Workshop on Natural History Studies of Rare Diseases:
Meeting the Needs of Drug Development and Research

NIH Campus • Bethesda, MD — May 16–17, 2012

WORKSHOP SUMMARY

Sponsored by:
Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA)
Office of the Commissioner, Office of Orphan Products Development (OOPD), FDA
National Institutes of Health (NIH) Clinical Center
Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS), NIH
Therapeutics for Rare and Neglected Diseases (TRND) Program, NCATS, NIH
National Institute of Neurological Disorders and Stroke (NINDS), NIH
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), NIH

Overview:
Natural history (NH) studies are an important tool for understanding the etiology, range of manifestations, and progression of rare diseases. Well-conducted NH studies can yield information on biomarkers and other correlates of clinical outcome. Obtaining maximum value to support drug development programs depends on conducting these NH studies early, often long before potential therapeutic agents are identified for development. Comprehensive, good quality NH studies designed with an eye toward supporting drug development programs can avoid some of the common problems that lead to stalled, slow, or inefficient drug development for rare diseases. This workshop aims to bring together thought leaders in the design, conduct, and evaluation of natural history studies to discuss the role of these studies in the development of therapeutic candidates.

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Executive Summary

Welcome and Opening Remarks

Stephen C. Groft, Pharm.D., National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH), welcomed participants and thanked the workshop sponsors. Gayatri Rao, M.D., J.D., Food and Drug Administration (FDA), explained that FDA's Office of Orphan Products Development supports researchers who are starting the FDA phase of development for products for rare diseases. Christopher Austin, M.D., NCATS, hoped that the workshop would lead to a new plan for collecting natural history data to support the development of interventions for rare diseases. John Gallin, M.D., of the NIH Clinical Center, reported that approximately half the patients who come to the Clinical Center have a rare disease and called for the development of a phenotype atlas for rare diseases.

Concept and Importance of Natural History Studies: Expectations for the Workshop

Anne Pariser, M.D., FDA, explained that natural history studies track a disease's course over time and identify demographic, genetic, environmental, and other variables that correlate with the disease and its outcomes in the absence of treatment. In rare cases, patients in natural history studies or registries can serve as historical controls.

Nuria Carrillo, M.D., NCATS, reported that for investigators, regulatory agencies, funders, and industry, natural history studies are the cornerstones of research plans. For patients and their families, natural history study sites offer a medical home. When planning a natural history study, investigators should identify knowledge gaps, study objectives and design, specimens to collect, and how to monitor study progress and modify the study based on the lessons being learned.

Theoretical Considerations in the Design of Natural History Studies

Marc Walton, M.D., Ph.D., FDA, explained that natural history knowledge can guide several design features of therapeutic studies. Investigators should identify all of their study's objectives from the beginning. Types of natural history studies include published medical literature reviews, retrospective chart reviews, and prospective cross-sectional and longitudinal studies.

Jeffrey Krischer, Ph.D., University of South Florida, reported that the NIH Office of Rare Diseases Research sponsors the Rare Diseases Clinical Research Network (RDCRN). When designing a natural history study, investigators should identify who owns the data, who has access to the data, and how to protect patient confidentiality. Cross-sectional data typically provide information on prevalence, whereas longitudinal studies shed light on incidence.

Edward Kaye, M.D., AVI BioPharma, explained that biotechnology companies conduct natural history studies of rare diseases to determine a disease's incidence, understand its variability, identify causes of morbidity or mortality, and determine effects on patient lifespans. Investigators should ensure adequate geographic representation of patients to avoid bias, ensure that sites enter data in an accurate and timely way, and learn from the mistakes of previous studies.

Patricia Furlong, Parent Project Muscular Dystrophy, explained that patients with rare diseases and their families are eager to participate in natural history studies to learn about the disease and its likely effects over time, current treatments, and ways to improve quality of life and lifespan. Families should receive information on how the study results might be used, who will have access to the data, and when and how the investigators will communicate what they are learning.

Case Studies: Academic Prospective Longitudinal Studies

Basil Darras, M.D., Children's Hospital Boston, described a prospective natural history study of 5q spinal muscular atrophy. The investigators developed, validated, and tested three outcome measures and collected an extensive biomaterials repository. Lessons learned included the need to schedule research and clinical visits on the same day and for all study sites to conduct the outcome measures in the same order at each visit.

Marshall Summar, M.D., Children's National Medical Center, described Urea Cycle Disorders (UCD) Consortium, which works to better understand the pathophysiology and outcomes of UCD, conduct clinical trials of promising new drugs, develop information resources on UCD, and train the next generation of investigators in UCD. Lessons learned include that a good data coordinator is critical, collecting too much data degrades data quality, and capturing specific data on events that occur between research visits is difficult.

Jane Paulsen, Ph.D., University of Iowa, described a prospective longitudinal study of people who had undergone genetic testing for Huntington's disease. The study is collecting biospecimens and data on more than 80 variables, and the investigators share all of the data they collect to maximize the study's utility. Lessons learned include the need to make participation convenient to patients and families and to use standardized methods so that the data are comparable and of high quality.

David Pearce, Ph.D., Sanford Health, commented that natural history studies have helped identify biomarkers that could be applied to therapeutic interventions for rare diseases in clinical trials. Craig McDonald, M.D., University of California Davis, emphasized the importance of evolving study designs over time in response to the data collected and of conducting biomarker studies in parallel with natural history studies.

Case Studies: Industry-Sponsored Prospective Longitudinal Studies

Lawrence Charnas, M.D., Ph.D., Shire Human Genetic Therapies, described a planned natural history study of Krabbe disease that was stopped before recruiting any patients, primarily because of the inability to recruit patients due to lower than expected incidence of Krabbe disease and its rapid progression.

P.K. Tandon, Ph.D., Genzyme, reported on a natural history study of Niemann-Pick disease Type B (NPB) to determine the prevalence and range of abnormalities in patients with NPB, evaluate disease progression over time, and improve the design of future clinical trials of enzyme

replacement therapy. The study provided new information about the spectrum of NPB manifestations and identified differences in manifestations in patients from different countries.

Patrick Haslett, M.D., Shire Human Genetic Therapies, described a natural history study of mucopolysaccharidosis IIIA to understand the disease spectrum, measure disease progression, help identify appropriate patients and candidate endpoints for therapeutic trials, and generate a high-quality dataset with potential utility as a historical control group. The cerebrospinal fluid biomarkers identified by the study and brain magnetic resonance imaging patterns might be useful adjuncts to clinical evaluation in assessing the impact of therapy.

Annette Stemhagen, Dr.P.H., F.I.S.P.E., United BioSource Corporation, urged researchers to start natural histories early in the therapeutic-development process because these studies can add valuable information to these development programs. Karen Chen, Ph.D., SMA Foundation, stated that foundations and patient advocacy groups can help reduce the risk of developing interventions for rare diseases by sponsoring and spearheading natural history studies.

Case Studies: Retrospective Chart Reviews

Robert Fiorentino, M.D., FDA, described a pilot cross-sectional and longitudinal study to characterize symptoms in patients with eosinophilic esophagitis using existing site-based registries and datasets from three sites. The results showed that pilot studies can inform future natural history data extraction studies. Cross-sectional studies can help identify potential age-related symptom "targets" for developing patient-reported outcome measures to demonstrate that therapies used in future clinical trials have a meaningful clinical benefit.

Richard Moscicki, M.D., Genzyme, explained that after FDA approved Fabrazyme® (agalsidase beta) for Fabry disease, Genzyme conducted a Phase 4 trial to demonstrate the product's clinical benefit. The company conducted a retrospective natural history study in parallel with its Phase 4 study. Genzyme suggested to FDA that if some patients in the placebo group dropped out of the Phase 4 study or began active therapy, the natural history study patients could serve as a control group. However, FDA did not agree.

Priya Kishnani, M.D., Duke University Medical Center, reported on a natural history study of infantile Pompe disease that documented the frequency and age of onset of important clinical milestones, age of death, and factors associated with longer and shorter survival. The investigators identified 62 untreated patients from the natural history study to serve as a historical control group in the open-label study of Myozyme® (alglucosidase alfa). Based on the results of this study, FDA approved intravenous alglucosidase alfa for Pompe disease in 2006.

Case Studies: Prospective Cross-Sectional Studies

Elsa Shapiro, Ph.D., University of Minnesota, explained that pilot studies are small-scale preliminary studies used to plan longitudinal natural history studies. Pilot studies can provide information on the feasibility, recruitment potential, and costs of a natural history study. Cross-sectional studies can include large single-visit studies that are stand-alone studies or part of a

natural history study. Cross-sectional studies typically include more patients and have broader goals than pilot studies.

Maria Escolar, M.D., M.Sc., Children's Hospital of Pittsburgh of UPMC, described the Program for the Study of Neurodevelopment in Rare Disorders (NDRD), NDRD has established a registry and conducts natural history studies of rare neurodegenerative genetic diseases of the brain. The challenges of conducting natural history studies include geographically dispersed and chronically impaired populations, variable onset of presentation and spectrum of disease involvement, and loss of opportunity to conduct a true natural history study once a treatment is available.

Florian Eichler, M.D., Massachusetts General Hospital, described a natural history study of GM2 gangliosidosis to help plan a study of intracranial adeno-associated virus-mediated gene delivery. This survey-based study showed that caregivers can recall distinct clinical findings, but their reports on milestones might be tainted by subjective impressions. The investigators used the natural history study data to develop a disease-specific clinical scoring system that they are using in prospective studies.

Meral Gunay-Aygun, M.D., Staff Clinician, National Human Genome Research Institute, NIH, reported that she is conducting prospective longitudinal studies of celiopathies.

Summary, Conclusions, and Moving Forward

John McKew, Ph.D., NCATS, said that this workshop will start a dialog on natural history studies of rare diseases that addresses funding sources, shared resources, incentives for academic collaborators, and patient group involvement. A follow-up meeting will focus on a key challenge identified at this workshop. A longer term outcome might be the formation of a consortium or compendium of guidance for unified natural history study design and execution.

Dr. Austin and Dr. McKew thanked participants for attending the meeting and invited them to join the group that will plan the next steps after this workshop.

Day 1: May 16, 2012

Welcome and Opening Remarks

Stephen C. Groft, Pharm.D., Director, Office of Rare Disease Research (ORDR), National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)
Gayatri Rao, M.D., J.D., Acting Director, Office of Orphan Products Development (OOPD), Food and Drug Administration (FDA)
Christopher Austin, M.D., Scientific Director, Division of Pre-Clinical Innovation, NCATS, NIH
John Gallin, M.D., Director, NIH Clinical Center

Dr. Groft thanked participants for coming to this meeting. He also thanked the meeting's cosponsors:

- Center for Drug Evaluation and Research (CDER), FDA
- Office of the Commissioner, OOPD, FDA
- NIH Clinical Center
- ORDR, NCATS, NIH
- Therapeutics for Rare and Neglected Diseases (TRND) Program, NCATS, NIH
- National Institute of Neurological Disorders and Stroke (NINDS)
- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

Dr. Groft advised researchers to consider starting a natural history study when they first identify a patient with a rare disease to increase knowledge about these diseases. The goals of natural history studies include identifying clinical endpoints, potential participants for clinical trials and other studies, and research hypotheses for basic and clinical research as well as contributing to the drug research and development continuum. The meeting sponsors hoped that the workshop would lead to the development of a critical mass of investigators and research sites to form consortia that adhere to common study protocols, accept patients from all age groups and disease stages, and conduct extensive front-end planning for natural history studies. Patient advocacy groups should play a major role in these consortia.

Dr. Rao explained that FDA's OOPD supports researchers who are ready to start the FDA phase of development for products designed for rare diseases. FDA celebrated the fifth annual Rare Disease Day on March 1, 2012, by hosting the FDA Rare Disease Patient Advocacy Day to educate and engage the rare disease community in regulatory processes related to rare diseases. An important message that FDA delivered during this event was that patients and family members who are eager to make a contribution can help establish registries and participate in natural history studies.

