

Global Rare Disease Drug Development: *Understanding and mitigating its complexities*

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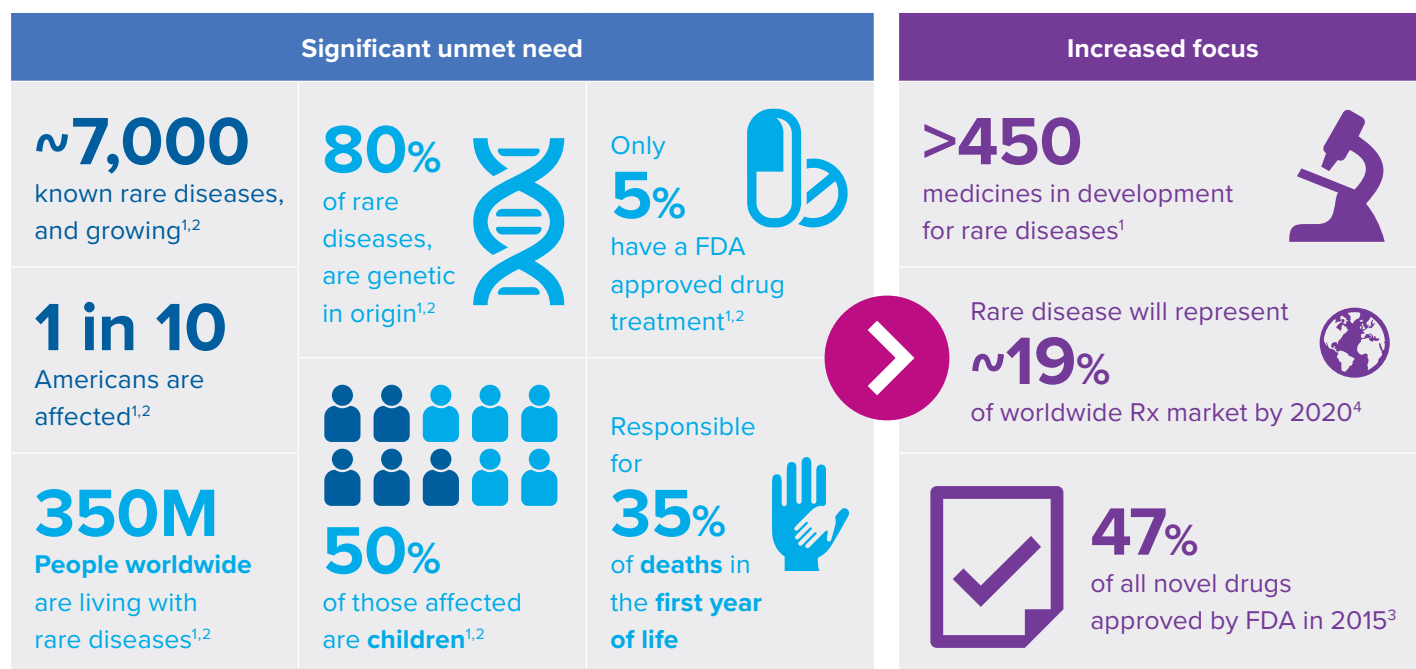
TABLE OF CONTENTS

Introduction	3
Definitions and complexities of rare disease drug development	4
Patient-centric study planning	8
Developing an efficient site strategy for faster patient recruitment	8
Importance of real-world evidence in rare disease research	13
Conclusion	14
References	15
About the authors	16

Introduction

There are at least 7,000 known rare diseases, affecting 1 in 10 Americans and a total of 350 million people worldwide, and causing 35% of deaths in the first year of life (*Figure 1*).^{1,2} Only 5% of rare diseases have a Food and Drug Administration (FDA)-approved therapy, and more than 450 rare disease therapies are currently in development. It has been estimated that rare diseases will account for around 19% of the worldwide prescription drug market by 2020.³ This insight brief examines the varied definitions and regulatory pathways for rare disease therapies. The authors describe QuintilesIMS's proven patient-centric approaches to study planning, innovative ways to accelerate patient recruitment through an efficient site strategy, and the importance of real-world evidence.

Figure 1: Rare diseases: A huge impact



QuintilesIMS is committed to accelerating development efforts to bring new treatments to patients.

