

Good Clinical Practice (GCP)
&
Clinical Trial Registries

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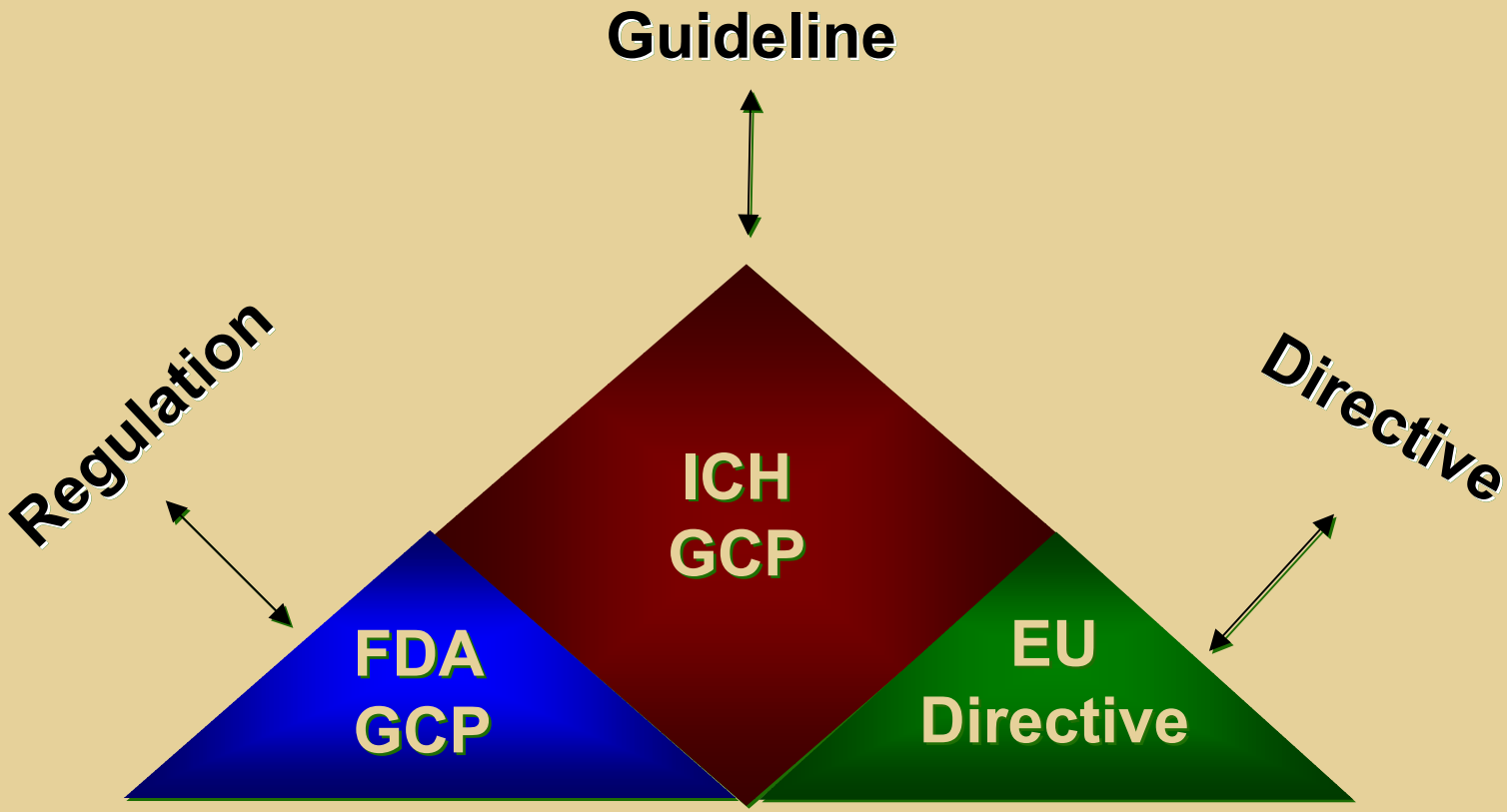
Good Clinical Practice

