Rare Disease Clinical Research: Collaboration the Key to Success

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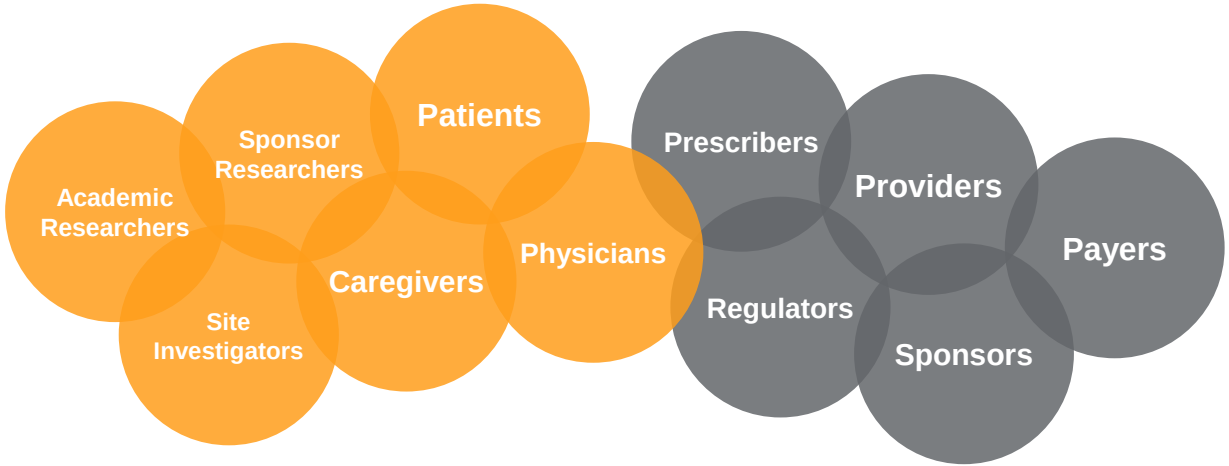
- Full time employee of Syneos Health

Collaborative approach to address the challenges of rare diseases clinical research

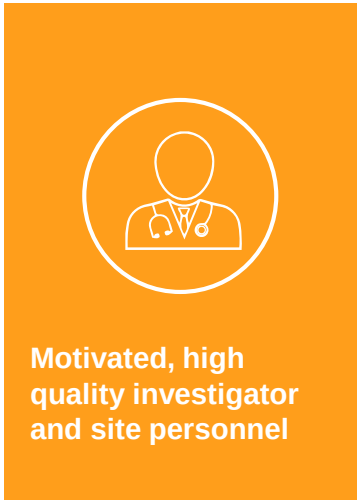
Rare Diseases Clinical Research

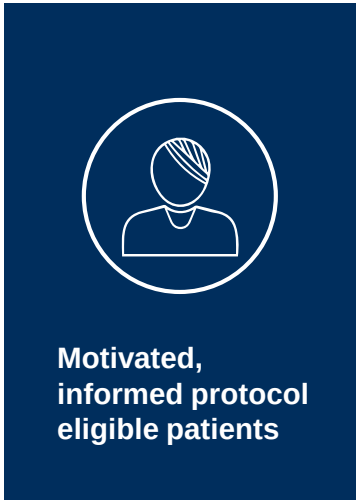
High complexity – Multiple stakeholders



Focusing basic, clinical, operational, and regulatory science towards the acceleration of clinical research and availability of meaningful therapies for patients with Rare Diseases

Pillars of clinical research – keys to success





What's different in Rare Disease Clinical Research

Strong Rationale for MOA/Target

Impassioned, dedicated investigators and site staff

Valid scientific hypothesis and ability to run a trial

Operationally valid and feasible protocol

Motivated, high quality investigator and site personnel

Motivated, informed protocol eligible patients

Extremely motivated and passionate, patients and families

Protocol complexity driven by:
- Scarcity of patients
- Complexity of IP, administration/handling procedures
- Novelty of and unfamiliarity with assessments