Sources: ¹2005-2015: A Decade of Innovation in Rare Diseases, PhRMA. ²<http://globalgenes.org/rarefacts>. ³<http://rarediseases.org/fda-approves-21-orphan-drugs-for-rare-diseases-in-2015/>. ⁴2014 Orphan Drug Report, Evaluate Pharma.

Definitions and complexities of rare disease drug development

There is no globally harmonized definition of a rare disease. For example, the FDA’s Orphan Drug Designation program⁴ defines rare diseases as those affecting fewer than 200,000 people in the U.S., or affecting more than 200,000 persons.⁵ A rare disease is also defined as affecting 4 per 10,000 people in the U.S. or 5 per 10,000 people in the EU.⁶ An ultra-rare disease affects at least 1 in 50,000 people, but may affect as few as 1 in 1 million.⁷ *Figure 2* provides definitions of rare diseases from various geographies.

Figure 2: Rare disease populations defined by regulatory agencies

Jurisdiction	Organization	Definitions adopted
U.S.	FDA	(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
EU	EMA	Rare diseases are defined as life-threatening or chronically debilitating conditions that affect no more than 5 in 10,000 people in the EU

Country	Affect fewer than	Prevalence figures
U.S.	200,000	<6.4 in 10,000
EU	250,000	<5.0 in 10,000
Japan	50,000	<4.0 in 10,000
Australia	2,000	<1.2 in 10,000
Canada	—	<5.0 in 10,000
Mexico	—	<5.0 in 10,000
Argentina	—	<5.0 in 10,000

DEFINITIONS

- Orphan drugs are for rare diseases.
- “Orphan disease” is a synonym for “rare disease”.
- There is a global trend toward a harmonized definition for “rare disease”.
- Currently a disease can be rare in 1 geographic region and not in another.
- Definitions are generally rigorous with respect to prevalence.
- Most definitions of “rare” use a prevalence of 4 per 10,000 people.
- “Ultra-rare” diseases affect 1 in 50,000 people; many affect as few as 1 in 1 million.⁸
- Other criteria in addition to prevalence need to be considered and defined.

It is important for biopharma sponsors to choose a partner with the expertise to select the most applicable designations and approval mechanisms for the particular therapeutic and rare disease: not every strategy will be applicable to every product.

Based on QuintilesIMS’s experience with 245 rare disease studies conducted in 96 countries since 2011, there has been a clear change for the better in the regulatory landscape for rare and orphan disease therapeutics in the past few years. Depending on the region, several designations and approval methods can be applied. It is important for biopharma sponsors to choose a partner with the expertise to select the most applicable designations and approval mechanisms for the particular therapeutic and rare disease: not every strategy will be applicable to every product.

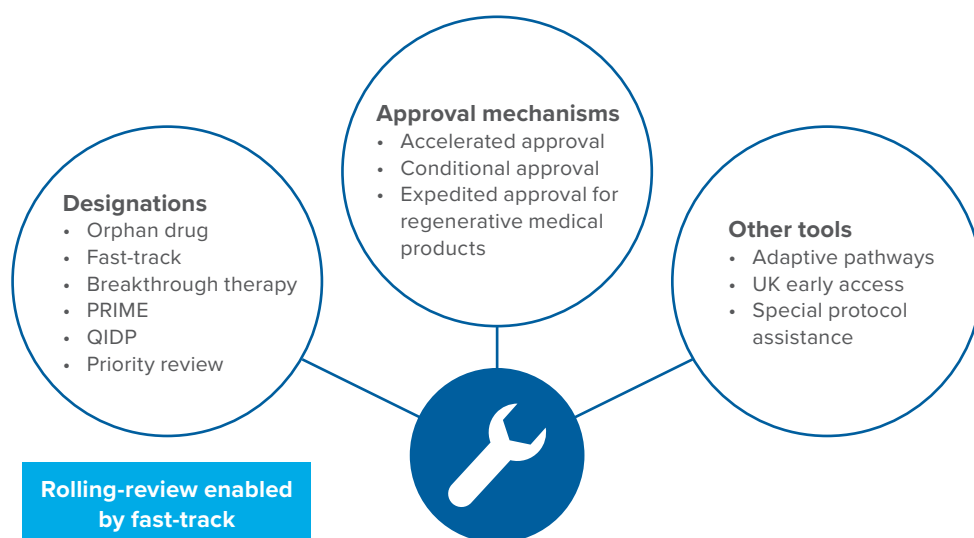
Orphan designations do not directly translate into a reduced regulatory requirement. Regulators may be more amenable to non-standard approaches, but this is not guaranteed by the orphan designation. Fast track designation facilitates frequent interactions with FDA, providing for a rolling review where the FDA reviews new information as it comes in. A product can have both fast track and orphan designation but it is fast track that allows for rolling review.

