IACRN Meeting – Role of a CRO in Rare Disease Trials

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Executive Director, Study Management
CTI Clinical Trial and Consulting Services
Introduction
Objectives

1. Role of a Clinical Research Organization (CRO) vs. Industry Sponsor in the conduct of clinical trials

2. Role of a CRO in managing trials in rare disease populations

3. Importance of collaboration and partnership between the Sponsor, CRO and site staff in the successful conduct of rare disease trials
Activities to Meet the Objectives

1. Overview of the role and responsibilities of Industry sponsor and CRO
2. Overview of a CRO organizational structure and roles of the CRO team
3. Overview of Rare Disease Designation
4. Specific aspects of trial management in rare disease trials
5. Enrollment and retention, and strategies to enable patients to be able to participate in clinical trials
6. Present a case study – Managing a trial in a rare disease population
7. Importance of collaboration between the Sponsor, CRO and site staff
What is a Clinical Research Organization (CRO)
Clinical Research Organization

CROs

- Provides support to the pharmaceutical, biotechnology, and medical device industries
- Services outsourced on a contracted basis
- Grew when Pharma companies needed to decrease overhead
- Opted for outsourcing solutions – transfer of services to outside vendors (Monitoring, Safety, Data, Regulatory)
- Range from large, international full-service organizations to small, niche specialty CROs
Responsibilities of Sponsors, CROs and Investigators and Keys to Success
Responsibilities in Clinical Trials
The Ultimate Goal

- Improvement in Patient Care
- Subject Safety
- Efficacy
- Quality/Integrity

Sponsor
Regulatory Authority
CRO
IRB/IEC
Site
### Who is Who…and What Do They Do?

<table>
<thead>
<tr>
<th><strong>Sponsors</strong></th>
<th><strong>Regulatory Authorities</strong></th>
<th><strong>IRB/IEC</strong></th>
</tr>
</thead>
</table>
| Pharmaceutical Companies  
Biotech Companies  
Individual Investigators | FDA  
EMEA  
HealthCanada | Central  
  - WIRB  
  - Shulman  
Local: Per institution  
  - Ensure the safety of patients using IP in their institutions |
| ✓ **Develop products to effectively and safely treat patients** | ✓ **Ensure the safety and efficacy of any drug utilized to treat patients in their country** | |

<table>
<thead>
<tr>
<th><strong>Sites</strong></th>
<th><strong>Vendors</strong></th>
<th><strong>CROs</strong></th>
</tr>
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</table>
| Academic Center  
  • Hospitals  
  • Clinics  
Research Centers  
Practioners  
Phase 1 Units | Central Labs  
Drug Depots  
IWRS  
Home Health | CTI Clinical Trial and Consulting  
PPD  
Quintiles  
MedPace |
| ✓ **Secure best tx options, care and safety of their patients** | ✓ **Perform required patient research services that protect integrity of specimens, assessments, and data** | ✓ **Perform all contracted services to secure quality, integrity and safety of patients and data** |
### General Responsibilities: Sponsor

<table>
<thead>
<tr>
<th>Sponsor Responsibilities</th>
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<tbody>
<tr>
<td>✓ Protocol and IB: Develop, maintain and distribute</td>
</tr>
<tr>
<td>✓ IND: Submit and maintain the IND (Investigational New Drug Application)</td>
</tr>
<tr>
<td>✓ Investigators: Select and ensure they are qualified and provide essential information</td>
</tr>
<tr>
<td>✓ Financial Disclosure: Ensure no investigator bias from financial gain</td>
</tr>
<tr>
<td>✓ Compliance: Ensure investigation is conducted according to the protocol</td>
</tr>
<tr>
<td>✓ Monitoring: Ensure compliance through proper monitoring</td>
</tr>
<tr>
<td>✓ Safety: Ensure Regulatory Authorities and investigators are informed of significant adverse events and risks associated with drug – stop study if needed</td>
</tr>
<tr>
<td>✓ Drug Accountability: Control of the Investigational Product</td>
</tr>
<tr>
<td>✓ Records: Maintain adequate records (Medical Records, ISF, TMF, trial documents)</td>
</tr>
<tr>
<td>✓ Access: Allow Regulatory Authority inspection of records and reports</td>
</tr>
<tr>
<td>✓ Annual Reports: Keep Regulatory Authorities apprised of study progress</td>
</tr>
</tbody>
</table>
## General Responsibilities: Investigator

