Fundamentals of International Clinical Research Training Course

6-11 September 2015
Bangkok, Thailand
Training course

• Funded by NIH

• Organized by The International Clinical Studies Support Center (ICSSC) of FHI360

Participants

• International clinical investigators who are funded by Division of Microbiology and Infectious Diseases (DMID), NIAID, NIH
Training Series organized by ICSSC

> The Fundamentals of Clinical Research Workshop

> Data Management Training

> Biostatistics Training

> Study Design Training

> Good Clinical Practice Training

> Laboratory Quality Improvement and Safety Training

> Research Ethics and IRB Operations Training

> Science Writing Training
CRF
cohort
Case-Control study
monitoring
ICH GCP
Sample Size
Source doc
RCT
SOP
GLP
IEC
Informed Consent
IRB
QC
QA
Participants at Bangkok 2015 workshop

5 from FTM
• Narisara Chantratita
• Suparat Phuanukoonnon
• Wanlapa Roobsoong
• Wang Nguitragool
• Rungnapa Phunpang

30 more from
Thailand, Myanmar, India, Kenya, Sri Lanka, Taiwan, Malasia, China, Ethiopia, Uganda, South Africa, Malawi, USA,
Lecturers

• Mario Chen, PhD  
  (Biostatistics)  
  Lead Statistician of ICSSC

• Michelle Immelman, PharmD  
  (Field Operations)  
  Director of Clinical Operations,  
  Global Research and Services at FHI360
Lecturers

- **Kenneth Schulz, PhD, MBA**  
  (Study Design)  
  Distinguished Scientist,  
  Quantitative Sciences, FHI360

- **Jeremy Sugarman, MD, MPH, MA**  
  (Research Ethics)  
  Professor of Bioethics and Medicine, Johns Hopkins University
Erik Jolles (Data management)
Senior Data Manager of Research Informatics

Laura Phillips
Administrative manager
Materials covered (5 days)

1. Study design & biostatistics
   - Types of study design, biostatistics, sample size
calculation, analysis plan, etc.

2. Ethics
   - Ethics in design of clinical research, assessing risks and
benefits, inform consent process, IRB, Safety oversight, etc.
Materials covered (5 days)

3. Data management
   - Source documents, Case Report Form (CRF), Standard Operating Procedure (SOP), others forms, etc

4. Field Operation & regulation
   - ICH GCP, Staffing, Quality Control (QC)/Quality Assurance (QA), site monitoring
Course materials distributed

- All power point presentations on different topics

- Sample Essential Regulatory Document Binder

- Handbook of essential Concepts in Clinical Research
Clinical Study

Planning → Conducting

- Objectives
- Study Design
- Sample size
- Analysis Plan

- Ethics approval
- Safety monitoring
- QC/QA
- Reporting
Study Design
Taxonomy
Prospective Cohort Design

**The Present**
- Population
- Sample
  - Exposure present
  - Exposure absent

**The Future**
- Outcome
- No Outcome
- Outcome
- No Outcome
Case-Control Design

The Past or Present

Exposure present
Exposure absent

The Present

Outcome
Sample of cases
Population with disease (cases)

No Outcome
Sample of controls
Much larger population without disease (controls)
RCT PARADIGM

Population of Interest

Sample (Subset)

Randomize

Unexposed

Exposed

Outcome Assessment

Other Allocation Approach?
Retention, Retention, Retention!

“Loss to follow up” in a cohort/RCT study is a bias and can invalidate the study.
Get a good biostatistician involved early on.

Role of Lead Study Biostatistician (LSB)

• Study design & Sample size calculation
• Protocol Development
• Data Management
• Study Implementation
• Study Monitoring
• Data analysis
• Report/Manuscript writing
Good Data Analysis Plan is essential.

- Provides the statistical methodology for the assessment of the primary objective(s):
  - Statistical Hypotheses and testing procedures/analysis strategy
- Discusses statistical methods to be used in planned interim analyses.
- Should be written prior to un-blinded review of the data or even prior to data collection:
  - Helps you prepare for report and manuscript writing
  - Helps in the validity and credibility of the results
Data Analysis

- Fishing Expedition
- Data Mining
- Data Dredging
- Data Torturing
- Data Driven Analysis
- Shotgun Approach
- Exploratory Analysis
If you torture the data long enough, it will confess.
Ronald Coase
Performing Clinical Study: 
ICH GCP Guidelines

GCP is
“An international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involved participation of human subjects.

ICH is
“International Conference on Harmonization of the Technical Requirements for the Registration of Pharmaceuticals for Human Use (www.ICH.org)”
The Principles of ICH GCP

**Ethical**

- Well-being of participants
- Benefits versus risks
- Ethics committee approval
- Voluntary informed consent
- Participant confidentiality

**Scientific**

- Scientifically sound study design
- Study conducted by qualified individuals
- Quality assurance and quality control systems
ICH E6
Document describing key elements of clinical studies.

