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Clinical research for rare disease: Opportunities, challenges, and solutions

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ABSTRACT

Over 7000 rare diseases, each <200,000 US residents, affect nearly 30 million people in the United States. Furthermore, for the 10% of people with a rare disease and for their families, these disorders no longer seem rare. Molecular genetics have characterized the cause of many rare diseases and provide unprecedented opportunities for identifying patients, determining phenotypes, and devising treatments to prevent, stabilize, or improve each disease. Rare disease research poses challenges to investigators requiring specific approaches to: (1) the design of clinical studies; (2) the funding of research programs; (3) the discovery, testing, and approval of new treatments, and (4) the training of clinical scientists. Rigorous, statistically-valid, natural history-controlled, cross-over, and n-of-1 trials can establish efficacy and support regulatory approval of new treatments for rare diseases. The U.S. Orphan Drug Act of the U.S. FDA has stimulated industry investment in clinical trials to develop treatments for rare diseases. For trainees interested in finding a treatment for a rare disease, a commitment to longitudinal care of patients provides a base for the characterization of phenotype and natural history, a stimulus for innovation, a target population for research and helps fund training and research. The scientific methodology, financial resources, and logistics of clinical research for rare diseases have changed dramatically in the past two decades resulting in increased understanding of the pathophysiology of these disorders and direct benefit to patients.

Introduction

The clinical presentation, natural history, pathophysiology, and often mysterious nature of rare diseases have fascinated physicians for centuries. Rare diseases provide opportunities to study human physiology and biomedical science from unique perspectives. Major scientific breakthroughs resulting from investigation of rare diseases have often provided insight into more common disorders. The satisfaction of diagnosing a patient with a rare disorder successfully is often rapidly countered by the realization that the ability to understand and treat the patient's condition is limited by ignorance and the difficulties of studying the disease. Moreover, for the "interesting" patient with a rare disease, being a "fascinoma" to physicians may intensify suffering. Patients may feel that their physicians are in league with the "interesting" disease. Furthermore, for patients with a rare disorder, the disease is no longer rare—it is a constant part their lives and the life of their families.

There are several definitions of "rare" or "orphan" diseases and these definitions may differ among countries. Common to all definitions is the low prevalence of a disease and the perception that treatments and research related to a specific disease are inadequate. In 1983 the United States (U.S.) Congress passed the "Orphan Drug Act" (since amended several times). This landmark act instructs the U.S. Food and Drug Administration to label a disease as "rare" if it has a prevalence of <200,000 persons in the U.S. Using this definition, it is estimated that over 7000 rare diseases affect an estimated 25–30 million people with a rare disease in the U.S. (8–12% of population). The Orphan Drug Act also designates diseases as "rare" if they affect more than 200,000 persons in the U.S. if "…there is no reasonable expectation that the cost of developing and making available in the U.S. a drug for such disease or condition will be recovered from sales in the U.S. of such drug" [1].

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The awareness of rare diseases by the general public has grown over the last three decades. This increased awareness is the result of changes in society including: the marked expansion in the size, number, and influence of patient advocacy groups focused on a specific rare disease; groups promoting awareness of rare diseases in general (e.g. the National Organization for Rare Disorders [2]; the ability of the internet to allow patient groups to organize and educate and reach millions of people world-wide inexpensively; the growing interest by mainstream media in human interest stories about people, especially celebrities, with rare diseases; increased government attention to, and funding of, rare disease research and targeted drug development; and academic medical institutions' support of specialized centers organized to treat patients with rare diseases and conduct research on these disorders. This paper reviews important issues facing clinical investigators studying or training to study rare diseases.