<table>
<thead>
<tr>
<th>Investigator Responsibilities</th>
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</thead>
<tbody>
<tr>
<td>✔ Protect the rights, safety and welfare of subjects</td>
</tr>
<tr>
<td>✔ Ensure subjects provide informed consent prior to participation</td>
</tr>
<tr>
<td>✔ Conduct and provide oversight of the investigational plan</td>
</tr>
<tr>
<td>✔ Ensure compliance with all requirements of the protocol</td>
</tr>
<tr>
<td>✔ Ensure all colleagues are informed and trained in their study responsibilities</td>
</tr>
<tr>
<td>✔ Control drug under investigation</td>
</tr>
<tr>
<td>✔ Maintain adequate records (Drug, Medical Records, ICF)</td>
</tr>
<tr>
<td>✔ Ensure IRB/EC review and approval</td>
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</table>
CRO: Clinical Trial Operations and Project Execution
General Responsibilities: CRO

- CROs are contracted to assume any responsibilities or obligations that are transferred from the sponsor
  - Should be described in writing (contract) and in Transfer of Responsibility (TORO)
  - CROs are responsible and held to the same standards as the sponsor making the CRO subject to the same regulatory actions
- Assist sites with meeting their obligations as well
Typical Clinical Trial Services Provided by a CRO

- Clinical Monitoring
- Biostatistics
- Contracting & Budget Negotiation
- Data Management
- Trial Management
- Regulatory Affairs
- Medical Monitoring
- Global Drug Safety
- Quality Assurance Audits
# Typical CRO Contracted Services

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>CRO</th>
<th>Other Third Party Vendors</th>
</tr>
</thead>
</table>
| • Oversight of Trial  
• Investigational Product  
• IND Management  
• Regulatory Authority Submissions (FDA, EMEA)  
• Investigational Brochure  
• Protocol Development  
• ICF Development | • Day to Day Operations  
• Site ID and Qualification  
• Development of Study Materials  
• Clinical Monitoring  
• Medical Monitoring  
• Regulatory - Sites  
• Site Contracting/Budget  
• Data Management  
• Biostatistics  
• Safety  
• Trial Master File  
• Vendor Management  
• Site Payments | • Central Lab  
• Drug Depot  
• Home Health Care  
• IWRS |

![Diagram showing the relationship between Strategy, Plan, and Transition phases with Oversight Management and Vendor Management nodes]

- **Strategy**: This phase involves defining the overall plan and objectives of the project. It sets the stage for the rest of the project and ensures that all stakeholders are aligned with the project goals.

- **Plan**: The plan phase is where the detailed project activities are outlined. This includes the development of timelines, resource allocation, and task assignments. It's crucial for ensuring that everyone understands their roles and responsibilities.

- **Transition**: The transition phase marks the handover from the project team to the stakeholders or operational team. It involves ensuring that all the project deliverables are documented and transferred to the appropriate departments or individuals for ongoing maintenance and support.
Typical US Study Team

- Sponsor
- CRO Study Director
- CRO Study Manager
- CRO Study Coordinator
- Quality Assurance
- Study Site
  - Safety
  - Data Management
  - Medical Monitor
  - Lead CRA
    - CRAs
  - Regulatory
  - Legal
  - Biostatistics
Some would say that a Study Manager is…. 

A person with responsibility for doing something that has never been done before for people who don’t always know exactly what they want, who is often placed in a position of predicting the unknown, making a plan for the unforeseen and executing the plan with resources that they cannot always control but who is usually completely help responsible for the results!
Study Management

Seriously Though….What is a Study Manager?