Clinical Research Naïve Sites:
- Inexperience with clinical trials and associated procedures and requirements
- Additional equipment/processes for IP preparation

Rare patients in complex environments:
- Parents/pediatric, advocacy groups
- Complexity of IP difficult to understand
- Geographic distribution

Driving Connectivity in Clinical Research

Convergence of patients/advocacy – specialized sites – scientific experts
→ Accelerated medicine development and patient access to therapy

Operational Solutions in Rare Diseases Clinical Research

Scarce and dispersed population requires specific operational strategy

- Creative leverage of multiple sources to identify the right patients
- Site selection driven by patient geographic distribution and strategy
- Collaboration with patients associations and specialized networks
- Use available and current registries
- Collaboration with genetic or specialty laboratories
- Engagement of centers of excellence for specific rare diseases

Study start-up considerations

- Site selection strategy, timings and regulatory concerns
- Appropriate capabilities, training, regulatory/safety approvals for IP in place
- Accurate sample size assumptions and rationale
- Endpoint selection and clinical assessments in new indications
- Appropriate Informed consent/assent in pediatric population
- National Coordinator responsibilities

Investigational Site Issues

- Clinical trial Inexperienced sites might require training plan for GCP compliance
- Clinical trial Inexperienced sites might require additional equipment/facilities to deal with complex IP
- Provide operational support when necessary
- High intensity data review plan to ensure data quality and adequate follow-up of early withdrawals

Focus on the individual patient

- Take a patient centered approach
  - Early engagement in clinical development cycle
  - Collaborate with advocacy groups
    - Ensure patient needs and concerns captured in the clinical protocols and development plans
    - Partner to raise awareness of clinical trials as access to medicine
  - Develop patient recruitment strategy as first intent
    - Include educational material on complex gene and cell therapy

- Partner with quality sites that know their patients, the protocol, and the Investigational Product
  - Select sites based on recruitment strategy
  - Enable sites to focus on patient experience
  - Provide training and education on specifics of handling advanced therapeutics
  - Provide operational and infrastructure support
  - Ensure quality despite complexity

Collaboration with advocacy groups

- Appoint a **Patient Advocacy Lead** who facilitates interactions between their advocacy group and the other stakeholders to drive a partnership model for delivery of the clinical program. Ensures advocacy group:
  - Protocol input, review, and finalization to ensure inclusion of patient considerations
  - Support for sites engagement and cooperation
  - Endorsement of multi-channel outreach (web-based platforms, email, messages and other communication mechanisms) to promote study awareness and participation
  - Facilitation of connecting potential patients with the selected investigational sites
  - Support for logistic management of patients to facilitate access to the study
  - Education for patients, parents and community about the specific rare disease manifestation, progression and quality of life with the rare disease as well as information about complex therapies

Overcoming recruitment and retention challenges

Focus on the patient experience

Enable sites to cater to each individual patient's needs

Patient Associations and Site Advocacy Groups	Genetic / Specialty Testing and Processing Laboratories	Medical and Clinical Experts	Informed Consent/Assent Training
Special issues with travel logistics – support patients and caregivers	Minimize burdensome site visits – Maximize home nurse support	Site support and training through for high intensity visits and management of IP	Disease and patient specific recruitment plan including education on complex therapies

