Clinical Trials & Ethics

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Good Clinical Practice

What does GCP mean to You?

Good Clinical Practice

An international ethical and scientific quality standard for designing , conducting, recording and reporting trials that involve the participation of human subjects

(Cont.) GCP is…

- Compliance with this standard provides public assurance that the rights, safety, and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki .

Why GCP ?

Tuskagee Experiment (1932-1972)
– On Natural history of Syphilis (400 patients with Syh and 200 without syh)

- Nazi camp trial (During WWII,1940's)
- Fabricated data (US, 1990's) - New Jersey

- The Jewish chronic Disease Hospital Study 1963 (involved the injection of foreign, liver cancer cells into patients)
  - oral inform consent
  - no discussion on method
  - no Ethical clearance
- The Willow brook study involving injection hepatitis virus in mentally defective children(1963-1996)

- Nurember Code (1947)

"Voluntary consent of human subject
is absolutely essential"

Declaration of Helsinki

- Revised five times
- Recently in October 2000
- "the benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods."

Development of Ethical Guidelines

1900	The Directive on Human Experimentation
1947	Nuremberg Code
1964, 1975, 1983, 1989, 1996, 2000	Declaration of Helsinki
1979	Belmont Report
1982, 1993, 2002	International Ethical Guidelines for Biomedical Research Involving Human Subjects

http://www.patientcenters.com/trials/news/ethics_of.html, Emanuel, Ezekiel, et al. "What Makes Clinical Research Ethical?" ,Talbot, David and Joan Perou. "Ethical Issues"

Why GCP ?

Avoidance of fraud and error

- Protection of human rights

ICH GCP ….

What is ICH ?

ICH

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

Aim

Have a single dossier
accepted every where in the world

Philosophy/Purpose of ICH

- Eliminate Duplication in Tests to meet Different Regulatory Requirements
- More Efficient Use of Resources
- Timely Access of Patients to Safe and Effective "New Drugs"

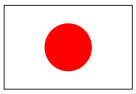
ICH Sponsors and Regions

EMEA: The European Commission

EFPIA: European Federation of Pharmaceutical Industries Association

FDA: CDER & CBER

PhRMA Pharmaceutical Research and Manufactures of America



JMHW: Japanese Ministry of Health and Welfare

JPMA: Japanese Pharmaceutical Manufactures Association

ICH Topics

- Safety [S] - *in vitro* & *in vivo* preclinical testing
- Quality [Q]- chemical & pharmaceutical QA
- Efficacy [E]- clinical studies in humans
- Multidisciplinary [M]- terminology, electronic standards, common documents

ICH Efficacy Guidelines *(1)*

- E1: Exposure (to assess clinical safety)
- E2: Clinical Safety (includes data management)
- E3: Study Reports
- E4: Dose Response Studies
- E5: Ethnic Factors (acceptability of foreign data)

ICH Efficacy Guidelines *(2)*

- E6: Good Clinical Practices
- E7 & 11: Special Populations
- E8,9,10: Clinical Trials Design
- (including biostatistics)
- E12: Therapeutic Categories

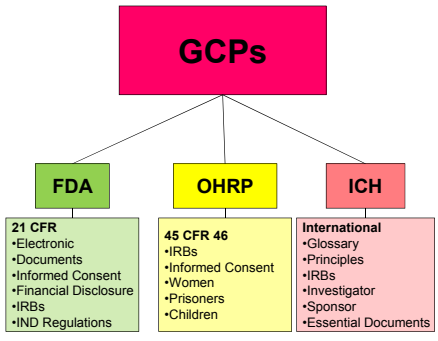
GCP adoption in the Asia Pacific Region

- Original ICH GCP 1996

JAPAN 1/4/97; USA 9/5/97; EU 17/7/97

Since then:

