Chapter 1
Rare Diseases: Joining Mainstream Research and Treatment Based on Reliable Epidemiological Data

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Abstract Despite growing acceptance of patient registries and natural history studies to provide useful information, the rare disease community suffers from the absence of reliable epidemiological data on the prevalence and incidence of most rare diseases in national and global populations. Likewise, the patients and health care providers lack adequate information on the pathophysiology of rare diseases and expected outcomes of these disorders. The rare diseases community includes all of the stakeholders involved in the research and development and dissemination of products and information for the diagnosis, prevention or treatment of rare diseases or conditions. To replace many of the perceptions with realities, several global efforts have been implemented to sustain and increase the reported progress with the thousands of rare diseases. The first efforts is to develop a global research infrastructure of qualified investigators to stimulate and coordinate research efforts by seeking ways to provide access to clinical trials at multi-national research sites with common protocols and multi-disciplinary research teams. Next, is the continued identification and expansion of worldwide partnerships and collaborations of Patient Advocacy Groups (PAGs), research investigators, the biopharmaceutical and medical devices industries, and the government research and regulatory agencies for a specific rare disease or group of related diseases. Gaining access to information about rare diseases, patient advocacy groups, ongoing and planned research studies and products in research protocols continue to improve the lives of patients and their families. Many basic, clinical and translational research investigators, public and private sector funding organizations, patient advocacy groups, foundations, and the pharmaceutical, biotechnology, and medical devices industries are committed to translating research discoveries that will be useful in the treatment and care of

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patients with rare diseases over their lifespan. Evidence from well-constructed epidemiological studies will provide the evidence that point to the value of additional clinical studies to increase the understanding of rare diseases.

Keywords Rare diseases • Clinical research networks • Epidemiology • Information systems • Patient advocacy groups • Orphan drugs • Orphan products

1.1 Introduction

The rare disease community suffers from the absence of reliable epidemiological data on the prevalence and incidence of rare diseases in the national and global populations to support additional public health measures to address these tremendous needs. The rare diseases community includes all of the stakeholders involved in the research and development and dissemination of products and information for the diagnosis, prevention or treatment of rare diseases or conditions. Translation of basic research discoveries and information gained from patient registries and natural history studies continues to occur at a relatively rapid rate and is leading to research hypotheses generation in clinical research studies and trials of products for rare diseases. Despite this increased emphasis by the private and public sectors and successful research accomplishments leading to increased regulatory approval for orphan products, approximately 95% of rare diseases lack an adequate intervention. Reluctance to become involved in research and development efforts is frequently attributed to the need for more reliable information about the rare diseases from epidemiological and natural history studies. Significant efforts have been made by the rare diseases community to develop procedures and methods to enable rare diseases to enter mainstream research and provide better information for treatment options.

The majority of rare diseases are inherited conditions but a significant number are acquired through various interactions including the effects of environmental factors. As perceptions are replaced by reliable data and information from the community we can address these needs more appropriately. We know there are an ever increasing number of disorders falling under the term rare disease. The exact number of rare diseases remains unknown. Estimates approaching and exceeding 8000 conditions have been expressed. As sophisticated analytic capabilities continue to improve to identify genetic variability, more and more diseases will be subcategorized into distinct rare disorders and conditions. The proposed International Classification of Diseases -11 from the World Health Organization provides the opportunity to increase the number of Rare Diseases with specific classification codes to approximately 5400 in their nomenclature [2, 31, 32]. Expanded genomic analyses will explain many of the phenotypic differences observed in patients. Frequently, those involved with larger numbers of patients in their practice or in their research protocols recognize the phenotypic expression of a rare disease varies from patient to patient. In many instances, it is the active patient advocacy group leader who

describes the differences in patients. Data from appropriate epidemiologic studies are required to confirm the opinions offered by clinicians, patients, and families.

The discussions that follow address many of the perceptions, barriers and the successful activities responding to these needs. The lack of access to appropriate information to aid in the informed decision making process remains a major barrier to an improved quality of life for patients and their families, and caregivers. High costs of products to treat rare diseases are now viewed as a barrier to ready access to care. When no interventions are available for treatment, most patients and families with rare diseases are extremely happy to have a product available regardless of the costs of the products. They are often reluctant to voice concern about the costs of treatments for rare diseases. Collaborative research efforts involving academic investigators, government research and regulatory scientists, the biopharmaceutical industry and patient advocacy groups are vital in all phases of research for rare diseases.