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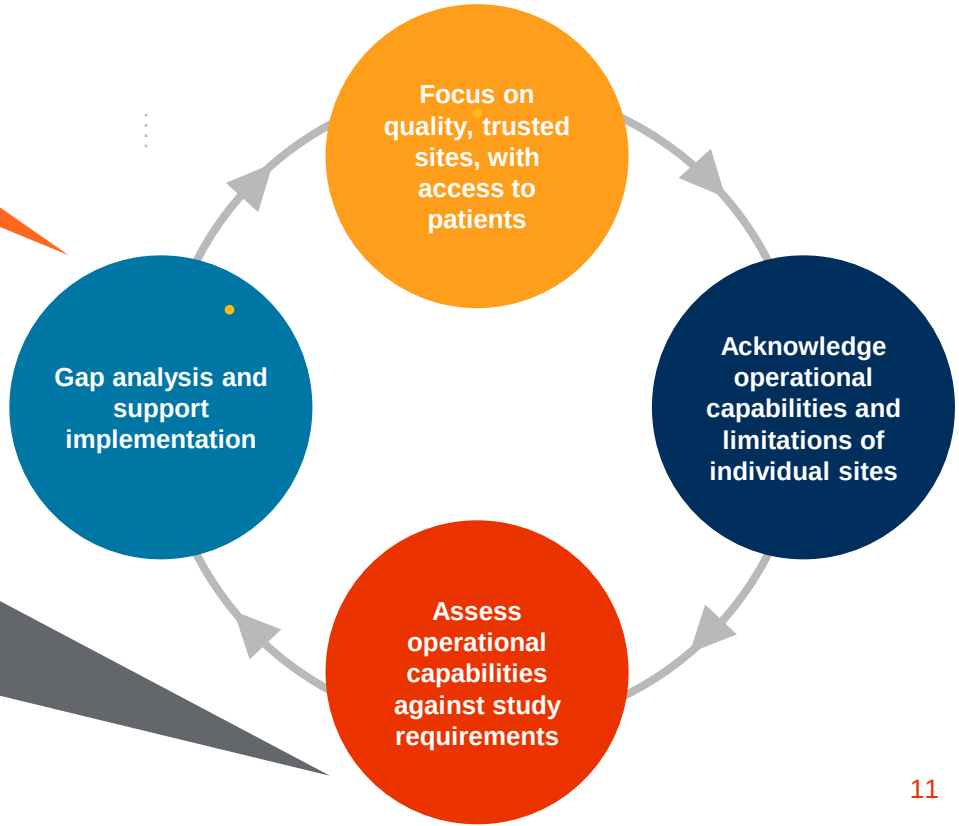
Partner with quality sites: Overcome operational barriers

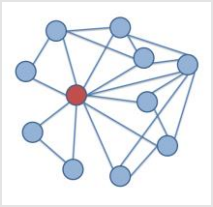
- Address within protocol

- Complexity of investigational product
  - Cell based therapy, gene editing
  - Storage and administration issues
- Complexity of laboratory assessments
  - Specialty labs and special handling
- Intensity of screening and visit days
  - May require staff augmentation
- Focus on recruitment AND retention
  - May require additional support (on site and in the field)



Examples of site collaboration

- Specialized training for sites and investigators with limited clinical research experience
- Site and study specific implementation of logistical support to optimize delivery and ensure data quality