A well-informed regulatory strategist – such as those employed by QuintilesIMS – has access to a regulatory toolbox for rare diseases including multiple elements (*Figure 3*):

- **Designations:** These include orphan drug, fast-track, breakthrough therapy, priority review FDA qualified infectious disease product (QIDP) from the FDA, or Priority Medicines (PRIME) designation from the European Medicines Agency (EMA).
- **Approval mechanisms:** Examples include accelerated approval (where the drug can be approved on basis of a surrogate marker), conditional approval or expedited approval for regenerative medical products (Japan).
- **Other tools** that may be helpful include adaptive pathways, early access (UK), and special protocol assistance meetings.

Figure 3: A regulatory toolbox for rare diseases

More than one, but not all tools will apply for a particular product.



Due to new understanding of disease physiology and pathways, in addition to novel molecules, new treatments may also repurpose products already marketed in another indication. In such cases, a large volume of data may be available from a different patient population.

Challenges for clinical trial design

Several overarching challenges should be discussed and mitigations agreed to before a trial is designed. In many rare and ultra-rare conditions, the natural history is unknown and registries will be required to determine the clinical course and assist in future development of outcome measures. Such natural history studies enable researchers to learn about the disease and suitable outcome measures, generate hypotheses, support study logistics planning, help build a network of investigators and patients, and potentially serve as a control group.

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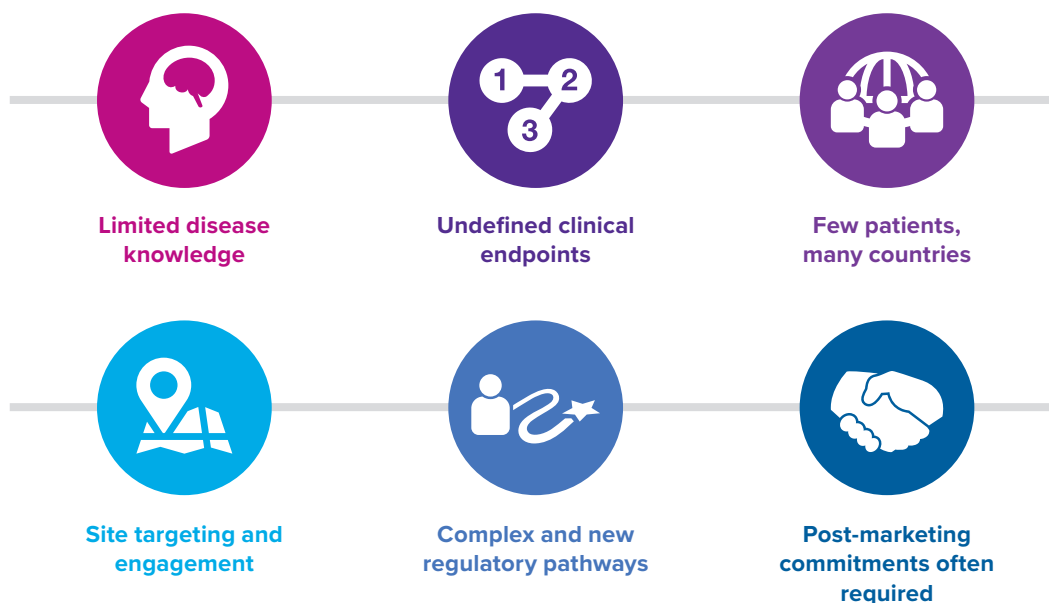
Innovative trial designs⁹ are needed to collect a large volume of information on primary, secondary and exploratory endpoints from a small group of patients. Modeling and trial simulation also have a role in determining the optimal randomized trial design, with options including:

- **Randomized, parallel group**, with active arms vs. a placebo arm
- **Crossover factorial**, where 2 or more treatments are compared by randomly assigning participants to receive study therapy in different sequences
- **Randomized withdrawal**, where patients who respond positively are randomized to placebo or continued active treatment
- **Early-escape**, which minimizes a patient's exposure to placebo by removing them from the study if they do not respond.