1. Glossary
2. Principles of GCP
3. IEC/IRB Responsibility
4. Investigator Responsibilities
5. Sponsors Responsibilities
6. Protocol and Amendments
7. Investigator’s Brochure
8. Essential Documents
The regulation of research ethics is a public activity

• Attention to the ethics of research is essential to respect those who choose to participate
• Although investigators and sponsors retain significant moral responsibility for protecting the rights and interests of participants in research,
• ‘external’ bodies are positioned to provide additional protection
Oversight

- Institutions
- Federal agencies
- Accrediting bodies (eg, AAHRPP)
- DMCs, DSMB
- IRBs
Good Clinical Practice

- Protection of participants
- Credibility of results
  - Scientific design
  - Responsible conduct of research
  - Responsibilities of sponsors
  - Responsibilities of investigators
Design the clinical research

• Randomization
  – Why Use Randomization?
    • Minimize observer bias
    • Minimize patient selection bias

• Placebos

• Confidentiality

• Selection of Subjects
Confidentiality

• Why?
  — Protect participants from social risks: insurance, jobs, housing, and the law

• When?
  – Any research posing potential social and some economic risks

• Challenges?
  – Must be considered in the design of research
  – Strategies may be expensive
Subject Selection

• Why?
  – Generalizability
  – Justice

• When?
  – Disease or condition is of relevance to the population or population subgroup

• Challenges?
  – Statistical power
  – Recruitment and retention
Risks and Benefits

• Recognized by numerous international bodies
  – Risks to subjects are minimized
  – Risks to subjects are reasonable in relation to anticipated benefits, if any, and the importance of the knowledge that may be expected to result

• Attention to welfare as well as rights
Minimizing Risks

- Qualified personnel
- Substitution of procedures
- Monitoring
- Exclude especially susceptible subjects
Risks and benefits may affect different domains of health status

- Risks may be born by one individual to benefit another
- Risks may be born by individuals to benefit society
- Risks may be born by society to benefit individuals
Balancing risks/benefits

Although balancing risks and benefits can be difficult, or impossible, there is an obligation to minimize risks and maximize potential benefits in research

- Requires evaluation of risks
- Such an evaluation not only promotes the welfare of subjects but also enhances consent and the accuracy of claims about justice
Advertisements

• No claims that test article is safe or effective
• No claims that test article is equivalent or superior to any other drug, biologic or device
• No use of terms such as “new treatment”, “new medication”, “new drug”
• No promise of “free medical treatment” when intent is that subjects won’t be charged for participation
• If subjects will be paid, no emphasis on payment
Informed consent

• Autonomous authorization
  – Ethical principle of respect for persons
  – Right to liberty

• Social rules of consent
  – Consent of minors
  – Special forms
  – Witnesses
Process of informed consent: Beyond consent forms

• **Threshold**
  – Decision-making capacity
  – Voluntariness

• **Information**
  – Disclosure
  – Understanding

• **Authorization**
  – Indication of agreement
  – Consent forms:
    • Consistent with Disclosure
    • Readable
The need for oversight

• Responsible parties
  – IRBs (aka, REBs, RECs, etc)
  – DMCs (aka DSMBs)
Internal Review Boards

IRB Membership

• At least 5 members

• Diversity of the members
  – Race
  – Gender
  – Cultural
  – profession/specialty
  – members who are not clinicians or scientists
  – members who are not from the Institution
IRB Continuing review of research

• At intervals appropriate to the degree of risk
• Not less than once a year
• Should be done at convened meetings except if eligible for expedited review - When is this permissible?
How is continuing review date determined?

• Continuing review must occur “on or before the date when IRB approval expires”
• Focus on date of convened meeting at which IRB approval was granted and NOT date of letter
• Review of a change in a protocol does not alter the continuing review due date
What occurs if there is a lapse in continuing review?

- The research must STOP, unless the IRB finds that it is in the best interests of subjects to continue participate in the research

- Enrollment of new subjects cannot occur
Essential documents

• **IRB/IEC records**
  – Copies of protocols and informed consent forms
  – Minutes of meetings
  – Records of continuing review
  – Correspondence with investigators
  – List of IRB/IEC members

• **IRB/IEC records to be retained for 3 years after completion of study**
Removing the I from IRB?

• Inherent conflicts of interest with institutional review
• Level of expertise may exceed that of the institution
• Multicenter trials more common
  – Multiple reviews can be confusing and unnecessary
  – Difficulty with conducting meaningful continuing review
Suspension of IRB Approval

• IRB approval may be suspended if there is undue harm to subjects or evidence of not following IRB rules

• If IRB suspension occurs, the IRB must document the reason, notify investigator, institutional officials and the government
What is a DMC?