1.2 Very Few People Have the Rare Condition

One of the first issues a patient encounters at the time of obtaining a diagnosis is the conclusion presented that very few patients are diagnosed with their disease. The response is usually based on the publication of results in very narrowly defined populations from a single or a few studies. Unfortunately, most of the results published do not include a sufficiently large population to draw realistic conclusions about the incidence or prevalence of a particular disorder. Only after an individual or a family becomes aware of the availability of services from a patient advocacy group or a link to a social media group with other families are they convinced there are many others living with the same disease. These patients frequently provide vital information about the symptoms and anticipated outcomes of the disease and how best to live with their condition. The lack of ready access to patient advocacy groups is troubling to many patients who are lacking such representation. These connections help eliminate the stigmatization that frequently occurs, whether they are developmental, psychological or physical expressions of the disease. Stigmatization of children with rare diseases remains a major concern. In recent years, we are seeing a reduction of the problem due to the willingness of the families, patients, or parents to address the disease openly and to educate the public about their disease.

One of the major barriers to removing the stigmatization is the lack of adequate incidence and prevalence data for the thousands of rare diseases. Estimates of between 6% and 8% of the population may experience a rare disease [29]. In the USA, an estimated 25–30 million patients have a rare disease. Estimates from the European Union are even higher of between 27 and 36 million people due to a larger population base. Global estimates have been reported as high as 350 million people with a rare disease. When a multiplier of 3–4 people who are affected significantly by rare diseases including family members or caregivers, the number of people directly affected by rare diseases begins to approach and may even exceed 100 million people in both the USA and the European Union and approximately 1.05 to 1.4 billion people worldwide.

Most rare diseases do not recognize geographical, historical or political borders. However, some diseases may occur more frequently in selected populations or in individual countries. The possible occurrence of different inherited conditions points to the need for families to establish and maintain an extensive family history of the health and illnesses of their family members through multiple generations. In the absence of information from longitudinal or natural history of diseases studies, extensive family history studies and environmental exposure studies may be very good predictors of the occurrence of genetic and acquired disorders until the time when large data sets of information from significantly larger patient cohorts can be mined for more reliable information [10]. One of the confounding issues is the occurrence of co-morbidities affecting patients with rare diseases. This can contribute to the increased difficulty to obtain the correct diagnosis.

If a diagnosis is obtained through genetic testing, whole genome or exome sequencing, it is critical for the individual and the family to receive adequate interpretation of the results and an explanation of the health implications for the individual, related family members, and future generations. Access to genetic counseling services is essential to maintain emotional and psychological well-being of the family members whether affected by the genetic disorder or not. Counseling services should be made available prior to the decision of whether or not to have the diagnostic procedure done and after the results are received regardless of the outcomes. Each individual and family must be considered separately and the resulting decision must be respected by other members of the family and the health care providers.

1.2.1 Precision or Personalized Medicine

Genomic Information and Genomic Medicine is now an integral part of patient recruitment and enrollment in clinical trials and study design. This integration of data has led to the development of compounds with a greater likelihood of success in selected patient populations. In Precision Medicine, it is important to engage in research with each product and patient as an individual. Development of specific clinical endpoints and appropriate bio-markers and companion diagnostics is leading more quickly into the full integration of research and product development. Major pharmaceutical breakthroughs continue to facilitate the development of precision medicine products for the care of individuals with rare diseases and conditions. NIH has provided significant resources to develop research partnerships and infrastructure to implement a Precision Medicine Initiative (PMI) emphasized by former USA President Barack Obama [1, 20]. Funds have been provided for cohort projects and to include a Data and Research Support Center to gain access and help organize access to information from more than 1 million Americans. There will also be a Participant Technologies Center to support enrollment of patients in the study. Current product approvals such as for Vertex's Lumacaftor and Ivacaftor suggest the level of specificity of products for patient populations with specific genetic variability. With the sophistication of information presented to patients, a greater

understanding of the principles behind genetics and genomics and precision medicine will require a greater public education effort to increase science and health literacy in the global populations [27].

1.2.2 International Classification of Diseases

One of the persistent requests from the rare disease community has been the need for appropriate classification of rare diseases in standard diagnostic coding resources. Having this information readily available is a key to many of the uncertainties related to an absence of reliable prevalence data. These codes are available and utilized by the health care providers and are essential for reimbursement from third-party payers and national governments after establishing medical necessity. A Rare Diseases Technical Advisory Group for the World Health Organization's (WHO) efforts assisted in the revision of the International Classification of Diseases (ICD). Obtaining an appropriate ICD classification and coding will assist in determining the prevalence of rare diseases. Adopting these codes and integrating them into medical records system will increase the ability to obtain useful data from summary information in patient records and particularly from those using an electronic health record format. Adequately designed natural history studies of rare diseases should also benefit from the improvements to be offered in coding revisions. However, the difficulty of obtaining the correct diagnosis may require several years of visits to practitioners, clinics, and hospitals. In many cases, coding of symptoms of a disease may continue until an agreed upon diagnosis is obtained. At the time of obtaining the correct diagnosis, clinicians need to have a diagnostic code to address the uniqueness of individual patients. The assignment of an appropriate code for rare diseases is also crucial if we are to monitor global health trends by the use of reliable statistical data as mentioned previously. As mentioned previously, a Beta version of ICD – 11 is available for public review and comment at the website of the WHO.