Pursuing a career in rare disease research

Once interested and engaged in research into a rare disease, an investigator faces a number of opportunities and challenges. The scientific and career opportunities for researchers specializing in rare diseases are excellent. Unanswered questions about the pathophysiology of many rare diseases have the potential to make possible a major impact on a clinically and scientifically underserved population. The advances and availability of powerful tools for studying genetics has been of particular benefit to students of rare diseases. The internet has been a key and expanding method for recruiting clinical study subjects and publicizing the services of new centers for care and research in specific diseases. In addition, funding agencies in many countries now recognize the benefit for the general scientific community of supporting research in rare diseases. Many patient advocacy groups now provide support for young investigators focusing on specific rare disorders. Investigators can quickly carve out their own research niche when studying a rare disease.

Clinical investigators in rare disease research also regularly face challenges specific to the study of uncommon disorders. Perhaps the most frequent problem is the recruitment of a requisite number of study subjects for an observational cohort or a clinical trial. This need requires the creation of multi-institutional and international collaborations to conduct clinical investigation in rare diseases. These recruitment challenges and reduced study sample sizes also directly lead to the need for adoption of specialized study designs and biostatistical techniques developed to maximize data from small numbers of subjects. Additionally, studying rare diseases requires greater vigilance in protecting the privacy of study subjects as the publication of family pedigree information or detailed clinical descriptions can lead to identification of a specific individual. Successfully obtaining adequate research funding by government agencies and stimulating the interest of biopharmaceutical industry partners are greater problems for researchers involved in rare diseases as more common diseases have greater economic impact. Thus, trainees in rare disease research need to seek out mentors with a different subset of skills from those for individuals engaged in research in common disorders.

Orphan-drug designation program

The Orphan Drug Act (Public Law 97-414) was enacted in 1983 to provide sponsors incentives to develop promising drugs to treat, prevent, or diagnose rare diseases or conditions affecting less than 200,000 persons in the United States (US). These incentives include: protocol assistance (written recommendations from the US Food and Drug Administration (FDA) on the preclinical and clinical studies necessary for marketing approval); tax credits equal to 50 percent of the qualified clinical testing expenses; waiver of Prescription Drug User Fee Act marketing application fee; orphan product development grants; and, most importantly, seven-year marketing exclusivity once the drug is approved by FDA [3]. Drugs intended for common diseases are also eligible for the same incentives if the sponsors can show that no reasonable expectation of recoverable profit occurring from sales in the U.S. in the first seven years of marketing.

To be eligible for these incentives, a sponsor must submit to the Office of Orphan Product Development (OOPD) an orphan-drug designation request prior to the submission of a marketing application of the drug for the intended orphan use. The request should contain information on the disease and its prevalence, the drug and its rationale for use, and estimates and justifications of non-recovery of cost, if applicable. A previously unapproved drug, a new orphan indication of a previously approved drug, or the same drug as a previously approved drug, but potentially clinically superior, are eligible for designation. A drug may also be designated for use in an "orphan" subset of a common disease, if the sponsor can present a medically plausible rationale why the drug could be used in only that particular subset and not in the remaining patients. The sponsor should refer to the FDA Orphan Drug Regulations for more information on orphan designation [4].

The FDA OOPD has granted 1705 (71%) of the 2394 designation requests received between 1983 and 2006. To date, over 300 designated orphan products have been approved for marketing, serving over 12 million Americans and numerous patients in other countries. In the decade preceding the passage of the Orphan Drug Act, only 10 drugs were approved for orphan indications. From 1996 to 2006, the average number of FDA orphan drug approvals per year was 16 (range 6–25). Over the last decade, drugs with orphan indications accounted for 0.7% of all original new drug approvals and supplemental applications combined, 11% of original new drug approvals alone, and 24% of all new molecular and biological entity approvals. Over the same period, the number of FDA orphan-drug designations per year increased 143% [5]. Updated cumulative lists of designated and approved orphan drugs are available on the OOPD Website [6].