• A group charged with reviewing the progress, conduct and outcomes of an ongoing RCT

• Other names:
  – Data Safety and Monitoring Board (DSMB)
  – Treatment Effects Monitoring Committee (TEMC)
Who is on a DMC?

• Clinical experts
• Biostatistician/trialist
• Ethicist? Patient advocate? Investigators?
• Representative of sponsor?
• Must be independent
Purpose of Safety Monitoring

• Provide an independent and objective review in timely fashion
• Monitor safety, study conduct, study progress, and when appropriate, interim analysis of efficacy data
• Particular emphasis on “serious and unexpected” events
• Ad hoc members as appropriate
• Must be able to meet on an Ad hoc basis when safety issues arise
• Typically used in early phase, low risk trials such as PK and immunogenicity studies
• Availability in real time
• No conflicts of interest, impartiality is critical to independent decision making
• Communication with DMID primarily through the Safety Oversight Committee Support (SOCS) staff
Adverse Events

• An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. (GCP)
Reason for Adverse Event Collection and Reporting

- The most important responsibilities of investigators and sponsors of clinical research studies:
  - Protection of study participants.
  - Collection of accurate and reproducible data.

- All clinical studies greater than minimal risk must have an AE collection and reporting system in place.
Detecting Adverse Events

- Symptoms (headache, nausea)
- Physical findings (elevated BP, lump)
- Abnormal lab values
- Behavioral changes
- Toxicities
How Would You Describe an AE?

• Wherever possible, describe AE in terms of a change in the status or diagnosis, NOT the symptoms.
• Example: “decrease in Hb from 10.1 to 7.3”
• Example: “influenza” rather than stomach cramps, fever, chills.
What Is a Serious Adverse Event?

- Death
- Congenital anomaly or birth defect
- Permanent Disability
- Hospitalization or prolongation of hospitalization
- Life threatening (at immediate risk of death)
- Condition that requires medical or surgical intervention to prevent one of the above
Severe vs Serious

• Severe:
  – How intense was that particular condition (mild, moderate, severe)

• Serious:
  – How threatening to the existence of the person?

• Severe AE ≠ Serious AE
SOP

- Promote consistency and efficiency on how work is performed and checked
- Internal training material
- Meet regulatory guidance requirements
- Opportunity to examine and improve processes
- Accountability for performing tasks
SOP

• First draft should be written by staff who perform the task
• Pilot the first draft with several staff when task is performed.
• Update the draft based on the results of the pilot
• Review each SOP yearly
• Control the documents with approval dates, applicability dates, and version numbers
Data management

What Information Should be Contained in a DM Plan?

- Definition of Source Data/Documents
- Data Capture/Case Report Forms
- Data Transfer
- Data Entry System/Validation
- Data Entry/Filing
- Data Querying
- Data Set Creation
- Data Storage/Archiving

- External Data (e.g., lab data)
- Protocol Violations
- Serious Adverse Events
- Coding of Medical Terms
- Data Safety Monitoring Board (DSMB), and other regulatory reports
- Data Assessments
- Data Audits
LIMS

• Laboratory Information Management System
• Software that is used in the laboratory for the management of samples, laboratory users, instruments, standards and other laboratory functions.
• Differ greatly in functionality but can include sample tracking, QC, reports, results and data export.
• Systems should be in place to track collected lab samples
• Process should be set up for data transfer from lab to data center to ensure that participant confidentiality is not compromised
• Need personnel responsible for each step of the process
• All steps and responsibilities should be documented in the DM plan
Quality management

• QC: the “day-to-day” observation and documentation of the site’s work processes to ensure that accepted procedures are followed

• QA: periodic, systematic, objective and comprehensive examination of the total work effort

• QM: QA+QC

• Sponsor is responsible for quality

• Sponsor must implement and maintain QC and QA systems with written SOPs
Essential documents

- Documents that permit evaluation of the conduct of a trial and the quality of the data
- Auditable
- Before/ during/ after trials
- Document retention, by who and how long
## Examples

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<thead>
<tr>
<th>Indicator</th>
<th>Criteria</th>
<th>Yes/No</th>
<th>Comments</th>
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<tr>
<td>Consent</td>
<td>Consent form signed and dated in ink by subject/legally authorized representative prior to study procedures being performed?</td>
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<tr>
<td>Missed visits</td>
<td>Has subject missed any visits? If yes, documented?</td>
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<td>AE/SAE reporting</td>
<td>AEs and SAEs recorded and reported properly?</td>
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<td>Documentation standards</td>
<td>Source documentation complete and accurate?</td>
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<td>Are handwritten chart notes legible, signed &amp; dated by clinician?</td>
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<td>Errors corrected: single line, initialed, dated, reason?</td>
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More sources

• [www.ICH.org](http://www.ICH.org)
• Check with ORS