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DESIGNING CLINICAL TRIALS TO STUDY RARE DISEASE TREATMENT

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This paper provides an overview of the design of clinical trials for rare diseases and the impact of the Orphan Drug Act on the successful study of diseases found in small, widely dispersed patient populations. Orphan drugs are defined. Randomized, placebo-control trials may not always be an option for studying orphan drugs; designs which may work better include: open protocol, open label, historical control, crossover trials, withdrawal design trials, or trials with surrogate endpoints. Each of these is discussed. The benefits of studying orphan drugs and the procedure for approval of trial design by the Food and Drug Administration are outlined.

Key Words: Orphan drugs; Clinical trial design; Orphan Drug Act; Office of Orphan Products Development; Rare diseases

SINCE 1983, THE Orphan Drug Act has encouraged clinical research for the treatment of rare diseases and disorders, and has played a major role in bringing treatment and diagnostic products for those disorders from the laboratory bench to the patient. Rare disease research calls for clinical trial design that accommodates the study of diseases found among small, widely dispersed patient populations. Prior to the Orphan Drug Act, researchers and drug sponsors often felt that clinical trials targeting minuscule patient populations could not possibly derive results sufficient for Food and Drug Administration (FDA) market approval. Over the past 15 years, this legislation has proven that in many many instances, products for rare diseases can successfully be studied, and ultimately achieve FDA approval.

Due to the small number of patients affected by most rare,"orphan" diseases, an appropriately designed trial is imperative; but methodologies for studying orphan drugs are, in general, not significantly different from the methodologies for studying any other drug. Exactly what are the barriers to orphan drug development? They are not terribly surprising: the small number of patients affected by the disease; the small market for the product; the wide dispersement of patients throughout the United States, and—frequently—throughout the world; and products that frequently are not patentable, or require a lengthy patent process. These barriers all influence the development of drugs for rare diseases.

In the 10 years before the Orphan Drug Act was enacted, it is estimated that 10 products were approved for rare disorders. Because of the high cost of drug development, and the perceived lack of return on investment, incentives were needed to encourage

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development of products for rare diseases—and the Orphan Drug Act provided them. Orphan legislation established the public policy that the federal government would become involved in the development of drugs for rare diseases. That was a new role for the federal government and was a particularly new and different function for the FDA. At the time, there was concern that such involvement would amount to the "fox" watching the "chicken house," and was not an appropriate way to handle drug development. Today, most would agree that the Orphan Drug Act has clearly demonstrated it is indeed a good way to handle drug development.

An orphan drug is defined by the Orphan Drug Act as one that "treats a disease affecting fewer than 200000 people in the US, or which will not be profitable for a period of seven years following FDA approval." The population size for a rare disease may range from that of adenosine deaminase (ADA) deficiency, affecting 12 children in the United States, to chronic renal failure which—at the time erythropoietin was approved—affected 192000 people. The scope of patients affected with these rare diseases is also widespread. Although 200000 patients may sound like a lot, dispersed among a United States population of 265 million, it is a small number of people, who may easily be lost. Without an established registry, interested researchers cannot easily find these patients for studies. Patients with end stage renal disease were a clearly defined population, since they were treated under Title 18/19 of the Medicare Act, and practically all were registered and known by name and number, for easy location. This is not often the case.

Since 1983, more than 173 orphan products have been approved by FDA to treat rare diseases. The total population treated by these 173 products in the United States is more than eight million. That is an impressive accomplishment for 15 years of commitment to the mission of assisting and encouraging identification, development, and availability of safe and effective products for patients with rare diseases and disorders. Of the 173 products that have been approved, 49 are for pediatric indications—with a total patient population of close to a million; more than 125 are for rare diseases that represent life-threatening illness.

The Office of Orphan Products Development has the authority and responsibility for designating a drug or biological product as an orphan. OPD staff verify the prevalence of the disease at the time the sponsor applies for orphan designation, and reviews the rationale for using the product in this condition. Although drugs, biological products, medical devices, and medical foods are eligible to receive orphan grant funding through the orphan products development program of the FDA, only drugs and biologicals may be designated as orphan products. The term "drug" is used interchangeably here to denote drugs and biologics.

There are some advantages to studying a small disease population: small population studies involve less data to review, so products may be approved more quickly. On the other hand, with very few data points, the product must work well. Orphan products are just as safe and as effective as any other products approved by FDA for marketing. They are subjected to the same review and approval criteria as nonorphan drugs. Although many patients with rare disease may be willing to accept greater risks to receive treatment for a life-threatening illness, FDA does not consider such risk appropriate except under extreme circumstances.

Randomized, placebo-control-designed trials provide the best study result with the least number of patients, however, this trial design may not always be an option for orphan products. Due to the nature of the rare disease, researchers may determine that open protocol, open label, historical control, crossover trials, or withdrawal design trials, or surrogate endpoints are the most appropriate to their investigations.

At the time Orphan Drug Act was passed, investigators thought using an open protocol was the only way they could approach rare disease treatment. It was felt that populations were too small to achieve market approval; the primary objective was to provide treat-

ment to patients. Open protocols were used in the investigation of such products as cysteamine for nephropathic cystinosis and sodium phenylbutyrate for urea cycle disorders. The term "study" may have been used somewhat euphemistically. All eligible patients were given the drugs. Information was gathered; sometimes it actually was data. Today, cysteamine and phenylbutyrate are approved orphan products. But the approval process for them was very, very difficult, and involved determining from all the evidence what was data and what was anecdotal. Open protocols may actually obscure important information, and hinder FDA market approval of a product. In certain situations, however, so many patients are already on the drug that it is very difficult to conduct any other type of study.