Humanitarian use device designation program

The Safe Medical Devices Act of 1990 (Public Law 101-629) authorizes the FDA to exempt makers of medical devices developed for the diagnosis or treatment of diseases or conditions affecting a relatively small number of people in the US from the requirements to show effectiveness prior to marketing approval. This provision is also known as the humanitarian device exemption (HDE). As a prerequisite to HDE approval, the sponsor must submit to OOPD a request for humanitarian use device (HUD) designation of the device in question at the earliest possible time [7]. The request should contain an adequate description of the device and a demonstration that the disease or condition (or a subset thereof) of interest affects or is manifested in fewer than 4000 persons in the US per year. The FDA may approve a designated humanitarian use device through the exemption marketing application if the sponsor can show that: (1) the benefit outweighs the risk from its use; (2) no comparable approved device is available on the market; (3) the device is to be used with institutional review board approval; and (4) the device is sold at cost.

Between 1996 and 2006, OOPD received 174 HUD designation requests of which 117 (67%) were granted. A total of 42 medical devices were eventually approved for marketing under HDE in that time.

Orphan product development grants

The aim of the orphan product development (OPD) grant program is to assist sponsors in defraying the costs of clinical trial

expenses incurred in the development of drugs, medical devices, and medical foods for rare diseases and conditions [8]. The program has an annual budget of approximately $14 million. Domestic or foreign, public or private, non-profit or for-profit entities (excluding those engaging in lobbying activities), state and local units of government, and non-HHS federal agencies may apply. To be eligible, the clinical investigation of the drug or the device must be conducted under an active investigational new drug application or investigational device exemption, respectively.

Applicants may apply for OPD grants electronically via http://www.grants.gov/. Beginning in fiscal year 2009, funding levels for these grants will be up to $200,000 per year for up to three years for Phase 1 clinical investigation and up to $400,000 per year for up to four years for Phase 2 or 3 clinical investigation.

Between 2000 and 2006, OOPD received an average of 69 grant applications annually. Of these, about 17 were funded each year. The majority of grantees (76%) were affiliated with universities and medical centers. Approximately 19% of grants were awarded to pharmaceutical companies. A quarter (24%) of grants were for oncologic drugs, 14% for metabolic disorders, and less than 10% for each of a number of other disease categories. To date, OPD grants have supported clinical development of 41 approved orphan drugs and medical devices.

Academic partnerships with industry for orphan diseases

Probably the first question an academician interested in orphan disease should ask before dealing with a biotechnology or pharmaceutical company is "why should a biopharmaceutical company be interested in a rare disease?" The answer relates to some of the history of orphan diseases. The Orphan Drug Act gave financial incentives for companies to consider working in the rare disease field. There was also the incentive of 'less competition' and the more likely probability to demonstrate 'proof of concept' in these rare disease populations. One of the first corporations to utilize this new 'Orphan Disease Legislation' was Genzyme Corporation who in 1991 successfully registered alglucerase (Ceredase) for the treatment of Gaucher disease. The initial drug development was performed at the NIH.

Academic–industrial relationships provide a synergy of activity that cannot be obtained if each component works in isolation. Academic groups provide the intellectual catalyst that is required for an industrial partner to feel confident enough to expend the capital to further the development of a new drug product. Industry brings the rigor and resources to confirm initial findings and provide the resources required for manufacturing and toxicological studies. The final clinical trials are rigorous and expensive and usually require a partnership with a pharmaceutical entity before completion. It is essential that each party understands its responsibilities and strengths of both parties before a successful 'partnership' can begin. A well demarcated 'pre-nuptual' agreement is necessary so that each party understands the benefits and risks of the partnership. Disagreements can be significantly reduced if the early 'groundwork' can be established. It is critical to understand that both the academic and pharmaceutical partner brings invaluable assets to any agreement.

Working with patient advocacy groups for rare diseases

Patients with rare diseases often form advocacy groups as a way of sharing information and encouragement, supporting research, and helping patients and their families obtain needed services. These groups have played an important role in the history of the orphan product movement and they continue to provide substantial support to rare disease researchers today. Patient advocacy groups often help with patient recruitment, research funding, administration of patient assistance programs, and facilitation of patient–doctor communication. For example, the National Organization for Rare Disorders (NORD)—which is a federation of patient advocacy groups—provides assistance with patient recruitment, including "Clinical Broadcasts" that notify patients and family members of opportunities to participate in clinical trials. NORD also administers grants and fellowships for the study of rare diseases, and early access programs for investigational drugs.