Dr. Austin reported that the top reason why rare disease development programs fail at FDA is the lack of natural history information. Natural history studies can shed light on the full spectrum of genotypic and phenotypic features associated with a rare disease, how the disease develops over time, and potential biomarkers. These studies can also collect biospecimens. Another reason why rare disease therapeutic development efforts fail is that natural history studies that are designed

to result in academic journal publications do not address the requirements for regulatory submissions. The organizers of this workshop brought together representatives of academia, industry, and government to develop a new plan for collecting natural history data in ways that are sufficiently robust to support the development of therapeutic or diagnostic interventions and that address several rare diseases at once to generate economies of scale.

Dr. Gallin characterized the NIH Clinical Center as one of the great gifts that Congress has given to the American people. The Clinical Center has served approximately a half million patients since opening its doors in 1953. Approximately half the patients who come to the Clinical Center have a rare disease, and the Clinical Center probably sees more patients with rare diseases than any other institution in the world. Rare diseases as a whole are not all that rare; according to some experts, up to 30 million Americans have a rare disease. With the increasing use of genotyping technology, this number is likely to expand rapidly. Dr. Gallin called for the development of a phenotype atlas for rare diseases, with links between this phenotyping information and genotyping information.

Concept and Importance of Natural History Studies: Expectations for the Workshop

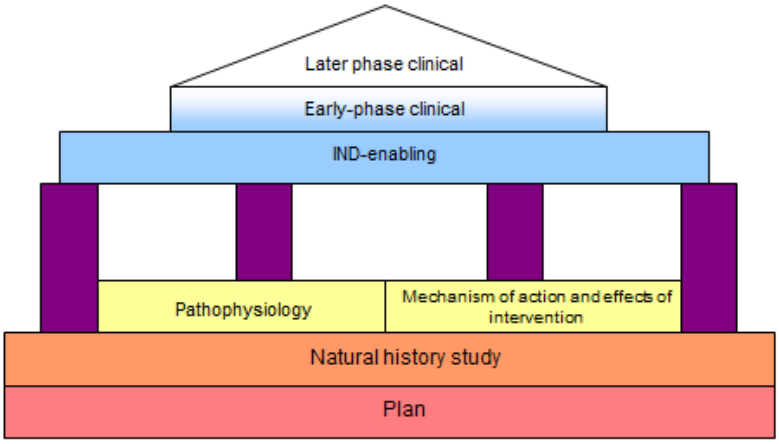
Importance of Natural History Studies in Rare Diseases

Anne Pariser, M.D., Associate Director for Rare Diseases, Office of New Drugs, CDER, FDA

FDA Approval Process

For an intervention to receive FDA approval, research needs to demonstrate that the intervention has a clinically meaningful effect on patients through adequate and well-controlled studies. These studies must be based on a scientific foundation that includes knowledge of the disease's natural history.

The traditional drug development process follows a linear trajectory that begins with basic science and proceeds to translational research, pre-Investigational New Drug (IND) studies, and clinical studies. Much of the planning takes place during the clinical study phase. After FDA approves the New Drug Application (NDA), the last phase is post-marketing surveillance. Natural history and other studies often take place during the translational phase of drug development. For rare diseases, a more appropriate model is built on a foundation of careful planning and natural history studies, as shown below.



In this foundation-based model, every piece builds on what came before and everyone involved in the different steps works together.

What Is a Natural History Study?

Because only small numbers of patients have a given rare disease, the opportunity to study these patients and replicate these studies is limited. Approximately 7,000 rare diseases exist and these diseases are highly heterogeneous, with substantial phenotypic diversity within many individual disorders. Little precedent exists for drug development within most rare disorders. For these reasons, intervention development for rare diseases often requires more (and more careful) planning than for more common diseases.

Natural history studies need to be distinguished from registries. The term "registries" is very general and can refer to collections of contact information for patients or post-marketing data (e.g., on an intervention's safety). In contrast, natural history studies have a specific purpose and are intended to explore a disease in a comprehensive way.

According to Manuel Posada de la Paz and Dr. Groft, a disease's natural history is "the natural course of a disease from the time immediately prior to its inception, progressing through its presymptomatic phase and different clinical stages to the point where it has ended and the patient is either cured, chronically disabled or dead without external intervention."[1] By definition, natural history studies track a disease's course over time. These studies identify demographic, genetic, environmental, and other variables that correlate with the disease and its outcomes in the absence of treatment. According to the Institute of Medicine, natural history studies serve as a "pillar of epidemiologic research on rare conditions."[2]

[1] *Adv Exp Med Biol*. 2010;686:3-14.
[2] *Rare Diseases and Orphan Products: Accelerating Research and Development*. Washington, DC: The National Academies Press; 2010.

Use of Natural History Study Data to Create Historical Control Groups

In rare cases (such as for diseases with high and predictable mortality rates or for which a drug's effects are self-evident), patients in natural history studies or registries can serve as historical controls. The purpose of any control group, whether historical or concurrent, is to measure what would have happened without the intervention and this is typically much clearer with concurrent control groups. Historical control groups often include patients from a different time or place than the patients in the study, and the data on these patients must be comparable to the data on the study's participants.

Two types of historical controls exist. Informal or implicit controls are based on general knowledge and are reasonable when the intervention has a rapid and dramatic effect that is unlikely to have occurred spontaneously. The second type of control group involves specific experiences of the type available, for example, in retrospective chart reviews. These types of control group are only appropriate when objective, verifiable measures are available and the control group data can be fairly compared to data from the interventional study population.

Examples of Using Natural History Studies to Inform Clinical Development

In 2012, the FDA approved Voraxaze® (glucarpidase) for the treatment of toxic plasma methotrexate concentrations due to impaired renal function. This drug, which had no disease precedent, received full approval based on a pharmacodynamic endpoint—the proportion of patients with an elevated methotrexate level who achieved a rapid and sustained clinically important reduction in their methotrexate level to less than 1 μmol/l.

The evidence for the drug's effectiveness came from an analysis of data on 22 patients with evaluable methotrexate levels after glucarpidase administration. These patients were part of a National Cancer Institute-sponsored prospective, open-label, historically controlled compassionate use trial in 184 patients with high-dose methotrexate-induced nephrotoxicity and delayed methotrexate excretion. Randomly assigning patients to an intervention or control group was not ethically feasible.

A large volume of long-term clinical experience was available on glucarpidase. Its effects, mechanism of action, toxicity, excretion, and metabolism were well understood. FDA determined that rapid and sustained plasma levels of methotrexate levels below the 1-μmol/l threshold could be used as a valid surrogate endpoint for organ toxicity. Because the drug was so well characterized, a historical control group could be used to assess the treatment's effects.

A second drug approved in 2012, Kalydeco™ (ivacaftor), also had no disease precedent. This drug is indicated for the treatment of cystic fibrosis in patients aged 6 years or older who have a *G551D* mutation in the CFTR gene. Two randomized, double-blind, placebo-controlled trials robustly showed the drug's clinically meaningful benefit on lung function, pulmonary exacerbations, and weight. A cystic fibrosis registry and care network had been established in 1960, and extensive disease history data had been prospectively collected.

Key Points

Dr. Pariser closed her presentation with the following key points:

- Natural history studies describe a disease in the absence of investigational agents.
- Rational, scientifically based drug development requires an understanding of the disease, which natural history studies can provide.
- Natural history studies are most informative when their data are available early in the drug development process, ideally before efficacy trials are designed.
- Patients and caregivers must be involved in natural history studies, including in planning and overseeing studies.
- Rare diseases are a highly diverse collection of disorders, requiring different types of clinical development programs based on an understanding of the intervention and its likely impact on the disease.
- Drug development for rare diseases is a continuum in which data on natural history, pathophysiology, mechanisms of action, and intervention effects inform the design of efficacy, early-phase clinical, and IND-enabling studies as well as endpoint identification and development.

Natural History Studies of Rare Diseases: Concepts and Elements
Nuria Carrillo, M.D., Staff Clinician, TRND Program, NCATS, NIH

Purposes of Natural History Studies

Natural studies for rare diseases have several purposes. For investigators, regulatory agencies, funders, and industry, natural history studies are the cornerstones of research plans. For patients and their families, natural history study sites offer a medical home.

Possible objectives of natural history studies are to:

- Define the disease.
- Improve diagnosis.
- Identify biomarkers.
- Develop outcome measures.
- Collect biospecimens.
- Create centers of expertise.
- Provide foundations for drug development.

To support clinical research, natural history studies can define a disease's clinical features and complications, progression rate, pathophysiology, incidence, and prevalence. The clinical information collected in natural history studies should guide basic research. This information can also help identify the types of patients to study in a clinical trial, the duration of the trial, and the types of biomarkers and outcome measures to use in the trial.

Challenges

The challenges for natural history studies in rare diseases include limited knowledge of these diseases and lack of a standard of care or validated measures of disease activity. For some rare diseases, the only information in the literature comes from a few case reports. In addition, the numbers of patients with a given rare disease are limited, as are time and resources.

The best way to address the challenge of limited knowledge is to conduct a well-planned, comprehensive, and efficient natural history study. Because the numbers of patients with the rare disease will be small, this study must include sensitive evaluations and the researchers must design the study carefully, with appropriate biostatistics. Because resources and time are limited, this study must be cost effective.

Natural history studies can also address other challenges of rare diseases. For example, rare diseases are usually misdiagnosed or undiagnosed. Natural history studies can help develop screening and diagnostic tests and inform patients and the medical community about the disease.

Planning

Natural history investigators should plan to evaluate as many potential outcome measures and biomarkers as possible to understand their feasibility, reproducibility, variability, and sensitivity. Natural history studies should also assess the correlation of each outcome measure and biomarker with clinical and patient-reported outcomes, progression, and prognosis. This process should lead to a focus on one or two outcome measures or biomarkers that could be used in clinical trials.

Planning is a key step for natural history studies. During the planning phase, investigators should identify:

- Knowledge gaps.
- Study objectives.
- Study design.
- Evaluations.
- Potential collaborators.
- Data-collection and reporting procedures.
- Specimens to collect.
- Ways to monitor study progress and modify the study based on the lessons being learned.

Discussion

In response to a question about guidelines for natural history studies, Dr. Carrillo said that no consolidated set of guidelines on natural history studies is available, but guidelines would be a powerful tool. Dr. Pariser added that developing a set of best practices is one of the goals of this meeting.

A participant noted that autopsies can play a critical role in natural history studies. The use of autopsies is a cost-effective approach to collecting data on natural history and unanticipated manifestations of a disease.

Dr. Carrillo answered a question about assessing outcome measures by recommending that researchers collect as much data as possible on potential outcome measures and correlate the results of outcome measures to as many outcomes as possible because determining in advance where correlates will occur is not possible. As the study progresses, which outcome measures to focus on will become clearer.

Dr. Pariser explained that natural history studies are often used for post-marketing surveillance, especially for interventions for rare diseases. Drugs for rare diseases are often approved on the basis of studies in small populations and a condition of approval is the establishment of a registry to monitor the drug's effects on the disease and its safety over time. Several longstanding registries of this type exist, such as the Gaucher disease registry established by Genzyme.

A representative of a patient advocacy group asked whether an "idiot's guide" to conducting natural history studies with a limited budget is available for small patient advocacy groups. Dr. Carrillo commented that registries do not offer an inexpensive alternative to natural history studies because registries are not inexpensive. Planning is key to minimizing the costs of natural history studies, and this meeting should provide many examples that could be used to create guidelines for natural history studies. Dr. Pariser added that this meeting should increase the recognition that natural history studies are important for drug development and good logistical approaches for these studies are not available. If natural history studies become more common, perhaps more conversations will occur about how to fund these studies in a comprehensive way.

A participant commented that some approaches to natural history studies that are appropriate for adults are not appropriate for young children. Identifying the disease's developmental trajectories early on is important. A treatment that is not effective in adults might work in children in whom the disease progression is less advanced. Dr. Pariser agreed that natural history studies need to describe the entire spectrum of each disease. Dr. Carrillo added that natural history studies in children might lead to the development of a newborn screening test that will make describing a disease's natural history from birth possible.

