Orphan Indications and Clinical Trials: Why Rare Diseases Warrant Special Treatment

By Dr. Stephan de la Motte, Chief Medical Advisor, SynteractHCR

To begin a discussion about orphan indications and why clinical trials are special for the development of drugs to treat these indications, one must first understand what rare diseases and orphan indications are. Rarity depends on the frequency of a disease in the general total population. The definition is arbitrary; authorities in different countries or regions use different cut-off values.

The Rare Disease Act of 2002 (HR 4013) and the US Orphan Drug Act defines a rare disease or condition as one that "(A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug." Statistically speaking, with a population of about 300 million, that means roughly .07% of the US population or less than one in 1,500.

The European Commission on Public Health, on the other hand, defines rare diseases as "life-threatening or chronically-debilitating diseases which are of such low prevalence that special combined efforts are needed to address them." Generally speaking, low prevalence is taken as an incidence of less than one per 2,000 in the European Union, calculated as about .05% of the overall population.

An "orphan" disease is a disease that is "forgotten" by treatment, a disease for which there is no definitive, convincing treatment. Orphan is used mainly in the context of an indication, with emphasis on "intervention" or its absence. There may be measures available to attenuate the symptoms or risks for complications, but there is nothing to change or prolong the natural course of the disease or to eliminate the damage caused by the disease.

A disease can be rare, but not orphan, if there is an effective treatment available. A rare disease, if harmless and with good self-healing prognosis, is not an objective for industrial drug/treatment development at all. In a rare disease, the costs for development of a new therapy are seen in relation to a very small number of individual patients. The price per prescription may become astronomical.

A frequent disease can be orphan, if there is no treatment.

The overlapping of these two terms occurs when the cost of normal drug development is in conflict with the frequency (market size). An "orphan drug" then is one for a rare disease for which there are no adequate drugs available, according to the US Orphan Drug Act definition.

Recently, there has been a rapidly-growing demand for trials in orphan indications because of orphan drugs legislation in both the US and the EU that have established incentives to increase research in these areas. Public incentives and facilitations make drug development for rare diseases more financially viable.

AT SYNTERACTHCR, WE WORK FREQUENTLY ON STUDIES THAT HAVE NEVER BEEN DONE BEFORE.

- 94 clinical trials in rare diseases
- 30+ different rare diagnoses
- Strong feasibility group works globally
- Conducts an integrated assessment of project feasibility

WE HAVE WORKED ON:

- blood/lymphatic system diseases
- infectious/parasitic diseases
- neurological, metabolic and immunological/inflammatory diseases
- and other rare and orphan diseases

Unique characteristics of clinical trials in rare diseases

Typically, our rare diseases are chronic, because in an acute disease, the medicine is given only for a very short time (meaning: very few products sold, exceptionally small market). Rare, chronic-deteriorating disease creates damages with secondary conditions and symptoms, which need additional treatments. Clinical trials for these chronic, rare diseases have **some unique characteristics**, including:

Complex case report forms are required to deal with both the primary and secondary conditions.

High number of study sites are needed because patients are scattered across wide regions. Even a big medical center in a high density area may have only a few patients.

Proactive recruitment efforts are required because the incidence of newly-diagnosed patients is extremely low; therefore, a study must rely on patients who are already known. As an example, the emergency treatment of attacks of a disease like hereditary angio-edema: A pool of patients is contacted, informed and regularly reminded of the study, increasing the likelihood that patients will contact the study site in case of an attack. A study site that is just passively waiting until a patient comes along may not recruit a single patient.

There are **scientific limitations** as well. Due to rarity, a statistically-powerful study with a high sample size may not be feasible. Statistical significance may be limited. Two studies may not be feasible either, because the existing patients may hardly be sufficient to fill one study.

True surrogate variables may not exist; accepted biomarkers may be available, but not truly validated as prognostic factors or disease course indicators. Therefore, analysis of individual patients and comparison with historical data may be acceptable. Luckily, Internet access has made doing this research easier than before.

In working with regulatory authorities, the path to drug development and registration is highly individualized. Each situation is assessed on a case-by-case basis and deviations from a scientific "gold standard" may be acceptable. This is why clinical drug development in these cases should always be conducted based on extensive, thorough, pre-IND (US) or Scientific Advice (EU) from authorities.

