Principles and Practice of ICH GCP

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2012 HA Practical Workshop on Clinical Research Compliance
Objective of this session:

To understand:
- Clinical Development
- GCP History
- Good Clinical Practices
- Investigator and EC Responsibilities
- Audit and Inspection Procedures and findings
The Long Road to a New Medicine

**Discovery**
- Project Team and Plans
- Synthesis of Compounds
- Screening

**Exploratory Development**
- Studies in Healthy Volunteers (Phase I)
- Candidate Formulations Developed
- Extensive Safety Studies

**Full Development**
- Clinical Data Analysis
- Large Amounts of Candidate Medicine Synthesized
- Candidate Medicine Tested in 3-10,000 Patients (Phase III)
- Studies in 100-300 Patients (Phase II)

**Registration**
- NDA/MMA
- Extensive Safety Studies
- Clinical Data Analysis

The Long Road to a New Medicine
Attrition is High in the R&D Process

Millions of Compounds Screened

Preclinical Pharmacology

Preclinical Safety

Clinical Pharmacology & Safety

~100 Discovery Approaches

High Risk Process
12-15 years, $800MM+

1 - 2 Products

Discovery
Exploratory Development
Full Development

Idea
Drug

0 5 10 15
11 - 15 Years
Why Conduct Clinical Trials?

- Un-met medical needs
- To determine efficacy
- To confirm its safety

...............Many reasons
What is a Clinical Trial?

An investigation in human subjects intended to:

- discover or verify the clinical, pharmacology and/or other pharmacodynamic effects
- identify any adverse events
- study absorption, distribution, metabolism, and excretion of an investigational product(s)

Full definition: ICH-GCP Section 1.12
What is Health Outcomes?

- Measures the costs and outcomes of alternative treatments, such as Pharmacoconomics (PE) and patient quality of life (QOL)

- Health Outcomes in an *active* component in clinical trials, from Phase II through to Phase IV
EXAMPLES OF TYPES OF COSTS CONSIDERED IN HEALTH OUTCOMES STUDIES

- Cost of a medical team
- Lost earnings and productivity
- Cost of drugs and drug administration
- Cost of a hospital stay
Grouping of Components of QoL

Mental State

Social relations

Functional Competence

Physical Health
Pharmacogenetics

- To identify patients who will respond to our drugs
- To identify patients at risk of adverse events
- Correlating response to “genetic make-up”
- To target therapy more accurately

“The Right Medicine For The Right Patient!”
GCP Timeline

1938 – US Food, Drug, and Cosmetics Act
1947 – Nuremburg Code
1962 – Kefauver-Harris Drug Amendment
1964 – Declaration of Helsinki
1974 – National Research Act
1979 – Belmont Report
1981 – US FDA regulation on ICF and IRBs
1986 – National GCP guideline
1997 – ICH-GCP Guidelines
2001 – EU Clinical Trials Directive

1930s
1940s
1960s
1970s
1980s - Present

Elixir of Sulfanilamide
Nuremburg Trials
Thalidomide
Tuskegee Experiment

US FDA Investigator Inspections
Elixir of Sulfanilamide Tragedy

- In 1937, a toxic solvent was accidentally used to create a liquid formulation of the sulfanilamide drug.
- Resulted in deaths of >100 Americans from acute renal failure.
- Many victims were children.
US Federal Food, Drug and Cosmetics Act

- Increased the FDA’s authority to regulate drugs. This act was the 1st regulation of cosmetics and therapeutic devices.

- Required drug manufactures to provided scientific proof that new products were safe

- Provided authority for factory inspections
Nuremberg Trials

- After WWII, war criminals were brought to trial.
- Nuremberg Germany was a site where the unethical medical trials were taken place in 1945 and 1946.
The Nuremberg Code

- Published in 1947. It sets out 10 standards for the review and conduct of human research, the most significant for which are:

  - Voluntary consent of subjects
  - Justifiable reason for experiment
  - Ability of the subject to withdraw from the research
Thalidomide Tragedy
Thalidomide

- Drug sold to public as a hypnotic in Europe, but investigational in U.S. (1961 – 1962)

- Prescribed to pregnant women to combat morning sickness symptoms.

