21st Century Cures: Incorporating the Patient Perspective
U.S. House of Representative
Energy and Commerce Committee
Subcommittee on Health
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Good morning, Mr. Chairman and Members of the Committee. I am Dr. Marshall Summar. I have the good fortune to be the Chief of Genetics and Metabolism and a Professor of Pediatrics at Children's National Medical Center here in Washington, D.C. I have spent the last 29 years working in the field of rare diseases as a physician and researcher. I am the parent of a child with Down Syndrome. I am here today in my capacity as a member of the Board of Directors and Chair of the Scientific Advisory Committee of the National Organization for Rare Disorders, or NORD.

On behalf of the estimated 30 million men, women, and children affected by one of more than 7,000 known rare diseases, NORD thanks you and the Energy & Commerce Committee for your continuing strong support of the rare disease community. We view the 21st Century Cures Initiative as a great opportunity to move the process of therapeutic development and approval forward. This is particularly important for Rare Diseases where need is often acute and classic approval models can delay life-saving treatment.

NORD is a unique federation of over 200 patient advocacy groups and voluntary health organizations dedicated to helping all people with rare diseases. NORD provides resources, research, advocacy, education, community, and infrastructure support to the rare disease community that small individual organizations cannot. NORD's support allows its member groups to focus on their primary mission, progress towards understanding, treating and curing their diseases.

NORD was founded in 1983. NORD's founders played an active role in the creation of the Orphan Drugs Act, which is a successful model of how to incentivize the development of treatments and is saving lives. Analysis of data in the United States shows that years of life lost to rare diseases declined at an annual rate of 3.3% after the Orphan Drug Act due to the development and deployment of new treatments. Without these new drug approvals, years of life lost would have increased at a rate of about one percent [ref 1]. The annual growth rate of the orphan drug market between 2001 and 2010 was 25.8 percent, compared to only 20.1 percent for non-orphan drugs [ref 2]. Since 1983 more than 450 drugs have been approved by the Food and Drug Administration (FDA) for rare diseases.

Speaking personally, without the treatments resulting from Congress and NORD's efforts many of my patients would not have survived, and I thank you for what has already been done. These efforts represent a good beginning but there is much more we can do to improve the lives of our patients and NORD views the 21st Century Cures Initiatives as a great way to do it.

Using our experience as patients, physicians, researchers and families working with rare diseases and the development of new treatments, we have developed a series of recommendations that we believe will advance not only the development of new orphan drugs and devices but non-orphan ones as well. We have provided the Committee with our recommendations and today I would like to emphasize a few of them, and to place them in the record of this important hearing. These proposals are intended to accelerate the pace of medical innovation, and improve the lives of our patients and families.. We look forward to discussing these ideas with the Energy & Commerce Committee as the 21st Century Cures Initiative continues.

Our recommendations are as follows:

1. Establish a Commission and National Plan to Determine Priorities, Methods, Resource Needs and a Consistent Agenda on Rare Disease Registries and Natural History Studies

Natural history studies and registries play a critical role in the drug discovery and development process. Without the information on the existence, frequency and severity of clinical findings, the efficacy of any treatment cannot be assessed. Without determining effective markers and surrogates of outcome, the potential for long term benefits of a treatment cannot be determined. Before a clinical trial can begin this information must be obtained but it significantly slows the development and approval process and dis-incentivizes work in the field.

We propose the creation of programs to create, curate, and standardize registries and natural history studies which can pre-populate this needed data. Not only will needed data be available for therapeutic development and approval, but previously unidentified treatment targets would become known. This effort could be one of the most important accelerators of the treatment development and monitoring process.

Patient registries represent one of the best resources to collect prevalence, demographic, natural history, and comparative effectiveness data on rare diseases. This is an area where patients can have a major and cost-saving impact on the process. Patient entered data has been clearly shown to be accurate and useful when collected properly. This data can be collected for less cost than more traditional researcher centric models. Creative hybrids using physician, patient, and other health professional collected data can greatly speed the understanding, discover, approval, and monitoring process. Standardized natural history registries, tied to tissue banking, facilitate the generation of research leads, and accelerate studies.

In collaboration with the National Institutes of Health (NIH) and the Food and Drug Administration (FDA), NORD has built and is in the process of testing a rare disease patient driven registry/natural history program. This program will ensure that rare disease patients have adequate natural history information in order to spur drug discovery and development and shorten the process. The NIH's Rare Disease Clinical Research Network has already demonstrated the benefits of this approach with three new drug approvals for one disease in a 10-year span with a group of only 700 patients. The Patient Centered Outcomes Research Institute is developing new statistical methods and models to use data from rare disease patient studies.