Unique characteristics of clinical trials with orphan treatments

Use of placebo can be an issue. In a non-orphan indication, a working "rescue" treatment can be given or the investigational product is given as an add-on to a somewhat working baseline treatment. But when there is no treatment available at all, the disease will inevitably create damage, and the new drug is the only hope (even if only theoretically), how can you justify not giving it? Study designs where each patient gets the active drug at least once (cross-over) or open-label extensions for everyone in the study are usually a big help. The disadvantage is that this creates difficulties for biostatistical analysis and for correct interpretation of results. But it may create additional safety data.

Motivation of patients can be extreme. Patients are aware that they have something rare so they are pro-actively looking for information on how to deal with it. Formal and informal interest groups are often formed. Once they learn of a study, they are anxious to get into it. Patients are willing to try something new, provided it is sound and serious. They are also willing to take on the burden of longer travels to a study site or other constraints imposed by the study.

Patients are **responsive to advertisement.** The challenge is to place the advertisement so that they can see it. Often, the advertisement is seen by a relative or by a friend who tells the patient.

Compliant, stabilized patients may have "learned to live with it." When patients are stabilized, they may not visit a doctor regularly. Patients know their condition, and they know that the doctor can't do anything about it. As long as there is nothing acute, why should they see their doctor? The study can be done only if the investigator or a nurse is searching through the patient database and proactively calling patients to inform them about the study. Even if the patient's current condition is not fit for the study, this may change in the near future. Therefore, proactive recruitment is critical or the trial is bound to fail.

Ways to conduct proactive recruitment for rare and orphan studies

We recommend a proactive, visible, recruitment strategy.

- Conduct database searches at study sites to see if there are patients known to the site who might fit.
- Contact special interest groups, self-help groups and Internet forums to inform them of the study; they will spread the word among themselves.
- Make presentations at medical congresses. Some doctors may tell their patients about the study or may even want to participate in the study as an investigator.
- Create a study website, using search engine optimization, so that when prospective patients are searching for information about their illness, your site will come up.
- Advertise in suitable media. Even if the patients don't see it, a friend or relative may.
- Contact universities with medical schools as they may have patients with early diagnosis coming to them to find out what treatments are available.
- In cases of children's diseases, make sure that pediatricians are aware of the study. Children see their pediatricians regularly in the early years and they may be able to refer patients to the study.
- Use social media. The viral nature of this medium may be what is needed to spread the information far and wide.
- Make it easy for patients to participate by taking the trial to them if possible. Visiting nurses who can come to the patient's home to handle an infusion, for example, would help to boost recruitment of patients who may be too sick to travel.

Mental agility required by investigators and trial clinicians

Biotechs and CROs that work in these rare diseases and orphan indications use resources that are typically highly educated and have the mental flexibility to use creative thought processes. Not only do they conduct extensive research on diseases that show a similar pathophysiology and response, but they also must be able to assess each situation on a case-by-case basis. The ability to deal with all kinds of diverse illnesses is perhaps more important than experience in the particular indication. After all, when a disease is rare, how much experience could a team have in it anyway? Look for a team that knows how to think outside the box and has had a diverse range of experience in multiple indications.

Further information can be found in Milestone Legislations:

- 1983: US Orphan Drug Act
- 2000: EU Parliament and Council Regulation EC 141/2000
- 2000: EU Commission regulation 847/2000
- 2002: US Rare Diseases Act

About SynteractHCR www.SynteractHCR.com

SynteractHCR is a full-service contract research organization with a successful two-decade track record supporting biotechnology, medical device and pharmaceutical companies in all phases of clinical development. With its "Shared Work – Shared Vision" philosophy SynteractHCR provides customized Phase I through IV services collaboratively and cost effectively to ensure on-time delivery of quality data so clients get to decision points faster.

About the Author

Dr. Stephan de la Motte, Chief Medical Advisor

Dr. Stephan de la Motte provides medical and scientific input as the Chief Medical Advisor at SynteractHCR. Dr. de la Motte has been the Principal Investigator for numerous clinical studies involving indications in Phase I, II, and III studies. Dr. de la Motte's therapeutic experience includes general medicine, clinical pharmacology, pharmacology and toxicology, anesthesia, internal medicine, psychiatry, neurosurgery, neurophysiology, and military medicine. Licensed since 1985, Dr. de la Motte's scientific and medical background and clinical trial experience provide SynteractHCR customers an expert resource to support their drug development needs.