1.3 Gaining Access to Available Information About the Rare Disease or Condition

With ready access to the Internet and World Wide Web and social media connections, patients and their families now have ready access to the extensive collection of information available from numerous sources including disease-specific PAGs. Even though there are significant sources of educational materials available to most people in the developed nations, lack of ready access to these resources remains a major need for millions of individuals and families in the developing nations around the world. Developing methods to convey the increased body of knowledge available from groups around the world is a key to increasing access to the

ever-increasing, reliable and useful information developed by numerous sources. These sources include the National Institutes of Health, the National Library of Medicine, the Office of Rare Diseases Research, the Genetic Alliance, Global Genes, the National Organization for Rare Disorders (NORD), Eurordis, Orphanet, Office of Orphan Products Development (OOPD) at the United States Food and Drug Administration (FDA), European Medicines Evaluation Agency (EMEA), patient organizations, industry, foundations, health care provider organizations, and other government sources.

Extensive use of data sources is sought by the public MEDLINE/PubMed. The NLM's database recorded almost a 2.8 billion searches in FY 2015. On an average day in April 2015, approximately 3.5 million searches were performed on the PubMed Web site. (9) [14] An additional 5.2 million searches were done by scripts, e.g., by application programming interfaces (APIs).The NLM indexes 5618 biomedical journals for the MEDLINE/PubMed database to assist users in identifying articles on specific biomedical topics. A combination of staff, contractors, and cooperating USA and international institutions indexed 806,000 articles in FY2015, bringing the total number of MEDLINE citations to over 22 million. A growing number of Medline citations contain an active link to the free full text articles contained in Pub Med Central or other sites such as the publisher of the articles. Many of these articles may be freely available depending upon the publisher's access requirements. Considerable information on rare diseases is readily available to those with access to the world-wide-web from the Genetic and Rare Diseases Information Center and Orphanet [8, 23].

The most recent figures from the Genetic and Rare Diseases Information Center supported by the ORDR/NCATS and NHGRI reveal that information has been made available for over 6800 rare and genetic diseases to requests from 120 countries in their 14 year history. Orphanet, located in France's INSERM, continues to provide useful and reliable information to the European Union member states and worldwide from multiple sources for over 5600 different rare diseases. Recently, GARD and Orphanet announced plans to share information gathered from their resources to increase the amount of information readily available from their websites [3].

New sources of useful information appear regularly from help-lines established by individual countries and organizations to supplement currently available information. Traditional sources of information continue to expand their information base as improved search engines enable the identification and collection of more information from many sources and presented in a more systematic fashion to potential users. For some rare diseases, it is not a lack of information, but information overload that can be overwhelming to patients and their families. It is important with multiple sources presenting information to the patients or their families to remain aware that not all patients are capable of accepting and absorbing the same amount of information and at the same pace as others. Facilitating or guaranteeing access to useful information is a major step to assist and to enable patients to understand their disease better, to live with their disease, and to learn about the numerous aspects of their disease on their time schedule. When accomplished on each indi-

vidual's own schedule, it is expected to improve the understanding and acceptance of the disease with or without available treatments.

Types of information generally recognized as significant for patients and health care providers are available from numerous other sources such as academic centers, patient advocacy groups and foundations, the biopharmaceutical industry, health care providers, and information services, hotline and social media resources with individual and group interactions. Lack of ready access to information frequently leads to other misunderstanding about the disease and anticipated outcomes. The information falls into several major categories and include but are not limited to information about the disease, expected cause of the disease, prognosis, inheritance potential, available treatments approved by regulatory agencies or products in investigational status, and ongoing or planned research studies. As more clinical trials and natural history studies are completed, results from completed studies presenting both positive and negative results in understandable terms to patients and families are helpful. Gaining access to knowledgeable health care providers or specialty clinics is essential, Availability of links to patient advocacy groups and social media organizations provide real life or real world experiences with a rare disease are beneficial to patients and families and treating physicians and other health care providers. Results from Phase 4 or post marketing surveillance studies conducted by biopharmaceutical industry sources are required more frequently by regulatory agencies as part of the regulatory approval of products prior to entering the marketplace. This information is extremely useful to monitor safety and efficacy in larger patient populations.