Rare diseases present several challenges in developing new treatments:

- **Limited knowledge** about the underlying disease mechanisms and clinical progression; there may be many subtypes with different clinical manifestations and progression.
- **Undefined clinical endpoints**, due to a lack of adequate preclinical models and knowledge of potential biomarkers; outcome measures may not exist and need to be developed upfront.
- **Few patients, dispersed across many countries**, with patients often not located near sites, resulting in frequent, long distance travel and lodging.
- **Site targeting and engagement challenges**, since there are often few, if any, investigators experienced in the indication who have experience in good clinical practice (GCP) for research. High costs and large number of zero-enrolling sites can be an issue; there is a need to consider different models for site targeting and site strategy.
- **Complex and new regulatory pathways**, with varying global incentives and pathways to approval that can be difficult to navigate.
- **Post-marketing commitments** often required, due to smaller sample sizes and accelerated approval pathways; post-marketing registries and benefit-risk management are often mandated.

Figure 4: What makes rare disease development so different?



Patient-centric study planning

QuintilesIMS's broad experience in rare diseases confirms that patient-centricity is particularly important in this type of clinical research. Many questions need to be answered during the planning process, such as:

- Is the rare disease an inherited condition, and if so, what is the mode of inheritance?
- Are there regional “pockets” of affected patients? Are cultural issues involved?
- How are patients diagnosed and when? Prenatal screening? Newborn screening? Does the child present in first few days of life or after several months?
- Is there a known standard of care (SOC)?
- Who are the primary treating physicians and where do they practice?
- Are there Key Opinion Leaders (KOLs) or treatment centers?
- Do site networks exist?
- Is there a patient advocacy presence and how mature or sophisticated is it?
- What is the patient pathway to care?
- What relevant literature is available?

In designing a study, QuintilesIMS can offer its partners expertise in balancing regulatory requirements with practicality, obtaining patient input early in the process via groups such as patient and/or family advisory boards. Biomarkers should be used for pre-identification if possible. Endpoints should be utilized to determine the visit schedule, keeping visits to a minimum, bundling in-patient and/or study-site procedures when possible, and using home-health vendors to perform visits off-site where possible. Technology can be helpful, such as mobile data capture, e-diaries, telephone or video-streamed visits, and wearables. Assistance should also be provided with logistics for any necessary travel, including cross-border transportation planning.

Developing an efficient site strategy for faster patient recruitment

Rare disease trials are complex and require extensive support from the study team. We believe the most critical aspects of structuring an appropriate team are finding staff passionate about rare diseases and building strong relationships with sponsors, patients and caregivers; and finding project managers who understand the increased level of site support required for a relatively small sample size.

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EXPERIENCE NEEDED FOR RARE DISEASE TRIALS

Specialized project teams with rare disease and therapeutic expertise are vital for the success of rare disease trials. Key factors that drive QuintilesIMS project team successes include:

- Strong relationships cultivated with sponsors, patients and caregivers
- Project leaders skilled in rare diseases
- Rare disease delivery units, aligned therapeutically
- Specialized roles to drive clinical delivery and vendor logistics
- Flexible resourcing matched to study needs
- Special attention and oversight via rare disease operations heads
- Laser focus on recruitment
- Heightened on- and off-site support by seasoned CRAs
- Additional clinical support as needed – medical science liaison (MSL)-like resources to help identify patients in the community
- Resources and oversight for new investigators
- Site training
- Ability to up-skill research naïve sites

Develop a rare disease study strategy

Important elements of the rare disease studies include both strategic and operational considerations unique to rare diseases. QuintilesIMS has expertise in key strategic elements such as relationships with patient advocacy groups; identification of indication-specific KOLs, site networks and treatment centers; understanding the patient pathway; facilitating patient and caregiver ability to travel; understanding the method and complexity of drug preparation and administration; and developing a schedule of visits that makes use of home health services; and allowing the maximum time from patient identification to first dosing.

From the operational perspective, tailored approaches are needed for site identification; personalized patient support services; centralized monitoring technology and analytics for increased data quality; drug supply and lab kit logistics; patient recruitment, engagement and retention; and team resourcing models aligned with the scale and complexity of rare disease studies.