Open label trials, on the other hand, can be controlled. Ganciclovir intravitreal implants were used in open label trials of cytomegalovirus (CMV) retinitis in AIDS patients. Implant treatment results were compared to standard treatment. While difficulties may occur in evaluating the efficacy of a product, open label trials can and do provide information regarding the safety of the drug.

Patients with rare life-threatening illness frequently urge approval of treatment for their disease based on historical controls; they feel it is unethical to withhold a possible cure from patients with greatly limited life expectancy. They assume that the product is effective, and frequently insist that a placebo-controlled trial is out of the question. They sometimes forget that the purpose of the trial is to show efficacy.

Since no placebo control is used in historical controlled trials, patients are easier to recruit, however, interpreting the results of such studies may sometimes be extraordinarily difficult. Conducting a trial using historical controls may actually take longer, because endpoints must be controlled against what is historically known about the effectiveness of the product. In order to conduct a trial using historical control, the disease must be well differentiated, with steady and rapid progress, and be free of additional interventions during the study period.

Enrollment is also fairly easy in crossover designed trials, since patients know that at some time they will receive the drug. This study design is well-suited to small groups of patients with a rapidly responding disease, since the same patients may serve both as treatment and control subjects. Difficulties occur when the "washout" period—at which patients return to baseline—is too long, or nonexistent.

In rare instances, FDA has looked at randomized withdrawal design trials for orphan disease studies. During randomized withdrawal trials, all available patients receive the drug. In this trial design, the drug is initially assigned in open fashion to test toward a desired endpoint. Those patients who respond at the end of a period of treatment are randomly assigned to either continued treatment or to placebo, and the two patient groups are compared. This trial design likewise cannot be used in testing drugs with a long half-life, and is undesirable for studying serious or life-threatening disease.

Surrogate endpoints must sometimes be used in rare disease studies, but results are really only valid when probability is linked to clinical outcomes. In orphan grant studies using Lorenzo's oil for Adrenoleukodystrophy (ALD), reduction of serum long-chain fatty acids seemed to be an appropriate surrogate endpoint, but unfortunately it was determined not to be very closely associated with reduction in disease progress. In a study of beta interferon for multiple sclerosis, the number of plaques observed through magnetic resonance imaging was the surrogate endpoint. The number of plaques was lower in patients receiving beta interferon.

The Orphan Products Grant Program, administered by the Office of Orphan Products Development (OPD), provides a valuable perspective on clinical trial design in rare diseases. Orphan product grants offer a unique opportunity to researchers to study rare diseases and develop products to treat them. FDA funding provides support to develop treatment for diseases affecting very small populations. Investigation into treatment for rare diseases provides benefit to patients'

quality of life beyond the actual study. Many positive results originate from the involvement between patients and the doctors undertaking rare disease studies. Through the grants program, FDA is able to attract investigators and allow them to develop skill and experience that can only be acquired by studying these rare disorders. A total of 22 products have received FDA market approval as a result of orphan grant studies.

The design of a clinical trial for a product being reviewed by FDA for market approval is determined, and approved, by the individual FDA review divisions. The OPD staff—working with expert review panels, as well as the FDA reviewing divisions—examine protocols and trial designs that are part of orphan grant applications. Requirements for clinical trials to determine the safety and effectiveness of all treatments are likewise established by the FDA review divisions: Center for Drug Evaluation and Review, Center for Biologic Evaluation and Review , or, in the case of devices, the Center for Devices and Radiological Health. Staff in review divisions provide constructive feedback and protocol assistance to researchers, and may negotiate with investigators to determine study endpoints prior to Phase III trials. Then, along with ad hoc reviewers, OPD staff carefully analyze each proposed trial design.

The concentration of a minute population of patients with a rare disorder that takes place during a study allows physicians to observe greater numbers of patients with the disease than might otherwise occur. Thus, they are able to elucidate factors that may contribute to the disease and influence the effect of the drug being studied. Even if a study does not lead to FDA approval, information published in peer-reviewed journals greatly assists other physicians treating patients with this disease.

Very small populations of geographically isolated patients often require multicenter studies. The investigation of botulism immunoglobulin (BIG), funded by the orphan products grant program, involved 59 study sites. This study, to compare the effectiveness of BIG in reducing morbidity in infantile botulism to that of standard supportive therapy and placebo, included 120 patients. The results of this double-blinded trial were recently unmasked and found to be significantly positive.

Orphan product investigations must sometimes be conducted at foreign sites, due to the rarity of the disease in the United States: A pertussis immune globulin is being studied in several foreign locations where vaccination requirements are different than in the United States, and occurrence of the disease is more frequent.

Conducting studies at multiple sites requires coordinating institutional review board (IRB) approvals from each. Procedures must be consistent, and interrater variability must be overcome. When study sites are located outside the United States, the researcher must be assured that standard care and procedures are followed. Grants that include large numbers of foreign patients require State Department approval.

With the stimulation of the Orphan Drug Act, philosophy has shifted. Manufacturers and sponsors are more familiar with developing drugs with limited commercial markets; drug companies have become interested in producing treatment for orphan diseases, and the emphasis is now on clinical trials to provide data to the FDA to obtain approval.

The Orphan Drug Act has been tremendously successful, and has helped many patients. FDA's next goal is to move ahead in cooperation with its European, Japanese, and Australian counterparts to benefit even more of the world's patients with rare diseases.