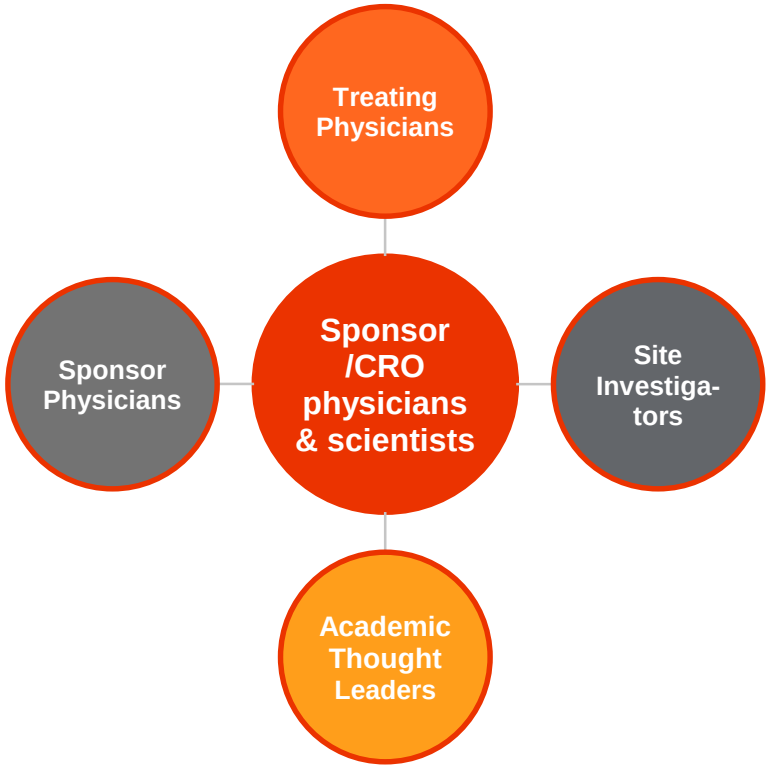


- Develop site networks and partnerships to drive study efficiency
- Leverages site knowledge and experience to shorten start-up timelines, improve patient access to trials, and improve subsequent trials and protocols

- Identify critical operational adjacencies and partner with specialized vendors
  to provide seamless trial execution
- May include travel logistics, home-nurse visits, and coordination with local primary care or specialists to optimize data integrity and patient retention

Drive Collaboration: Peer to peer relationships ensure right patient for best protocol

- Leverages shared training and passion for the patients and disease
- Ensures multiple clinical perspectives represented in protocol design
- Drives connectivity between the sponsor and the investigational sites, surfacing operational issues early
- Allows timely review of emerging data so that any protocol adjustments can be made in a nimble fashion
- Facilitates insight sharing from cross sponsor clinical research
- Advances clinical research critical to developing treatments for these underserved diseases.



Case Study: Enrollment

Situation

- Some patients must travel long distances and even across countries for treatment
- Patients may be seen by different physicians in different clinics for study treatment vs.follow-up
- Assessment schedule often more intense at the central (treatment) sites are higher than that of the satellite (follow-up) sites

Challenge

- Study requires patients to stay for extended periods in another country for IP administration presenting not only logistical challenges but also linguistic and cultural challenges
- Some countries do not allow health information to be transferred between countries (i.e. Italy)
- Two sites in two countries must access the patient's clinical database to enter and assess the subject's data

Solution

- Engaged a specialty vendor to arrange patient travel logistics (flights, hotel, etc.) and provide translation services
- Established site-specific communication plans to ensure appropriate sharing of patient data and safety information
- Ensured strategies were accounted for in the site budgets

Case Study: Start Up

Situation

- Higher regulatory scrutiny and additional committee/approval requirements
- Investigational therapy had special handling and manufacturing requirements
- Irreversible gene therapy making informed consent challenging and even more important.
- Educational material from sponsor highly specialized and complex

Challenge

- Larger and more complex regulatory dossiers with more submissions and committees involved
- Longer start-up timelines as a result of additional regulatory requirements
- Variable regulatory requirements by country
- Extensive qualification and auditable technical expertise needed for each site to allow dosing and administration
- Translation of lengthy and complex site SOPs required
- Maintaining readability of the ICF while providing all elements required

Solution

- Ensured additional time budgeted for team to accommodate submission needs
- Ensured start-up timelines for ATMPs taken into account in start-up projections
- Understood country specific requirements prior to start up process
- Trained pre-site selection visit staff on specialized site capabilities needed
- Supported creation and translation of complex ICFs
- Provided for external expert involvement in the consent process as required by some countries

Summary

- Clinical development and research in rare diseases is challenging, difficult, and rewarding work driven by committed and passionate people
- Success requires collaboration across many different stakeholders with broad needs and priorities
- Patient centered research approaches are critical to ensure the voice of the patient and their caregivers is incorporated in both the scientific design and the operational execution of clinical trials
- Recognizing the tactical complexities for investigational sites participating in these trials and devising solutions to enable them to focus on optimizing the patient experience is critical for patient participation and retention