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

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
What’s different in Rare Disease Clinical Research

Strong Rationale for MOA/Target

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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

Impassioned, dedicated investigators and site staff

Extremely motivated and passionate, patients and families
Driving Connectivity in Clinical Research

Focus on the patient experience – collaborate with patient advocacy

Lead with the best clinical and operational science – drive interface between clinical goals and operational excellence

Partner with quality and experienced sites – support through complexity

Driving connectivity

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
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

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

Focus on quality, trusted sites, with access to patients

Gap analysis and support implementation

Assess operational capabilities against study requirements

Acknowledge operational capabilities and limitations of individual sites
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
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.