All of these efforts will help our patients but a national plan and standards would help prevent wasted effort and resources. An added benefit of these efforts will be a better and more accurate understanding of the incidence and impact of these diseases on the American population.

2. Significantly Reform the Institutional Review Board (IRB) System for Assessing New Therapies

All clinical trials for new treatments -- whether a drug, biologic, or medical device -- must receive approval from an IRB. Each institution typically requires approval and protocol adjustment to its own IRB. Any changes to the study design must go through the IRBs.

This process is one of the greatest impediments and costs to rare disease clinical trials or indeed any clinical trials. One recent study required approval by more than 30 IRBs taking almost two years. The cost of our current system in hours, lost-productivity, delays, and frustration literally cannot be calculated. Surveys show that a majority of young investigators view the IRB process as a significant barrier and reason not to do research or pursue it as a career. The documents have evolved into a risk defense system with consent forms for simple studies often exceeding 20 pages.

NORD recommends that Congress develop legislation that would de-risk the process and foster the creation of an IRB system that is portable across institutions. The de-risking of the IRB process and the encouragement/requirement of reliance agreements between institutions receiving federal funding would accelerate the clinical trials and clinical research process greatly.

A system in which studies approved by the IRB at any institution that meets appropriate standards, can be performed at any other interested institution without modification will significantly increase the pool of study sites, speed the process, and allow greater patient participation. Simplifying the process to focus on information for the patient rather than risk mitigation will shorten the process and better serve the participant in research.

3. Ensure All Current Laws that Increase the Patient's Involvement are Implemented Fully

NORD believes that the patient's voice must be strengthened in the drug development and approval process. We first need to assure that current laws addressing patient involvement are being implemented fully. The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 made groundbreaking strides in encouraging that patients play a greater role during the drug approval process. The FDA has implemented many of these changes admirably but there are various other measures contained within FDASIA that are not being implemented to the fullest extent, or not at all.

The FDA must include a patient or patient representative on the drug review committee as mandated by section 903 of FDASIA. While the FDA has increased patient involvement in other aspects of the drug approval process, such as in advisory committee meetings, the FDA has yet to include patients on a review panel. The FDA should be required to fulfill this mandate. Rare diseases are an excellent place to start.

While the FDA has conducted several patient-focused drug development meetings, it has yet to demonstrate how it intends to use the information to inform the drug review process. While NORD appreciates the FDA's efforts in implementing the patient-focused drug development initiative, we are particularly eager for the findings from these meetings to be incorporated within the drug review process.

NORD requests that the FDA develop a guidance advising patient organizations on how they can administer their own patient-focused drug development meetings and provide data that will be useful to the drug approval process. Under current law, the FDA is holding 20 patient-focused drug development meetings. The information derived from these meetings can be broadened substantially if FDA provides guidance on how patient organizations can independently conduct their own patient-focused drug development meetings in a manner that would enable the FDA to use the findings of these meetings to enhance the drug review process.

We advocate that patients be regarded and treated as partners with the FDA in the drug review process. At present, despite progress, patients are regarded as outside participants who are asked to occasionally consult on drug efficacy and effectiveness, usually under the auspices of the drug companies.

We urge FDA to standardize patient input within the drug review process. Currently, the level of patient involvement varies among review divisions. Patient contribution at regular and predictable times must be built into the process.

Rare disease patients, their families, and their caregivers can be most useful for the FDA when assessing the benefit-risk of a therapy. In its "Patients" white paper, the 21st Century Cures Initiative asks, "How should regulators evaluate benefit-risk? How do you work with regulators regarding benefit-risk? Can this process be improved?"

It is NORD's opinion that patients can make significant contributions in helping to evaluate the benefit-risk of a drug. Patients must be partners with the FDA and companies in making this assessment.

4. Ensure Sufficient and Consistent Resources, Direction and Funding for the Food and Drug Administration and National Institutes of Health.

The FDA is underfunded, given the wide array of regulatory responsibilities it maintains. The FDA is continually charged by Congress with additional regulatory and oversight responsibilities, not to mention the expansion of existing responsibilities due to globalization and increasingly diverse scientific innovations. As part of the acceleration process and the changing landscape of the drug approval and monitoring landscape, the FDA will have new responsibilities. Providing the appropriate resources to these tasks is a key element to their success.