Many patient advocacy groups have developed sophisticated and highly effective fund-raising techniques to support the study of rare diseases. For example, when researchers at the University of Pennsylvania announced in 2006 that they had identified the gene associated with fibrodysplasia ossificans progressiva (FOP), they credited the International FOP Association with providing major funding for their work [9]. Several patient advocacy groups have also assisted academic researchers in the creation and maintenance of tissue banks and patient registries.

A growing spirit of internationalism among patient advocacy groups may also be helpful to researchers. Organizations within the U.S. work closely with their counterparts in Europe, Asia, and elsewhere. In the world of rare diseases, where the number of patients in any one locale may be quite small, such international linkages can be extremely beneficial.

Clinical trial design

Trial designs for rare diseases must meet the same rigorous standards as those for trials for more prevalent diseases [11]. They must ask important scientific questions, minimize bias and have appropriate likelihood of achieving a scientifically acceptable answer. Indeed, designs for rare diseases are equally applicable to any other category of diseases. However, many different types of study designs exist, some of which require only a fraction of the number of subjects required to conduct a randomized controlled trial, which might make them particularly attractive for studies of rare diseases [12–16].

A randomized controlled trial is considered the gold standard because inherent in its design is the minimization of bias. Thus the results are often regarded as providing the strongest evidence in testing a hypothesis. However, randomized controlled trials are not easy to do in that many potential participants object to the concept of randomization and investigators may sometimes feel that randomization, in of it itself, is unethical [17]. Randomization requires that the investigator and the subject consider themselves in the state of equipoise in that they truly feel that the treatment received from either arm of randomized trial is equivalent unless proven otherwise. This is difficult for participants who want to believe that their treatment will be based upon what is best for them and not the 'flip of a coin' and difficult for physicians who also think that they are ethically bound to provide the 'best' treatment. Equipoise is made the more difficult as trials are often developed because an investigator feels that an experimental therapy is better and they wish to test that hypothesis in a rigorous fashion. Some subjects object to the trials if they have a likelihood of being assigned a potentially inferior arm (i.e. the non-experimental therapy) or being randomized to a placebo. Appropriate patient education by investigators intimately aware of the specific rare disease often diffuses their concerns.

Alternate designs can address concerns about randomized controlled trials by using external or historical controls or with participants serving as their own control [18]. In the case of external or historical controls, all patients recruited for a proposed study receive the new or experimental therapy and their outcomes are compared to a population that had already been treated by a standard therapy. If historical data are valid and available, this is an efficient design because it requires fewer patients to be accrued.

Table 1
Cross-over trials for rare diseases. The administration of one or more experimental therapies (often including placebos) one after the other in a specified or random order to the same group of subjects.

Advantages
All subjects serve as their own controls and error variance is reduced thus reducing sample size
All subjects receive treatment (at least some of the time)
Statistical tests assuming randomization can be used
Masking can be maintained
Disadvantages
All subjects receive placebo or alternative treatment at some point
Washout period can be lengthy or unknown
Cannot be used for treatments with permanent effects or in diseases that change over time

The downside of such a design is that the selection of historical controls must be made with extreme caution so as not to bias the study results. Often it is difficult to know whether bias has been introduced by factors that have not been reported in the historical series or through changes in practice that may affect clinical assessments or outcomes.

A design that avoids the biases of historical controls is the use of concurrent controls for which participants serve as their own control. Such designs are desirable if there is less within-patient variability in a treatment response than there is between-patient variability. In such cases, outcome estimates will have less variance and the study design will require less accrual. Examples of these designs include cross-over designs (Table 1) and "N-of-1" designs (Table 2) [19–21]. These study designs are applicable, however, only in the situation where there is a relatively rapid response to the intervention, the response disappears relatively soon after the intervention is withdrawn, and the participant's overall condition does not change during the intervention or post-intervention periods. These designs can work well for chronic diseases, but in many settings these assumptions can not be justified.