- >10,000 children in 46 countries were born with deformities as a consequence
Kefauver-Harris Drug Amendment

It required:

- Manufacturers to prove efficacy and safety before marketing a new product
- Informed consent from participants
- Registration of clinical investigators (FDA 1572 form)
Tuskegee Syphilis Experiment

- Conducted by the US Public Health Service from 1932-1972.

- 400 low-income African American males who infected with syphilis were medically monitored but were not told of a proven cure becoming available in 1950s.

- As a consequence, many subjects died during the study
Tuskegee Experiment

• Stopped by the US Dept of Health, Education and Welfare only when its existence was publicized.

• A similar study was conducted by the same group in Guatemala which was only recently unearthed.
Good Clinical Practice (ICH GCP)
ICH Definition

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
International Conference on Harmonization

- Established in 1990
- A constructive forum among the EU, USA and Japan
- Identify areas for mutual acceptance of technical requirements
- Over 60 guidelines written and approved by participants
ICH Guidelines – Four Areas of Focus

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<th>M</th>
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<td>&quot;Quality&quot; Topics, i.e., those relating to chemical and pharmaceutical Quality Assurance (Stability Testing, Impurity Testing, etc.)</td>
<td>&quot;Safety&quot; Topics, i.e., those relating to in vitro and in vivo pre-clinical studies (Carcinogenicity Testing, Genotoxicity Testing, etc.)</td>
<td>&quot;Efficacy&quot; Topics, i.e., those relating to clinical studies in human subject (Dose Response Studies, Good Clinical Practices, etc.)</td>
<td>&quot;Multidisciplinary&quot; Topics, i.e., cross-cutting Topics which do not fit uniquely into one of the above categories (MedDRA, ESTRI, M3, CTD, M5)</td>
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</table>
Impact of ICH

- Global development programs
- Single standard for conduct
- Acceptability of foreign data by FDA
- GCP audits by foreign regulatory authorities
What is Good Clinical Practice (GCP)?

GCP is an international ethical & scientific quality standard for designing, conducting, recording & reporting trials that involve the participation of human subjects.
Two Pillars of GCP

Compliance with this standard provides public reassurance that:

- The rights, safety and well-being of trial subjects are protected
- The data resulting from the trial are complete, accurate and unbiased
ICH GCP components

- Section 1: Glossary (62 definitions)
- Section 2: Principles of ICH GCP (13 points)
- Section 3: IRB / IEC (4 topics)
- Section 4: Investigator (13 topics, consent)
- Section 5: Sponsor (23 topics, monitoring)
- Section 6: Protocol (16 topics)
- Section 7: Inv. Brochure (5 topics)
- Section 8: Documents (Before, during & after)
Basis

- FDA regulations
- EU GCP guidelines
- Japanese GCP
- Nordic guidelines on GCP
- WHO GCP
General Principles of ICH GCP

Follow the ethical principles in the Declaration of Helsinki; GCP and applicable regulatory requirement(s)

Benefit > Risk & Inconvenience

Right, Safety & Well-being > Interest of sciences & Society
Investigator Responsibilities
“Investigator”

“A person responsible for the conduct of the clinical trial at a trial site. The investigator is the responsible leader of the team and may be called the principal investigator”

ICH GCP E6, 1.34
INVESTIGATOR RESPONSIBILITIES

1. Investigator Qualifications and Agreements
2. Adequate Resources
3. Medical Care of Trial Subjects
4. Communication with IRB / IEC
5. Compliance with Protocol
6. Investigational Product(s)
7. Randomisation Procedures and Unblinding
8. Informed Consent of Trial Subjects
9. Records and Reports
10. Safety Reporting
11. Premature Termination or Suspension of a Trial
1 – Investigator Qualifications and Agreements

- Provide evidence of appropriate education, training and experience
- Be thoroughly familiar with the investigational product(s)
- Be aware of and comply with GCP/regulatory requirements
- Permit sponsor monitoring and auditing and Regulatory Authority inspection
- Maintain a list of qualified designates
2 – Adequate Resources

- Be able to meet requirements and schedule
- Have time to conduct the trial on schedule
- Have adequate staff and facilities
- Ensure all trial assistants are adequately informed
3 – Medical Care of Trial Subjects

- Provide adequate care in event of AEs/ significant abnormal lab values
- Inform the subject when medical care of an intercurrent illness is needed
- Inform subject's primary physician of subject participation (recommended)
- Make a reasonable effort to ascertain reason for subject withdrawal
“The “medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.”