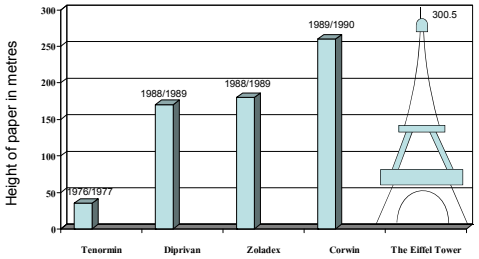
- Singapore GCP 1998
- Malaysian GCP 1999
- Chinese GCP 1999
- Thailand 2000
- Indonesia 2001
- Malaysian GCP 1999 and 2nd edition 2004



Research in the various fields emphasises the use of standardized practices

- Good Agriculture Practice in domesticating plantation of potential plants
- Good Storage Practice in storing the raw materials
- Good Manufacturing Practice in producing the products
- Good Laboratory Practice in performing laboratory testing
- Good Clinical Practice in conducting clinical trials

www.ich.org



Summary E6 in ICH guideline

2. THE PRINCIPLES OF ICH GCP

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki

2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society

2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB) / independent ethics committee (IEC) approval/favorable opinion.

2.7 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.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

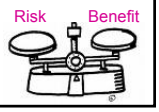
2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

The Principles of ICH GCP

Ethical Principles

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



Key Elements

- Protection of subjects
- Adherence to standard operating procedures
- Verifiable data
- Correct archiving of data
- Proper reporting of adverse events

Principles of ICH Good Clinical Practice (1)

All individuals conducting trial must be "qualified"

- Each subject must give informed consent freely
- Informed consent must be approved by IRB/EC

Principles of ICH Good Clinical Practice (2)

- All trial information must be managed under a document control system
- Subject confidentiality must be maintained
- Investigational product should be cGMP
- Quality assurance must be in place at study sites

Concept

Good Clinical Practice (GCP) is an international ethical and scientific quality standard

Designing
Conducting
Recording
Reporting

Trials that involve human subjects

Designing

Protocol

Detailed written plan about the way to conduct, monitor, audit and report the study.

Role of placebo
According to New Declaration of Helsinki

Conducting

Conducting

Written in the Protocol &
Standard Operating Procedures

Protection of Trial Subjects

Informed consent

"freely given"

Why do we need informed consent?

- Ethical concerns-Nuremberg Code
- Good Clinical Practice
- Informed consent is legally effective by code of federal regulations in the USA

As a tool to confirm "GCP" compliance

- Volunteer must be *fully informed* of the research such as test articles or test procedure, roles of volunteers, benefits, disadvantages, etc. before voluntarily making decision to participate in the study
- No coerce, *voluntarily participate*

Medical care

Will always be the responsibility of a qualified physician

Recording

- Regulatory documents
- Source documents
- CRFs

Regulatory documents

- Informed consent / information
- Investigators' CVs
- Authorized signature form
- Product importation authorization
- Lab. certificate / normal values
- TSA
- Agreement - not using product prior to IM

Source Documents

Original documents or certified copies containing data related to the trial

Direct Access to Source Data / Documents

- Clinical Monitor
- Audits
- IEC / IRB
- Inspection

Source Documents

Storage and Retention of the Documents:

- Safe & secure place; limited access
- 2 y after last approval for marketing
- 15 y for identification list

CRF Completion

- Use point ball pen
- Complete all items
- Print - for all entries

CRF Completion

Enter initial & allocated No. at recruitment (against name on subject identification)

Result
- first entry to subject's file

CRF
- complete during participation

Data
- consistent with SD
- discrepancies ??