The case-control design is well-suited to study rare events and rare diseases. [22] In this design, individuals in whom a certain outcome has been observed (e.g. specific level of disease severity or a particular event) are matched to controls that did not have such an outcome and then the two groups are compared with respect to a particular intervention or exposure. Case-controlled studies can utilize either prospectively or retrospectively collected data. Case-control studies are particularly efficient but suffer because of the reliance on historical data. Such designs can be particularly useful in rare diseases in which there is a long lag time between genotype and phenotypic expression or between exposure and the particular events or outcomes of interest. When conducting case-controlled studies, investigators have to be extremely careful in selecting appropriate controls to avoid introducing bias. This design is not ranked as high as the randomized controlled trial in terms of the strength of evidence.

Table 2
"N-of-1" trials for rare diseases. Randomized, multiple cross-over trials (often includes placebo) in which an individual subject serves as her/his own control. Consecutive periods are paired and treatment order is randomized independently for each period.

Advantages
All subjects receive treatment (at least some of the time)
The benefit and side effects of the treatment are determined for the specific subjects
Masking can be maintained
Disadvantages
All subjects receive placebo or alternative treatment at some point
Wash out period lengthy or unknown
Requires that disease and outcome variables be stable or linearly progressive
Provides poor information on the benefits/side effects in a larger population of subjects

Different designs can be used even when treatment arms are prospectively randomized to reduce sample size requirements. Examples include cross-over designs as well as factorial designs [23]. In the former, participants are randomized to a treatment arm for a period at the end of which the outcome is assessed and then 'crossed over' to the other treatment. The cross-over design makes the same assumptions as does 'N-of-1' trials where participants are randomized to pairs of therapies given in random sequence and a washout period is assumed to eliminate the effect of the treatment after the intervention is withdrawn. Factorial designs involve a double randomization in which two questions are asked in the same participant population. This essentially results in a sample size savings of an appropriate 50%, but also assumes no interaction between the two treatments. By interaction we mean that the effect of treatment A over its comparison group (placebo) is in the same direction regardless of whether the patient received treatment B or not. Again, this is an assumption that is hard to verify.

Finally, designs for ranking and selection procedures are often helpful and generally require a smaller sample size than randomized controlled trials [24]. In a ranking design, the objective is to maximize the likelihood of selecting the better therapy from a number of therapies as opposed to designing a trial that actually compares therapies directly and measures how much better one is as compared to another. Subjects are prospectively randomized to different treatment arms and response rates measured as in a randomized clinical trial. Instead of direct comparisons, the results are ranked in terms of the desired outcome. Ranking statistics are often used when information about underlying parametric distributions are unknown. It could be argued that less is learned in such an experimental design and a subsequent experiment is required to measure the actual difference between treatment outcomes. That is because a randomized clinical trial design is to detect a minimal clinical significance between treatments whereas the ranking statistics only seeks to determine which treatment has the better outcome. Because fewer subjects are necessary to establish the superior treatment, this design is suitable for evaluating multiple treatments.

In some instances the arguments against randomized controlled trials are convincing exclusive of the difficulty of recruiting a sufficient number of subjects. For a disease in which the natural history is one of invariably relentless progression and death, the improvement and survival of a relatively small number of subjects is persuasive evidence of efficacy and is sufficient for regulatory approval. Similarly, a major benefit of a treatment vs. placebo in a small number of n of 1 trials with repeated, confirmatory observations in each subject gives definitive information for individual cases. In both instances two major limitations are noted: (1) It is uncertain what proportion of patients will benefit from treatment, and (2) insufficient data on adverse effects of treatment are generated.

The design of a clinical trial for evaluating an experimental treatment for a rare disease may follow many approaches: a number of them can achieve certain economies in terms of the required number of participants. However, the options are not without their drawbacks and require investigators to make a number of assumptions, some of which cannot be verified. It is clear that careful consideration needs to be made regarding those assumptions to identify the study design that best fits the research question [25–28].

