertise in the genesis of the registry, its elements and contributing their established treatment protocols from which to build a consensus on anticipated research questions. A metabolic disease clinician “state lead”² was identified in each state to represent metabolic centers and metabolic specialists within their state. They assure ongoing communication among their colleagues, actively participate as members of the Workgroup in monthly conference calls, work to recruit participation of all metabolic clinics in their state and attend planning meetings of the Region 4 genetics collaborative.

The IBEM-IS was developed as a registry that allows all clinical centers and clinicians access to their data. Each individual site holds the link to the identified and de-identified patient data from that particular site. All other participating sites have read-only rights to de-identified patient data from other sites.

Over the next three years the IBEM-IS registry will continue to evolve as a registry and data system for all MS/MS screened diseases. As the data registry becomes populated and clinical outcome data are available, the Priority 2 Workgroup (which includes genetic-metabolic and follow-up experts from each Region 4 state) and epidemiologist staff will explore and define

² Clinical State Lead

research questions to examine specific clinical questions and to contribute to the ongoing development and evaluation of treatment protocols.

Efforts also are underway to extend collaboration on this project to other genetics regions, thereby enhancing communication among metabolic-genetic specialists and state Departments of Health across regions, building capacity to increase the number of rare disorders added to the registry, supporting accurate and consistent data collection, and enhancing the overall project scope. Six clinicians from the Heartland Genetics Region are currently in various stages of IRB approval for participation in the IBEM-IS.

Objective 1: Implement the Inborn Errors of Metabolism Information System

Building on activities of the past five years, the Priority 2 workgroup (P2WG) continues to develop and work toward implementation of a comprehensive inborn errors of metabolism information system. The existing DocSite platform for MCADD was extensively reviewed and revised to assure more accurate, consistent and comprehensive data collection. In order to do this, data entry at centers was halted until changes were made in the platform. Currently, at this time, eight centers have completed their IRB review and approval process and seven Centers are finalizing IRB materials or waiting for an IRB decision. Clinical State Leads continue working to bring the remaining Region 4 metabolic centers on board. Recruiting activities are reported in their bi-annual reports.

The P2WG members who have successfully completed the IRB process have shared materials and resources for adaptation by other centers seeking IRB review and approval in preparation for participation in enrolling patients in the registry. Materials are available on the Region 4 website. Based on feedback from the clinicians, Region 4 now provides additional resources to facilitate the IRB process including completing drafts of center specific IRB forms.

In Year 1 of this grant cycle, much of the focus was on developing and refining processes to facilitate implementation of the IBEM-IS, resulting in development of the following products: IBEM-IS Quick Reference; Getting Centers Started (a guide to complying with IRB requirements, identifying users and providers, requesting and obtaining user names and passwords, and scheduling initial IBEM-IS training); Communication with DocSite; Case Enrollment Reporting Form; Case Enrollment Invoice Form; Role of State Clinical Lead (revised); Metabolic Centers and Specialists in Region 4 (revised); Research Proposal Submission Guide (draft); Sample Research Proposal Form (draft). During Year 2 the P2WG has focused on the addition of disorders to the IBEM-IS; and engaging additional metabolic clinics within Region 4 in the project.

Objective 2: Refine research and intellectual questions that can be explored employing the data in the disease registry

The Priority 2 workgroup and epidemiology staff will assess the clinical practice data elements from the registry to establish a portfolio of potential research questions that can be addressed from this data. Initially the group will focus on defining research questions using the data encompassed in the registry, undertaking the comparative analyses implicit in reviewing our

differences in practice and examining the emerging natural history for treated screened patients. For example, we may undertake evaluating service level interventions, determining comparative clinical outcomes based on differential uses of medications, or exploring correlations between genetic test results and disease expression. It is our intention to encourage the development of formal prospective clinical trials, soliciting the participation of patients enrolled in the database.

At our initial Clinical State Lead meeting in January 2005 (Chicago), the group agreed to fundamental principals for initiation of research activities based on mutual respect and sharing of both responsibility and credit for participation. Since the opportunity to accomplish research is an anticipated outcome of the IBEM-IS, this issue was revisited in greater detail during the Minneapolis meeting in November 2007. The clinical state leads discussed a research proposal review process to include rules for research, use of materials, and authorship. Two types of research likely to be proposed were identified as data mining (de-identified information in the IBEM-IS) and cohort data (research that requires contact with a family for purposes of gathering additional information and/or testing and intervention. A detailed review process is being outlined by the workgroup. The Region 4 Project Director will serve as a conduit for investigators wishing to use Registry data for study. As a group, we will discuss and initiate research proposals examining outcomes of our enrolled patients. A committee will be identified to review brief proposals for their scientific merit and appropriate engagement of enrolled patients, resulting in recommendations for the Priority 2 workgroup in responding to the proposals. Input from the Region 4 Advisory Group on the final process will be sought.