CRF Correction

Authorized staff Do Not obscure the original entry

To make correction :

~~PAZ CL~~
PAT 9/11/98 *jk*

Date of vaccination
2/10/98

Sex :

Male = 1

29/11/98 *jk*

Female = 2

Reporting

Safety Reporting

SAEs :

- FATAL
- Life threatening
- Permanently disabling
- Hospitalization for Rx of

AE

- Congenital anomaly
- Require intervention

Safety Reporting

Perform Causality Assessment

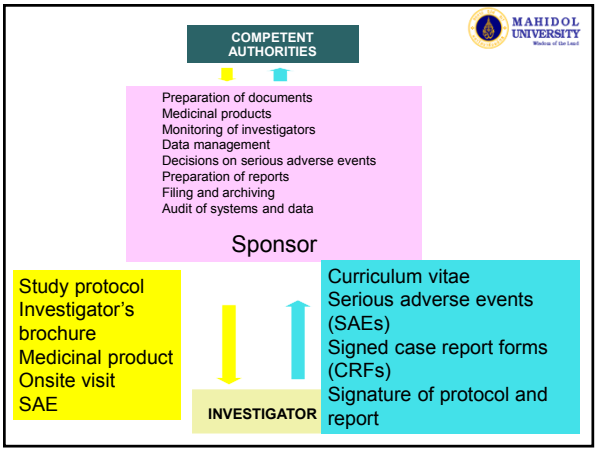
- Not related
- Unlikely
- Possible
- Probable
- Most Probable

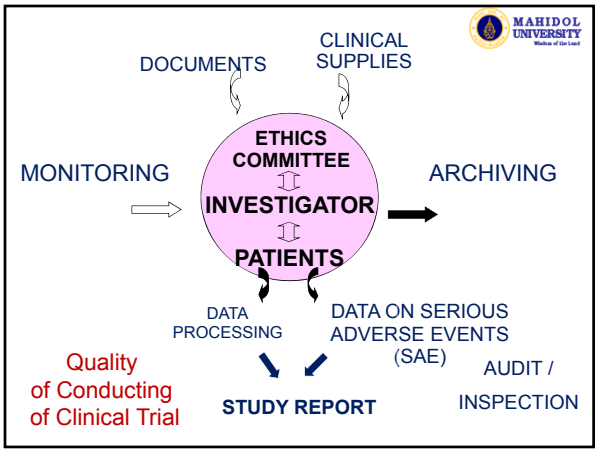
Safety Reporting Procedures

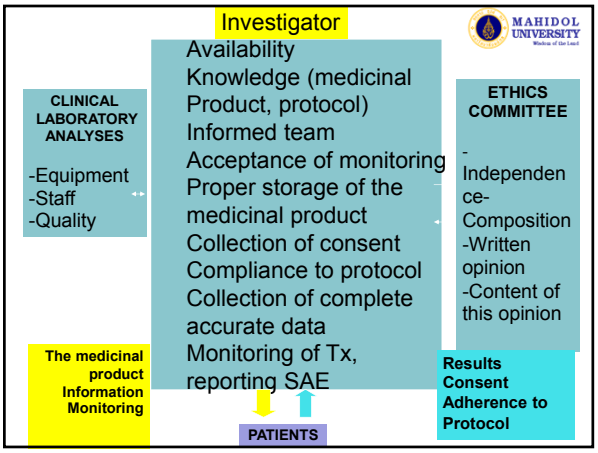
All AEs - Report in CRF

SAE :

- Report immediately - w / 24 h
- Fax initial SAE report form (Alert form)
- Send SAE form - w /5d
- Send relevant information (when available)
- Information for Death Report







The Investigator' s Role

- Before the trial
- During the trial
- After the trial

Pre study activity : INITIATION VISIT

Objective :
- To ensure that the site for testing is adequate
- To present the trial and its conduct in detailed to all personnel

- Occur after the site has been formally selected and before study subject enrollment
- After the initiation visit, the monitor will prepare a report of all activities

ITEMS TO BE ADDRESSED AT STUDY INITIATION VISITS

- Detailed review of the protocol and the requirement to follow/adhere to the protocol
- Overall review of the study medication/ device, handling and prescribing, and procedure associated with the randomization and blinding
- Verify receipt and explain management of the supplies to the site personnel

