Global Clinical Trials: Operational and Regulatory Challenges

Society for Clinical Trials

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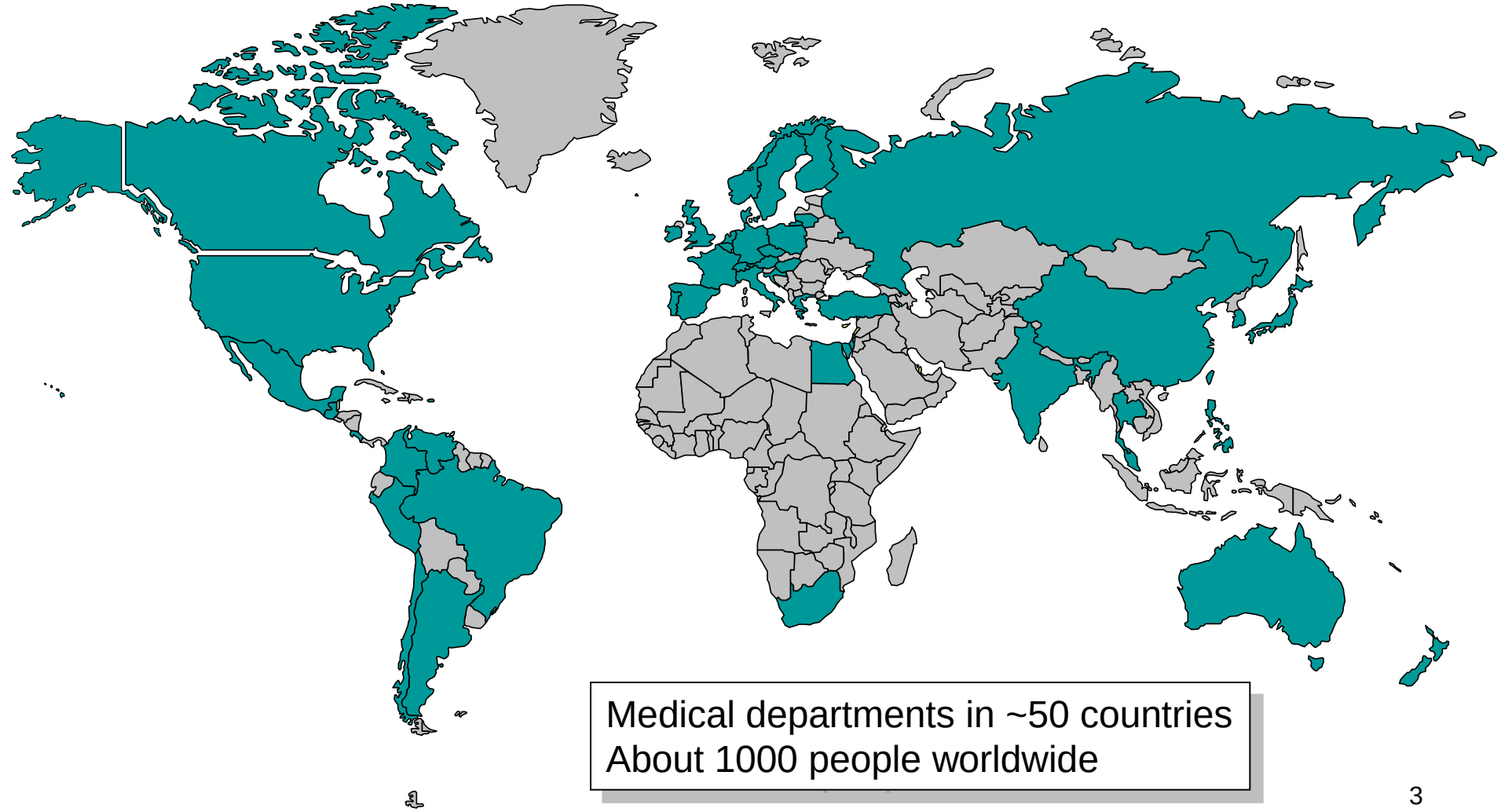
Outline