When faced with enrollment challenges in rare disease trials, opening more sites may not be the most efficient strategy, due to low numbers of patients who may be located in diverse geographic regions. QuintilesIMS has successfully applied a “hub and spoke” concept to deliver the most challenging of rare/ultra-rare disease studies (*Figure 5*) and is partnering with leading global institutions to expand this capability for a broader range of trials. QuintilesIMS’s model addresses the following:

- Using specialty vendors to provide travel concierge services and home health to reduce the patient burden involved in trial participation.
- Maximizing data quality by using analytics and centralized data monitoring.
- Streamlining the supply of investigational product and lab kits to reduce storage and logistical burdens for sites.
- Recognizing the clinical trial will often be the only option for treating a rare disease patient. As a result, tailored patient recruitment strategies and a heightened focus on engagement and retention throughout the trial are necessary.

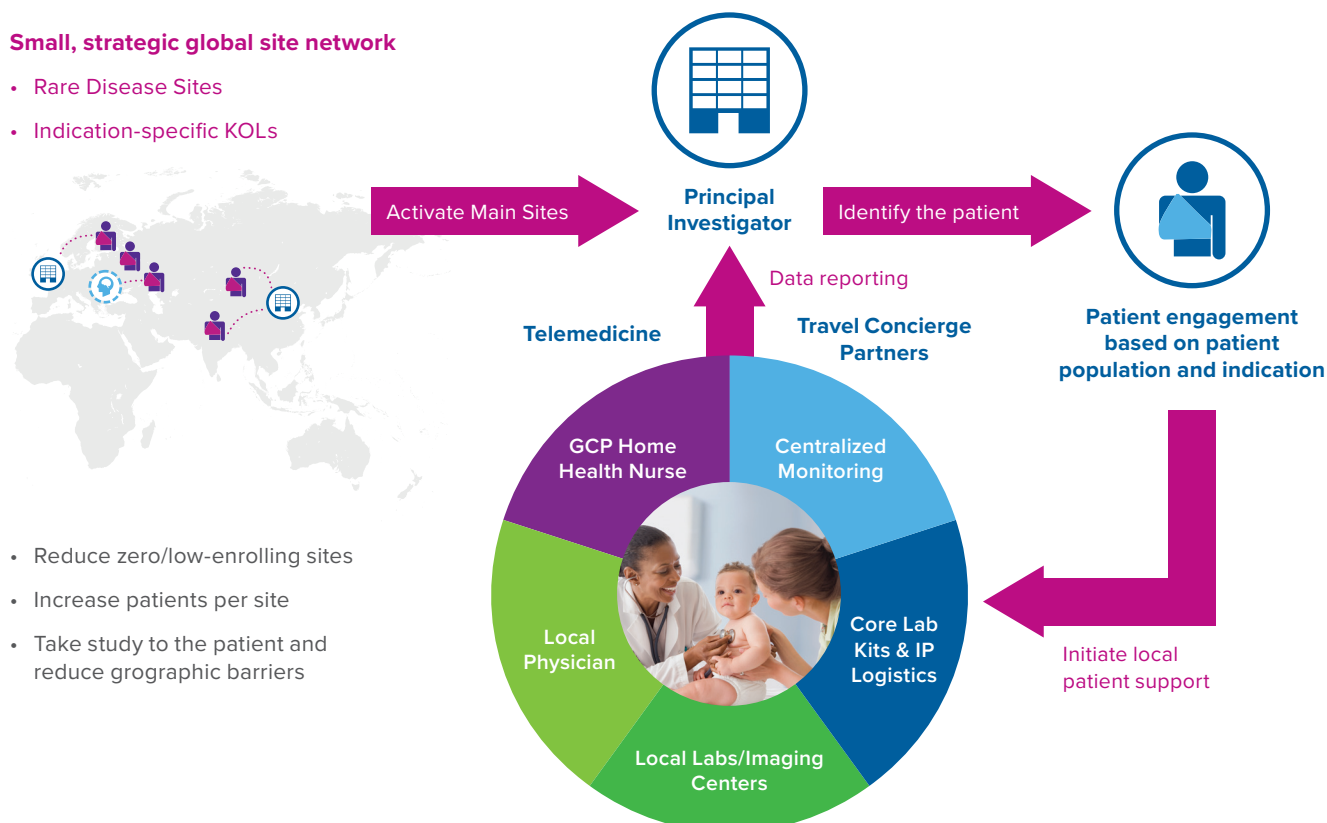
The goal of QuintilesIMS’s “hub and spoke” model is to reduce the number of zero/low-enrolling sites, helping to minimize costs; increase the number of patients per site so more dedicated resources can be assigned to the trial; and to take the study to the patient, helping reduce geographic barriers to trial participation (*page 11*).