IRB and HIPAA issues regarding research in rare diseases

Navigating the requirements of domestic Institutional Review Boards (IRB's), international ethics boards, and the U.S. Health

Insurance Portability and Accountability Act (HIPAA) regulations are daunting for both new and experienced investigators in rare disease as the complexity of adherence to HIPAA regulations is amplified when conducting clinical trials in rare diseases. An understanding of the fundamentals of human subjects protection regulations relevant to clinical research and the role of government agencies (e.g., the Office for Human Research Protections, the Food and Drug Administration, and the Office of Civil Rights) is a critical foundation for efficient, high-quality, and ethical research, in rare diseases.

Maintaining the anonymity of participants is a particular challenge for rare disease research due to inherently smaller affected populations, yet is germane as those afflicted with rare diseases and their families can be more vulnerable to discrimination (e.g. insurability, employability, etc). Some strategies to protect the anonymity of research participants and their families include: physical controls (limited and centralized access to data), restricted use and disclosure of protected health information (PHI), and employment of Certificates of Confidentiality. Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level [10].

Research registries are an important part of conducting rare diseases research. However, access to and utilization of the information collected by registries includes complicated ethical and privacy issues. The utilization of a central data coordination center can lower IRB and HIPAA hurdles by providing standardized controls for what data are collected, who/what entities have access to data, and specifications for how/by whom registrants can be contacted.

Solution-based discussions on human subjects issues specific to rare diseases research also require special attention. These include strengthening investigator relationships with patient advocacy groups and successfully navigating local IRB review of multi-center studies by volunteering/providing much needed expertise in rare disease areas.

Research training for rare disease research

Research training strategies, including curricula and mentoring requirements for clinical investigators in rare diseases do not necessarily differ from those employed for other clinical research. However, the absolute requirement that training prepares the investigator for the challenging task of supporting a research program mandates distinct considerations for rare disease research (Table 3). It could be argued that those interested in a rare disease should consider the option of studying both a common as well as a rare disease in order to cross-subsidize their focus on a rare disease.

The curriculum for research training includes biostatistics and epidemiology and can often occur within a masters program in clinical and translational research or public health. The bedrock of training is the mentoring team: a single mentor who is a role model, well-funded for rare disease research and has demonstrated mentoring success; a biostatistician with time and interest in the trainee's focus; and a basic scientist interested in the trainee's specific disease focus. An essential quality common to all ideal mentors is generosity (Table 4). The selection of the right mentor is essential for all trainees—basic or clinical. For rare disease research training, this means working with a mentor who has learned the research strategies essential to pursue study of a rare disease, including garnering support.

Table 3
Skill sets essential for research on rare diseases.

Recruiting and retaining subjects
Developing multiple streams of extramural research funding
Ability to achieve disease-centered development/philanthropy
Developing therapeutic agents with small "markets"
Obtaining/gaining access to therapeutic agents
Establishing equipoise in investigators and patients

Table 4
Assessing the generosity of mentors.

Quality (vs quantity) time—available when needed?
Authorship of papers (group, first, final)—are they usually first or final author on all papers?
Reviews for journals frequently
Mentoring with journal reviews—Willing to help you review articles
Grant recognition/inclusion—are previous mentees PI on their own grants?

Training strategies for clinical scientists are different from those for basic scientists (Table 5). For basic scientists a single supervisor/mentor and a single focus are ideal. For clinical/translational training a mentoring team is essential; and it is often important to pursue one or more clinical projects at the same time since some of the highest quality clinical studies are longitudinal—making it difficult to publish the results within a reasonable period of time from the initial design of a project. Working collaboratively on several longitudinal studies at various stages is often the key to high productivity. Trainees can often have their own individual projects based on data-mining, subset analyses, or ancillary studies based on ongoing or completed longitudinal studies. Rare disease research training ideally occurs in an environment rich in ongoing, well-funded investigators and longitudinal projects.