- Study subject cannot be enrolled until study medication/ device have been checked by the monitor
- Completion and management of CRFs, requirements for submission of CRFs
- Arrangement with clinical laboratories, pharmacists, ward etc.
- Obtaining of subject informed consent, submissions to ethics committee/ IRBs during the study

- Procedures for reporting AEs,
- Proposed schedule for monitoring and the need for access to source documents
- Requirement to retain records securely for specified time periods

ITEMS TO BE PROVIDED TO THE STUDY SITE BEFORE THE STUDY BEGINS

- Current IB
- Protocol (signed) and protocol amendments (signed)
- Other signed agreement (e.g. confidentiality agreement, financial agreement)
- Sufficient study medication/ device
- Sufficient CRFs, subject information sheets and consent forms

- Regulatory notification/ approval documentation
- Guidelines for GCP
- Special equipment (if require)
- Ethics committee/ IRB review and approval letter
- Investigator CV and/ or other statement of qualifications, CVs and training records of all site staff
- Pre-study correspondence and assessment reports
- Clinical laboratory reference ranges, clinical laboratory certification/ accreditation

The Investigator' s Role

- Interest in the scientific aspects of the study and ensures that the study is benefited to the study population
- Put the welfare and interest of the subjects as foremost priority
- Sufficient time to conduct the trial
- Ensure the confidentiality of the product, protocol ,trial procedures and patients

Before the trial

- Qualifications and agreements
- Resources- staff
  facilities
  appropriate subjects
  archives

Qualifications and agreements

- By education/training
- Has knowledge of GCP and regulatory requirement
- Has knowledge on the drugs (IB, Protocol)
- Permit monitoring, auditing and inspection

Resources- staff

- Have adequate number of qualify staff (authorized signature form , CV)
- Ensure that all persons assisting with the trial are adequately informed about the protocol, study drug, their related duties and functions

Resources- facilities

- Site/ facility resources are adequate
  - confidentiality
  - safety condition/treatment and care of the subject
  - lab assay
  - product storage

Resources-Document archiving

Safe, secure, and maintain subject confidentiality

✓ IRB/EC - members, documents, minutes ,correspondence
✓ Documents, during the trial
✓ Subject ID list retained for minimum of 15 years
✓ Source documents, CRF >10 years

Communicate with IRB/EC

- Obtain written approval for
  - Trial protocol
  - Written patient information sheet
  - Written inform consent form
  - Subject recruitment procedures

Documents to be submitted to IRB/EC

- IB
- Trial protocol
- Consent forms and patient information sheet
- All educational materials
- CVs
- Others requested

Responsibilities during the trial

- Screening and recruitment of study participants
- Inform consent from participants
- Protocol compliance
- Trial participants' medical care
- Randomized procedure and unblinding
- Safety reporting
- Product storage and accountability

A Study of Asthma, UK ,10 Patients

- Patient were not informed that the study was double blinded randomized –placebo controlled trial.
- The ethics committee was informed that the patients would receive minor compensation (But they received 300 USD)

A STUDY OF AN ANTICO-AGULANT,15 PATIENTS

- Patients were not informed that the study medication had become available in the market during the time of the study. Consequently patients continued to be treated with placebo.

- Maintain study subject clinical notes (e.g. source document) separately from CRFs
- Maintain a confidential list identifying the number/ code and names of all subject entered into the study
- Allow authorized representatives of sponsor/ CRO and regulatory authority in order to verify the data records on CRFs
- Ensure CRFs are complete and accurate

- During the monitoring visits, the monitors must be allowed to communicate with all site personnel
- Preparing and submitting progress reports of the study
- Handling premature termination of a trial
- Reporting trial results
- Allow an independent audit and/ or inspection of all study documents and facilities

Closed out

- Source data verification completed documented
- But cleaning of data continues
- Clarification of all queries especially on safety profiles
- Medication accountability form completed
- Return all unused medication and empty containers per sponsor's recommendation

- Maintain the security and accountability of clinical study supplies
- All CRFs should be completed and collected
- Archive all CRFs, and document associated with the study for a minimum of 15 years
- Maintain the records of study medication dispensing and return or disposition (as instructed by the sponsor/ CRO) after completion or termination of the study

- Notify IRB of study completion and plan to submit final report
- Review the final clinical report, and sign and date signature page after review
- Agree to the publication policies
- Agree to the Sponsor/ CRO' s ownership of the data

A study of diabetes,Canada,21 patients

- The sponsor archives were protected from fire by water sprinklers.