ICH GCP E6, 2.7
Some examples of medical care:

- Diagnosis
- Obtaining IC
- Direct supervision of investigational treatment
- Assessment of clinical progress
- Evaluation of AE, including abnormal lab. values
- Decisions about changes in dosing
- Decisions about concomitant treatment
- Assessment of outcome and follow up
Delegating responsibilities - is this allowed? Yes, and...

- For all physician-investigator related responsibilities, delegation must be to another physician.
- IRB must be aware of who is doing what.
- Investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.
- The Declaration of Helsinki states that consent should be obtained by a physician.

Bohaychuk W & Ball G. Applied Clinical Trials Sep 1999: pp. 68-76 or http://ourworld.compuserve.com/homepages/gcrp
4 – Communications with IRB/IEC

- Obtain written approval of IRB/IEC for:
  - Trial Protocol
  - Written Informed Consent and any updates
  - Subject recruitment procedures (e.g. advertisements)
  - Any other written info to the subject
Communications with IRB/IEC

Provide IRB/IEC with:

- a copy of the Investigator Brochure
- any revised/updated study documents
- progress and final study report
- local SAEs; SUSARs and protocol deviation as per EC requirement and timeline
No study start without written Ethics Review Committee approval
5 – Compliance with Protocol

- Agree to comply and sign the protocol

- Obtain prior sponsor and IRB/IEC approval for protocol amendments

- Document any protocol deviation
  - Immediate subject hazards do not require prior approval but the IRB/IEC, Sponsor and Reg Authority should be informed ASAP
Familiar with the properties of the investigational product(s) (IPs)

System in place to ensure that IPs are:
- received by a designated person
- recorded upon receipt
- handled and stored as per study requirement
- dispensed to trial subjects in accordance with the protocol
- returned to the sponsor for destruction
7 – Randomisation and Unblinding

- Treatment code is only broken in accordance with the protocol
- Consult/inform monitor before unblinding
- Notify sponsor promptly of premature unblinding
- Document all codes broken with explanation
8 – Informed Consent

- Comply with ethical principals of the Declaration of Helsinki
- Obtain IRB/IEC approval before use
- Include current information
- Timely re-consent patients on new information
- Simple and non-technical language
Patient Informed Consent must be obtained prior to initiation of any clinical trial procedures.
Basic Elements (ICH 4.8.10)

- Information on the drug / treatment & randomisation
- Fact that Subject is involved in research
- Explanation of study including purpose and duration; no. of trial subjects
- Right to withdraw/terminated
- Contact name and number
- Statement that participation is voluntary, refusal will not affect future treatment
- Any payment / expenses to the subject
- Compensation in case of injury
- Aspects of the trial that are experimental
- Subject responsibility
- Timely informed of new information
- Confidentiality and access to notes
- Any risks or discomforts or benefits
- Alternative procedures or therapy and associated risks and benefits
- ICF

Information on the drug / treatment & randomisation
- Fact that Subject is involved in research
- Explanation of study including purpose and duration; no. of trial subjects
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- Confidentiality and access to notes
- Any risks or discomforts or benefits
- Alternative procedures or therapy and associated risks and benefits
- ICF
9 – Records and Documents

- Ensure accuracy, completeness, legibility and timelines of the data reported to the sponsor in the CRFs and all required documents.

- Any change or correction to a CRF/source documents should be dated, initialed, and explained (if necessary) and should not obscure the original entry.

ABC  ACB

10 May 2004
9 – Records and Documents (Cont.)

- Maintain trial documents (data archiving until at least 2 years after the last approval of a marketing application in an ICH region... In fact, most sponsors would have their specific retention period)

- Allow direct access to all trial-related records upon request of monitor, auditor, IRB/IEC, or regulatory authority
• Submit progress to IRB/IEC at least annually or more frequently if requested

• Upon completion, investigator will provide IRB/IEC with a summary of the trial’s outcome ± any reports required by regulatory authorities
11 – Safety Reporting

- Report all AEs/SAEs to sponsor and EC as per required timeline
- Promptly follow-up with detailed written reports
- Comply with local regulations
12 – Premature Termination or Suspension of a Trial

- Promptly inform all subjects
- Assure appropriate therapy and follow up of subjects
- Inform regulatory authority, where required
What is an Institutional Review Board/Independent Ethics Committee?