A participant stated that phenotypic information collected in natural history studies must be correlated with genotypic information. Dr. Carrillo agreed, saying that natural history studies should collect genotypic information on all patients and this information could be useful for clinical trials.

A participant wondered whether natural history studies should start in parallel with clinical trials. Dr. Pariser said that the timing of natural history studies should depend on the disease. Natural history studies do not necessarily need to be completed before clinical trials start. However, the lack of a potential therapeutic candidate should not prevent an investigator from starting a natural history study.

A participant asked about the use of newborn screening data to inform the natural history of a disease and to inform the planning of clinical studies. Dr. Carrillo said that states determine which tests to include in their newborn screening panels based on such criteria as the availability of good biomarkers and whether early detection can change disease outcomes.

Theoretical Considerations in the Design of Natural History Studies
Chair: John McKew, Ph.D., Chief, Therapeutics Development Branch, TRND Program, NCATS, NIH

Natural History Studies: Form Follows Purpose
Marc Walton, M.D., Ph.D., Associate Director for Translational Medicine, Office of Translational Sciences, FDA

Orphan diseases are those that affect fewer than 200,000 patients in the United States. Dr. Walton defined "rare diseases" for his presentation as a subset of orphan diseases about which little is known and for which the small numbers of patients make therapy development difficult.

Applications for Natural History Knowledge

Natural history knowledge can guide the selection of several design features of therapeutic studies, including:

- Which population to study.
- Which outcome assessments to evaluate.
- Which objectives to target.
- How long the clinical trial should last.
- Which biomarkers to use.

Unless natural history studies guide these types of decisions, the wrong decisions might be made and, as a result, a therapeutic development program can fail.

Critical natural history information is not available for many rare diseases, but successful therapy development may require this information. Natural history studies are not part of drug treatment studies, but natural history knowledge must be used in therapeutic development programs. Natural history studies are most useful if they are conducted and their data are available before the treatment development program starts. Natural history study information is usually used during the drug development (IND) period but this information is not usually a major part of the NDA or Biologics License Application processes. Critical regulatory decisions (such as approval of a treatment) do not typically depend on natural history data.

Natural history study data do not need to be of verifiable good clinical practice quality, but the data do need to be of high quality. Investigators should monitor their data quality during the study to ensure that the quality is adequate for the study's purposes.

Natural history knowledge is disease specific, not therapy specific. For this reason, conducting natural history studies outside drug development programs is appropriate. The data from natural history studies should come from a broad base of patients and sites and the data should be

available to everyone who can apply that information, so that the information can be used in several different treatment development programs.

Design Considerations

As with any clinical study, natural history studies need careful, prospective planning. The investigators should identify all of their study's objectives in consultation with experts in drug development from the beginning, and these objectives should drive the study's design. Investigators should aim to collect information that could inform the development of a broad range of potential therapies.

Types of natural history study designs include:

- Published medical literature review.
- Retrospective chart review: a common starting point for natural history studies. These data are typically not comprehensive and the types and quality of information recorded in charts usually vary. However, these studies can guide subsequent studies in the knowledge-development program.
- Prospective cross-sectional study: provides a moderately detailed understanding of a disease and can be valuable for developing outcome tools. However, cross-sectional studies do not usually provide details on the disease's pace, unless the disease's onset is reliably identifiable.
- Prospective longitudinal study: provides the most comprehensive understanding of a disease and its course and pace. Sustained commitment from patients and investigators is essential, and these studies provide valuable information for designing clinical trials.

Investigators should regard their natural history protocols as evolving, not fixed. They should analyze the data they are accumulating periodically and refine their study questions, hypotheses, and designs based on these data.

Information to Gain from Natural History Studies

The types of information to collect in natural history studies can include:

- Major and minor disease features, including survival and physical, sensory, and neuropsychological impairments.
- Pathophysiology subsets (including genetic subsets).
- Diagnostic criteria.
- Standard of care (including supportive or unproven treatments).
- Biomarkers of disease course and pharmacologic responses to therapy.

Investigators should collect data on all levels of severity of disease manifestations, the pace of manifestation development, and the frequency of these manifestations. They should also measure intra- and inter-patient variability in disease manifestations.

Although many investigators hope to use their natural history study data to create a historical control group, this is not feasible for most rare diseases. Using natural history data for this purpose is most suitable for highly homogeneous disorders or phenotypes for which uniform,

rigorously recorded patient evaluations from multiple sites are available that are not easily influenced by variations in patient care.

A Community Endeavor

The most successful natural history studies are community endeavors involving everyone who is interested in the disease. Limiting access to data can impair progress as much as the lack of data, so natural history studies of rare diseases need investigators at multiple sites who jointly design and conduct these studies. Other key players include:

- NIH to ensure that natural history studies are communal endeavors.
- Industry to provide drug development expertise and identify the questions that natural history studies need to answer.
- Patient groups to identify potential study participants, educate patients and families about the value of natural history studies, sustain patient involvement, and assist with data collection and management.
- FDA to provide advice on rare disease treatment development programs.

Operational Issues

Natural history study investigators need to make decisions about several operational issues, including whether data will be managed centrally or at different sites. Multisite studies reduce the need for patients to travel long distances for their evaluations and allow patients to be monitored by their usual physicians. However, when several sites or physicians use the study protocol for only a few patients, they might not follow the protocol consistently. A centralized model ensures that the data site has experience with the protocol and collects the data in a consistent way. However, this model is the least convenient for patients.

Other operational designs include:

- Mixed model, with several clinics conducting evaluations and one central site conducting less frequent but more intensive evaluations.
- In-home model, in which visiting health care providers or other trained persons conduct more frequent and less intensive evaluations in patients' homes.
- Patient-reported model, which requires training for patients and families and a reporting tool with known reliability; this model is most suitable for less quantitative evaluations.

Much work is still needed to understand how to collect natural history information most efficiently and effectively, which operational structure is best suited to a given study design, and how to train people to collect high-quality natural history data.

Practical Considerations in the Design of Natural History Studies

The View from the Rare Diseases Clinical Research Network
Jeffrey Krischer, Ph.D., Professor, University of South Florida College of Medicine

Rare Diseases Clinical Research Network

The NIH Office of Rare Diseases Research has funded the Rare Diseases Clinical Research Network (RDCRN) since 2003. The network currently consists of 19 consortia of 167 institutions around the world. The RDCRN is studying more than 200 diseases and has enrolled almost 10,000 patients in 78 studies.

The network facilitates clinical research by creating consortia focused on related diseases, establishing a cost-saving research infrastructure and uniform protocols for data collection, and making meaningful large-scale studies possible. The network engages patients and advocates and trains new investigators in rare diseases research. All RDCRN studies have defined eligibility criteria for participants, specific aims, uniform clinical assessments within the context of usual care, and uniform follow-up frequency. Network studies use data standards (pertaining, for example, to drug coding, diagnoses, or dietary supplement use) to ensure that study results are generalizable, and all studies have analysis plans.

When a network site identifies a population to study, the investigators try to develop an enrollment plan that will find patients with a given set of characteristics for a future clinical trial. Studies are also planned to estimate event rates and determine correlations between genotypes and phenotypes. Studies identify factors that contribute to heterogenous outcomes and test hypotheses.

Natural History Study Design

Design considerations are as critical for natural history studies as for clinical trials. When designing a study, investigators should determine:

- Who owns the data.
- Who has access to the data.
- How to protect participant confidentiality.

Natural history studies are often expensive, partly because outcomes of interest take a long time to become manifest. In addition, primary care providers and subspecialists need compensation for the effort required to collect data for the studies. However, if assessments are not clinically indicated, physicians might not be reimbursed for conducting them. Standardized assessments are necessary to minimize bias. Electronic health records might become robust sources of data for natural history studies in the future, but this is unlikely to happen in the short term.

The RDCRN does not reach all patients with a given diagnoses, so its investigators need to identify potential differences between study participants and other patients with the diagnosis. All sites need to report on the same events in the same ways so that their data are comparable.

Cross-sectional data typically provide information on prevalence, whereas longitudinal studies shed light on incidence. Some creative statistical approaches can be used to generate longitudinal data from cross-sectional studies. For example, if a study has a large population but few follow-up data and a longitudinal study would not be feasible, the investigators might be able to use their cross-sectional data to predict changes in weight or other disease outcomes by age.

Investigators need to monitor their data on an ongoing basis. For example, they should determine whether all members of the initial cohort are being followed in the same ways because patients who are more seriously affected by a disease might be followed more closely. Investigators can make adjustments for any differences they identify or at least keep these differences in mind when interpreting the data.

Importance of Natural History Studies for the Biotechnology Industry
Edward Kaye, M.D., Chief Medical Officer and Senior Vice President, AVI BioPharma

Biotechnology Company Perspective

Small biotechnology companies are chronically underfunded, so they have little tolerance for risk. A failed clinical trial could mean the end of a company. One way to minimize risk is to understand a disease, which can be accomplished with natural history studies.

The reasons why a biotechnology company might conduct a natural history study of a rare disease include to:

- Determine the true incidence of the disease.
- Understand the disease's phenotypic, genotypic, and geographic variability.
- Identify causes of morbidity or mortality.
- Determine the disease's effects on patient lifespans.

Natural history studies should take place in "precompetitive space." When natural history studies are noncompetitive, competitors and foundations can work together, which can reduce costs and yield information that is valuable to all partners.

Design Issues

Natural history studies can inform clinical trial design by identifying the population to study and the disease's natural progression and to assess whether a particular endpoint can be used in a rare disease trial. Endpoints must be measurable by study centers, and the changes measured must be noticeable and relevant to all subpopulations.

In some cases, natural history data can be used to create a historical control group. The endpoint for these studies must be simple and reproducible. Death is a reliable endpoint that is readily recognizable and is documented in medical records. However, time to ventilation in infantile Pompe disease is not a suitable endpoint because different sites define "ventilation" differently.

Data collected by different centers for a natural history study might not always be comparable because, for example, different centers use different imaging equipment. In addition, changes in

the standard of medical care during a natural history study can affect the study results. For example, steroids have changed the natural history of Duchenne muscular dystrophy in the past decade by prolonging patients' ability to ambulate for approximately 2 years.

Other tips for natural history studies include:

- Collect data that can provide insights into clinical trial design. For example, natural history studies can help determine the endpoints, number of patients required, and sites with potential study participants for a clinical trial.
- Collect data over the Web, which makes the data easy to monitor.
- Ensure adequate geographic representation of patients to avoid bias.
- Ensure that sites enter data in an accurate and timely way.
- Learn from the mistakes made in previous natural history studies.
- Collect data on as many patients as possible because large datasets can sometimes compensate for data collection weaknesses.

Natural History Studies to Inform Drug Trials in Duchenne Muscular Dystrophy: Lessons Learned and the Role of Patient Advocacy

Patricia Furlong, Founding President and Chief Executive Officer, Parent Project Muscular Dystrophy

Role of Patients and Families in Natural History Studies

The reasons why patients and families should participate in natural history studies include the opportunity to learn about the disease and its likely effects on the patient over time, current treatments, and ways to improve quality of life and lifespan. Participating in natural history studies also gives families the opportunity to contribute to the development of future clinical trials. Families are highly motivated to participate in natural history studies because they want to change the trajectory of the disease and to help make safe and effective drugs available for the disease. The knowledge gained from natural history studies can help families plan for a loved one's future. For example, knowing that a child with Duchenne muscular dystrophy is likely to lose the ability to walk allows families to make the necessary adjustments to their homes in advance.

In return for the time and effort patients and families spend undergoing testing, they should receive information on:

- The reasons for any changes to the protocol.
- How biotechnology and pharmaceutical companies and other researchers might use the results of the natural history study.
- Whether the study data will be publicly available.
- Whether patients and families will have access to their data.
- Whether the aggregate data will be incorporated into a larger dataset.
- When and how the investigators will communicate what they are learning.