All items were in paper

A study of an anticoagulant,Italy,10 patients

- The on-line computer system for randomization required the investigator to provide subject's full name to CRO to issue of treatment allocation.
- Full names were maintained in the data base of the CRO.

SPONSOR/CRO SHOULD NEVER RETAINED
ANY DOCUMENTS WITH SUBJECT'S NAMES IN THEIR ARCHIVES

SETTING UP CLINICAL STUDY

- A lengthy process (it may take more than a year to set up a multi-centre trial)
- Prepare many documents (e.g. Protocol, CRFs, Investigator Brochure)
- Assess study facilities (e.g. Study sites, CROs, Clinical laboratories)
- Consider regulatory review
- Undertake negotiations and agreement with study sites (e.g. Contracts, finance, confidentiality, indemnity, insurance)

- Consider ethical aspects of the study (ethics committee, IRB review, Informed consent requirements)
- Organize study medications/ devices (e.g. requisition, purchasing, labeling and shipment)
- Site initiation process by the monitors must be done before any study subjects can be treated

IRB/IEC review

Are the investigator and staff familiar with IRB/IEC requirements and processes?

Does the IRB/IEC have special document requirement?

Can the site obtain IRB/IEC approval according to the sponsor's schedule?

Essential Documents (I)

- EC & Regulatory approval
  - Date of submission
  - Which version of documents
  - EC comments
  - EC reviewing comments (individual member comment during the reviewing process) : asked by authority !
  - EC member lists
  - Import license

Essential Documents (II)

- Protocol, amendment, patient information sheet, informed consent, study questionnaire
  - Date of development, receipt
  - Date of distribution to investigator
  - Signature & date of receipt acknowledgement
  - Date of validation of questionnaire (if applicable)
  - Comments from each party on the development of protocol
  - Any changes of the protocol

Essential Documents (III)

- Investigator file :
  - Protocol, Patient information sheet, informed consent : version approved by EC & use in the study*
  - EC approval letter*
  - Copy of signed & dated informed consent (can be kept in the CRF in case study is on going)*
  - Import license (if applicable)*
  - Investigator agreement
  - Financial agreement
  - Investigator & team member CVs*

Essential Documents (III) cont.

- Correspondence between site & monitor (study manager)*
- Investigator brochure*
- Role & responsibility of each member*
- Sample of signature*
- Patient enrollment log*
- Drug dispensing log, accountability

Essential Documents (IV)

- Case record form : CRF
  - Signed & dated informed consent
  - Completeness of CRF
  - Investigator signed & dated in the assigned pages
  - Accuracy of data compared with source data
  - Black ball point pen
  - Logical date according to protocol !
  - Source data has to be available (can be randomly checked)

Essential Documents (V)

- Source data
  - Patient note (OPD card) : should document the information required by the protocol (monitor can prepare the check list page & attach to the OPD card)
  - Other documents : lab test, ECG, X-rays, CT scan,
  - Translator is required in case local language is not English (FDA inspection might ask for an independent translator)

Essential Documents (VI)

- Correspondences
  - E-mail, letter, telephone note
  - Internal : between operational team
  - External : to sponsor, to sites, biometrics
  - Comments from each party
  - Project manager following log

Next-Treatment and follow-up stage

- Prepare periodic data reports for safety monitoring committee
- Prepare periodic reports on performance of clinical and resource centers
- Carry out periodic training sessions to maintain high level of proficiency at clinics in treatment and data collection procedures
- Evaluate data processing procedures and modify as necessary
- Develop and test data collection forms for close-out stage