Congress must recognize the importance of the FDA and significantly increase its annual appropriation. The 21st Century Cures Initiative can accelerate the pace at which treatments reach the patient by helping FDA make the expedited review pathway the default for all treatments that qualify. These new pathways not only will accelerate the process but also will change the risk profile of the drug approval process. This is highly important to the rare disease community where the often drastic clinical picture significantly changes the risk/benefit ratio for our families in considering new treatments. FDA needs the ability to expand not only its own expertise but the available pool of experts needed in the approval process to evaluate new products and provide knowledgeable research advice.

With regard to NIH, for the U.S. to maintain its position as the world leader in biomedical research, we need to assure that the basic, translational and clinical research system remains strong. The extramural and intramural programs at NIH have created a community of biomedical scientists and knowledge that we must have to develop new treatments and understand the diseases we can't treat yet. The bulk of human biomedical research in the U.S. is funded through the NIH and the success of the peer-review process and collaborative work this has fostered is evident in the improvement in the human condition we have seen.

To maintain this system requires consistent and sometimes increased levels of funding. Downward or sporadic fluctuations result in the loss of researchers, knowledge and infrastructure that is either irreplaceable or engenders a much greater cost to replace. To incentivize the best and brightest to devote their lives to biomedical research requires consistency and predictability.

The NIH operates several programs and initiatives that are critical to rare disease research. The National Center for Advancing Translational Sciences (NCATS) conducts various initiatives that advance innovation in rare disease research. NCATS collaborates with industry partners and academia to find new therapeutic uses for existing molecules, many of which may be effective in treating rare diseases.

NCATS operates the Clinical and Translational Science Awards (CTSA) program which funds and coordinates clinical and translational research in more than sixty research institutions across the Unites States. NCATS also operates the Therapeutics for Rare and Neglected Diseases (TRND) program which collaborates with academic researchers, patient organizations, and industry to speed the development of therapies for rare diseases. Finally, the Office of Rare Diseases Research (ORDR) within NCATS supports the Rare Diseases Clinical Research Network (RDCRN) and operates a rare disease database with nearly 7,000 diseases included.

If the 21st Century Cures Initiative is to succeed in strengthening the medical research framework of this country, it must strengthen NIH funding and then remove the unpredictability of funding levels each year.

5. Commission a "National Plan for Rare Diseases"

The U.S. needs a consensus document that sets for a National Plan for Rare Diseases. We advocate that Congress commission a comprehensive agenda that evaluates the entire rare disease healthcare ecosystem, and makes recommendations on how to improve the discovery, development, and delivery of treatments to rare disease patients. Congress can follow the precedent of other National Plans it has commissioned, such as the National Plan to Address Alzheimer's.

This plan must be comprehensive and cover the entire spectrum of the rare disease landscape. It should address the duties of each public agency involved in rare disease treatment discovery, development, and delivery. This plan must also address how these public agencies can collaborate with private entities to improve the rare disease ecosystem.

Congress can strengthen the basic and translational rare disease research ecosystem by requesting the Orphan Products Board, which we believe should be reinvigorated, to publish a yearly agenda with recommendations for rare disease research and products development. A reinvigorated Orphan Products Board would be beneficial for the entire rare disease community. It would facilitate greater communication and collaboration between the FDA and the NIH, and with the Federal agencies that are instrumental in the delivery of orphan products, such as the Centers for Medicare and Medicaid Services (CMS) and the Department of Defense (DOD). These collaborations will assist in ensuring that critical orphan therapies will actually reach the rare disease patients who need them.

The Orphan Products Board should work, in consultation with the NIH and FDA, to recommend advances in innovative clinical trial designs for orphan therapies. The Orphan Products Board should also work with the Centers for Disease Control and Prevention (CDC) on epidemiological techniques and advances.

As part of the National Plan, Congress should commission a study on how better funding and coordination of rare disease research will benefit the economy and the healthcare system, as well as lower the Federal government's healthcare expenditures. Greater coordination of research will foster a more efficient use of public and private resources.

6. Enhance the Focus on Clinical Trial Design and Endpoint Development within the NIH Division of Clinical Innovation within the National Center for Advancing Translational Sciences (NCATS)

NORD also advocates enhanced focus on rare disease clinical trial design and clinical endpoints within the NIH Division of Clinical Innovation. Clinical trial design is of a paramount importance when developing any therapy, but is especially important for orphan therapies, where innovative trial designs are often needed to accommodate the small disease population. Many companies that are developing orphan therapies are small, inexperienced companies that have little practice in designing clinical trials in general, let alone trials for diseases that require an innovative trial design because of factors such as small or geographically dispersed patient populations.