"Protected-time" is the mantra of the academic clinician whose mentors have argued that an excessive service load—for either revenue support or to help a department meet "clinical mission"—can interfere with research-skill development and productivity. However, it is critical for the rare disease trainee to gain extensive clinical experience in "their" disease. Moreover, the support of a patient population is needed for clinical research initiatives.

The proliferation of graduate degree-granting programs for clinical research has fostered organized curricula that provide both didactic and mentored, hands-on training in skills needed for a successful career. Formal, practical courses in grant writing are particularly helpful.

Successful training prepares the trainee to secure extramural support and resources to fund an independent research program with the recognition that clinical research is labor- and personnel-intensive. Optimal training includes seeking and receiving government, private foundation, and industry support as well as experience in philanthropic support development. Developing and fostering relationships with patients and advocacy organizations is essential. Finally, funding is inherently cyclical: academic institutions are rarely in a position to provide substantial programmatic maintenance support and funding agencies have lean years. Finding or creating a position which has substantial "reserves" has to be the goal.

Conclusion

The scientific methodology, financial resources, and logistics of clinical research for rare diseases have changed dramatically in the past two decades with these changes resulting in substantially increased understanding of the pathophysiology of these disorders, many new treatments, and direct benefit to patients with many of these diseases. There are many other resources which can be brought to bear on rare disease research (Web Table 1).

Table 5
Comparisons/contrasts: basic vs clinical/translational research training.

	Laboratory scientist Ph.D., or M.D., Ph.D	Clinical scientist M.D.
Mentors/faculty Resources	Usually one	3 (or more): clinician, biostatistician, basic scientist
Course work	Extensive	Extensive
Duration	3 years + post-doctoral position(s)	3 years + 3–5 years mentoring
Focus	One (or two) major project(s)	Often multiple projects
Target outcome (after 3–5 years)	Positioned for grant application	1–5 funded grants
Debt	Variable (minimal if Ph.D. training supported)	Up to $250,000
Clinical work	Minimal (<10%)	Substantial (25% or more)
Survival skill	Writing ability	Writing ability, ability to build a collaborative team

Web Table 1
National resources for rare diseases research.

Scientific conferences	http://rarediseases.info.nih.gov/html/workshops/scicon.html
Genetic and rare diseases information center	http://rarediseases.info.nih.gov/html/resources/info_cntr.html
Angel flight America	http://aircharitynetwork.org
CETT (Collaboration, education and test translation) program	http://www.cettprogram.org/
Bench to bedside program in rare diseases	http://clinicalcenter.nih.gov/ccc/btb/awards.shtml
Commercial licensing	http://www.ott.nih.gov/licensing_royalties/raredisease_ovrvw.asp
National gene vector biorepository and coordinating center	http://www.ncrr.nih.gov/clinical_research_resources/resource_directory/national_gene_vector_biorepository/
Human genetics resource center	http://locus.umdnj.edu/ninds/genetic.html
UC Davis/NINDS/NIMH NeuroMab facility	http://www.neuromab.org
Mutant mouse regional resource center	http://www.mmrrc.org/catalog/StrainCatalogSearchForm.jsp
NIDDK-sponsored central repositories for biosamples and data	http://www.niddkrepository.org
NEI-sponsored national eye disease genotyping network	http://www.nei.nih.gov/resources/eyegene.asp
Cogan ophthalmic pathology collection	http://cogancollection.nei.nih.gov/
NIH knockout mouse project	http://www.nih.gov/science/models/mouse/knockout/index.html
NIH-RAID program (rapid access to interventional drugs)	http://nihroadmap.nih.gov/raid/
NCI's clinical proteomics technologies initiative for cancer	http://proteomics.cancer.gov/
Outside NIH—human proteome organization	http://www.hupo.org/research/hai/
Clinical and translational science awards	http://www.ncrr.nih.gov/clinical_research_resources/clinical_and_translational_science_awards/

Although challenges specific to studying rare diseases remain, the opportunities for contributing to exciting scientific discoveries, forging successful research careers, and, most importantly, improving the lives of people with rare diseases have never been better.

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