Lessons Learned

Parent Project Muscular Dystrophy is a partner in a multicenter, longitudinal natural history study by Dr. Craig McDonald on Duchenne muscular dystrophy. Many companies are about to conduct trials of therapies for Duchenne muscular dystrophy.

Some lessons learned from the organization's experience with natural history studies are:

- These studies need funding from a broad range of sources, such as foundations, government agencies, and industry.
- Patients and their families are eager to participate in these studies because they understand the role of natural history studies in supporting clinical trials that can lead to approval of a new treatment.
- Families want studies to include patients of different ages and disease stages.
- Families enjoy and benefit from the exposure to research and clinical experts.
- Investigators need to keep patients and families informed of study progress to sustain their participation.

Once the analysis is complete, the data collected from natural history studies must be accessible to patients and investigators. An embargo can be placed on subsequent publications using the aggregate data until the original investigators have published the study results.

Investigators should consider ways to integrate natural history data collection into routine care. Families must often travel long distances to a study site, which requires taking time off work, incurring other expenses, and making arrangements for their other children. If participating in a study is too costly, the study will only include patients whose families have education and money. Investigators need to find ways to bring in all patients and families to ensure that the study sample is not biased.

Discussion

In response to a question about the use of natural history data to create a historical control group, Dr. Walton emphasized that using natural history data for this purpose to develop definitive proof of efficacy is very difficult and can only be done in a small number of disorders. Relying on historical control data for additional claims of benefit is probably even more difficult.

A participant asked whether natural history studies that meet good clinical practice standards could be used to create historical control groups. Dr. Walton explained that the reason why natural history control groups for rare diseases are not suitable is not that these studies do not meet good clinical practice standards. Patients in natural history data can only be used to create historical control groups for highly uniform disorders or a subset of patients with uniform characteristics and the outcome measured in the natural history must be the same as in the interventional trial. Furthermore, all of the supportive care in the natural history study and interventional study must be provided in the same way. In FDA's experience, the natural history data available for most rare diseases are not reliable enough to serve as a comparator.

The participant commented that in some circumstances, a retrospective analysis of data from a prospective natural history study could identify a homogeneous set of patients who could serve as a historical control group. Dr. Walton said that investigators should identify clear objectives for their natural history studies at the outset, and this requires identifying all of the possible uses for the data they will collect to ensure that the study has the best chance of answering the questions that will arise during drug development. If investigators focus on collecting data from natural history studies that could form the basis of a historical control group, they might miss opportunities to advance interventional drug development for the disease.

A participant said that results from natural history studies might be valuable for FDA's clinical development guidelines. Dr. Walton said that FDA's disease-specific guidance documents do explain the value of natural history study results for informing clinical trials, although these documents tend to focus on more common diseases. One purpose of this meeting was to find ways to communicate the importance of natural history studies for drug development in the absence of disease-specific guidance documents.

A participant called for companies to prioritize rare diseases to study based on the potential for reimbursement for an intervention. Dr. Kaye said that his company tries to collect data, including data on quality of life, in its clinical trials that will be important for reimbursement once the intervention is approved. In some diseases, an intervention that provides a small improvement might be eligible for reimbursement. For rare genetic diseases that result in early death, however, interventions will only be eligible for reimbursement if they can improve survival. Dr. Walton added that mortality is a good endpoint for intervention development, and natural history data on a rare disease that is associated with early mortality can make a disease more attractive for drug development by a company.

A participant asked about potential drug-development paths for rare diseases in which a placebo arm is not possible for ethical or design-related reasons. Dr. Walton said that each situation must be addressed individually.

Case Studies: Academic Prospective Longitudinal Studies

Chair: Petra Kaufmann, M.D., M.Sc., Associate Director, Office of Clinical Research, NINDS, NIH
Co-Chair: Edward Kaye, M.D., Chief Medical Officer and Senior Vice President, AVI BioPharma

Spinal Muscular Atrophy Natural History: Lessons Learned
Basil Darras, M.D., Associate Neurologist-in-Chief, Children's Hospital Boston

5q Spinal Muscular Atrophy

Decreased levels of survival of motor neuron protein cause 5q spinal muscular atrophy (SMA), an autosomal recessive disorder that is one of the most common neuromuscular conditions in infants and children. Type I SMA develops in infants aged 0–6 months and is associated with an inability to sit unsupported and a lifespan of less than 2 years without aggressive treatment. Type II SMA develops at ages 7–18 months, these children can sit but never stand or walk, and

approximately 70% are alive at 25 years. Type III SMA typically begins after 18 months, these children can stand and walk at some time, and their lifespan is almost normal.

Natural History Study of SMA

The SMA Foundation created the Pediatric Neuromuscular Clinical Research Network to study the natural history of SMA, collect data for trial planning, develop and validate outcome measures, and provide comprehensive care integrated with research.

The Network's natural history study was a prospective, comprehensive, observational study of patients with SMA Types I, II, and III. All cases of SMA were genetically confirmed and had been diagnosed before age 19 years. The study did not exclude patients taking drugs or supplements for SMA treatment. All patients visited a study site every 2 months through Month 6, every 3 months through Month 12, and then every 6 months. The study collected data on clinical outcome measures (including measures of motor and pulmonary function), demographic and clinical variables, medication use, and quality of life.

The network enrolled 118 subjects in its natural history study over 4 years and an additional 65 patients for a minimal dataset study. The investigators developed, validated, and tested 3 outcome measures and collected an extensive biomaterials repository.

Lessons Learned

Recruiting patients to the natural history study and maintaining their participation was challenging because the study involved extensive testing procedures, including some that were painful. The investigators ultimately decided to schedule research and clinical visits on the same day to make participation more convenient for families.

The investigators learned that they had to instruct all study sites to conduct the outcome measures in the same order at each visit; administering the most tiring tests first could affect the results of subsequent tests. The equipment used at each site had to be chosen carefully to ensure technical uniformity across sites.

Using the same evaluators for every patient was difficult, so the network assigned some backup evaluators. To compensate for the use of different evaluators, the network held regular training sessions and monthly conference calls for evaluators.

Additional lessons learned were:

- Include only tests that are necessary.
- Develop, test, and validate outcome measures during the natural history study.
- Collect biomaterials.
- Include a follow-up period lasting several years because the disease progresses slowly in many patients.
- Use a Web-based management system, which is the easiest way to store and analyze data.
- Create a system for central quality control and evaluation of certain test results to increase data quality.

- Identify missing data early on.
- Use a disease-specific clinic to recruit patients.
- Establish governance policies, including bylaws regarding authorship, from the outset.
- Maintain relationships and communication channels with patients through investigator participation in parent events, fundraising events, and newsletters.
- Reimburse families for travel expenses.

The Utility of Longitudinal Studies: Examples from the Urea Cycle Disorders Consortium
Marshall Summar, M.D., Chief, Division of Genetics and Metabolism, Children's National Medical Center

Urea Cycle Disorders Consortium

When the Urea Cycle Disorders (UCD) Consortium, part of the RDCRN, began, it was led by researchers and clinicians who had good working relationships with one another. The consortium's long-term goals were to better understand the pathophysiology and outcomes of UCD; conduct clinical trials of promising new drugs; develop information resources on UCD for clinicians, researchers, and patients; and train the next generation of investigators in UCD. The consortium's research is expensive, requiring funds from NIH and other sources.

The consortium's leaders hold monthly teleconferences and meet in person once a year. Coordinators also meet with one another regularly. When the consortium held too many meetings, fewer researchers attended. Similarly, if the study's testing is too burdensome for patients, they drop out. Of the 511 patients recruited to the consortium's natural history study, the study lost 26 patients over 8 years, primarily because patients were fatigued, lost to follow-up, or died.

Lessons Learned

Lessons learned included:

- A good data coordinator is more precious than gold.
- Fewer patients will enroll in the study than the investigators originally expect (the study had originally been designed to recruit 1,200 patients but its recruitment goal was dropped to 550).
- Paperwork (even if it is completed digitally) is the rate-limiting step for most activities.
- Collecting too much data degrades the quality of the data—the great is the enemy of the good.
- Extensive neuropsychological testing wears patients out and degrades performance.
- Capturing specific data on events that occur between research visits is difficult.
- Dietary data are difficult to standardize and reported dietary data are not always reliable.
- Patients are often noncompliant with their medications.
- Some of the best ideas are not raised until a few years after the study begins (such as collecting data on immunizations, seizures, and drug trials).
- Investigators should plan their studies to achieve the desired outcome based on the assumption that they will receive funding for a long time.

- Consensus regarding treatment builds over time and outcomes improve.

Dr. Summar advised researchers to collect only data that they can consistently obtain. They should spend some time defining the criteria for the disease of interest and involve parent groups and industry early on. Another critical early step is developing criteria for opening new sites and closing unproductive ones. Some additional tips are to bank DNA, develop consensus guidelines, use the study's webpage for recruitment and communications with families, and schedule team-building events to maintain the researchers' cohesiveness. In addition, senior investigators should listen to junior investigators, who often spend more time with patients and have interesting ideas.

The European Union's Registry and Network for Intoxication Type Metabolic Diseases is based on the UCD Consortium's database. As a result, the European Union's registry data will be comparable to the consortium's data. Other groups in Japan and South America are collecting natural history data on patients with UCD.

Lessons Learned from Prospective Longitudinal Study of Healthy Persons at Risk for Brain Disease: Neurological Predictors of Huntington's Disease (PREDICT-HD)
Jane Paulsen, Ph.D., Professor of Psychiatry, Neurology, and Psychology, University of Iowa

Huntington's Disease

Huntington's disease is a neurodegenerative disease with a known genetic pathology. Mean age of onset is 40 years, and patients typically develop signs and symptoms 15 years before their motor diagnosis. In general, patients die within 15 to 20 years of disease onset, and the disease has no known cure.

PREDICT-HD

PREDICT-HD began after families of patients with Huntington's disease had been asking for natural history studies of the disease, especially once the gene that causes the disease had been identified. The leaders of PREDICT-HD decided to recruit only people who had voluntarily undergone the Huntington's disease genetic test. Although many experts argue that people do not want to know if they have a disease for which no treatment is available, data from PREDICT-HD suggest that this is not the case.

PREDICT-HD is collecting data on more than 1,300 people who have undergone genetic testing for Huntington's disease from 32 sites in the United States, Canada, Australia, and Europe between 2001 and 2014. To date, 187 participants have received a diagnosis of Huntington's disease. The study is collecting biospecimens and data on more than 80 variables, including cognitive, motor, and psychiatric functioning and patient-reported outcomes. All of the data are sent to specialty sites for quality control and quality assessment.

PREDICT-HD shares all of its data to maximize the utility of this work, and investigators have virtually no embargoed time to write their papers. Several investigators have indicated an interest in using data on the cohort to answer questions that this study could not address.

Lessons Learned

Sites that recruit fewer than 10 participants a year have much poorer data integrity than sites that recruit more than 80 participants a year. To minimize the amount of travel required of participants, sites conduct many of their measures from a distance. Another lesson learned was that people with a family history of Huntington's disease are eager to participate in a natural history study.

The study showed that many new markers of disease developed for the study, including decrements in tapping speed, decision making, and planning, are present many years before diagnosis. Clinical trials of interventions for Huntington's disease have failed, possibly because they included "presymptomatic" patients who probably had some signs and symptoms of the disease. Furthermore, traditional measures did not detect changes in function prior to diagnosis.

Challenges

The primary challenges that PREDICT-HD has faced include:

- Recruitment—For people clinically affected by Huntington's disease, research visits must be combined with clinical visits or research staff must visit patient homes at times that are convenient to participants.
- Communication and dissemination of information—Top-down guidance is needed from NIH and FDA regarding authorship, who should have access to the data and under what circumstances, and related issues.
- Methodology—Top-down guidance is also needed on standardized methods to ensure that natural history studies collect high-quality, comparable data.
- Resources—Resources needed include funding for principal investigators, other investigators, advisory and steering groups, and indirect costs.