Good Clinical Practice



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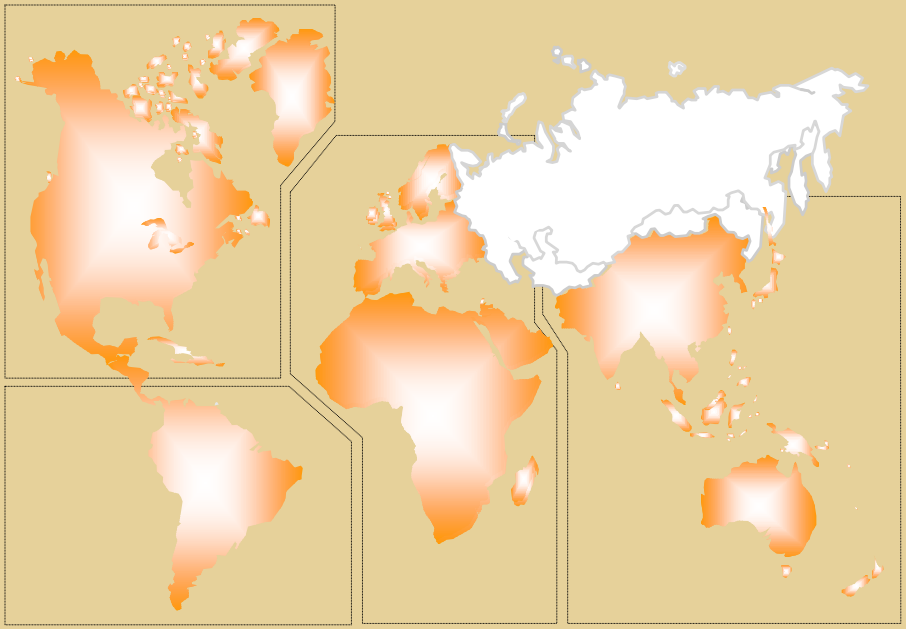

ICH GCP Guideline Objective

"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"

Source: pharmacos.eudra.org

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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[1]
  - Accounted for 70% of market in 2003 – expected to grow to almost 80% by 2008[2]

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

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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

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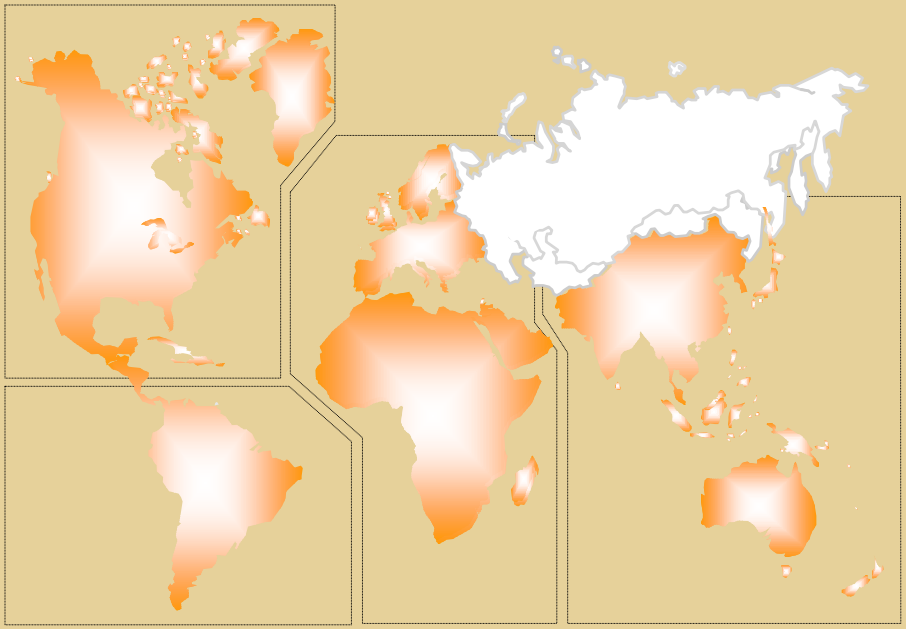

Nearly 4,000 clinical trials, Phase I, II, or III, are taking place worldwide

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

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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

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- 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

Register	Comment	Website
Government		
National Institutes of Health (NIH)	Includes trials of serious and life-threatening diseases	www.ClinicalTrials.gov
NIH and the Food and Drug Administration	GemCRIS. Gene therapy trials from 1989-present	www.gemcris.od.nih.gov
Collaborative Efforts		
Cochrane Central Register of Controlled Trials	Comprehensive register of controlled clinical trials	www.cochrane.org
TrialsCentral	Online register of 200+ US-based trials registers	www.trialscentral.org
Current Controlled Trials	Meta-register compilation of individual registers	www.controlled-trails.com
Industry Register		
CenterWatch	Over 41,000 active industry & government-sponsored trials	www.centerwatch.com