We would encourage enhanced focus within the Division of Clinical Innovation on providing leadership and expertise in clinical trial design as well as consultation with sponsors on clinical trial design. In the field of rare diseases, the cost and failure rate of clinical trials could be substantially reduced by making expertise, advice and guidance readily available to those developing new therapies. The barriers for interaction need to be lowered for the NIH, FDA, PCORI and other relevant agencies.

In addition, all clinical trials must have agreed-upon endpoints. The role of the NIH Division of Clinical Innovation should include enhanced emphasis on helping develop appropriate endpoints for studies. The Patient Centered Outcomes Research Institute can help develop the tools and should be encouraged to interact closely with the Division of Clinical Innovation. This leadership early in the research process would be helpful in preventing companies and/or patient organizations from spending years and millions of dollars on biomarker research only to receive a rejection from the FDA. It would be especially beneficial to the rare disease patient population, as clinical endpoints and biomarkers are particularly difficult to establish within rare, genetic diseases.

7. Create an "Orphan Protected Class" within the Medicare Part D Program

Recently, CMS proposed the removal of three protected classes from the Medicare Part D drug coverage system. After a unified outcry from the patient community, CMS withdrew the proposal.

NORD acknowledges the need for reform within the Medicare Part D Protected Class system, and would welcome a discussion with CMS. NORD also proposes that CMS add a Protected Class for orphan therapies. There are rarely alternatives to orphan therapies that patients with rare diseases rely on, yet these drugs are no more protected than any other drug within the Medicare Part D program.

By ensuring coverage of orphan therapies within the Medicare Part D Program, Congress will assure rare disease patients that they will receive the live-saving coverage they need under the Medicare program.

8. Establish Clearer Federal Policies with Regard to Off-label use of Drugs

Many rare disease patients use drugs outside of FDA-approved uses, based on the judgment of their physicians that the drugs will benefit them and will not be harmful. Recently, reimbursement for off-label uses has been denied. Congress needs to address this issue aggressively, as many drugs will never be tested for the rare disease patient and, without reimbursement for appropriate off-label use as determined by the physician, these patients will be denied access to approved therapies that may change or save their lives.

At the same time, the government severely restricts what drug companies can say about new research and about off-label uses, thus cutting off information from the most knowledgeable sources. The Congress should seek new policies that permit drug companies to share appropriate information without fear of enforcement action.

9. Ensure Reimbursement for Medical Foods

In NORD's comments on the 21st Century Cures Initiative white paper titled, "A Call to Action", we highlight the issue of high cost-sharing within drug formularies for specialty drugs, many of which treat rare diseases. We also discuss off-label reimbursement issues, and the importance of off-label use of therapies for rare disease patients.

These are several of many reimbursement issues facing patients with rare diseases, including lack of coverage of orphan therapies under the Medicare and state Medicaid programs.

While reimbursement problems exist for all orphan therapies, we are particularly concerned about issues surrounding medical food treatments, especially the lack of reimbursement for such products.

Each year, approximately 2,550 children in our country are diagnosed with inborn errors of metabolism, requiring them to access life-saving treatments such as medical foods, foods to be modified as low protein, supplements and amino acids. These costly medically necessary foods and supplements are often not covered by insurance or public assistance, causing irreparable mental and physical damage. Families continue to struggle with the tremendous financial burden associated with these medically necessary foods.

Insurance coverage of medical foods is vital to children and adults in order to access medically necessary foods and supplements; however, there is tremendous inequity in coverage amongst the states. Although there are currently 35 states that have legislation in this regard, the legislation is subject to interpretation and more often than not, families have to pay out-of-pocket to ensure their child's well-being and survival. As there is no current cure for these inborn errors of metabolism, these treatments are necessary during the entire lifespan of the individual.

As Congress addresses the discovery, development, and delivery of treatments for rare disease patients, NORD requests that Congress stay particularly mindful of diseases that require medical foods.

Mr. Chairman and Members of the Committee, thank you for considering these and other proposals from NORD. The continued leadership of this Subcommittee on Health is critical to the rare disease community. We welcome continued collaboration.

References:

1. Lichtenberg , The European Journal of Health Economics, 2013, vol. 14, issue 1, pages 41-56
2. Thomson Reuters, *The Power of Rare Drugs*

Respectfully Submitted,

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