Panel Member Remarks
David Pearce, Ph.D., Vice President, Sanford Research, Sanford Health
Craig McDonald, M.D., Professor and Chair, Department of Physical Medicine and Rehabilitation, University of California Davis

Dr. Pearce commented that natural history studies have helped identify biomarkers that could be applied to therapeutic interventions for rare diseases, such as juvenile Batten disease, in clinical trials.

Dr. McDonald has conducted natural history studies of Duchenne muscular dystrophy, with a focus on developing clinical endpoints. A recurring theme from the presentations at this meeting was the importance of evolving study designs over time in response to the data collected. Dr. McDonald and his colleagues were not satisfied with the existing measures used for Duchenne muscular dystrophy, so they developed and validated the 6-minute walk test in a natural history study for use in clinical trials. The test has subsequently been refined to take maturational effects into account. Biomarker discovery is another important theme from this meeting, and biomarker studies should be conducted in parallel with natural history studies. As more mature data become available, researchers will be able to correlate clinical endpoints with clinically meaningful

milestones and patient-reported outcomes to answer important questions, such as how important a 10% decline is in walking function over 12 months.

Discussion

In response to a question about ethical issues of genetic testing in presymptomatic individuals, Dr. Paulsen said that the ability to study many rare diseases at an earlier stage would allow researchers to have a more substantial impact on people's lives. Most of the objections to genetic testing of presymptomatic individuals come from professional groups, not patients or families. Families want researchers to have their genetic information.

A patient organization representative asked about the feasibility of completing clinical and research visits on the same day, given that the services provided for these purposes are funded by different sources. Dr. Summar said that when a patient undergoes routine clinical care, these services are charged to the sources of clinical care funding. If a component of a visit involves tests that are not part of the standard of care, these services are funded by the research funding source. Dr. Darras added that the SMA natural history study also scheduled research and clinical visits on the same day, but kept the two visits separate, and insurance carriers reimbursed the costs of the clinical visit. For example, one visit took place in the morning and the other in the afternoon. Dr. Paulsen gives clinical patients the opportunity to sign a consent form permitting the use of their clinical data for research, and she warned researchers to avoid collecting data during both the clinical and research visit.

A participant asked about the value of using measures developed for other diseases as opposed to creating a new disease-specific measure. Dr. McDonald said that the Quality of Life in Neurological Disorders (Neuro-QOL) is a patient-reported measure for neurologic diseases with a core set of questions for all patients and domains that are specific to certain diseases and can be added as needed. Dr. Paulsen said that anyone who wants to create a disease-specific tool should talk to others who have done this in the past. Furthermore, FDA has created guidelines on developing these types of tools, and researchers can start by using items from existing tools. A participant commented that standardized measures for cognitive function are often not useful for rare diseases, so developing more refined, disease-specific measures is important.

In response to a comment about statistical methods and the importance of involving statistical experts in natural history studies, Dr. McDonald and Dr. Summar reported that the teams that lead their natural history studies include biostatisticians. Dr. Summar added that power calculations are difficult for longitudinal natural history studies because these studies do not have a defined outcome.

Dr. Kaufmann advised researchers considering a natural history study to plan all activities with the study goal in mind. If the study's ultimate goal is to develop better treatments, then all of the study's findings should be useful for drug development for the disease. Biomarkers can allow the field to answer questions more quickly, without waiting for a clinical outcome. The goal of therapeutic development is also important to keep in mind when planning a study's statistical analyses.

Dr. Kaufmann asked whether natural history studies typically require different consent forms for each site. Dr. McDonald said that different protocols and consent forms from different sites in a multicenter natural history study often must be reviewed by several institutional review boards (IRBs), which tends to cause delays. The use of a central IRB would help move natural history studies forward more quickly. Dr. Paulsen agreed that IRB reviews are one of the top "rate-limiting steps" in multisite studies and that central IRBs are needed. However, many sites will not agree to have their protocols reviewed by a central IRB, even though research has not found that local IRB review is necessary.

Case Studies: Industry-Sponsored Prospective Longitudinal Studies

Chair: Edward Kaye, M.D., Chief Medical Officer and Senior Vice President, AVI BioPharma
Co-Chair: Petra Kaufmann, M.D., M.Sc., Associate Director, Office of Clinical Research, NINDS, NIH

An Observational Study of Pediatric Subjects with Globoid Cell Leukodystrophy
Lawrence Charnas, M.D., Ph.D., Medical Director of Translation Medicine, Shire Human Genetic Therapies

Krabbe Disease

Globoid cell leukodystrophy (GLD), also known as Krabbe disease, is an autosomal recessive disease caused by a deficiency of lysosomal galactocerebrosidase (GALC) with resultant toxicity from psychosine (galactosylsphingosine) and galactosylcerebroside. Krabbe disease is usually diagnosed in infants younger than 6 months with extreme irritability, feeding difficulty, developmental regression, and stiffness. The disease progresses rapidly to a decerebrate condition.

Natural History Study

New York State screened all newborns for Krabbe disease between 2006 and 2010. Of more than 900,000 infants screened, 11 had very low enzyme activity but only 3 were believed to be at risk of developing clinical disease. These data raised questions about how to define GLD.

The Hunter's Hope Foundation developed a registry of people with GLD. The registry data showed that the disease had several forms. The investigators decided to focus on the infantile form, typically diagnosed at 0–6 months, because this form is most common and most severe, and it has a high mortality rate.

Dr. Charnas began a natural history study of GLD with a review of the literature. The natural history study was to use a nontraditional design, with home-based measures and frequent investigator contact. The study's primary objective was to evaluate the natural history of disease progression in infants with GLD. Primary endpoints were changes from baseline in growth parameters and, as a surrogate measure of survival, the onset of inadequate oral nutrition, hydration, and/or ventilation. The secondary endpoints included other clinical parameters of disease progression.

The study's inclusion criteria were a documented diagnosis of GLD based on GALC enzyme activity or a GALC genotype that is predictive of GLD, clinical signs and symptoms consistent with a diagnosis of infantile GLD, onset of signs and symptoms of GLD prior to age 12 months, and ability to maintain oral nutrition and hydration without a feeding tube and to maintain ventilation without a breathing tube (to ensure that infants were recruited early in the course of their disease). The investigators planned to exclude patients who had been treated with a bone marrow transplant or who were scheduled to undergo one during the study so that they could understand the natural history of the disease prior to the administration of therapy.

Some of the challenges included variability that could not be interpreted, the need to establish relationships with local sources of care because the study would not deliver clinical care, and the difficulty of enrolling patients with a rapidly progressive disease.

The study was stopped before it enrolled its first patient, primarily because of the inability to recruit patients due to the lower than expected incidence of infantile GLD and its rapid progression.

A Prospective, Longitudinal Study of the Natural History of Niemann-Pick Disease Type B
P.K. Tandon, Ph.D., Senior Vice President and Clinical Science Officer, Genzyme

Niemann-Pick Disease Type B

Niemann-Pick disease is an autosomal recessive lysosomal storage disorder that is chronically debilitating and can be life threatening. The disease is caused by an acid sphingomyelinase (ASM) deficiency, resulting in the accumulation of sphingomyelin and cholesterol. The disease's clinical spectrum appears to be related to ASM activity.

Genzyme is developing an enzyme replacement therapy for Niemann-Pick disease Type B (NPB). The company completed a Phase 1 trial of the therapy in 2009 and a Phase 2 trial is in development. The company is also conducting a 12-year natural history study of NPB.

Natural History Study

This natural history study has enrolled 59 patients from the United States, 3 European countries, and Brazil. The study's objectives are to determine the prevalence and range of abnormalities in patients with NPB, evaluate disease progression over time, and improve the design of future clinical trials of Genzyme's enzyme replacement therapy for the treatment of NPB. All participants visited study sites at baseline, in Year 1, and once again in Years 5–11. The investigators are collecting data on demographics, medical history, laboratory test and imaging results, functional status, and quality of life. The investigators have developed a disease-specific quality-of-life instrument that is used during patients' final study visit.

The natural history study has provided important new information about the spectrum of NPB manifestations. The study also identified differences in disease manifestations in patients from different countries. Degree of splenomegaly, one of the disease's cardinal features, correlates with other signs of disease severity.

Future Research

After all participants complete their final study visits this year, the investigators will analyze their longitudinal data. Genzyme will then initiate a Phase 2 clinical trial using spleen volume as the primary efficacy endpoint. Changes in this endpoint will be useful for assessing the dose-response relationship, and its correlation with disease severity might predict clinical benefit.

A Natural History Study of Mucopolysaccharidosis IIIA
Patrick Haslett, M.D., Medical Director, Translational Medicine, Shire Human Genetic Therapies

Mucopolysaccharidosis IIIA

Mucopolysaccharidosis IIIA (MPS IIIA), also known as Sanfilippo syndrome type A, is progressive disease caused by mutations in the *SGSH* gene, which encodes heparan N sulfatase. This enzyme defect causes an accumulation of heparan sulfate, resulting in developmental delays, severe behavior disturbances in middle childhood, progressive dementia, and death in the late teens or early 20s.

Natural History Study

Shire Human Genetic Therapies is developing an enzyme-replacement product for MPS IIIA. Dr. Haslett conducted a natural history study of MPS IIIA to understand the disease spectrum, measure disease progression, help identify appropriate patients and candidate endpoints for therapeutic trials, and generate a high-quality dataset with potential utility as a historical control group.

The investigators initially decided to enroll only patients who were 3 years or older because younger children might not tolerate treatment and the median age at diagnosis is 4.5 years. However, the researchers ultimately lowered the minimum recruitment age to 1 year. Patients need to have a developmental age of at least 1 year, and evaluations take place at baseline and at 6 and 12 months. The study is collecting data from comprehensive neurodevelopmental assessments, brain imaging, and cerebrospinal fluid measures.

The investigators created a developmental assessment tool based on data from 25 children enrolled at a single site. Results with this developmental quotient tool indicated an age-related decline, and the results of this somewhat subjective tool correlate with the more objective measure of cerebral cortical volume. These results show that cerebral volume correlates with an important measure, suggesting its potential utility as an endpoint in a clinical trial. The study's baseline data on 25 patients also suggest that MPS IIIA has two phenotypic patterns based on age of diagnosis.

Future Research

The investigators are planning to conduct additional studies to identify the disease's genotypes and phenotypes. The developmental plateau reached by many patients suggests that for maximal

efficacy, treatment should begin as early during the plateau phase as possible. The cerebrospinal fluid biomarkers identified by the study, along with brain magnetic resonance imaging (MRI) patterns, might be useful adjuncts to clinical evaluation in assessing the impact of therapy.

Panel Member Remarks

Annette Stemhagen, Dr.P.H., F.I.S.P.E., Senior Vice President, Safety, Epidemiology, Registries, and Risk Management, United BioSource Corporation
Karen Chen, Ph.D., Chief Scientific Officer/Chief Operating Officer, SMA Foundation

Dr. Stemhagen explained that United BioSource Corporation is a contract research organization that has conducted many natural history studies of rare diseases for biotechnology and pharmaceutical companies. She urged researchers to start natural histories early in the therapeutic-development process because these studies can add so much valuable information to these development programs. Some sponsors choose not to conduct natural history studies and later realize that they need natural history data to determine whether adverse events are due to the disease or its treatment.

Dr. Chen stated that foundations and patient advocacy groups can help reduce the risk of developing interventions for rare diseases by sponsoring and spearheading natural history studies. The SMA Foundation has used its natural history database to validate some biomarkers, and several industry partners are using the database to identify appropriate patient populations for clinical trials. One of the themes of this meeting was the importance of designing academic natural history studies with the same goals as industry-sponsored natural history studies.

Discussion

Dr. Kaye asked why the GLD study ended before recruiting any patients. Dr. Charnas replied that the study did not proceed primarily because the disease's prevalence is so low. Investigators should not assume that their studies will be able to achieve their goals.