- Prepare summary of study results for presentation to participating investigators for use in close-out stage
- Assume responsibility for location of patients lost to follow-up
- Take initiative for reviewing study priorities and for proposing changes in the organizational or operating structure of the trial
- Assume major role in writing paper on design and methods

Patient close-out stage

- Monitor for adherence to agreed-upon patient close-out procedures
- Develop plans for final data editing
- Design and test computer programs needed for final data analysis
- Develop plans for final disposition of study data
- Coordinate logistics of patient disengagement from treatment
- Un-blinding
- Assume key role in writing papers summarizing results of the trial

Termination stage

- Perform final data edit and undertake final analysis of data according to plans outlined by study leadership
- Implement study plans for disposition of study records
- Assume leadership role in paper writing activities
- Undertake extra measures to locate patients lost to follow-up

- Supervise collection and disposal of unused study medications
- Distribute draft manuscripts and published papers to participating centers
- Serve as funding center for activities in the trial after termination of support for clinics

Monitoring

"The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)"

ICH-GCP [1.38]

Monitor

- a professional
- a valuable resource and partner to the study team
- the main line of communication between the sponsor and the investigator
- a key contact for trial-related issues

Role of the monitor (1)

When planning a clinical trial, use the skills of the monitor for:

- communicating with the sponsor and project team
- site management advice
- problem solving
- provision of practical support
- training team members

Role of the monitor (2)

During the trial the monitor will review:

Protocol adherence
- SDV (Source Data Verification)
- AE reporting
- deviations

Subject recruitment
- informed consent process
- recruitment schedules
- drug accountability

Site management issues
- trouble shooting
- motivating the team

Record management
- Essential documents
- CRFs

Audit

Why quality matters

"Good Clinical Practice (GCP) is an international ethical and ***scientific quality standard for designing, conducting,*** *recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that:*

- the rights, safety, and well-being of trial subjects are protected and that the clinical trial data are credible."

Introduction to ICH–GCP

Quality Control (QC) versus Quality Assurance (QA)

	QC	QA
Role	Part of the process of ensuring quality	Third-party assurance of quality
Responsibility	Study team	Audit group
Examples	• Monitoring − Data check of CRFs against source documents	• Audit − Sample check of CRF data
Summary	Procedures that ensure that the process is in control and 'makes things correctly'	Procedures that verify that QC procedures are effective and 'the correct things are made'

Quality is teamwork

Investigator and study team
- Protocol compliance
- Standard proceses
- Local regulations

Sponsor
- On-site monitoring
- Audits
- SOPs

Regulatory authorities
- inspections

Data protection agencies
- inspections

IRB/IEC
- SOPs

Quality at the investigator site (1)

"The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements."

ICH–GCP [4.1.3]

Quality at the investigator site (2)

The investigator must:

- train the study team
- ensure that documentation is in accordance with ICH–GCP and the sponsor's requirements
- instil a culture of openness and accountability
- make sure that appropriate procedures are in place and are followed
- make sure that everyone understands their role and the importance of quality

Monitoring

Definition of Monitoring

"The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)"

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Role of Monitor (2)

During the trial the monitor will review:

Protocol Adherence	Subject recruitment
• SDV (Source Data Verification) • AE reporting • deviations	• informed consent process • recruitment schedule • drug accountability
Site management issues	**Record management**
• trouble shooting • motivating the team	• essential documents • CRFs

Role of Monitor (3)

After the trial:

- making sure that all study data have been collected
- informing the site of its archiving responsibilities
- checking the return/destruction of the investigational product
- making sure that the IRB/IEC is notified of study closure

Frequency of monitoring

The number and timing of monitoring visits is dependent on:

Study issues

- Objective
- Purpose
- Design
- Study phase
- Complexity
- Blinding/masking
- Size
- Endpoints
- data collection

Site issues

- experience of the investigator and study team
- Logistics
- Problems encountered
- Number of subjects enrolled