According to the ICH Guideline glossary:

An independent body ... constituted of medical / scientific professionals and non-medical / non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of subjects and to provide public assurance of that protection ...
What are IRB/IEC Responsibilities?

IECs / IRBs should:

- review the qualifications of the investigator.....
- maintain / provide a list of members & qualifications
- function as per SOPs
- make decisions at announced meetings with quorum
- maintain adequate records!
IEC / IRB Membership (ICH)

- At least 5 members
- At least 1 member independent of site
- At least 1 member whose primary area of interest is non-scientific
- Ensure that only independent members vote/give opinion - not the investigator!
Information Required by IEC / IRB

- **Safety Information** - IB + any other information

- **Protocol/amendments** - objectives, exposure, placebo use, number/duration/ invasiveness of assessments, etc.

- **Suitability of investigator** - CV or other documents showing qualification

- **Subject Recruitment Procedures** - walk in, GP referral, advertising (copy needed)
Information Required by IEC / IRB

- **Informed Consent** - the ICF and any written information for subjects
- **Compensation arrangements** - for patients in cases of injury-death as a result of the trial
- **Finance** - amount and method of any payment to subject
- **Other** - Anything else the IEC may need e.g. an application form, copy of the CRF
Audit & Inspection
Annual Growth in Clinical Investigations (by country)

41% of principal investigators in FDA regulatory submissions were based outside the US (2007)

Dr. Ken Kaitin, Tufts Center for the Study of Drug Development (2008)
Off-Shoring To Reduce Costs of RCTs

**Overall Indexed Clinical Trial Costs**

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<td>Germany</td>
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Within the next 3 years, up to 65% of clinical studies in FDA regulatory submissions will be conducted outside the US.

RCT results depend on:
- drug
- study design
- study conduct
- subgroups
- local culture

Source: Adopted from FDA website

*Dr. Ken Kaitin, Tufts Center for the Study of Drug Development (2008)*
Number of Phase III Trials Started in 2008

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<td>Philippines</td>
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*CAGR=Compound annual growth rate

Source: www.clinicaltrials.gov.

India’s Phase III is growing seven times faster than the global average.
International Clinical Investigator Inspections* (CDER, FY 2002-2009)

*Based on Inspection start date [1/5/2010]

Source: Adopted from FDA website
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*Conducted for FDA/CDER from 1980 through 08/4/08; total:889
**data reviewed in U.S.

Source: Adopted from FDA website
Drugs GCP Inspection Experience By Region

1980-2008
n=889

45%
17%
15%
11%
1%
7%
4%

2006-2008
n=252

31%
12%
12%
11%
3%

*CI inspections performed for CDER

Source: Adopted from FDA website
FDA is Coming!
FDA Guidance

- 21 CFR 314.106 and 21 CFR 312.120

- Compliance Program Guidance Manuals
  - Sponsors, CROs and Monitors – 7348.810
  - Clinical Investigators – 7348.811
  - Institutional Review Board (IRB) – 7348.809

- Guideline for the Monitoring of Clinical Investigations

- Information Sheets
  - Informed consent
What Do They Inspect?

- Protocol (original & revisions)
- Investigator agreements & financial disclosures
- Case report forms
- Inclusion/Exclusion criteria
- Informed consent forms
- Adverse events
- Other required reports
- Electronic records
- Other study subject records
What Do They Inspect?

- Qualification records for Clinical Investigators
- Training records
- Study delegation sheet
- Correspondence
- Device accountability records
- Standard operating procedures for conduct of study
## Common CI Deficiencies

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<th>Issue</th>
<th>Description</th>
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<td>Inadequate safety reporting</td>
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<tr>
<td>Failure to maintain case histories</td>
<td>Failure to submit progress reports</td>
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<td>Inadequate IP accountability</td>
<td>Failure to follow conditions of approval imposed by an IRB</td>
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<tr>
<td>Inadequate informed consent process</td>
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</table>
Some Interesting Phrases...

- “In God We Trust, From Everyone Else We Want to See the Data!”
- “If it is not documented, it didn’t occur!”
- “Trust, but verify”
THANK YOU