Dr. Chen commented that SMA, GLD, NPB, and MPS IIIA are diseases of childhood with substantial phenotypic variability. If natural history studies enroll patients with different forms of a disease, average outcome data might not be very informative. Dr. Haslett said that investigators could begin with a large cross-sectional study to determine where to focus their longitudinal study. Dr. Tandon emphasized the need to identify different endpoints for children and adults.

A participant commented on the importance of using a statistical design that can show different developmental and growth trajectories in different groups of patients. Dr. Tandon said that the study of NPB began as a cross-sectional study, but the investigators converted it to a longitudinal study because the cross-sectional study was not sufficiently informative.

Dr. Stemhagen remarked that longitudinal natural history studies can slow down product development. Dr. Haslett said that companies face enormous pressure to develop treatments quickly for the types of rare diseases discussed in this session because their effects on patients are so drastic. If Genzyme had known that it would need to conduct a natural history study for 11

years on NPB before developing its therapy, the company might not have pursued this therapy. For this reason, precompetitive consortia that can conduct natural history studies are necessary.

A participant noted that once a therapy receives FDA approval, the opportunity to study the natural history of a rare disease is lost. Furthermore, because the natural histories of different forms of a disease, such as MPS IIIA, are so different, each form of the disease might require its own natural history study.

Day 2: May 17, 2012

Case Studies: Retrospective Chart Reviews

Chair: Priya Kishnani, M.D., C.L. and Sue Chen Professor of Pediatrics, Duke University Medical Center
Co-Chair: Marc Walton, M.D., Ph.D., Associate Director for Translational Medicine, Office of Translational Sciences, FDA

Dr. Kishnani explained that retrospective chart reviews are not typically sufficient to meet all objectives of a natural history study, but they can serve as a guide for designing a prospective natural history study.

Clinical care records are not designed for natural history studies, and their data are not typically comprehensive. Furthermore, what is recorded and how that information is provided can vary by site. In some cases, the data in medical charts are erroneous, and charts do not typically include data that are not useful for clinical care.

Making the most of retrospective chart reviews requires:

- Realistic expectations about the challenges.
- Careful thought about which data elements to extract.
- Care when obtaining data because different sites might use different norms.
- Collaboration with experts, including patient organizations and foundations.
- Attention to data quality and remembering that quantity does not always equal quality.
- An early start, often before a drug candidate is available.

FDA Perspective: Eosinophilic Esophagitis
Robert Fiorentino, M.D., Medical Team Leader, Division of Gastroenterology and Inborn Errors, FDA

Eosinophilic Esophagitis

Patients with eosinophilic esophagitis (EoE), an allergic inflammatory disease, have high eosinophil levels in the esophagus. Infants and children with EoE often have feeding difficulties, whereas school-aged children often have vomiting or pain, and dysphagia is the predominant symptom in adolescents and adults. FDA has not approved any therapy for EoE treatment, the existing dietary and corticosteroid treatments do not always eliminate EoE symptoms, and many dietary regimens are difficult to use on a routine basis. Furthermore, the disease has no precedent for approval or pathway to approval.

Pilot Natural History Study

A pilot cross-sectional and longitudinal study was designed to characterize the symptoms and symptom clusters in adult and pediatric patients with EoE using existing site-based registries and datasets from two sites in the United States and one site in Europe. Each site used an extraction template to collect information on a sample of their patients with EoE.

FDA, participating sites, and University of Florida faculty members designed the extraction template to identify symptoms derived from the definition of EoE used in published guidelines.[3] This Microsoft Excel template included six worksheets to collect information on each patient's EoE history, index visit, and up to four follow-up visits. The template had fields for date of birth; estimated year of symptom onset; predominant, secondary, and tertiary symptoms at onset; procedures performed prior to diagnosis; and family history of the disease. The template also provided free-text fields to allow sites to contribute supplementary information or elaborate on their entries. FDA stratified patients into six age groups for analysis.

The study included 88 patients, and the results confirmed reports in the literature that symptom prevalence at the index visit varied by age group.

Lessons Learned

Lessons learned included:

- Pilot studies can be critical for informing future natural history data extraction studies.
- All site investigators need to use the same clearly defined and agreed-on terminology.
    - The extraction template did not initially define "dysphagia."
    - FDA could not verify that sites had correctly classified symptoms as predominant as opposed to secondary or tertiary.
- Sites need to make a substantial time commitment to ensure completeness of data collection at the source.
- The frequency and severity of symptoms (or possibly treatments) can be difficult to ascertain retrospectively but might be critical for understanding the disease course.
- Adequate longitudinal natural history data would take much longer to collect than the time available for this retrospective chart review study.
- Cross-sectional studies can help identify potential age-related symptom "targets" for developing patient-reported outcome measures to demonstrate that therapies used in future clinical trials have a meaningful clinical benefit.

[3] *J Allergy Clin Immunol*. 2011 Jul;128(1):3-20.

A Retrospective Natural History Study in Fabry Disease: Challenges and Uses
Richard Moscicki, M.D., Senior Vice President and Head of Clinical Development, Genzyme

Fabry Disease

Fabry disease is a rare and lethal inborn error of metabolism caused by a deficiency in α-galactosidase A activity, leading to progressive globotriaosylceramide accumulation in several cell types and tissues and end-organ impairment. The key pathology of Fabry disease is vascular endothelial deposition and disruption of small vessel activity. The manifestations of the disease include acroparesthesia, renal failure, and central nervous system (CNS) and cardiac disease.

FDA granted accelerated approval for Fabrazyme® (agalsidase beta) based on a study that used a surrogate endpoint, the clearance of substrate from key areas. FDA required Genzyme to conduct a Phase 4 randomized, placebo-controlled trial to demonstrate the product's clinical benefit.

Natural History Study

Fabrazyme was available for Fabry disease when Genzyme initiated its Phase 4 trial, so the company was concerned that patients randomized to the control arm would drop out of the study because they would recognize that they were receiving a placebo. The company therefore decided to undertake a natural history study in parallel with its Phase 4 study as a backup. Because a treatment was on the market, a longitudinal study would not be possible, so Genzyme's natural history study consisted of a retrospective chart review.

The objectives of this natural history study were to:

- Estimate the event rates of renal, cardiac, and cerebral vascular diseases and/or death in patients with Fabry disease.
- Characterize the natural history of Fabry disease.
- Provide a historical control group for comparison to data from the Phase 4 study.

To minimize bias, an independent clinical research organization with expertise in epidemiology and survey data collection methodology collected the data using prospectively designed case record forms. Genzyme invited all domestic and international sites that might be able to contribute data to participate in the study. The study took place in 2001–2002, and the final dataset included 447 patients from 27 sites, primarily in the United States and Canada, but also from 3 sites in Europe. The study collected all clinically relevant information on Fabry patients at participating sites, with no preselection of data points.

The investigators identified 103 patients who met the eligibility criteria for the Phase 4 study. The records of most of these patients included at least 3 serum creatinine test results. The investigators measured the incidence of renal, cardiac, and cardiovascular disease events and of death in these 103 patients. However, the number of deaths in this group was too small to use for this evaluation, so the investigators decided to focus on renal outcomes and serum creatinine level progression.

Use of Natural History Study Data to Create a Historical Control Group

The Phase 4 study was a multinational, multicenter, randomized, double-blind, placebo-controlled trial in patients with mild-to-moderate renal disease. The study was designed to compare the effectiveness of Fabrazyme and placebo in prolonging time to clinically significant deterioration in renal function, cardiac function, CNS disease, or death.

Genzyme had suggested to FDA that if some patients in the placebo group dropped out of the Phase 4 study or the investigators moved some of these patients to active therapy, the patients in the natural history study could serve as a control group. However, FDA did not agree because only a minority of patients in the natural history study qualified for the Phase 4 trial and it was not possible to ensure that patients from the historical database were comparable to patients in the prospective study. FDA was also concerned about the difficulty of adequately determining and adjusting for important baseline characteristics as well as the potential influence of selection bias.

Results

Genzyme was able to conduct its Phase 4 study without using the natural history study patients as a historical control group because patients assigned to the placebo arm stayed in the trial. However, this natural history study did show that even though records of serum creatinine levels and major events were not as extensive in the natural history database as the investigators had expected, statistical modeling made the data useful for estimating placebo and treatment effects and for identifying the sample size for the Phase 4 study.

Lessons Learned from Pompe Disease
Priya Kishnani, M.D., C.L. and Sue Chen Professor of Pediatrics, Duke University Medical Center

Pompe Disease

Pompe disease is a progressive, multisystemic, debilitating, and often fatal neuromuscular disease characterized by a deficiency of acid alpha-glucosidase (GAA), a lysosomal enzyme. The infantile form of the disease typically presents in the first few months with hypotonia, generalized muscle weakness, macroglossia, and hypertrophic cardiomyopathy leading to death. In contrast, the late-onset form in children and adults is characterized by respiratory and limb-girdle muscle weakness, resulting in significant morbidity and mortality, but the disease has no severe cardiac effects in these patients.

Two open-label studies in small numbers of patients with infantile Pompe disease showed that recombinant human GAA (now known as Myozome® by Genzyme) improved motor and cardiac function. However, a double-blind study seemed unethical because some patients who were likely to die soon would be assigned to a placebo group.

Natural History Study

Prior to conducting pivotal clinical trials, Genzyme decided to conduct a multinational natural history study on infants younger than 6 months with infantile Pompe disease to characterize the natural history of disease progression and provide a historical control for clinical studies. A clinical research organization screened data from 300 cases and abstracted chart and case report form data on 168 patients from the United States, Canada, and 7 other countries who met the study's inclusion criteria of symptom onset by 12 months and documented GAA deficiency or positive genetic testing results. The study collected data on a broad range of disease manifestations, including cardiomyopathy, respiratory symptoms, growth parameters, and survival.

The data showed that feeding tubes, ventilators, and supportive care for cardiac manifestations had no impact on survival. The results confirmed that infantile Pompe disease has a spectrum; although most patients die within the first year, some survive for 3 years or more.

The natural history study of infantile Pompe disease made it possible to document the frequency and age of onset of important clinical milestones, helping investigators understand treated disease. The study also answered questions about the age of death in infants with Pompe disease, identified factors associated with longer and shorter survival, and identified patients with classical infantile Pompe disease who could be used as a comparator group for a pivotal trial.

Historical Control Group for Open-Label Therapeutic Study

Genzyme subsequently conducted an open-label study of Myozyme in patients who had been diagnosed with Pompe disease and had developed their first symptoms and cardiomyopathy before age 6 months, had minimal GAA activity, and were not using a ventilator. The primary endpoint was survival without invasive ventilator use compared to survival in the untreated historical control group. Other endpoints were changes in left ventricular mass index (LVMI), growth, and motor development. The investigators identified 62 untreated patients from the natural history study who closely matched the patients in the pivotal trial to serve as a historical control group.

At age 18 months, all 18 cases were still alive after 52 weeks of therapy compared to only of 1 of 62 patients in the historical control group, and 15 cases were not on invasive ventilation compared to 1 patient in the historical control group. Levels of cardiomyopathy and failure to thrive were much lower in the treated group than in the historical control group. Based on the results of Study 1, FDA approved intravenous alglucosidase alfa for Pompe disease in 2006.

Discussion

A patient advocate asked how patients can become better research participants. Patients with rare diseases and their families are willing to go to extraordinary lengths to advance research, including relocating to a different city to participate in a clinical trial. Perhaps foundations could train patients and families to keep records of their symptoms, for example. Dr. Walton said that FDA would like patient and parent organizations to play a more active role in natural history

studies. Companies have difficulty investing in natural history studies if they have not developed a drug candidate, so someone else needs to take the lead in natural history studies. Companies and investigators might be willing to offer advice on how to plan prospective, longitudinal natural history studies. Dr. Moscicki suggested that consortia of interested parties initiate natural history studies, which are difficult for companies to develop on their own in diseases for which no intervention is likely to be available in the near future. NIH would probably need to take the lead in establishing these consortia.