Type of site visit

- Pre-study; Study initiation;
- Monitoring; Study close out

The frequency of visits will also vary before, during, and after the study

Communicating with the monitor

The monitor is a key contact for all trial-related issues

Practical issues:

- agree methods and timings of communication with the monitor and the sponsor
- obtain alternate contact details in case of unavailability
- appoint a suitably qualified individual as point of contact for the monitor
- log all contacts with the monitor

Good communication with the monitor is essential for the smooth running of a trial

Audit and Inspections

Definition of Audit

"A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)"

ICH–GCP [1.6]

Purpose of Audit

"The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements"

ICH–GCP [5.19.1]

Audit

Time

- During the study
- After the study

Whom

- Internal (Sponsor or CRO)
- External (Investigator site)

Type

- Routine
- For-cause: either has evidence of or suspect noncompliance

Differences between monitoring and auditing

	Monitoring	Auditing
Position	Part of study conduct	Independent third party
Focus	Study conduct	Study compliance
Timing	Study duration	One time point snapshot in time
Approach	Surveillance/partnering	Systematic
Interfaces	Sponsor and site	Regulatory authorities

Definition of inspection

"The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/ or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies)"

ICH–GCP [1.29]

Main Type of US FDA Inspection

1. **Surveillance/ routine**
- Conducted periodically
- Usually due pending application for market approval

2 . **For-Cause**
- Result of questions or problems noted
- Reviewer following review of study data (e.g.conflicting results submitted independently)

For-cause inspection

- Suspicion of wrong doing, questionable practices
- Large volume of work
- Outside field of specialty
- Efficacy too good
- No adverse events
- Too many patients
- Sponsor reports 'problems'
- Incongruous laboratory results

Differences between audits and inspections

	Audits	Inspections
Who conducts them?	Independent unit of the sponsor company	Regulatory authorities, IRB/IEC, Data Protection Agencies
What do they check?	Trial conduct and compliance with: • Protocol • ICH–GCP • Regulatory requirements: US FDA, EU (EMEA)	
When do they occur?	Any time before, during, or after the trial	
Why do they take place?	• randomly (Routine audit/inspection) • for cause (For-cause audit/inspection)	
How can you help?	• follow the protocol, ICH–GCP, SOP, regulatory requirements • document and file everything	

Conduct of audits and inspections

Process:
- scheduling of audit/inspection
- pre-audit review of sponsor file (by sponsor auditors)
- opening meeting
- review of study conduct
- discussions with the investigator and site staff
- closing meeting
- report

Audits and inspections (1)

What do they review?

Trial Issues

- protocol adherence
- compliance with ICH–GCP and applicable regulations
- compliance with SOPs
- trial documentation
- archiving
- product handling/accountability
- trial monitoring
- data validity
- IRB/IEC approvals/correspondence
- communications between the site and the sponsor

Audits and inspections (2)

Subject Issues

- rights and safety
- informed consent
- documents
- procedures
- AE/SAE reporting

Site Issues

- team qualifications
- delegation
- resources
- facilities
- certification
- interactions with external vendors

Conduct of audits and inspections (1)

Systems and facilities audit

- Policies and procedures that are often audited include
  - Frequency of monitoring visits
  - Documentation of monitoring visits
  - Conduct of pretrial meetings
  - Preparation and review of protocol
  - Process for reporting adverse reactions to the sponsor
  - Process for reporting adverse reactions to regulatory authorities
  - Validations of computers used in the clinical trial
  - Documents sent to the investigators

Conduct of audits and inspections (2)

Data Verification & Validation Audit

- Data validation is meant to provide the sponsor and regulatory authorities with greater assurance that the results are accurate and trustworthy
- Major questions addressed in this type of audit are
  - What was done
  - Why and when was it done
  - Who did it
  - How was it documented
  - What was the result or outcome

Conduct of audits and inspections (3)