1.4 Generating Research Interest

Because there are so many disorders under the rare diseases umbrella, it is frequently suggested there is little research interest in a particular disease. For most of the rare diseases there continues to be a major need for increased research emphasis in both the public and private sectors. However, we are observing shifts in emphasis in research portfolios to include a focus on rare diseases and orphan products. We continue to see a growing global emphasis on research of rare diseases. For example, the ClinicalTrials.gov database, developed and made available by the NIH National Library of Medicine and the US Food and Drug Administration, presents information on approximately 234,500 planned, ongoing and completed studies for rare and common diseases reported from more than 195 countries throughout the world [15]. This database highlights completed, planned and ongoing interventional phase 1, 2, 3, 4 of drugs, biologicals and devices, surgical procedures, observational, longitudinal, behavioral, and expanded access studies. In September 2016, results from completed studies receiving support from the USA government and the pharmaceutical industry are required to be provided in a timely fashion to ClinicalTrials.gov after the completion of the clinical studies. In an effort to make information about clinical trials widely available to the public, the U.S. Department

of Health and Human Services (DHHS) issued a final rule that specifies requirements for registering certain clinical trials and submitting summary results information to ClinicalTrials.gov. The new rule expands the legal requirements for submitting registration and results information for clinical trials involving U.S. Food and Drug Administration-regulated drug, biological and device products. The NIH issued a complementary policy for registering and submitting summary results information to ClinicalTrials.gov for all NIH-funded trials, including those not subject to the final rule. Requirements under the final rule apply to most interventional studies of drug, biological and device products that are regulated by the FDA. The requirements do not apply to phase 1 trials of drug and biological products, or small feasibility studies of device products. The final rule specifies how and when information collected in a clinical trial must be submitted to ClinicalTrials.gov. It does not dictate how clinical trials should be designed or conducted, or what data must be collected [19, 25].

1.4.1 Access to Research Funding Sources

Evidence exists that the research community will investigate special groups of rare diseases if priority is given by funding agencies. Research efforts have been known to follow research funds. As an example, 10 research consortia requiring multiple research sites and investigators received funds from five research NIH Institutes when the Rare Diseases Clinical Research Network was first funded in 2003. In 2016, 22 consortia received support from the ORDR and ten of the research institutes of NIH (NCATS, NINDS, NIAID, NICHD, NIDDK, NIDCR, NIAMS, NEI, NIDCR and NHLBI and the Office of Dietary Supplements) [18].

The European Union (EU) through their Framework Programs 6 and 7 and through the General Directorate of Health and Consumers (DG SANCO) funded different types of networks such as fundamental research consortia, European Reference Networks (ERN), surveillance networks, and translational networks. Member States of the EU have also funded at national level several consortia on rare diseases. It is important to mention the interesting experience of E-RARE action, a consortium of international European, Australian and USA agencies for funding rare diseases projects. E-RARE has funded in their two previous calls for proposals in 2007 and 2009 13 and 16 different rare diseases consortia respectively. The current emphasis is on the repurposing of existing products for rare diseases. The significance of the benefit offered by multi-institutional collaborative efforts and an expanded role of the patient advocacy groups has gained acceptance as a model for research of rare diseases. This is a desirable method to gain access to a critical mass of research investigators and patients. Many investigators and organizations are working to direct their efforts to establishing common protocols which ultimately increase the scientific understanding of the disease and the pathophysiology of specific diseases and molecular pathways of many other disorders. It is anticipated that the future expansion of these consortia and networks will compare favorably to the

sophisticated research and treatment networks developed in oncology and infectious diseases, and other more common diseases such as arthritis, diabetes, HIV/AIDS, and hypertension.

1.4.2 Identifying Rare Diseases Research and Orphan Product Development Projects

NIH provides ready access to a coded and monitoring system for selected rare diseases and orphan drugs. The Research, Conditions, and Disease Categorization (RCDC) system can now be easily found [17]. This system provides ready access to information on basic and clinical research projects receiving support from NIH, FDA, HRSA and CDC. This information is often the starting point to developing a systematic research agenda by identifying ongoing research projects and helps individuals and organizations identify the missing gaps in research. In 2015, NIH provided funding resources for numerous research projects research on rare diseases and conditions

- Rare Diseases ~ 9400 Research Projects ($3.639 Billion USD)
- Orphan Drugs ~ 1650 Research Projects ($785 Million USD)
- Gene Therapy ~ 615 Research Projects ($238 Million USD)
- Stem Cell ~ 3900 Research Projects ($1.429 Billion USD)
- Regenerative Medicine ~ 2500 Research Projects ($862 Million USD)

The NIH Clinical Center Hospital (CCH) also provides considerable resources and support for rare diseases research through the Intramural Research Programs of the 17 research Institutes and Centers (ICs)

- Number of Rare Diseases Under Investigation – 568
- Number of Active Rare Diseases Protocols and Total Study Protocols – 799/1630
- Number of NIH Investigators with Rare Diseases Focus – 315/495
- Patients with Rare Diseases in Studies at NIH – 15,653 (65% of all CCH Patients)

One observation from the experience gained with the focus on rare diseases is the relative lack of information from natural history studies of diseases to provide a better understanding of the disease across the lifespan. Knowledge from these studies is essential for the development or research hypotheses, identification of potential biomarkers, and phenotypic variations in patients. Due to the high costs of initiating and maintaining studies for many years, there has been a reluctance to support these studies. Only in recent years has the value of these studies been accepted by the research and regulatory communities as a generator of new research hypotheses and information for research and treatment for rare diseases. The FDA now considers adequately developed and implemented Natural History Studies with appropriate analysis and interpretation of study results to be one of the most essential steps in

generating information about clinical endpoints or to identify appropriate biomarkers to be developed and validated prior to initiating a clinical trial [24].