- Overview of a global medical organization
- Clinical Operations Challenges
- Regulatory Challenges
- Ethical Challenges

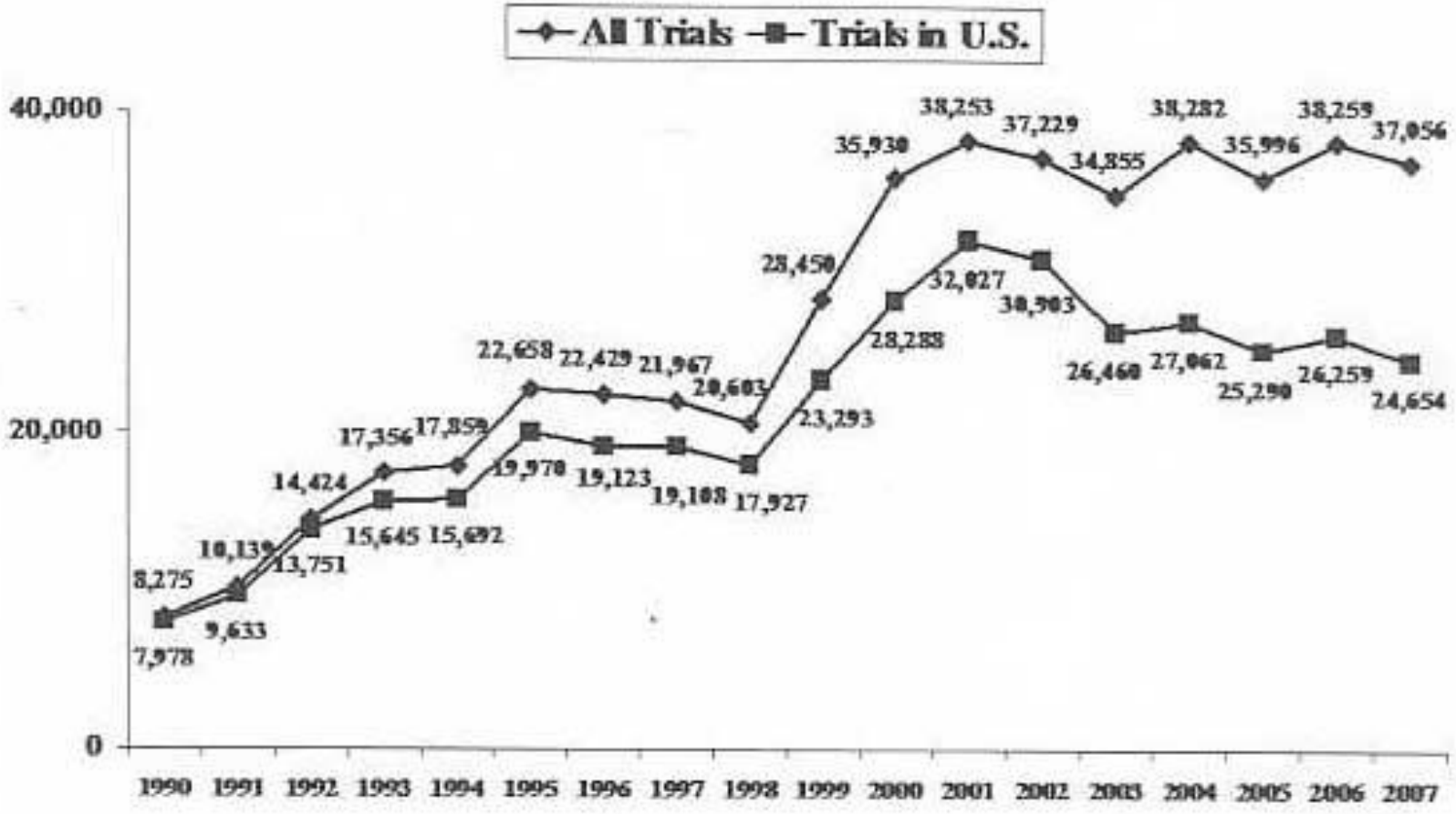
Global Medical Organization “Footprint”