- Strategically they set direction, provide support, anticipate and remove obstacles.
- They are a liaison between the various members of the study team, the sponsor and vendors.
- They provide leadership and are champions and advocates for their study.
- They carry all responsibilities associated with the study and its deliverables

Active Collaboration and Problem Solving throughout the Trial

Remove the Obstacles! Enable others success!
## CRO: Roles of Various Departments

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Data Management</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Partnering with Sites and Sponsor</td>
<td>o CRF and Instructions (w/ Study Management)</td>
<td>o SAE reporting procedures</td>
</tr>
<tr>
<td>o Site Visits (PSV, SIV, IMV, COV)</td>
<td>o Database development, testing and maintenance</td>
<td>o SAE review and development of patient narratives</td>
</tr>
<tr>
<td>o Problem ID and resolution</td>
<td>o Data cleaning</td>
<td>o Collaborates with Med Mon and Sponsor to assess for safety trends</td>
</tr>
<tr>
<td>o Informed Consent</td>
<td>o Query management</td>
<td>o Report to Reg Authorities</td>
</tr>
<tr>
<td>o Subject safety, well-being</td>
<td>o Database lock</td>
<td></td>
</tr>
<tr>
<td>o Integrity of the trial data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Protocol compliance</td>
<td></td>
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<table>
<thead>
<tr>
<th>Medical Monitor</th>
<th>Regulatory</th>
<th>Biostatistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Protocol expertise and support</td>
<td>o Collection and maintenance of required site regulatory documents</td>
<td>o Develop and manage randomization scheme</td>
</tr>
<tr>
<td>o I/E criteria questions</td>
<td>o Development/review of ICF</td>
<td>o Develop Statistical Analysis Plan</td>
</tr>
<tr>
<td>o Safety Assessments</td>
<td></td>
<td>o Data analyses/CSR</td>
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<tr>
<td>o DMC</td>
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So What is Involved in Trial Execution?
Begin with the End in Mind....
Key to Success in all Phases

- **Site Success = Study Success**
  - We cannot do this without you!
- **Open Collaboration with our Sites**
  - Enrollment
  - Protocol and GCP Compliance
  - Integrity of the Data
- Work to understand the needs and challenges
- Collaborate to find solutions:
  Sites + CRO + Sponsor
Trial Phases

- Study Start –up
- Enrollment
- Maintenance and Study Closure
Study Start-up Phase

From Project Award to First Patient Enrolled: the First 4 Months

Very Busy Time:

- Strategic Planning with Sponsor
- Site Qualification and Site Activation (Budgets, Contracts and IRBs)
- 3rd Party Vendor Contracting and Planning
- eCRF Development and Database Build
- Develop Study Management Tools
- Develop Study Reference Tools (Study Manuals, Pharmacy Manuals etc.)
- Design Study Specific Training
- DMC Planning and Coordination
- Site Initiation Visits
- First Patient Enrolls!
Start-up Process with Sites

All Activities Run in Parallel

IRB/Regulatory

Budget

Contract

Site Initiation

Speed of activation helps launch enrollment
Project Timeline: Enrollment Phase

Enrollment Phase: From First Patient In to Last Patient In

- Active site support and problem solving
- Interim monitoring visits
- Project management reporting to Sponsor
  - Site activities, recruitment efforts/challenges, protocol deviations
- DSMB Committee Meetings
- Drug Safety Management
  - SAEs and trends
  - Submission to Regulatory Authorities
- Data Management
  - Query resolution
  - Trends
- Medical Monitoring
## Maintenance and Close-out Phase

<table>
<thead>
<tr>
<th>Maintenance: Last Patient In to Last Patient Last Visit</th>
<th>Closeout Last Patient Visit to Study Close</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Active Site Support</td>
<td>➢ Final Query Resolution</td>
</tr>
<tr>
<td>➢ Continued Interim Monitoring Visits</td>
<td>➢ Database Lock</td>
</tr>
<tr>
<td>➢ Patient Safety Management</td>
<td>➢ Site Close-outs</td>
</tr>
<tr>
<td>➢ Query Resolution</td>
<td>➢ Clinical Study Report</td>
</tr>
<tr>
<td>➢ Study Management Coordination and Reporting</td>
<td></td>
</tr>
<tr>
<td>➢ Planning and Coordination to Database Lock</td>
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Sponsor and CRO Team Meetings

The Behind the Scenes Activity!