Frequently, research of rare and common cancers leads to the development of novel approaches to clinical trial design, patient recruitment, and analyses of results for both common and rare diseases. Rare diseases research benefits from these innovative approaches as they are adapted and adopted by the research community. Rare tumors like most rare diseases provide significant financial, physical, and emotional disease burden and present unique challenges in the research and development of potential interventions. Increased knowledge of the pathophysiology at the molecular level from basic research studies leads to potential new therapeutic treatments. Newer clinical trial designs such as BASKET or umbrella trials are leading to the evaluation of multiple potential agents in one trial or multiple different but molecularly-related disorders in trials of single agents or a combination of potential treatments. There are similarities in the requirements for the evaluation of oncology therapies and in the investigation of products for rare diseases that need to be explored, considered and implemented when appropriate [5].

1.5 Limited Access to Treatments for Rare Diseases

Even with the significant emphasis placed on rare diseases research and orphan products development by national governments, drug, biological and medical devices industries and foundations, adequate treatments for approximately 95% of rare diseases do not exist. Approximately 4045 Orphan Product Designations have been made by USA FDA since 1983 with 595 approved orphan product designations made during the same period. In recent years, an increase in orphan product designations and approvals in the USA and European Union have been noticed. There were 39 approvals in 2016 and 48 approvals in 2015. This is quite different from the two approvals in 1983, the first effective year of the Orphan Drug Act in the USA. The Pharmaceutical Research and Manufacturers of America (PhRMA) reported approximately 560 Compounds in Development for Rare Diseases and 836 Compounds and Vaccines in Clinical Trials for Common and Rare Cancers. The increase in approved products is likely to continue. There were 333 designations provided in 2016 and 354 designations in 2015 Again, this contrasts dramatically with the 26 designations provided in 1983. This lack of treatment can be traced to numerous causes including high costs of research and development, the high risk of failure of most potential compounds to reach the marketplace, the large number of diseases, small patient populations for many rare diseases, better return on investment with other projects and different regulatory requirements around the world. More recent evidence from data points to a different landscape for products for rare diseases. Nearly one-third of products approved for rare diseases have annual sales greater than $1 Billion USD [6, 12, 21, 22].

In recent years, FDA and EMA have initiated novel review programs to expedite review of New Drug Applications (NDA) and Biological License (Applications

Table 1.1 Expedited programs for serious conditions – drugs and biologics (2015 = 21/45 novel drugs approved or 47% for rare diseases)

Program	Qualifying criteria: Serious condition and…	Features
Fast track (14/45 = 31%)	Nonclinical or clinical data demonstrate potential to meet an unmet medical need	Actions to expedite development and review
		E.g., meetings
	Or, QIDP (qualifying infectious disease product)	Rolling review
Breakthrough therapy (10/45 = 22%) (EU PRIority MEdicine (PRIME)	Preliminary clinical evidence indicates drug may demonstrate substantial improvement on a clinical significant endpoint over available therapies	All Fast Track features
		Intensive guidance on efficient drug development
		Organizational commitment
Accelerated approval (6/45 = 13%) (EU Conditional marketing approval)	Provides meaningful advantage over available therapies	Approval based on a surrogate or intermediate clinical endpoint reasonably likely to predict clinical benefit
	Demonstrates effect on surrogate or clinical endpoint that can be measured earlier than IMM (irreversible morbidity or mortality)	
Priority review (24/45 = 53%) (EU Accelerated Assessment)	Would provide a significant improvement in safety or effectiveness	Shorter review clock goal for marketing applications (6 months vs. 10 months)
	Or, other qualifying programs	
	(*27/45 = 60% Used Expedited Programs)	

(BLA). Separate programs in the USA FDA and the EMA such as Fast Track, Breakthrough Therapy (EU Priority Medicine or PRIME) Designation, Accelerated Approval (EU Conditional Marketing Approval), and Priority Review Status (EU Accelerated Assessment). Table 1.1 provides highlights of the emphasis placed on the expedited regulatory review and approval processes. These programs have increased efficiency of drug development and regulatory review approaches for serious conditions, including rare diseases and rare cancers.

1.5.1 Repurposing Drugs: Gaining Access to Treatments and Investigational Products for Rare Diseases

The rare disease community still experiences some difficulty in gaining access to possible treatments through the development of new chemical entities. Other potential compounds could be identified by a global coordinated and systematic approach to the repurposing or repositioning of products approved for other rare or common conditions that might be useful for different rare diseases and conditions. To expand existing regulatory product approval processes, it would be necessary to develop

research and regulatory pathways to identify potential new uses from astute clinical observations and a systematic review of the published literature. Information on potential uses of products other than approved products may be gathered from well-constructed patient registries and Natural History Studies and even data gathered from PAGs and social media interactions of patients and families. Clinical trials may follow if clinical improvements are noticed in patients. Adopting this approach will require expanded efforts of the traditional pharmaceutical industry research and development activities. This process will also require a much broader approach to identify potential new uses for products other than existing indications for marketed products or products of little commercial interest. The magnitude of this approach for over 8000 rare diseases requires a globalization of efforts.