Figure 5: Rare disease site delivery model

Hub and spoke concept to deliver the most challenging of rare/ultra-rare disease studies

Small, strategic global site network

- Rare Disease Sites
- Indication-specific KOLs



SERVICES USED BY QUINTILESIMS TO ENHANCE THE PATIENT AND FAMILY EXPERIENCE

Travel logistics

Objective: Reduce travel burden for patients, caregivers and families through “white glove” end-to-end services

Services:

- Ground and air transportation
- Hotel accommodations
- Travel reimbursements
- Cross-border logistics, when required
- Door-to-door patient ambassador, when required
- Medical accompaniment, when required

Home health

Objective: Bring more of the study directly to the patient to reduce travel burden

Services:

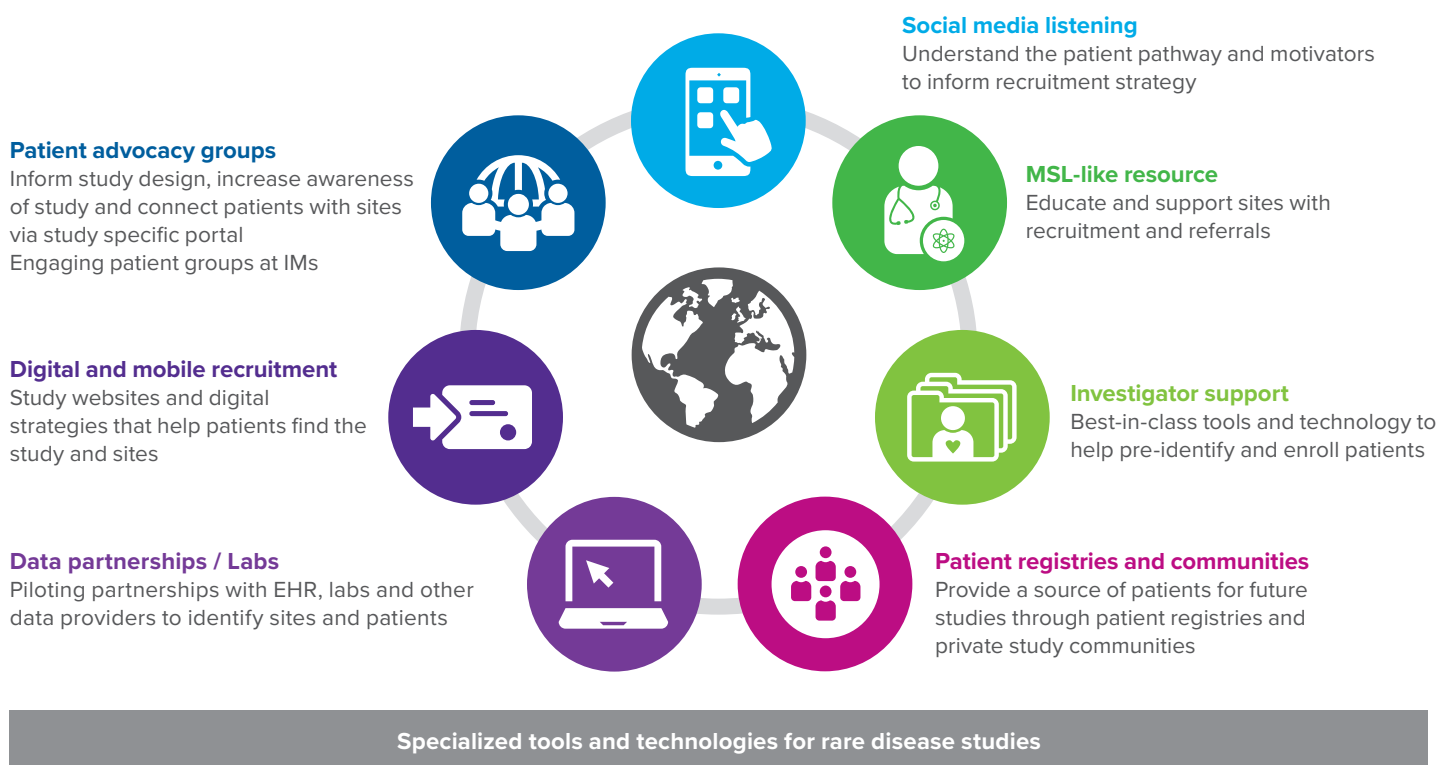
- Study drug administration (IV, injection, topical)
- Blood draws (safety labs, PK, genomics)
- Other biologic sampling
- Clinical assessments (vital signs, ECGs, concomitant medications, adverse events)
- Patient training and education
- Study compliance checks
- Patient questionnaires