Each Clinical State Lead has committed to assisting investigators proposing approved research activities. They will do this initially by enrolling patients in the IBEM-IS and by offering opportunities for inclusion in additional endorsed research activities to their patients. Ultimately, as researchers seek funding for such studies, the Leads will provide supporting documentation for the feasibility of the studies based on use of the larger numbers of patients that will be necessary for significance in analysis. The Clinical State Leads developed a process to report on their activities within their states to assist development and implementation of the Priority 2 project. The written reports allow an opportunity to capture progress, identify barriers and share strategies for moving the project forward. Some of the Region 4 states have provided written activity reports.

During the September 2008 Regional Meeting presentations of Regional Opportunities were entertained. Parent participant and P2WG member Dr. Darin Erickson proposed a research question to learn about the impact of having a child with a heritable disorder on the family. Carry forward funds were requested and approved to support discussion groups with parents in each of the seven Region 4 states. The discussion groups will result in a qualitative data summary that will be provided to the P2WG.

Objective 3: Expand the scope of the IBEM-IS

To achieve meaningful outcomes that document the utility of newborn bloodspot screening we need to monitor a large number of children with each of the screened conditions. This will necessitate both adding to the number of screened conditions in the IBEM-IS and increasing the numbers of enrollments in each disorder.

Over the next 4 years, we will continue to add conditions to the IBEM-IS by replicating the process employed in adding disorders to date – involving expert clinicians in review of the literature, published care plans and surveying genetic specialists about clinical protocols to decide on key data elements for the particular disorder. In the relational database that comprises the IBEM IS some core data elements remain the same or similar for all disorders, such as demographic information, genetic testing, and developmental testing, while other data elements to be collected reflect unique aspects of clinical treatment for each disease (disease-specific elements).

Region 4 also will continue to consider the work of the Mountain States Region to develop elements for minimum standards of care/treatment protocols for each of the screened conditions as we identify and define disorder specific data elements for the IBEM-IS. In turn, Region 4's experience in Registry activities will be shared with Mountain States as they plan their strategies for long-term follow-up analysis using their protocols.

Expanding the scope of disorders studied will result in the inclusion of disorder for which very few patients are available for participation. To expand the number of patients for each condition, other Regions will continue to be encouraged to join our Priority 2 WG and enroll their screened infants in the IBEM-IS. Clinical State Leads from the Heartland Region have been identified and are participating in P2WG activities. Interest has been indicated by states from other regions. Region 4 leadership is working with the leadership of those regions to extend partnership opportunities to the entire region.

Over the past five years, P2WG developed and implemented strategies for adding disorders to the information system. Disorders were selected and prioritized for adding by determining how they serve as paradigms for specific issues. To date, both enrollment and interval surveys for the following disorders are included in the IBEM-IS: CACT, CPT-I; CPT-II, CUD, IBD, LCHAD, MCADD, MSUD, SCAD, TFP, and VLCAD. The P2WG recently finalized elements for Glutaric Acidemia Type 1 and Galactosemia. These have been provided to DocSite to be added to the IBEM-IS. Currently, the P2WG is working on Tyrosinemia and Biotinidase is the next disorder targeted for addition to the IBEM-IS.

Objective 4: Integrate the IBEM Registry with other electronic systems, creating an IBEM Information System:

The IBEM-IS as a data set will provide both critical research measures and be highly useful as a record for each individual participant. Integration of IBEM-IS data with other programs - either import to the information system (e.g. as newborn screening data), or export of IBEM-IS data to secure, private data sites (e.g. an electronic medical record (EMR)) - will be a desirable expansion of the utility of the data gathered in this project.

By using a web-based product designed for clinical outcomes analysis we hope to integrate the IBEM-IS with other programs including emergency care plans, state newborn screening programs, and electronic medical records (EMR). It should be possible to design clinical decision-making tools to incorporate into this model. Extending collaboration with state health

departments will address issues of access and privacy, privacy and integrity of data, and systems needed that link particular data elements from the clinical center to the state for purpose of monitoring newborn screening follow-up and tracking and quality assurance. Using data from the IBEM-IS to supplement an EMR or prepare communications reporting a specialty care visit will facilitate interactions with families and their medical home and assist specialist providers in documentation of clinical care.