Medical departments in ~50 countries
About 1000 people worldwide

Clinical Trial Initiations

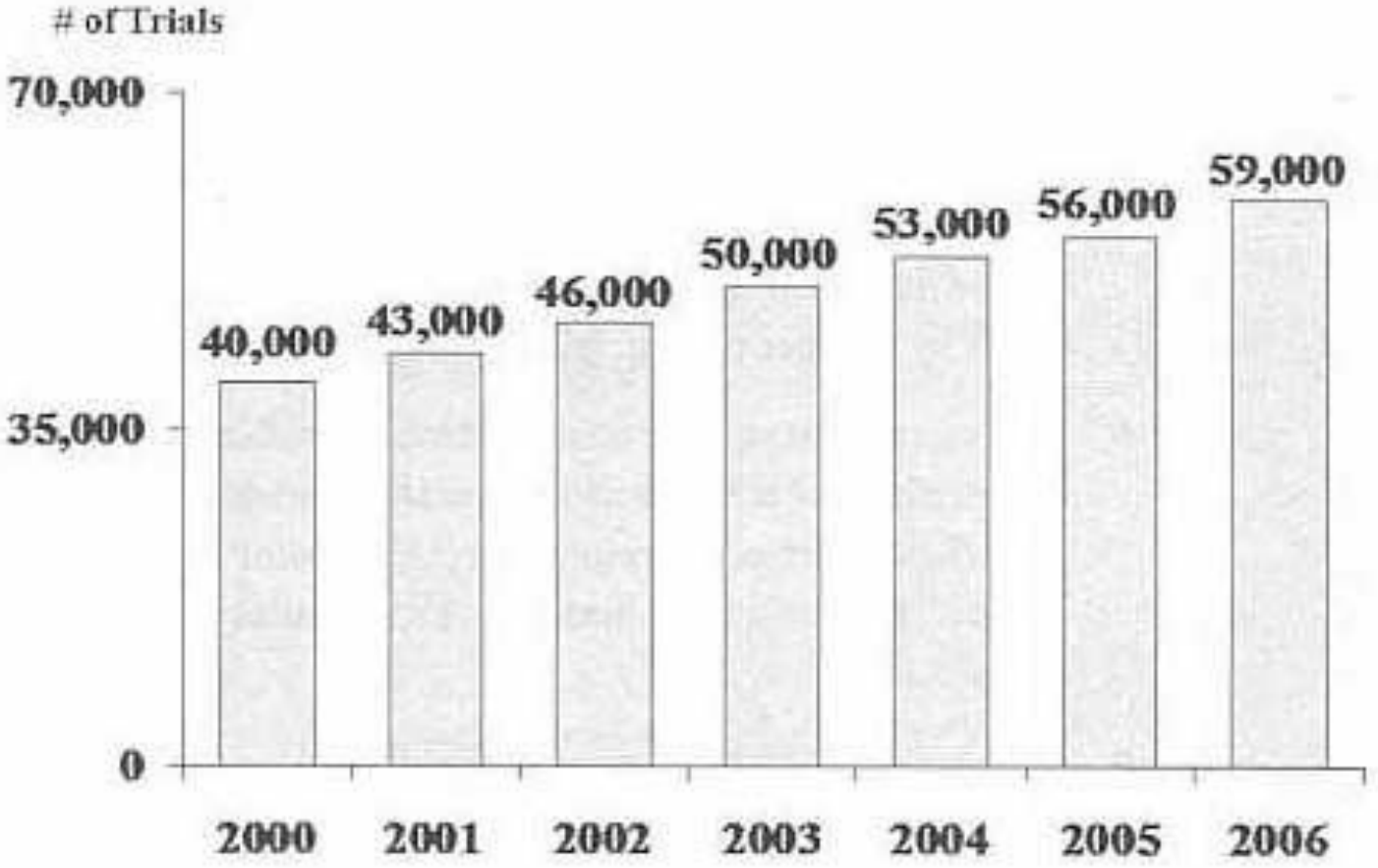
Based on FDA-1572, 1990-2007



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 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:

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