In response to a question about the definitions of terms, Dr. Kishnani called for consistency in the use of clinical definitions.

Dr. Walton cautioned that historical control groups are suitable for only a small minority of rare diseases, and collecting data to create a historical control group is not the objective of most natural history studies of rare diseases. Instead, these studies are typically designed to understand the disease better and identify distinct phenotypes and outcome measures that can be used in clinical studies. In some cases, natural history studies can also help experts define terms used to describe the disease more precisely.

Dr. Moscicki commented that in Pompe disease, an objective endpoint was available and the experiences of patients who underwent the treatment were clearly different from the disease's natural history. Furthermore, because Pompe disease is immediately lethal, a placebo-controlled trial of a treatment for this disease would not be ethical.

A participant asked how data from natural history studies can be used to determine whether an outcome in a clinical trial is typical of the disease's natural progression or is the result of a treatment if the trial does not have a placebo group. Dr. Walton said that when a trial does not have a placebo group, a natural history comparator group can be used in rare situations. FDA needs to determine whether the treatment's benefits outweigh its adverse effects. For Pompe disease, the treatment extended life and this type of effect can outweigh a fair amount of uncertainty about adverse effects.

Dr. Moscicki commented that once a treatment becomes available, the disease's major manifestations disappear or are mitigated. At that point, other aspects of the disease's natural history sometimes emerge (such as the Parkinson's disease-like symptoms in patients with Gaucher disease), although identifying these effects often takes years.

Dr. Kishnani stated that until recently, nothing was known about what happens to children with Pompe disease after their first year of life. Today, a cohort of children with the disease through age 13 years is available. Because a treatment for the disease is now available, sorting out which symptoms are due to the disease and which are results of treatment can be difficult. Dr. Kishnani recommended that investigators continue to collect natural history data after a treatment for the disease becomes available to learn more about the disease.

Case Studies: Prospective Cross-Sectional Studies

Chair: *Wendy Introne, M.D., Staff Clinician, Office of the Clinical Director, National Human Genome Research Institute (NHGRI), NIH*

How Pilot Studies and Cross-Sectional Studies Inform Natural History Studies

Elsa Shapiro, Ph.D., Professor of Pediatrics and Neurology, University of Minnesota

Pilot Studies

Pilot studies are small-scale preliminary studies used to plan longitudinal natural history studies. Pilot studies can provide valuable information on the feasibility, recruitment potential, and costs of a natural history study as well as how much time a longitudinal study might take, possible adverse events, and the effects of age and developmental stage on disease manifestations. According to the published literature, pilot studies should not be included in longitudinal studies, but this is unrealistic in rare diseases, which have a limited pool of potential participants. However, investigators need to consider the effects of including the same patients in pilot studies and longitudinal studies.

Dr. Shapiro described a pilot study she conducted on MPS I, II, and VI. All of the patients had undergone enzyme replacement study and some had had transplantation, so a natural history study was not feasible. Enzyme replacement therapy does not affect the brain, and the investigators wondered whether better brain treatments might be needed.

The pilot study include 10 patients with MPS I and 10 with MPS I H (also known as Hurler disease). This study helped the investigators develop expertise in using brain imaging analysis software. The data were also useful for establishing the feasibility, ease of recruitment, timing, and measures for a longitudinal study. For example, the investigators learned that neuropsychological testing and imaging could be completed in 1 day and they could recruit participants without difficulty even though participating in the study did not benefit patients directly. An unforeseen event was a scanner upgrade after 7 participants in each group had been examined, so the diffusion tensor imaging analysis included data only on these 14 patients. However, even with only 7 patients in each group, the study had valuable results, showing, for example, that the 2 groups had equivalent IQs but different attention spans and fractional anisotropy results.

Cross-Sectional Studies

Cross-sectional studies can include large single-visit studies that are stand-alone studies or part of a natural history study. These single visits can also be used as baseline visits in a natural history study. Cross-sectional studies typically include more patients and often have broader goals than pilot studies. These studies might be designed, for example, to develop expertise or a measure, explore a hypothesis, validate a scoring system, identify phenotypes associated with age at diagnosis and assessment, or identify important variables that were initially overlooked.

Dr. Shapiro is now conducting a multicenter cross-sectional study of baseline visits of patients with MPS based on the results of the pilot studies. The challenges of doing a multicenter study

include quality control and training as well as MRI comparability. Now that the study has enrolled 100 patients, the investigators have found that they need to collect more data on emotional and behavioral abnormalities and to raise funds to study DNA mutation data. In addition, MRI data cannot be collected on patients with orthodontic braces, programmable shunts, or cochlear implants. The study has yielded surprising findings that need further exploration, such as that patients with MPS I or MPS VI who have undergone hematopoietic stem cell transplantation have a smaller brain size but equivalent IQ compared to patients who have undergone enzyme replacement therapy.

A pilot study of patients with MPS IIIA (Sanfilippo syndrome type A) was designed to develop a disease-specific behavior-rating scale. This pilot study was associated with the cross-sectional study that Dr. Haslett had described to explore the behavioral phenotype. The investigators sent the first version of a disease-specific scale they had developed to 50 parents of patients with MPS III and then used the scale with 10 patients. The researchers are now using the scale in a natural history study of MPS III, although they are continuing to refine the scale.

A cross-sectional study to characterize the neurobehavioral phenotypes of Sanfilippo syndrome involved an analysis of data from the baseline visits of a natural history study. In this study, the investigators compared the behaviors (including fear, startle response, and activity levels) and autistic-like symptoms in patients with MPS IIIA and MPS I H. Children in the study spent 10 minutes with a parent in a "risk room" that exposed children to frightening items (such as masks) and sudden, loud noises. The differences between groups in most measures were statistically significant.

The study showed that the investigators could accurately measure cognitive function in very impaired children. The study also had unexpected findings, such as the ceiling for cognitive development in children diagnosed at a young age. Unexpected challenges included the need to develop methods to better delineate gray and white matter in younger children and to acquire control scans of typically developing children to determine the rate of change in patients.

Conclusions

Dr. Shapiro concluded that pilot and cross-sectional studies prior to natural history studies provide an opportunity to:

- Develop and validate new measures and techniques and test them for later natural history studies and clinical trials.
- Provide feasibility information.
- Develop expertise.
- Provide information on recruitment potential.
- Provide information on time and costs of future studies.
- Identify possible obstacles to data acquisition.
- Determine effect size to estimate sample size needed.
- Obtain significant new information, especially on the developmental growth trajectory.
- Develop new hypotheses based on unexpected results.

Practical Tips in Designing Natural History Studies for Rare Genetic Diseases of the Brain
Maria Escolar, M.D., M.Sc., Associate Professor of Pediatrics, Children's Hospital of Pittsburgh of UPMC

Program for the Study of Neurodevelopment in Rare Disorders

The Program for the Study of Neurodevelopment in Rare Disorders (NDRD) established a registry and conducts natural history studies of rare neurodegenerative genetic diseases of the brain. Since its establishment in 2002, NDRD has conducted 1,690 standardized multidisciplinary evaluations of 190 patients with MPS and 198 patients with leukodystrophies. The investigators have developed a set of standardized measures in consultation with experts in many disciplines to evaluate issues that affect the quality of life of patients from birth to age 17 years. Patients are evaluated every 3 months during the first year, every 6 months in the second year, and once a year thereafter.

Natural History Studies

An NDRD natural history study of MPS II (Hunter's syndrome) followed 50 patients aged 1 month to 25 years for 7 years. The study found that some patients have normal cognition, whereas cognition in other patients deteriorates rapidly. A retrospective review of patient charts identified early markers of CNS disease. The investigators used these data to develop a CNS index score to identify which children will develop CNS disease and, thus, which patients need early treatment.

A study of Krabbe disease focused on the infantile form because the investigators believed that interventions to help these children would benefit patients with other forms of the disease. A study of the infantile form could be completed quickly because the disease progresses rapidly, whereas a study in children or adults would take much longer. The investigators developed a staging system to predict disease progression at diagnosis based on a retrospective review of data from 42 patients examined in the NDRD. They correlated these stages with neurobehavioral, neurophysiological, and neuroimaging measures.

A natural history study is determining whether MRI can be used to detect subtle changes in the brains of young children with Krabbe disease. A cross-sectional pilot study showed a substantial difference in major cortical spinal tract measurements only in children with and without Krabbe disease at 30 weeks. Dr. Escolar is now determining whether MRI results can be used to identify which patients with Krabbe disease will develop motor disease.

Challenges and Tips

The challenges of conducting natural history studies include:

- Populations that are geographically dispersed and chronically impaired.
- Variable onset of presentation and spectrum of disease involvement.
- Very few specialists who understand the disease process.
- Variability in approaches to manage the disease and its complications.
- Expense of studies and difficulty of identifying funding sources.

- Loss of the opportunity to conduct a true natural history study once a treatment becomes available.

Dr. Escolar offered the following tips:

- Define the study's objectives.
- Determine whether the study will be a true natural history study.
- Compare the advantages and disadvantages of a single-site versus multisite study.
- Develop inclusion and exclusion criteria and data entry forms.
- Collect all available medical records.
- Identify where patients obtain clinical services and how their clinical symptoms are assessed and managed.
- Identify recurrent clinical problems and critical issues that affect patient quality of life.
- Include observations between appointments from several clinicians and from families.

In planning a study, investigators should:

- Base their inclusion and exclusion criteria on variables (such as interventions or concomitant diagnoses) that could influence their observations.
- Consider whether the timing of evaluations could affect the results of the tests they plan to use and whether these tests are standardized for patients in the target age range.
- Consider how the disease changes over time and the characteristics and age of disease onset.
- Determine how the study's variables are likely to change over time.
- Identify the issues that affect patient quality of life.
- Determine how to assess the effects of their variables on quality of life.
- Determine whether the tests they plan to use will be tolerable for patients.
- Identify which patients and how many patients to assign to the control group to provide an adequate power analysis for the estimated sample size.

If investigators want to use natural history data to develop biomarkers, they need to develop a protocol for obtaining samples in a standardized way and for tracking how the samples were obtained and processed. Biomarkers should be selected based on their ability to answer a significant question and correlate with function. Investigators should validate candidate biomarkers prospectively for predictive value.

Natural history studies are very challenging and expensive but necessary to understand phenotypic variability and evaluate the effects of new therapies. Predictive markers are extremely important to assess disease progression and response to therapy.

GM2 Gangliosidosis: Getting the Most out of Patient Surveys
Florian Eichler, M.D., Assistant Professor of Neurology, Massachusetts General Hospital, Harvard Medical School

GM2 Gangliosidosis

GM2 gangliosidosis is an inherited lysosomal beta-hexosaminidase deficiency that results in ganglioside accumulation in the brain, leading to neurodegeneration. The infant form is the most common and severe. No effective treatments are available, although some data on intracranial gene delivery in animals are promising.

Natural History Study

Dr. Eichler conducted a natural history study of GM2 gangliosidosis to help plan a study of intracranial adeno-associated virus-mediated gene delivery. The study was designed to determine whether the current animal work justifies a human clinical trial and, if so, which patient population to test, whether the target of administration is appropriate, and which endpoints to study. A well-organized patient advocacy group was eager to assist with the study, especially because this research could help move a potential intervention forward. A collaborative team of investigators was prepared to launch the study.

The investigators decided to focus on the infantile form of the disease because its rapid progression might be the most quantifiable and homogeneous. They developed an anonymous 18-page patient survey instrument to estimate survival and quantify gains and losses of specific developmental milestones. The advocacy organization identified and recruited parents. Initial response was poor, but follow-up emails from the advocacy group and promotions of the study at annual meetings and fundraising events led to the receipt of 97 completed surveys. The investigators complemented the survey data with lifespan data from patients whose families did not respond to the survey and from a literature search.