Our initial effort for integration will be to link entry into the IBEM registry with emergency care plans in a secure web-based environment for use not only by emergency physicians but also by parents, medical home and specialist providers. To accomplish this, we will collaborate with Region 4 base planning efforts for the project (see Region 4 Care Coordination Workgroup). Communication between the program vendors for these two web-based systems is currently underway. Region 4 staff will monitor progress toward linkages or interfacing between these systems. Our second anticipated integration will be direct population of newborn screening data from Departments of Health upon enrollment in the IBEM database. We have enlisted the consultative services of the DocSite programming staff to work on this project and other projects identified during the grant period. With the establishment of the, we anticipate additional opportunities for data integration projects. Additional opportunities for data integration efforts are anticipated, such as with the Newborn Screening Translational Research Network, though not yet defined. They will be added as the success of these initial efforts is assured.

Development of the IBEM-IS also included review of Emergency Care Plans used in the Region. A summary of emergency care plan elements was developed and compared to elements in the registry resulting in identification of additional elements to include in the data element template for the IBEM-IS.

Objective 5: Evaluate project progress:

The P2WG monitors of project processes and progress related to the workplan and objectives as a part of each meeting agenda. The Priority 2 co-leads and project coordinator develop quarterly reports of activities for each objective. These reports are shared with the Region 4 Advisory Group and HRSA. The Clinical State Leads have developed a reporting form and agreed to report on activities related to the role of the clinical state lead in the Priority 2 IBEM-IS project. The Clinical State Lead Reports are provided a minimum of every six months and are shared with the P2WG, the Region 4 Advisory Group; and incorporated into the Priority 2 quarterly reports. At designated six month intervals, participating centers complete case enrollment forms to provide a count of the number of persons consenting to participate in the IBEM-IS. (Those consenting may not yet be enrolled depending on the process the individual center has instituted for initial case entry, e.g. at time of next appointment. Consents may be obtained for disorders not yet “live” in the information system; which will be entered when the enrollment and interval surveys for those disorders are activated). At six month intervals, participating centers also provide case enrollment invoices which document the number of cases entered. Meeting notes, posted to the Region 4 website, document participants in telemeetings and face-to-face meetings. The process developed for approving use of the IBEM-IS data will include documenting requests, names of reviewers, and decisions made.

Carry forward funds were requested, and approved, to support additional evaluation of the Priority 2 Workgroup activities. Evaluation activities will include a telephone interview with P2WG members about the process, products, strengths and weaknesses, and sustainable change which has resulted from P2WG efforts to date.

Collaboration and Coordination

Membership of the P2WG includes the all 7 state public health agencies, two parent representatives, metabolic experts, hospitals, and universities from throughout Region 4 as well as clinicians from the Heartland Region.

Since initiation of the Long Term Follow-up Workgroup, from which this Priority 2 Workgroup evolved, collaboration has been an essential component of our achievements. Collaborative partners from all seven Region 4 states are engaged in Priority 2 workgroup activities and projects through monthly telemeetings, semi-annual face-to-face meetings, and frequent email correspondence. As with other Region 4 Workgroups, the Priority 2 WG engages a diverse group of stakeholders. In addition to our family member representative actively participating since the formation of the original workgroup, a second family member who approached the Region 4 Genetics Collaborative Director about participating specifically with the IBEM-IS project has been added to the workgroup. The family perspective is not only welcome, but also essential to insure that the IBEM-IS and its implementation is family centered, community-based and culturally competent.

The Priority 2 WG has committed to monthly conference calls and twice-yearly meetings (one occurring with an annual Region 4 Collaborative meeting in years 1, 3, and 5, the other specific to the Clinical State Leads, occurring six months after. In years 2 and 4, an additional semi-annual meeting of the Priority 2 WG will be held to ensure continuing communication and progress in years that the whole Collaborative does not meet.) Telemeetings are the forum for continuing review of the enrollment process and discussing operational issues for the P2WG.

During this grant year, 10 telemeetings of the P2WG and one face-to-face meeting of Clinical State Leads (Lansing, MI September 2008) were convened. All seven Region 4 States were represented at the face-to-face meeting.