- Information Sharing and Problem Solving:
  - Providing study and site updates…Developing solutions

<table>
<thead>
<tr>
<th>Sponsor Meetings</th>
<th>Internal CTI Team Meetings</th>
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<tbody>
<tr>
<td>Study Manager</td>
<td>Study Manager</td>
</tr>
<tr>
<td>Sponsor Project Manager</td>
<td>Medical Monitor/Medical Director</td>
</tr>
<tr>
<td>Medical Monitor/Medical Director</td>
<td>Regulatory</td>
</tr>
<tr>
<td>Regulatory</td>
<td>Safety</td>
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<tr>
<td>Safety</td>
<td>Data Management</td>
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<tr>
<td>Data Management</td>
<td>CRAs</td>
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<td>CRAs</td>
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Vendor Meetings

(Central Lab, IVRS, etc.)

<table>
<thead>
<tr>
<th>CTI Clinical Project Manager</th>
<th>Sponsor Project Manager</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor Project Manager</td>
<td>Vendor Project Manager</td>
</tr>
<tr>
<td>Vendor Project Manager</td>
<td>Other CTI or sponsor representatives (as needed)</td>
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</table>
# Importance of Vendor Management

<table>
<thead>
<tr>
<th>Investigational Product</th>
<th>Central Lab</th>
</tr>
</thead>
</table>
| • Availability from Sponsor manufacturer | • Central vs. Local  
  • Vendor Selection and Management |
| • Labeling                | • Specimen Collection Procedures                                           |
| • Distribution (drug depot) | • Shipping                                                                 |
|  • Shipping requirements  | • Specimen Tracking                                                        |
| • Storage conditions      | • Reports and Data Collection                                               |
| • Drug Accountability     | • Data Transfer                                                             |
|  • Chain of custody       |                                                                           |
|  • Site Responsibilities  |                                                                           |
|  • CRA Responsibilities  |                                                                           |
|  • Unblinded Monitoring (if applicable) |                                                                           |

**Early identification and resolution of issues!**
Managing a Trial in a Rare Disease Population
What Constitutes a Rare Disease?

Definition of Rare Disease:

- US: A disease or disorder that affects fewer than 200,000 Americans at any given time
- EU: A disease or disorder that affects fewer than 1 in 2000

Some Facts:

- 80% of rare diseases have identified genetic origins
- Others are the result of infections (bacterial or viral), allergies and environmental causes, or are degenerative and proliferative
- 50% of rare diseases touch children
- It is estimated that there are 6000 to 7000 rare disease affecting approximately 350 million patients globally (25-30 million in US)
- Typically these diseases are serious, progressive and often life threatening
- Most do not have treatment options

So what can be done?

- Government policies and incentives have lead pharmaceutical companies to the development of orphan drugs, leading to many new trials in the rare disease space

http://www.rarediseaseday.org
Rare Disease Trials
Some FDA Policies and Incentives to Help

- **Orphan Drug Designation**
  - Provides incentive through tax reductions and the exclusive right to develop the cure for a specific condition for a period of seven years to companies attempting to cure rare diseases.

- **Fast Track Designation**
  - Provides *expedited* review to facilitate development of drugs which treat a serious or life-threatening condition and fills an unmet medical need.
  - Drug must show some advantage over available therapy (Superiority, avoids serious side effects)
  - Enables more meetings and communications with the FDA re: protocol design

- **Breakthrough Therapy Designation**
  - Designation given if preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies
  - If designated, the FDA will expedite the development and review of such drug
Trial Execution:
Rare Disease Trials
Site Success is Study Success!