Repurposing of approved products and those previously included in clinical trials could entail a collaborative pooling of research and development assets with a sharing of research results and possible sharing of benefits to a number of potential commercial sponsors in emerging niche markets for specific rare diseases. In some respect this activity requires a re-visiting to the origins of the USA Orphan Drug Act looking at drugs of limited commercial value for the prevention, diagnosis and treatment of rare diseases and conditions not from a perspective of the 1970s but of the capabilities offered in the twenty-first century. These efforts could be assisted by more robust and powerful tools from information technology advances in searching large datasets over a very short time periods to determine potential uses from larger patient population samples. These processes would also be assisted by gaining access to chemical libraries and compounds not under development or not of further interest to the members of the biopharmaceutical industry. The transfer of compounds between the inventor and a company or between two companies is dependent upon successful completion of negotiations related to intellectual property and liability issues. This approach frequently requires an analysis of the current status of the compound and the completion of the necessary studies that will meet the requirements of the regulatory agencies. Absence of information for regulatory approval will be identified as noticeable gaps of required data. To fill these gaps, collaborative efforts require expanded utilization of resources from the public and private sectors.

The estimated costs of developing new indications for the 2nd and 3rd indications would be expected to drop dramatically from the costs of developing a new molecular entity for the first approved indication. Current estimates suggest costs for developing a new molecular entity exceed $1.2 Billion USD.

1.5.2 Recruiting for Clinical Trials and Managed Access Programs

About 1.7 million people participate in 80,000 drug company-sponsored clinical trials each year. It remains an extremely difficult task to recruit and retain an adequate number of study participants to meet the needs of opening and completing the

clinical trial in a timely fashion and within the proposed budget [28]. Increasingly, patient advocacy groups and social media groups are contributing to recruitment of patients into clinical trials. Meeting recruiting goals for all clinical studies is essential if we want to draw accurate conclusions from the clinical studies and if we want to make progress in the diagnosis, prevention, and treatment of rare diseases. Changes in clinical trial design such as a crossover design have improved the likelihood of obtaining active treatment for all patients during the clinical trial. Other trials have increased the ratio of patients expected to receive the investigational intervention.

The biopharmaceutical industry has maintained an emphasis on providing individual patient access to approved interventions when they are unable to pay for the treatments. Managed Access Programs include many different programs from different pharmaceutical companies and may be recognized with terms such as Named Patient, Compassionate Use, Early Access, Expanded Access and Pre-Approval Access programs. They may be defined differently in various countries but are generally for products not commercially available or approved by regulatory agencies. These programs enable the collection of Real World Data from a wider pool of patients who may or may not be included in a clinical trial. There are indications that regulatory agencies will utilize Real World data to assist in regulatory decision-making actions in the future [11].

1.6 Gaining Access to Experienced Rare Diseases Clinicians for Diagnosis and Care

Obtaining the diagnosis is not an easy task and often represents the first frustration encountered by patients and their families. Until a diagnosis is obtained, patients will continue to face barriers to obtain adequate information and treatments for their rare disease. The appropriate diagnosis of a particular rare disease may result after numerous visits to specialists at multiple locations. The difficulty in obtaining the correct diagnosis in the presence of co-morbidities is particularly challenging. For many patients ending the diagnostic odyssey is an accomplishment and relief to finally have a name for the constellation of symptoms that frequently leads to a separation and isolation from the traditional medical care systems. In a survey of patients with a rare disease, reported by the USA National Commission on Orphan Diseases (NCOD), 15% of patients indicated it took more than 5 years to obtain the correct diagnosis. The NCOD patient study results also indicated that gaining access to appropriate care can be very difficult to obtain and adequate information and clinical expertise is often insufficient to meet the unmet needs of patients and their families [16].

Eurordis reported in 2006, the results of a survey of diagnostic delays for patients with eight diseases in 17 European countries (Crohn's Disease, Cystic Fibrosis, Duchenne Muscular Dystrophy, Ehlers-Danlos Syndrome, Marfan Syndrome, Prader-Willi Syndrome, Tuberous Sclerosis and Fragile X Syndrome) [7]. Between 5 and 30 years had elapsed between the appearances of the first symptom to obtain-

ing the correct diagnosis for 25% of the patients. 25% of the respondents traveled to a location outside of their home region to obtain the confirmatory diagnosis. A review of inquiries completed by the Genetic and Rare Diseases Information Center supported by the USA ORDR and NHGRI at NIH discovered 6% of inquires related to undiagnosed diseases.