Data: Captured electronically and reviewed by study site

Multi-faceted approaches tailored to the specific indication, patient population, and protocol can help engage hard-to-find patients across geographies (*Figure 6*). As an example, social media listening can be leveraged to identify where patients are gathering online, understand the current patient treatment pathway, and understand the motivators to inform the recruitment and engagement strategy. When they exist, QuintilesIMS has found that an early partnership with patient advocacy groups can inform the core strategy and protocol design, increase awareness of ongoing studies, and even match patients with clinical sites. MSLs can also be deployed to support sites in managing their referral networks when appropriate.

Figure 6: Patient engagement strategies

Use multi-faceted approaches to engage hard-to-find patients anywhere in the world.



Risk-based monitoring

Even though samples sizes may be low, QuintilesIMS's risk-based monitoring (RBM) approach may offer advantages, providing an added level of data quality and support in trials where every data point matters. A combination of onsite and remote monitoring with centralized data surveillance is becoming recognized as the optimal approach for rare disease trials. Site and patient review and advanced analytics can be used to identify safety and other trends and outliers, allowing for near real time monitoring of data points through centralized data surveillance in addition to appropriate onsite review. However, sites still need a high level of support from CRAs.

POTENTIAL BENEFITS OF RBM

- 4x lower error rate in critical data in a head to head comparison of RBM to traditional 100% SDV from 2014 to 2015
- 45% reduction in the number of missing pages in RBM studies vs. traditional studies
- 28% improvement of aged queries in RBM studies vs. traditional studies in 2015 (queries > 10 days)

Just-in-time investigational product delivery

Drugs for rare disease trials are very expensive, driving the need to reduce wastage by early planning. Items to consider for just-in-time investigational product (IP) delivery to reduce overall site burden relating to storage, administration and destruction, include the need to: understand the patient pathway, differentiating between chronic and emergent rare diseases; take into account the duration of the screening period and any specific triggers; have up-to-date information on country importation limitations and local depots used; know the IP shelf life; carry out mock shipments to train sites on the IP process; and integrate key eligibility criteria into the system for triggering automatic supply.

Importance of real-world evidence in rare disease research

Patient registries are extremely important for rare disease drug development, as they may be the only way to determine the natural history of the condition. With experience developing and managing 18 rare diseases registries since 2011, QuintilesIMS has expertise in building and populating registries before commencing any clinical trials, helping inform trial design elements. The FDA does not require natural history studies be conducted but does say “a well-designed natural history study may help in designing an efficient drug development program.”¹⁰ In addition, the registry will allow a sponsor access to patients, physicians and advocacy groups, and build rapport with the broader patient population.

It is vital to begin the planning process for a registry early and define exactly what data points need to be collected. Additionally, the registry may be able to identify patients with particular characteristics. If the registry is developed early, it can facilitate collection of baseline data about clinical care which can then validate clinical trial endpoints, possibly eliminating the need for a placebo control. It can also provide insights into epidemiological research that might be needed post-authorization. There is often need to perform a post-authorization safety study, in which case, the registry can be used to generate evidence and data, especially if the drug was approved on the basis of use in very few patients. This type of situation usually occurs when the drug is approved via an adaptive or conditional pathway.

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CONSIDERATION IN SETTING UP A RARE DISEASE REGISTRY

- Set clear goals for the kinds of data you want to collect
- Start building the registry as soon as possible
- Determine the type of registry early:
 - **Prospective:** longitudinal natural history studies likely will generate the most useful information; need to use consistent medical terminology, and distinguish different phenotypes.
 - **Retrospective:** may be a little easier, and are usually collected from a clinical chart review; data collected may be incomplete and terminology inconsistent.