Rare disease trials REALLY require site, CRO and Sponsor to work together:

- Partnerships
- Collaboration
- Teamwork
- Commitment

Your Success is Our Success
Our Success is Your Success
Nuances of Rare Disease Trials

- Due to rareness of disease:
  - Patients can be very difficult to find
  - Patients not previously studied
- Assessment tools and outcome measures often not previously defined
- Natural progression of disease and expected clinical outcomes not always clearly characterized
  - Often need Natural History studies to characterize typical disease progression to inform expected clinical outcomes for protocol and endpoint development
- Often occurs in pediatric populations
  - Assessments of progression of disease complicated by impact of growth and development in pediatric population
- Access to patient population requires ability to expand geographic reach
  - Open more sites more countries or transfer patients to participating trial centers
  - Expense and logistics
- Importance of Site Engagement
  - Site involvement and engagement is everything!
  - Enrollment, Retention, and Protocol Compliance
Key Elements of Success
Rare Disease Trials

- Protocol Design
- Careful Site Selection
- Patient Identification
- Enrollment Strategies
- Patient Retention
CRO role:

• Utilize expertise in trial operations and rare disease populations to provide guidance in protocol review or development

• Need to know vs. nice to know – Collect only needed data
  • Site burden (protocol compliance)
  • Patient/family burden (enrollment and retention)

• Encourage KOL and site participation in protocol review
  • Comparison to standards of care or logistics of protocol execution
Critical First Step: Perform thorough assessment

- Access to targeted patient population
  - Or ability to accept patients from other regions
- Ability to conduct the required study procedures
- Availability of required medical records
- Early identification of potential site challenges and collaborate with site and sponsor to implement solutions
  - Each site and each patient is critical in rare disease
  - Work with sites to enable successful participation

Successful Sites = Successful Study
CRO Role: Enrollment

Many factors affect the enrollment rate:

- Rarity of disease and ability to identify patients
  - Ability to locate and recruit into the trial
  - Patient and family commitment to participation
  - Location of study sites or satellite sites, logistics management and compensation for travel
- Site engagement and staff workload
- Understanding the protocol and ability to perform required procedures

What can a CRO do to help?

- Understand the challenges – often requires individual site specific planning
- Liaise between the Sponsor and the Site to find solutions
- Provide site training (PSV, SIV, inservice training – ancillary services)
- Provide sites with trial educational materials for patients
- Study set-up – ease of execution
Additional Strategies to Patient Identification

- Face-to-Face Meetings with Potential Investigators
- Confirm Clinical Care Pathway
  - Understand point of entry for potential patients
- Patient Advocates – Formal Role
  - Assist with patient participation logistics and support
- Social Media Awareness
- Genetic Counselor Network
- Advisory Boards / Steering Committee
  - Seek out additional expertise as needed to find solutions
- PI/SC Teleconferences – Best Practices
  - Share knowledge and expertise
Subject recruitment and enrollment may be challenging but **subject retention is imperative**

- Ease of study procedures
- Informed knowledge about participation requirements and expected commitment
- Appropriate subject reimbursement and support for study participation
- Commitment of team to manage challenges that could impact the subject’s ongoing ability to participate
- Consider alternative solutions needed to enable continued participation
  - Home Health Care Visits
  - Transfer to another participating site

**Active collaboration between the Site, CRA, Study Manager and Sponsor**
Site Support: What are the Keys to Monitoring Success

• Knowledge of the protocol
• Knowledge of patient population
• Understanding of the critical data
  o Medical history
  o Medications
  o Adverse events
• Accountability
  o Partnering with Sites and Sponsor
• Timely responsiveness
  o Problem identification and resolution
• Study Updates, Newsletters, etc. – keeping the study in the forefront at the site
• Regular communication with Study Management and Sponsor

Whatever is needed to facilitate site’s success!
Case Study
To develop a treatment for a very rare x-linked genetic disorder that resulted in the inability for affected male infants to produce a protein that was linked to significant and life threatening abnormalities in development