1.6.1 Undiagnosed Diseases

The Undiagnosed Disease Program (UDP) was initiated at the National Institutes of Health (NIH) through a partnership consisting of the National Human Genome Institute (NHGRI), the Clinical Center (CC) Hospital, the Office of Rare Diseases Research (ORDR) and other NIH Institutes and Centers (ICs). Since that time, with funds provided by the NIH Common Fund, the UDP has expanded considerably and now includes the Undiagnosed Diseases Network and Undiagnosed Diseases Network International. These programs are now contributing their coordinated efforts to gather considerable information from the many organizations attempting to obtain the diagnosis for rare and common diseases [9, 13, 30].

After a diagnosis is obtained, patients and their families continue to search for specific information about their diseases. The quest for information about the cause, expected outcome, heritability, possible future manifestations, the availability of an investigational or approved treatments, learning how to live, cope and manage the condition over their lifespan is an important goal in the pursuit of optima care., Information on planned, ongoing, and completed research studies is considered essential. Recommendations from review committees in the USA and Europe have indicated the need to identify knowledgeable clinicians and locations of research and treatment centers with expertise in their disease.

1.7 Reference Centers of Excellence for Rare Diseases

In the European Union, with approval by the High Level Group on Health Services and Care, the European Rare Diseases Task Force has defined general criteria for Reference Centers of Excellence for Rare Diseases. DGSANCO designates reference centers for rare diseases. Identifying these centers should increase public awareness of possible centers of treatment and research excellence. Many research centers have transformed into treatment centers of excellence as information is gained from research and translated into clinical care as a result of having access to relatively large patient populations. Research or treatment centers of excellence frequently are considered regional or even national referral centers. Many centers of excellence provide active genetic counseling services to help educate the patient, their families, and public and health professionals about the rare diseases in their center. These research centers of excellence frequently serve as the optimal training

program for the new rare disease research investigator [4, 26]. The European Commission recently announced plans for the 24 European Reference Networks (ERNs) approved by The Commission in late December 2016. Through these networks, over 370 hospitals and nearly 1000 rare disease centers of expertise will be linked, connecting thousands of experts, researchers and doctors, across 25 EU Member States.

Resistance to the identification of reference centers of excellence is often heard due to concerns of appearances of inclusion or exclusion of one institution over another. This lack of access may impede gaining access to optimal care for many patients with rare diseases by not making information readily available to the patients in need of specialized treatments. There is recognition that due to current limitations on treatments, cures for most diseases are difficult to obtain. For many disorders, the staffs at these centers have assisted in the development of better care through a team approach to address all of the symptoms resulting from a multi-systemic disease treatments and an improvement in the quality of care of symptoms and the quality of life of patients. The patient advocacy groups have played a major role in improving the care of patients with rare diseases as well as educating health care providers about optimal care of patients. Frequently, the patient advocacy groups, utilizing their experiences with patients and health care providers, are able to identify the most skillful and knowledgeable clinicians who are able to provide the best services for their patient community. Developing and providing this information to the rare diseases community indicates the need for increased collaboration of patient advocacy groups, clinicians, and research investigators on a global basis. A major deficiency exists in identifying and addressing the needs of the many patients who do not receive benefits from the support of an organized patient advocacy effort for their diseases. Likewise, in developing nations, it has been suggested to provide centers of expertise at tertiary medical centers in each country to expand the knowledgebase for rare diseases and provide more ready access to expertise with rare diseases.

1.8 Training of Rare Diseases Research Investigators

To address the needs of training the next generation of research investigators, traditional research and training funding mechanisms from government and industry are used to foster the development of young investigators deciding on career choices or experienced clinicians who are seeking a career change. Continued emphasis on the value of research emphasis on rare diseases needs to be provided to pre-doctoral students, postdoctoral trainees and physician scientists.

Many patient advocacy organizations have found that a useful mechanism to initiate or expand research interest in their disease is to support research fellows who are seeking funds to support their continued research training or initiation of pilot projects. After receiving funding support, sufficient data can be gathered from pilot studies and proof-of-concept studies to support a grant application for an expanded research project that requires considerably more funds and more stable

funding. Generating interest with a particular disease can lead to a very rewarding career as new information is discovered and shared with others.

Consortia in the Rare Diseases Clinical Research Network supported by the ORDR/NCATS and other research ICs at NIH are required to have an active clinical research training component for new and usually younger investigators. In several of the research consortia the trainees have completed their research fellowships, moved to a different academic institution, and opened a new research site as part of the consortia.

The individual consortia are expected to offer a unique environment for clinical research in rare diseases for new investigators, post-doctoral or clinical fellows, junior faculty or established scientist investigators to re-direct their research careers to emphasize rare diseases research. Support from the academic institution or other outside organizations is allowed. The consortia are required to have two trainees in these positions at all times during the grant period. It is possible after the training period has been completed, the new rare diseases clinical research investigator assumes a position at a different institution and can join the consortia as a new research site as part of the anticipated expansion of the individual consortia. As mentioned previously, this has occurred and is an expected outcome of the research plan.