Results

The study showed that caregivers can provide a detailed recollection of distinct clinical findings, but their reports on milestones might be tainted by subjective impressions and these data cannot be objectively verified. Furthermore, details on the course of regression can help investigators choose outcome measures and design trials of interventions. Finally, the investigators used the natural history study data to begin developing a disease-specific clinical scoring system that they are now using in prospective studies.

Limitations of this study include its retrospective nature and dependence on self-reporting by family members. Features that are difficult to isolate (such as vocalizing) are prone to misrepresentation. The results might have been affected by recall or ascertainment bias as well as bias from missing data.

The survey results are valuable for designing a clinical trial. The results show, for example, that a trial might be able to measure retention of clinical function. However, more prospective studies

are needed. For example, the investigators are currently evaluating the use of the 6-minute walk test and gross motor function scales in children with GM2 gangliosidosis. They also plan to correlate an MRI scoring system they developed with the clinical course of the disease.

The natural history study provided an initial rough overview of the "GM2 landscape," helping Dr. Eichler understand the disease's clinical course, develop an MRI scoring system to describe anatomic burden, and design prospective studies. Many details on the natural history of GM2 gangliosidosis still need to be filled in, but casting a wide net in the retrospective natural history study did provide temporal and spatial benchmarks for future studies.

Panel Member Remarks
Meral Gunay-Aygun, M.D., Staff Clinician, NHGRI, NIH

Dr. Gunay-Aygun is conducting prospective longitudinal studies of celiopathies. Some of the patients are seen for only one visit, so Dr. Gunay-Aygun will publish their data as cross-sectional data.

Discussion

Registries

A patient advocate asked about the feasibility of designing questionnaires for neurological or psychological assessments that could be administered outside the clinical setting to a very small and widely dispersed population. Dr. Shapiro replied that questionnaires or telephone interviews can be used for psychological evaluations, but neurological parameters are more difficult to measure remotely.

Dr. Escolar recommended that advocacy organizations interested in collecting natural history data begin by creating a registry with demographic information. If a group wants to use a survey to conduct research, the group should collaborate with experts in this type of survey. How questions are asked in a survey can sometimes yield different responses, and the data should have as little error as possible.

Dr. Shapiro suggested that groups that are thinking about starting a registry find out what data other registries have collected and what survey questions they have used. If a survey is targeted to a small number of patients, consulting experts in the disease and in survey development is critical. Rachel Richesson, Ph.D., M.P.H., at Duke University is developing a library of data that registries should collect so that their data can be compared.

Dr. Escolar added that groups that are creating a registry should carefully consider the purpose of this registry. They should also be aware that creating and maintaining registries can be very expensive. Advocacy organizations should keep contact information on families up to date because this information is difficult for researchers to collect and it is useful for developing clinical trials and other research projects.

Dr. Groft reported that NCATS is developing templates for patient registries that will be available soon. The templates will include common data elements that registries should collect.

Other Issues

A participant asked how a study could determine whether a treatment affects all of the areas of the nervous system that the disease affects. Dr. Escolar said that neurological examination results are difficult to interpret, but brain parameters and neurophysiological study results can be examined to identify the source of the damage. In treatment studies that involve transplantation, evaluating the transplant's impact on the peripheral nervous system is difficult, so Dr. Escolar is using animal models to prospectively evaluate changes over time.

A participant commented that although development is typically linear, the developmental regression associated with rare diseases is not necessarily linear. Dr. Shapiro agreed that the developmental regression in patients with MPS is stepwise rather than linear. Her graphs of development in patients with MPS represent theoretical approximations.

Dr. Escolar cautioned against using MRI data to predict which patients with a rare disease will have better outcomes or as the basis for counseling patients. Researchers need predictive markers beyond imaging data to evaluate the extent of motor disability that a given patient is likely to develop and to move forward with newborn screening for these rare diseases.

A participant commented on the difficulty of conducting clinical trials that demonstrate the progression of renal function abnormalities in patients with polycystic kidney disease because these trials would need to be very long. Natural history studies are needed to validate renal volume as a predictor of renal outcomes. Dr. Gunay-Aygun said that kidney volume in her autosomal recessive polycystic kidney disease cohort has an inverse relationship with kidney function, but this relationship is highly variable.

Summary, Conclusions, and Moving Forward

Summary
Chair: John McKew, Ph.D., Chief, Therapeutics Development Branch, TRND Program, NCATS, NIH

Workshop Outcomes

Short-term outcomes of this workshop would include the archived webcast and the PowerPoint presentations on the workshop website.

Long-term outcomes of the workshop would include a white paper or journal article summarizing the presentations and discussions at the workshop. This document would explain the importance of natural history studies, share best practices and common pitfalls, and include data from the NICHD newborn screening panel. The document might be followed by a public call for input on common challenges. The organizers hoped that this workshop would be the beginning of an ongoing dialog on natural history studies of rare diseases that would address

funding sources, shared resources, incentives for academic collaborators, and the importance of patient group involvement. They also planned to organize a follow-up meeting focused on one of the key challenges identified at this workshop, such as retention of patients in studies, common data elements, or patient survey forms.

Longer term outcomes might include the formation of a consortium or compendium of guidance (and, possibly, funding) for unified natural history study design and execution. This effort would include representatives from NIH, FDA, advocacy groups, and industry. Participants could pool datasets to prepare data on control groups for natural history studies and therapeutic trials. This effort would also create an international compendium of registries organized by affected organ and collect and distribute information on the pitfalls of natural history studies. Another longer term outcome might be a rare diseases atlas, which will require a much better understanding of these diseases from natural history studies. This atlas could be built on the information collected by the consortium or compendium. A final longer term outcome would be a set of common data elements or terminology that natural history studies could use to allow their data to be pooled.

Lessons about Natural History Studies

Workshop presenters had given impassioned talks on the importance of natural history studies, which are critical for therapeutic development and clinical care. Speakers had offered several examples in which patient outcomes changed dramatically after a thorough natural history study had been completed, even without the development of therapies (such as in cystic fibrosis or urea cycle disorders). Natural history studies can also assist with the development of diagnostic guidelines and potential biomarkers for diagnostics. They can help identify patient populations for therapeutic trials. For many rare diseases, no regulatory pathway exists, so natural history studies are necessary to develop a regulatory pathway based on a thorough understanding of the disease. The presentations had also demonstrated the importance of continuing to study the natural history of a disease after a therapy becomes available, when new facets of the disease often become evident.

Natural history studies should benefit researchers, regulators, sponsors, caregivers, and patients. For example, natural history clinics can serve as a medical home for patients with a rare disease, and industry can use the natural history data to plan therapeutic development. In some cases, natural history study data can allow FDA to accept subpopulations for clinical development. Several presenters had emphasized the need for all stakeholders to make a long-term commitment to work together and to nurture the relationships they have developed. Active engagement of the rare disease patient community benefits patients and helps move therapeutic development forward. Researchers need to ensure that their study's demands on patients are realistic, and pooling natural history studies is more productive than conducting several individual studies.

The general principles identified during the workshop included:

- View natural histories studies as precompetitive, with the goal of learning about the disease.
- Avoid using a study design that depends on a specific therapy.

- Consider the study's ultimate goal, such as the potential therapeutic development plan for the disease, during the design phase.
- Remember that natural history studies tend to take several years and their protocols evolve over time in response to the data generated.
- Take potential sources of bias (such as whether only healthy patients tend to drop out of the study) into consideration.
- Negotiate data access and publication rights early.
- Create a plan to close out unproductive sites and bring on new ones.
- Try to combine research and clinical visits on the same day.
- Identify a good data coordinator.
- Avoid mission fatigue by not requiring investigators to meet too often.

In planning a study, investigators need to consider whether to collect data from one site or several sites. Advantages of single-site studies include assessments by a single group of investigators and good data control and quality. However, such studies require most patients to travel long distances or can only draw from a small geographic pool. Multisite studies must continuously train the individuals who conduct assessments to ensure that they collect high-quality data. These studies often need approval from several IRBs, which can lead to significant delays. A central IRB would greatly facilitate these studies and a central IRB protocol should be developed for multisite natural history studies.

The types of natural history studies include literature reviews, chart reviews, prospective cross-sectional studies (including patient surveys), and prospective longitudinal studies. Investigators planning a study should weigh the amount of time required for each design against the richness of the data that they are likely to collect. Investigators should also remember that the approach they use and the data they collect might evolve over time.

Discussion

A participant said that a survey of academic and industrial representatives should identify the highest priority diseases for therapeutic advances and the diseases in which natural history studies could be completed most quickly. Dr. McKew said that the rare diseases with the highest priority for therapeutic development might be appropriate targets for funding from industrial partners.

According to a participant, an international compendium of all rare disease registries would be valuable to learn what has and has not worked in the past. This information could be used to determine what information is available on a given disease, so that a new natural history study does not need to start from scratch. The compendium would also help groups that want to create new registries.

A participant called for the involvement of statisticians from the beginning in planning natural history studies. The way that instruments are scaled or data are captured can influence the scale's statistical properties and the types of information that the data can yield. A future natural history study meeting could focus on how to develop scales in ways that promote the collection of good data. Furthermore, although survival is a useful outcome to measure, studies need many patients

for survival data to achieve statistical significance. Researchers therefore need to identify other outcomes that can generate statistical power in studies with small numbers of patients.

Another suggestion was to avoid reinventing the wheel and to break down silos at NIH. Many of the issues discussed at this meeting have been addressed by the NICHD newborn screening program. For example, this program has created templates to describe diseases and identify the needed data elements.

Dr. Groft reported that some international efforts are ongoing to develop data elements and create tissue repositories for rare diseases. NIH is working closely with representatives of the European Union, for example, to ensure that data are collected in consistent ways. In addition, the Agency for Healthcare Research and Quality is developing a registry of registries and NCATS plans to develop templates for patient registries. Dr. Groft also emphasized the importance of maintaining the momentum created at this workshop to help move the agenda forward.

A patient advocate reported that groups like hers are desperate because they are worried about their loved ones and therapies might not be available for years. These groups want to make a difference for their families, so they need help identifying how they can contribute to natural history research on rare diseases. Too often, researchers and other experts underestimate what patient groups can contribute. Perhaps NIH could give some groups grants that they could use to teach other groups how to collect natural history data.

Dr. Austin provided the following summary points from the workshop:

- Enormous natural history study opportunities exist for scientific and structural reasons, including:
    - The revolution in gene sequencing technology.
    - The realization that FDA, NIH, and academic groups cannot make progress alone.
    - The creation of NCATS, which catalyzes expertise and tools from many different fields to study multisystem diseases, including many rare diseases.
- The NINDS approach to natural history studies, including the requirement that different stakeholders collaborate, provides a precedent for collaborative approaches to these studies.
- NIH is developing experience in large, ambitious, international projects, such as the Human Genome Project.
- An important outcome of this meeting would be multi-author publications in academic journals, which can help legitimize an approach or field of study.
- NCATS and NIH cannot fund all of the natural history research that needs to be conducted.
- The Clinical and Translational Science Awards should be key players in the types of studies discussed at this workshop by, for example, calling on clinicians to do phenotyping.

Dr. Austin offered the following recommendations:

- Given that 7,000 rare diseases exist, a practical approach to natural history studies might be to target groups of rare diseases instead of individual diseases.

- NIH should develop a consortium of all rare disease stakeholders that could provide shared services to the advocacy community for all rare diseases.
- An important activity is finding ways for the many different experts (such as neurologists and genealogists) who work with rare diseases to talk to each other.
- FDA should publish details on its experience with natural history studies and common pitfalls.
- A central resource should be created to collect diagnostic markers, biomarkers, and outcome measures as well as genetic screening measures.
- FDA and the European Union's regulatory body have very different criteria, and the need for international cooperation in the design and conduct of natural history studies is growing.

Closing

Dr. Austin thanked participants for attending this meeting and invited them to join the group that will plan the next steps after this workshop. Dr. McKew also thanked participants for attending the meeting and sharing their thoughts during the presentations and discussions.