- Incidence: 1:100,000 – fairly rare condition
- Sponsor identified the missing protein and demonstrated success in treating the condition in animal models
- Animal models who carried the genetic mutation, and were treated with an IV infusion of the recombinant replacement protein, developed normally
- Trials in a patient population were needed to see if these same results could also be achieved
- Challenge – Need to be administered within the first 2 weeks of life
  - Required identification of families with affected children
  - Required genetic testing of the amniotic fluid of pregnant mom to confirm diagnosis of neonate
Initiation of Clinical Trials

• Natural History Studies: initiated to characterize the natural progression of the disease
  • Initiated by the sponsor several years prior to Phase 1/2 and CRO involvement
  • Conducted in conjunction with National Family Conference Meetings
  • Conducted assessments of volunteers; collected data

• Phase 1: Initial study conducted in adult population
  • CRO contracted to run Phase 1 trial
  • Adult volunteers with the disorder tested IP for safety
  • Largely volunteers self identified through contacts at the National Family Conference or from clinicians in the field caring for individuals or family members with the disorder.
Phase 2 Initiation

- Phase 2: Initiated once Phase 1 data showed no safety concerns
  - Sponsor contracted CRO to conduct the trial
  - CRO worked with Sponsor to identify, qualify, and train key sites with PIs who were experts in the field
  - 3 sites in US and 3 sites in EU
  - Enrollment goal: 15 patients
  - LOS: 6 months / 15 visits (parent study) + LTFU Q6 months
  - Families of affected children identified – largely through social media and strong National Family Organization network
  - Families or clinicians notified treatment sites of participation interest (ClinicalTrials.gov)
  - CRO worked with Sponsor identified Patient Advocate to facilitate logistical arrangements (travel, scheduling)
    - Required travel across country and/or between countries
Study Challenges

- Identification of families with affected children
- Notification of upcoming pregnancy with genetic confirmation of the disorder
- IP needed to be initiated within 2 weeks of delivery
  - 5 doses over 2 week timeframe
- Logistics of transport of mom and baby to 1 of 6 sites that were open for treatment and provision of accommodations for their stay for duration of treatment and their return for follow-up appointments
- Assessments for short and long term safety and efficacy needed to be defined and agreed upon by the Regulatory Authorities
- Assessments were based upon findings in the NHS
- Research clinicians needed to be consistently trained on the assessments (not SOC).
Pharmacodynamic / Efficacy Evaluations

- Growth and Development
- Infections and Hospitalizations
- Physical Development
- Facial Development
- Sweat Gland Number and Function
- Dry Eye Assessment
- Thermoregulation
- Skin Biopsy

Not SOC - Needed to ensure consistency in training for measurements
CROs Role: How did we help.....

Besides Day to Day Operations…..

• Careful review of the protocol to eliminate any obstacles – streamline assessments and procedures

• Developed training materials and conduct of site training on protocol and procedures

• Relationships and engagement with the sites

• Highly orchestrated and coordinated enrollment effort (mom & baby)

• Liaison between the Sites and Sponsor

• Understanding and adherence to GCP principles

• Problem solving to keep trial moving forward – unchartered waters

• Support of sites in conduct of the trial – problem solving for success
So what have we learned....

- Importance of collaboration and communications between the site, the sponsor and the CRO
  - Partnership is key to success
  - Trials in rare disease can often involve the unknown and usually involve significant management of trial logistics
  - Need to over-prepare and consider all possibilities
  - CROs gain many experiences by working on many studies, with many sites and sponsors – important to utilize this knowledge to help problem solve, anticipate and remove obstacles to enable successful trial conduct
  - Training involved multidisciplinary teams such as physicians, research nurses, therapists, pharmacy, laboratory, geneticist and study coordinators – identify and work with all the players

Successful Sites = Successful Study
In Closing

Goal of this presentation…..support your understanding of:

1. Role of a Clinical Research Organization (CRO) vs. Industry Sponsor in the conduct of clinical trials

2. Role of a CRO in managing trials in rare disease populations

3. Importance of collaboration and partnership between the Sponsor, CRO and site staff in the successful conduct of rare disease trials

Thank you for all you do every day to support success of clinical trials
What you do matters and is appreciated!
Thank you

And remember......