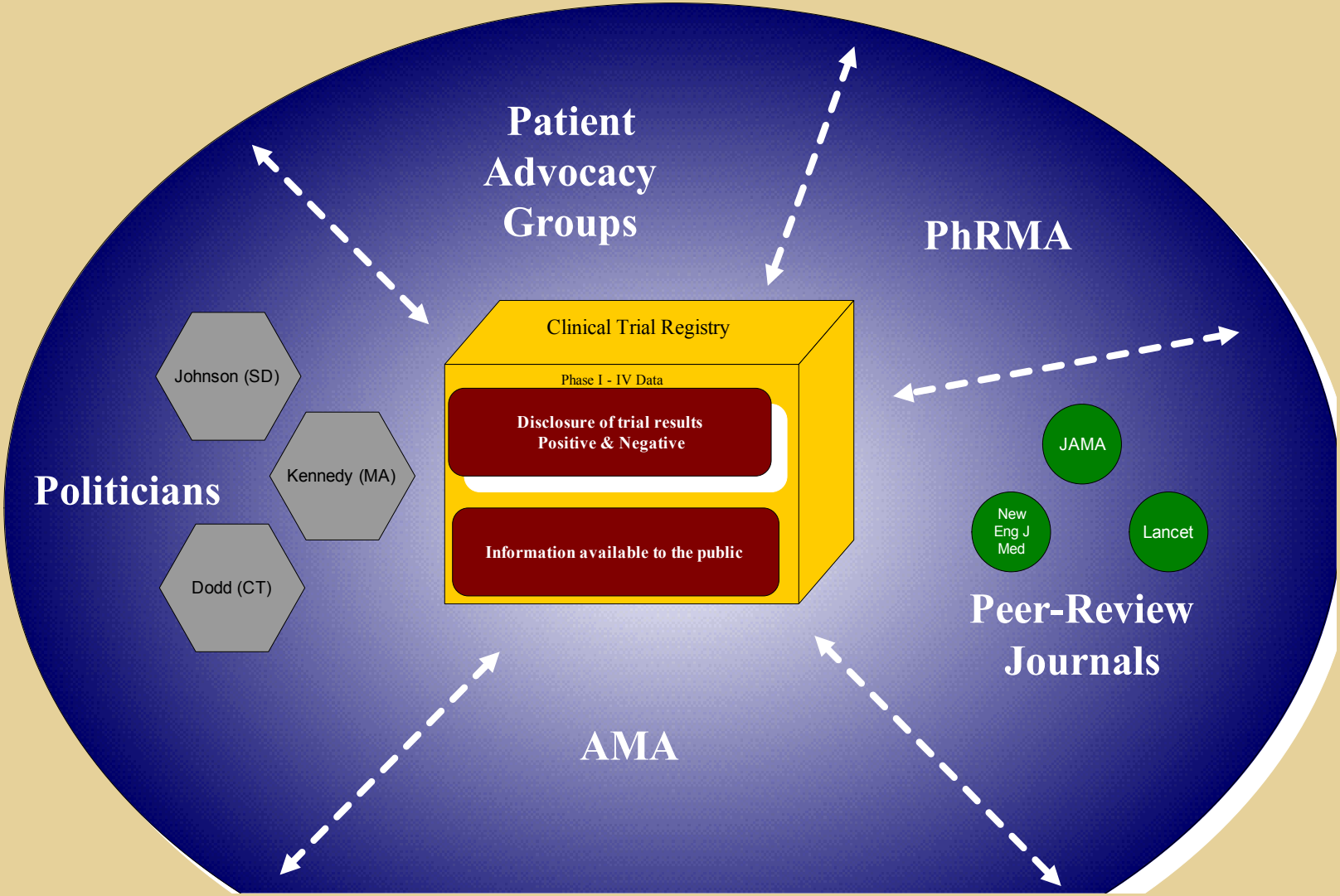
Clinical Trial Registry

In the United States

Registry

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

Clinical Trial Registry



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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

Clinical Trial Registry

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)

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

and more …

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

Source: Applied Clinical Trials. "The Future of Clinical Diagnostics. Oct 04

and more …

Computerized Systems in Clinical Trials

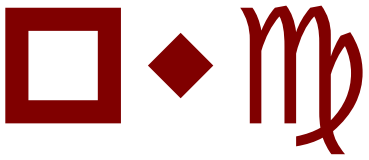
- FDA statement

"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



Your worlds  Our people