The Region 4 Genetics Collaborative Advisory Group will provides support, guidance and direction to this project by addressing barriers, assisting with conflict resolution, and ensuring the needs and concerns of the greater collaborative are considered as project decisions are made, practices and protocols developed and projects moved forward. Currently, the Advisory Group is considering a regional data sharing procedure, authorship issues, and the need to inform HRSA of upcoming publication and presentations.

Collaboration and Coordination across Regional Collaboratives

The Mountain States Region, which undertook the process of defining treatment protocols for each of the screened conditions; shared their emergency room and practice guideline templates

with us. The P2WG considered these templates in developing the IBEM-IS Region 4 disease-specific elements for each condition. To further this collaborative process, one of the Priority 2 Co-leads participated in the Mountain States Protocol Planning Meetings (Fall 2007 and February 2009). In turn, Region 4 is sharing our experience in the information system activities with Mount States as they plan their strategies for long-term-follow-up analysis using their protocols.

Recently, Region 4 and Mountain States decided to work together to explore the possibility of an interface between the IBEM-IS (clinician-based) with the Mountain States CHIRP database (public health-based) developed by the Colorado Department of Public Health and Environment and the Inherited Metabolic Disease Clinic at the Children's Hospital-Denver. Although similar in scope, there also are some significant differences in data elements. Establishing a working interface between the two systems could allow each to expand to include elements of the other as desired on a case by case-enrollment basis.

In order to expand the numbers of patients for each condition in the IBEM-IS, we will need to develop and implement a process for addition of other Regions and/or individual states in enrolling their screened infants in the IBEM-IS.

Susan Berry, Priority 2 Co-Lead has provided several presentations on the IBEM-IS and the Priority 2 workgroup process. Presentations have been provided within Region 4, for other regional collaboratives, to the Secretary's Advisory Committee on Heritable Disorders and in Newborns and Children, at a face-to-face meeting of the regional PIs and at conferences. These presentations have generated substantial interest, including both requests from people interested in participating in the Priority 2 project and invitations for our co-lead to participate on national and cross-regional workgroups and committees. There is sufficient interest for project leadership and staff to consider the implications of evolving as a national project. With the participation of states from other regions, there are plans to establish a National IBEM-IS Advisory Board. It is anticipated that this group will be formed and hold its first meeting in the coming year.

Resolution of Challenges

General project challenges:

Central to the successful accomplishment of this work is assurance of human subject protection. The IBEM-IS enrolls patients only with prior informed consent. Each metabolic center is required to obtain local IRB approval for the project. Template IRB documents have been provided. Individual centers are assisted as needed in preparing applications for IRB approval.

Some of the metabolic centers have experienced hurdles with their individual IRB processes. Challenges include: standardized IRB fees, presenting the IBEM-IS in a fashion that allows for approval of all disorders to be included in the information system, vs. individual reviews and approvals for each disorder; and standard IRB requests for consent language which may not be applicable to our target population. Issues are brought to the P2WG to address and forwarded to the Region 4 Advisory Group if additional input is needed. IRB materials used by working group members have been shared; Clinical State Leads receive a stipend for participation in Priority 2 activities and Centers receive a per-case entry stipend, either of these fund sources

could be used for IRB fees; and a standardized consent form and project protocol was developed and disseminated which serves as a template for requesting review and approval for participation in any disorder in the IBEM-IS. In addition, beginning this fiscal year, Region 4 has added staff support to assist with all phases of IRB application development.

Much of the activity over the past years has focused on development and continuous improvement of the IBEM-IS. This focus led state department representatives to question their role in the priority 2 project. The P2WG developed a statement of roles and responsibilities for the state follow-up/NBS representatives to strengthen the role and facilitate the workgroup actively considering the role of the state department representatives in the day-to-day activities of the workgroup. All seven states have designated a state follow-up lead in addition to a clinical state lead for participation in the Priority 2 workgroup. Currently, the state follow-up co-lead is developing a statement of IBEM-IS applicability to state follow-up. This document is intended to assist state follow-up representatives develop an understanding of how and under what circumstances examining the IBEM-IS data for their state might be informative.

Clinical State Leads continue to be actively involved, as demonstrated through participation in the monthly meetings, response to requests for action between meetings; and efforts to get their centers actively entering data. There has been minimal increase in efforts to engage additional centers throughout Region 4. Stakeholder meetings are being planned to occur in each of the seven Region 4 states prior to the end of the current fiscal year. Staff are working with state clinical leads to identify clinicians from non-participating clinics to participate in the stakeholder meeting in their state to learn about the IBEM-IS and opportunities for participating.