Data Verification & Validation Audit

- Study Master File audits
- Database audits during and near end of process (review database against source data)
- Tables, figures and listings audits
- Clinical Study Report (Safety Report, Expert Report) audits

Conduct of audits and inspections (4)

Site Audit

- Investigator obligations
- Sponsor/ monitor obligations
- Regulatory documentation
- Transcription accuracy of raw data into CRF
- Adequacy of drug accountability
- Site personnel
- Comprehensive reports

Conduct of audits and inspections (5)

Investigator's Adherence to a Clinical Trial

- **Administrative issues of the clinical trial being audited**
  - Protocol name and number
  - Sponsor
  - Names of investigators and staff
  - Addresses and telephone numbers
  - Name of monitors
  - Facilities used
  - Name of contact person at the site
  - Date of audit

Conduct of audits and inspections (6)

Investigator's Adherence to a Clinical Trial

- **Conduct of the clinical trial – technical points**
  - Details of IEC/ IRB approval
  - Adequacy of informed consent form
  - Appropriateness of methods for obtaining informed consents
  - Storage of medicine before, during and after use by patients
  - Adequacy of laboratories (e.g. certification, reference ranges)

Conduct of audits and inspections (7)

Investigator's Adherence to a Clinical Trial

- **Conduct of the clinical trial – patients**
  - Adequacy of patients enrolled
  - Number of patients enrolled to date and planned totals
  - Number of deaths and severe adverse events, plus a brief description of each
  - Reports on AEs and SAEs in accordance with protocol and regulatory requirements
  - Register of patient dropouts and discontinued patients

Conduct of audits and inspections (8)

Investigator's Adherence to a Clinical Trial

- **Conduct of the clinical trial – data collection forms**
  - Completeness of the records
  - Accuracy of the records
  - Comparison with original medical records
  - Patient informed consent present
  - Concurrent illness
  - Concomitant therapy
  - Dosage adjustments
  - Adverse event and reaction reports

Conduct of audits and inspections (9)

Investigator's Adherence to a Clinical Trial

- **Relationship between investigator and sponsor**
  - Frequency of visits by monitors and adequacy of reports
  - Speed of transmission of data to core facility, laboratory, and sponsor
  - Speed of correcting errors in data collection forms
  - Speed and completeness of reporting serious adverse events and reactions to the sponsor

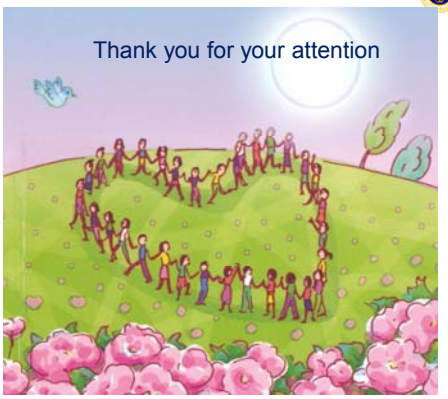
Possible outcomes of audits/inspections

Minor observation	Major observation	Critical observation
Deviations from accepted procedures or regulations that will not adversely affect subjects or data, but should be dealt with appropriately	The quality/integrity of data or rights and safety of subjects may be adversely affected if practices continue	The quality/integrity of data or rights and safety of subjects are adversely affected

The type of observation will determine the action taken by the sponsor or regulatory authority

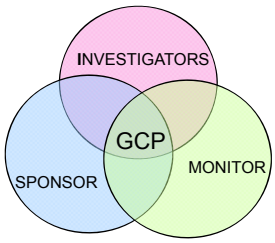
Observations in audits and inspections

- Non-compliance with protocol
- Informed consent problems
- Inadequate/missing source documents/CRF
- Inadequate record keeping
- Inadequate IRB/IEC process/documentation
- Inappropriate delegation/ inadequate PI oversight
- Fraud/misconduct



GCP : Our Responsibilities

(BANGKOK AIDSVACCINE EVALUATION GROUPS)



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