Global Clinical Trials: Operational and Regulatory Challenges

Society for Clinical Trials
18 May 2010
Mark A Bach, M.D., Ph.D.
Outline

• Overview of a global medical organization
• Clinical Operations Challenges
• Regulatory Challenges
• Ethical Challenges
Global Medical Organization “Footprint”

Medical departments in ~50 countries
About 1000 people worldwide
Clinical Trial Initiations
Based on FDA-1572, 1990-2007

Source: CenterWatch Analysis, 2008; FDA, 2008
Worldwide Clinical Trials
Estimated Ongoing Phase I-III Trials, 2000-2006

Note: Does not include phase IV, medical device, or non-medicinal trials

Source: CenterWatch Analysis, 2006
Elements of Clinical Operations

- Global trial management (HQ based)
- Trial oversight and monitoring (Country-based)
- Data management
- Clinical supplies and ancillary supplies
Operational Challenges

• Global Trial Management
  – Protocol design
  – Country selection
  – Language
  – Trial tracking and reporting
Operational Challenges

• Global Trial Management
  – Protocol design
    • Input into feasibility
      – Need to understand the local medical environment
      – Acceptability of placebo controls
      – Local standards of care
      – Disease incidence/prevalence
      – Variability in disease, drug metabolism
      – Cultural issues in patient reported outcomes
        » Need for translation/validation
Operational Challenges

• Global Trial Management
  – Country selection
    • Access to patients
    • Investigators
    • Proven quality
    • Speed (regulatory/IRB approvals)
    • Cost
Operational Challenges

• Global Trial Management
  – Language
    • Communication with country staff
    • Patient-reported outcomes – translation and validation
  – Time zones
    • Someone is working all the time
  – Trial tracking and reporting
    • Data from CTMS, EDC, IVRS . . . Requires one source of the truth
Operational Challenges

- Trial oversight and monitoring
  - Investigator selection
  - Sponsor capabilities
  - Enrollment issues
  - Regulatory environment
Operational Challenges

• Trial oversight and monitoring
  – Investigator selection
    • Must be well qualified, and understand clinical trials
    • Access to patients
    • Understand ICH GCPs
    • Must have IRB oversight
    • Sufficient trained staff to manage study procedures
    • Adequate facility for evaluating patients and performing study procedures
  – Regulatory environment
    • Must have good understanding of local regulatory requirements
    • Interaction with local regulatory agency for clinical trial authorization
Operational Challenges

- Sponsor capabilities
  - Act as liaison with HQ
  - Understand clinical trials
  - Understand ICH GCPs
  - Understand local healthcare environment
  - Visit investigator sites for monitoring and training
  - Factors for patient enrollment
Operational Challenges

• Local healthcare environment
  – Healthcare system
    • Nationalised
    • Regionalised
    • Funding – central/personal
  – Majority of patients in public insurance system with limited access to novel healthcare
  – Catchment areas
    • Large institutions with therapeutic focus
  – Accessibility of healthcare settings
  – Large population centers
Local Healthcare Environment

Max Super Specialty Hospital

G M Modi Hospital
Operational Challenges

• Site selection and monitoring
  – Confirm qualifications to participate
  – Confirm IRB/ERC approval and ongoing oversight
  – Ensure site staff are trained appropriately: AE reporting, sample shipping, data entry, etc.
  – Review proposed patient enrollment plan
  – Verify storage conditions for clinical supplies
  – Review emergency unblinding procedures
  – Perform source data verification

  • Site Monitoring is the process by which the sponsor fulfills the obligation to oversee clinical trials (ICH-GCP E6: 5.1.1, 5.1.3, 5.18.1, 5.18.3).
Operational Challenges

• Factors for patient enrolment
  – Eligibility
    • Meet the diagnosis
    • Naïve to excluded therapies
    • Exposed to appropriate standard of care
    • Standard of care
      – Compatibility with usual treatment protocols
      – Availability of comparator compounds
  – Participation
    • Lack of interest in trial participation
      – Availability of new/improved therapies
      – Placebo controlled studies
      – Fear of experimentation
      – Patient burden
Regulatory Challenges

• Impact
  – Timelines
  – Cost
  – Need for harmonization
    • Declaration of Helsinki
    • WHO
    • ICH GCP
    • National regulatory agencies
  – Resources
Regulatory Challenges

• Regulatory oversight is important
  – Patient protection
  – Transparency
  – Data integrity
• Global development is increasing as is regulatory burden
  – Increasing scrutiny of developing world/ex-regional data
• Clinical Trial Application timelines and requirements vary greatly
  – Intellectual property concerns (e.g., level of CMC data needed)
    - National and local ethical review committees
  – Variable timelines and requirements
    - Regulatory approach/timing must be coordinated with site/country choices
• Clinical trial registration and results posting
  – National and local requirements
• Clinical trial data need to support local registration requirements
  – Some countries specifically exclude FIM studies
Regulatory Challenges

• Importation issues, especially for biologics and comparators
• While not strictly regulatory, Health Technology Assessment (HTA) is becoming more important in many countries
  – HTA is done locally (e.g., no EU HTA authority)
  – Addressing HTA can impact study design and accepted/expected comparators
Ethical Issues in Global Trials

- Relevance to local health needs
  - Potential for benefit
- Standard of care
  - Disease under study
  - Concomitant/incidental health conditions
- Access to medicine post-study
  - Development stage/efficacy
  - Alternative therapies
- Consistent standards globally
  - Investigator
    - Training and experience
    - Payment: Conflict of Interest, Diversion of payments
  - IRB Quality
    - Local standards for patient protection
  - Global standards
    - International Conference on Harmonization (ICH)
    - Council for International Organizations of Medical Sciences (CIOMS)
    - Declaration of Helsinki (DoH)

Glickman et al; NEJM 360:8 Feb 2009
Ethical Issues in Global Trials

• Social Value
  – Relevance to health in the community
  – What are the benefits?
• Scientific validity
  – Validity overall and feasibility in the community
• Fair selection of study population
• Favorable risk-benefit ratio
  – Minimize risks
• Independent review
• Informed consent
• Respect for participants and communities

Emanuel et al; J Inf Dis; 189; 930 – 937; 2004: 22
Conclusions

• Multiple challenges in global clinical trials
  – Operational
    • Global logistics
    • Deep understanding of local environment necessary
    • Understanding of ICH-GCPs and other standards
  – Regulatory
    • Environment is complex and fluid
  – Ethical
    • Patient safety must come first
    • Adherence to key ethical principles