1.9 Conclusions

To establish realistic goals for the rare diseases community, numerous global efforts are required to sustain and increase the existing progress with the thousands of rare diseases.

The first is the identification and expansion of worldwide partnerships and collaborations of Patient Advocacy Groups (PAGs) for individual rare diseases and umbrella organizations representing numerous PAGs such as NORD, Eurordis, Genetic Alliance, Global Genes, Faster Cures, New Zealand Organization for Rare Disorders, IORD and ORDI in India, Korean Organization for Rare Diseases, Japan Patients' Association and ASrid (Japan), Rare Voices Australia, Taiwan Foundation for Rare Disorders, China Organization for Rare Diseases, Canadian Organization for Rare Disorders, the Geiser Foundation, Rare Africa and many others. Improving communication among the PAGs will also eliminate the feelings of isolation, loneliness or stigmatization that are reported by patients around the world. Knowing there are others with the same condition and connecting these individuals regardless of language barriers is often helpful to learn to live with a rare disease and maximize the quality of the life of the individual and their families and friends.

The next requirement is to develop a global research infrastructure of qualified investigators to stimulate and coordinate research efforts by seeking ways to provide access to clinical trials at multi-national research sites with common protocols and multi-disciplinary research teams. Several rare diseases organizations have discovered the value of encouraging these global interactions such as the Treat-NMD Network, Prader-Willi Syndrome Association and Progeria Research Foundation.

Many excellent research teams exist in individual countries. Expansion into global research networks will improve recruitment of patients into studies and increase the number of patients in research studies. The end result is increased access for all patients to clinical trials and the facilitation of the speedy completion of clinical trials. Partnering for Cures, Re(ACT), and organizations such as IRDiRC and ICORD are committed to expanding global and integrated research infrastructures and tools needed to meet the research needs of the rare diseases community. Activities such as those recently announced by NCATS and the Office of Rare Diseases Research such as the development of the Biomedical Translator and the Tool Kit with an emphasis on research tools are keys to future advances through research.

To provide easy access to useful and reliable information for patients, families, health care providers and the public is the goal of many government and non-government organizations. The development and dissemination of information through information centers, help lines, clearinghouses, government organizations, individual PAG, multi-disease organizations and the industry is a costly, but very helpful, process in terms of time, personnel and financial support. Excellent sources are readily available and provide information on a regular and updated basis in numerous countries. To avoid duplication of effort, organizations are encouraged to seek these sources of information and determine the usefulness of available information for their constituent members and then identify and fill in the missing gaps of information for their constituents. It is desirable to have the consolidation of information sources to ease the burden of the rare diseases community in their pursuit of information about their diseases.

Gaining access to research investigational studies frequently leads to an improvement in the quality of care available to patients from knowledge and experiences gained by the clinic staff treating many patients with rare diseases in the study. Improving communication and exchanging best practices information available between a referring physician and a rare disease specialist will increase the spread of best-care information to the local treatment facility or practitioner. It will also increase the likelihood of patients gaining access to approved treatments more quickly after approval by regulatory agencies.

For many rare diseases, the distinction between research and clinical care is very narrow and there is not always a bright line separating the two. The most novel treatments and most recent information from coordinated care efforts provided by health care teams from multiple countries and multiple medical and clinical specialties may be gained from research studies as part of the clinical care of larger populations of patients participating in clinical trials of rare diseases.

Providing ready access to the information about rare diseases practitioners knowledgeable about a particular rare disease, ongoing or planned research projects will help the patients, their families and practitioners gain a better understanding of their disease. By removing the existing misperceptions, patients and their families can adopt a realistic approach to the treatment of a rare disease that is based on the hope that others do care about their disease. Many scientists, government, private sector, and patient organizations, foundations and the pharmaceutical, biotechnology, and medical devise industries are committed to research discoveries that will

be useful in the care of patients with rare diseases over their lifespan. Evidence from well-constructed epidemiological studies will measure disease frequencies, distribution, and changes over time by identifying those affected, their location, when the diseases occur, and causes. They also will help to identify interventions that might affect outcomes and improve quality of life. Epidemiological studies will provide the evidence that point to the value of additional clinical studies to increase the understanding of rare disease. Perhaps our long–term goal should be incorporation of rare diseases into the mainstream of all research and development activities and not require a special emphasis to meet individual disease needs.

The future presents considerable optimism for the rare diseases community. At the heart of this optimism is data and information gathered from well-constructed patient registries, and natural history studies generating research hypotheses to be tested in clinical trials, and the continued emphasis on rare diseases research and orphan products development utilizing appropriate statistical methods and data analysis of results. Contributing to a better understanding of individual rare diseases from epidemiological studies will require collaborative efforts of all individuals and organizations involved in the public and private sectors.

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