Common Challenges in Conduct of Clinical Trials

8th Meeting with International Partners for Influenza Vaccine Technology Transfer to Developing Country Vaccine Manufacturers

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March 17, 2015

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Introduction

There are many parallel and competing factors when preparing for and conducting clinical trials:

- Coordination of manufacturing activities
- Clarity of trial protocol and case report forms
- Ethical/regulatory review(s)
- Site capacity, management, and experience
- Management of different partners
- Contracting and agreements
- Trial timeline
- Overlapping/parallel activities
Develop a realistic timeline

Include:

- Manufacturing and product readiness
- Length of time of review and approval of protocol dossier (various submissions)
- Contract negotiation and finalization
- Time to develop and rollout trial data capture system and site startup activities
- Trial recruitment/enrollment and implementation
- Time to complete clinical study report following database lock
- Awareness of regional influenza season
Align preclinical program, manufacture, and product release with trial timelines

- Preclinical requirements
  - Animal studies (safety, toxicology, and immunogenicity)
  - Stability studies (label claim and accelerated)
- Product
  - Availability (manufacture and release)
  - Adequate supply
  - Stability
    - To support preclinical studies
    - To support clinical program
    - Initiate stability programs prior to clinical trial regulatory submission (3 months stability needed)
- Expiry date
Plan trial protocol development

Plan to:

• Develop protocol synopsis early for review with partners (during site/CRO assessments)

• Develop full protocol and trial documents
  • Use format required by regulatory authority
  • Understand regulatory requirements
  • Prepare study instruments and recruiting/advertising materials based on local guidelines
  • Use informed consent form appropriate to the population in the study (vulnerable population, parental/spouse consent, language, etc.)

• Perform all appropriate training on protocol and study-related documents for clinical site staff, data management center, and sponsor
Perform in-depth clinical site assessment

- Engagement of Principal Investigator(s)
- Understand site capability
  - Staff qualifications/training
  - Experience with clinical trials, especially vaccine trials
  - Target population for participation
    - Ability to recruit, enroll, and retain appropriate volunteers
  - Assuring participant safety
  - Disease awareness (e.g. Influenza seasonality/mismatch)
- Investigational product, specimen, and document management
  - Processing, collection, tracking, chain of custody, appropriate storage, and capacity
- Infrastructure
  - Clinical, laboratory (safety), pharmacy
- Quality management plan
  - GCP, training in human subjects research protection
Perform assessment of laboratories

- **Safety laboratory**
  - Staff training
  - Certifications
  - QA and data management plan
  - Adherence to GCP

- **Immunological laboratory**
  - Assay(s)
  - Assay status (validation)
  - Access to reference controls/reagents
  - Adherence to GLP, GMP
  - Training
  - Equipment status (qualification, calibrations)
Understand data management needs

- CRO capabilities, flexibility, and costs
- Strong and effective QA/QC systems (e.g., safety and data quality)
- Regulatory authority compliant system (e.g., 21 CFR Part 11)
- Statistical support (statistical analysis plan)
- Timeliness and quality of study reports
- Compatibility/language of CRF design with site capabilities, ease of use
- Data entry (electronic/paper)
- Local representation/staff of CRO to communicate/work effectively with site staff
Understand safety monitoring

- PI, CRO, sponsor/medical monitor(s) capabilities and experience
- Develop safety oversight and medical management plans
  - Expedited and periodic safety reporting plan, as applicable (serious adverse event (SAE) and adverse event (AE) reporting)
  - Timeliness and quality of safety reports
- Safety review committee, independent data safety monitoring board (DSMB)
Understand site monitoring

• Develop trial monitoring plan
  • Frequency and format (risk based is preferable)
  • Compliance with GCP, local regulations, and trial protocol
  • Remote or onsite monitoring

• Develop plans for:
  • Lab monitoring
  • Pharmacy monitoring
  • Data monitoring
Ensure clarity of protocol and case report forms before trial implementation

Challenges that arise:

• Know how to handle *out of range* lab results
  • Interpretation of toxicity table
  • Handling out of range results
  • Determine when a lab result becomes a grade 1 or grade 2
  • Determine when to re-draw blood for lab retest(s)

• Predetermine relatedness of solicited (expected) adverse events to a defined period post immunization

• Prepare to follow up/discuss (at length) with CROs about trial data capture and data analysis
Challenge mitigation

Key factors for successful trial implementation and completion:

• Clear communication
• Consistent follow up
• Predefined roles and responsibilities
• Appropriate planning and timeline management