Good Clinical Practice (GCP) & Clinical Trial Registries

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Good Clinical Practice
ICH GCP Guideline Objective

“To provide a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions”
FDA GCP vs. ICH GCP

- The FDA maintains that ICH GCP guideline (E6) is entirely consistent with the agency’s GCP regulations and clinical studies conducted under these guidelines meet the GCP standards acceptable to FDA.

- Conventional wisdom … ICH GCP when doing studies for global NDA submission
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European Union Clinical Trial Directive

- Scope of legislation is much broader than strict GCP
- Encompasses:
  - Manufacture of investigational medicinal products
  - Laboratory testing services
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GCP Compliance Plan is essential

- Appx. ¾ of cost of drug development is in clinical trial phase
- Expanded globalization of studies
- Diversity of organizations involved in any trial can:
  - Be substantial
  - Difficult to manage
  - Expose sponsor to GCP compliance risk
- Outsourcing to CROs
  - R&D outsourcing expenditures rising at rate in excess of 14% per year
  - Accounted for 70% of market in 2003 – expected to grow to almost 80% by 2008

Sources: Pink Sheet, 2003; 65(50):30 / 2003 report by Kalorama Information
Clinical Trial Cycle

1. Sponsor + PI + Institution/CRO contact: Proposal & Budget Prepared
2. IRB approves study and informed consent form, Scientific & Regulatory Reviews approved
3. Contract Accepted by all parties - study initiated
4. Patients Enrolled by Proper Selection Criteria/Informed Consent Used, Trial Begins
5. Data Collected for Sponsor as patients receive treatment
6. Adverse Events Reporting Enrollment Continues Continuing IRB Reviews
7. Trial ends: All data submitted to Sponsor
8. Dossier prepared for NDA submission

Continuous Improvement of Medical and Business Practices
Regulators are focusing on “research compliance”

- The collection of evolving government requirements
  - Focus of complex rules and penalties from various federal and international agencies.
  - Can torpedo the reputation of even the most prestigious companies.
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Non-compliance exposes corporations to heightened risks

- Hefty fines
- Significant trial delays
- Endangered patient safety
- Wasted resources
- Lost profit margins
- Embarrassment
- Potential litigation
- Reputational damage
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FDA gearing up for:
- More Frequent
- Intensive
- Unannounced Inspections

Sponsor operational changes will undoubtedly have an effect
- Patient Recruitment
- Electronic Data Collection & Management
- Outsourced Clinical Activities
- Trial results disclosure

EU Directive enforcement will have direct impact
Nearly 4,000 clinical trials, Phase I, II, or III, are taking place worldwide

Source: Parexel’s Pharma R&D Statistical Sourcebook 04/05
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Clinical trials in developing nations

- “Ascending Markets”
  - Eastern Europe
    • Aligning with European practices, including ICH-GCP
  - India
    • Lags in GCP experience
    • Regulatory changes underway to promote GCP training
  - Asia
    • GCP practices and understanding “poor to fair”
    • Sponsors & CROs investing in GCP training
  - Latin America
    • Needs regulatory reform

- 20% - 30% of trials conducted in these markets

Source: Applied Clinical Trials, June 04
FDA priorities for the coming year

Focus on high priority safety areas

- Adverse Events (AE)
  - Improve efficiency & effectiveness of AE reporting system
  - Goal: Develop common reporting system used as single point of entry for patients, consumers, & health care providers to report all AEs and product problems
  - FDA Adverse Event Reporting System (FEARS)

Source: HHH/FDA Progress and Priorities 2004: Protecting and Advancing America’s Health
• Safety Reporting
  ▪ Codify expectations for timely acquisition, evaluation, & submission of relevant safety information

➤ Clinical Trials Registry
• ClinicalTrials.gov
  ▪ FDA checking compliance rates through April 03*
  ▪ Industry non-compliance has been on-going concern
  ▪ Survey of cancer INDs found only 47% listed

Source: FDA Pink Sheet V66(26)p30
Clinical Trial Registry
## Clinical Trial Registry

<table>
<thead>
<tr>
<th>Register</th>
<th>Comment</th>
<th>Website</th>
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<tbody>
<tr>
<td><strong>Government</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>National Institutes of Health (NIH)</td>
<td>Includes trials of serious and life-threatening diseases</td>
<td><a href="http://www.ClinicalTrials.gov">www.ClinicalTrials.gov</a></td>
</tr>
<tr>
<td><strong>Collaborative Efforts</strong></td>
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<tr>
<td>Cochrane Central Register of Controlled Trials</td>
<td>Comprehensive register of controlled clinical trials</td>
<td><a href="http://www.cochrane.org">www.cochrane.org</a></td>
</tr>
<tr>
<td>TrialsCentral</td>
<td>Online register of 200+ US-based trials registers</td>
<td><a href="http://www.trialscentral.org">www.trialscentral.org</a></td>
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<tr>
<td>Current Controlled Trials</td>
<td>Meta-register compilation of individual registers</td>
<td><a href="http://www.controlled-trails.com">www.controlled-trails.com</a></td>
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<tr>
<td><strong>Industry Register</strong></td>
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<tr>
<td>CenterWatch</td>
<td>Over 41,000 active industry &amp; government-sponsored trials</td>
<td><a href="http://www.centerwatch.com">www.centerwatch.com</a></td>
</tr>
</tbody>
</table>
Clinical Trial Registry

In the United States

Registry

Open clinical studies for serious or life-threatening diseases posted in ClinicalTrials.gov
Clinical Trial Registry

- Patient Advocacy Groups
- PhRMA
- AMA
- Peer-Review Journals
- Clinical Trial Registry
  - Phase I - IV Data
  - Disclosure of trial results
    - Positive & Negative
  - Information available to the public

- Kennedy (MA)
- Johnson (SD)
- Dodd (CT)
Clinical Trial Registry

What should be in the registry?

At least this “barebones info”

- Disease
- Investigational New Drug
- Pre-clinical information
- Location of studies
- Results of all studies done
- Contact information
In the European Union

Registry

All new trials must have a EudraCT number for tracking

Adverse Events Reporting

EudraVigilance Module
(linked to the EudraCT database)
Information included:

- Title of trial
- Sponsor identity
- Details & hx. of IND being tested/used as comparator (including pharmaceutical form, route of adm., all strengths used, provenance of active substance)
- Details of medical condition on which trial is focused
- Main and secondary objectives
- Principal inclusion and exclusion criteria
- Primary endpoints
- Scope and phase of trial
- Design of trial
- Sites
- Dosing and duration
- Population of trial subjects and details
- Principal and coordinating investigators
- Central technical facilities
- Duties subcontracted
- Trial monitoring facilities
- Ethics committee details
- Protocol details

Will not contain individual personal information relating to clinical trial subjects (provision of GCP)
Recent Update
Pharmacogenomics

- The study of variability in drug handling or response due to hereditary factors in different populations.

- If an argument can be made for genotyping subjects prior to enrollment in a clinical trial to reduce screening failures, the FDA may expect sponsors of clinical trials to incorporate pharmacogenetics testing in protocols.

Computerized Systems in Clinical Trials

FDA statement

“We recommend that each study protocol identify at which steps a computerized system will be used to create, modify, maintain, archive, retrieve, or transmit data.”

Source: FDA Draft Guidance on Computerized Systems Used in Clinical Trials. Sept 04
Conclusion

- Assess global clinical compliance risk
- Deploy resources to promote and achieve GCP
- Address issues preventing company from meeting compliance objectives