Conclusion

In conclusion, rare diseases have a huge impact on patients and their families that belies the “rare” terminology. QuintilesIMS has developed successful approaches to clinical trials in this area that are patient centric, minimizing the burden to patients and families of participation, and maximizing patient retention in a field where every data point counts. Data quality is also maximized using analytics and centralized data monitoring.

In terms of the regulatory landscape, a multi-pronged strategy must be tailored to each product, based on various designations (such as orphan drug, fast-track, breakthrough therapy or priority review); approval mechanisms (accelerated, conditional or expedited approval); and other tools such as adaptive pathways, early access, and special protocol assistance meetings.

The study design must balance regulatory needs while remaining practical, making early patient input essential. Multiple challenges must be addressed. For example, registries may be required to elucidate the clinical course of the disease, help develop outcome measures, generate hypotheses, support study logistics planning, and build a network of investigators and patients. They may also offer insights into epidemiological research that might be needed post-authorization. Based on QuintilesIMS’s extensive experience, suitable rare disease trial designs may include: randomized, parallel group, with active arms vs. a placebo arm; crossover factorial, where 2 or more treatments are compared by randomly assigning participants to receive study therapy in different sequences; randomized withdrawal, where patients who respond positively are randomized to placebo or continued active treatment; and early-escape, which minimizes a patient’s exposure to placebo by removing them from the study if they do not respond.

An efficient site strategy can accelerate patient recruitment. A proven approach is QuintilesIMS’s “hub and spoke” model, which works best in ultra-rare indications where there is no established treatment center, but where several KOLs treat most of the patients. The KOLs’ locations are used as hub sites, acting as centers for referrals and communicating closely with other physicians.

Taken together, all these elements can help sponsors understand and mitigate the complexities of rare disease research, accelerating the delivery of much-needed therapies to patients.

In developing tailored solutions to address the unique challenges of rare diseases, we draw upon extensive rare disease experience from across the organization, including:

- 245 rare disease studies since 2011 conducted in 96 countries
- >460 pediatric studies since 2010
- Centers of Excellence in Pediatrics and Rare Diseases to provide relevant insights to shape the development path
- Experience developing and managing 18 rare diseases registries since 2011

References

1. 2005-2015: A Decade of Innovation in Rare Diseases, PhRMA.
2. <http://globalgenes.org/rarefacts>
3. 2014 Orphan Drug Report, Evaluate Pharma.
4. <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm>
5. www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm
6. http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000034.jsp
7. <http://www.nice.org.uk/Media/Default/Get-involved/Citizens-Council/Reports/CCReport04UltraOrphanDrugs.pdf>
8. <http://www.nice.org.uk/Media/Default/Get-involved/Citizens-Council/Reports/CCReport04UltraOrphanDrugs.pdf>
9. Adapted from Nony, et al; A methodological framework for drug development in rare diseases. Orphanet Journal of Rare Diseases 2014, 9:164
10. Rare Diseases: Common Issues in Drug Development; Guidance for Industry, US Department of HHS, FDA, Aug 2015

About the authors



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Dr. Jackson has provided expertise and guidance for pediatric clinical trials in a variety of therapy areas, and has a broad understanding of regulatory requirements for pediatric research and a special expertise in global pediatric clinical trial strategy and clinical development planning. After graduating from Des Moines University College of Osteopathic Medicine, Dr. Jackson completed internships and residencies in Pediatrics and completed a fellowship in Pediatric Infectious Diseases at Duke University Medical Center and a medical fellowship in the Department of Virology, HIV Pathogenesis Lab at Glaxo Wellcome, Inc. She maintains an adjunct faculty appointment at Duke University in Durham, NC.



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Sheetal Telang has over 11 years' global clinical research experience within the pharmaceutical and CRO industry. In her current role, she applies rare disease operational and therapeutic knowledge to create strategies for our rare disease portfolio and provides strategic oversight to rare disease programs for emerging biopharmaceutical customers, in addition to her contributions to large partnership accounts. Telang has held several positions within clinical and project management, providing oversight to a global team of regional Clinical Project Managers, Clinical Monitors and Clinical Trial Assistants and various functions including Biostatistics, Data Management and Medical Writing to ensure consistency across global programs across 28 countries spanning five regions across all study phases.