Challenges specific to Objectives:

Challenges in Objective 1: Our biggest challenge continues to be DocSite's response to issues and completion of work in a timely fashion. MPHI, with input from the P2WG, developed and implemented a variety of strategies over the past two years to, on a steadily increasing basis, monitor DocSite progress and identify potential barriers before they caused significant delay. This has resulted in increased communication regarding the status of the work requested.

Challenges in Objective 2: Fair use and establishment of priorities and credit in research presentations could be a potential operational challenge in our efforts to define and generate research outcomes. We anticipate that this challenge can be mitigated by adherence to our mutual agreement that all participants will receive professional acknowledgement and mutual support for research activities and by our plans for regular review of all research related to the Registry. We have further agreed that all participants will assist in promoting the successful outcome of research that receives the endorsement of the State Lead review process. An additional challenge to the success of research may be limitations in numbers of cases. For this reason, initial research activities are likely to focus on the most common conditions with the anticipation that as other Regions or national activities progress questions about rarer conditions can be proposed.

During the January 2008 Telemeeting of the Region 4 Advisory Group, discussion on data sharing and authorship was initiated. The group has asked for additional time to consider the

issues and review additional resources. The Project Coordinator is collecting sample data sharing and/or authorship agreements from other web-based medical information projects beyond Region 4.

Challenges in Objective 4: To achieve the maximal utility of this Registry it will be essential to have all interested Regions ultimately incorporating the same data. Continuing efforts to define uniform elements will be important to success in extending the Registry. This will be achieved by enlisting collaboration with as many participants as possible in building the disease-specific elements required as the Registry expands. We will actively solicit plans from other regions as we have in collaboration with the Mountain States Protocol Planning Group and in using elements from the database created by metabolic researchers based in Oregon.

It is essential that cooperation emerge in concert with all others Regions. We anticipate that the establishment of the Newborn Screening and Translation Research Network (NBSTRN) will provide opportunities for the regional collaboration. Dr. Sue Berry, Priority 2 Lead, has been asked to Chair the data group for the NBSTRN.

Challenges in Objective 5: Achievement of Objective 3 transforms the IBEM from a dynamic database registry to an information system. Successful achievement of this objective will depend on the ongoing definition of appropriate vocabularies, careful attention to shared data elements with other Regions, and on emerging technologies in data management. Close collaboration with Departments of Health, DocSite, and ongoing efforts in enrollment and systems related to our Region 4 emergency care plan project (see Regional base activities) will be critical.

Administration and Organization

MPHI serves as the project administrator with the University of Minnesota as the scientific lead. Region 4 Genetics Collaborative Organization Information is addressed in the Base Grant Narrative (See also Region 4 Organizational Chart attachment 6.) Staff roles are outlined below.

Cynthia Cameron, Ph.D., Region 4 Director; provides overall administration for the project including contract compliance. Dr. Cameron will be the first point of contact for the research requests and oversee review process.

Susan A. Berry, M.D., metabolic-geneticist and Director of the Division of Genetics and Metabolism in the Department of Pediatrics at the University of Minnesota; is the scientific lead. Dr. Berry manages development and progress of the IBEM Registry, provides scientific direction and promotes participation in the project, both regionally and nationally. She leads the Priority 2 WG, identifying issues for discussion, selecting format and content for monthly meetings; coordinates the activities of the clinical state leads; and trains new users in the IBEM-IS.

Carolyn Anderson, Project Co-Lead; selects format and content for monthly telemeetings, serves as liaison to other state follow up designees to the workgroup; promotes participation in the project both within and beyond Region 4.

Kristi Bentler, in-kind; reviews IBEM-IS databases, identifies and documents issues and makes recommendations; assists with training new users.

Anne Jurek, epidemiologist; will advise the group regarding disease registry procedures and protocols to ensure valid, defensible data in support of best clinical practice and registry security

and assist in defining research analyses.

Sally J. Hiner, Region 4 Coordinator; coordinates all aspects of the project including meeting logistics, materials, records; facilitates ongoing communication with all Priority 2 participants; serves a liaison between workgroup members and DocSite; and monitors and maintains project activity reports.

Jodi Griffin, Project Coordinator; monitors and maintains records of IRB reviews, processing of project invoices and letters of agreement; provides direct assistance in development of IRB applications; coordinates access to approved user IDs and passwords; and coordinates new user and refresher training.