Good Clinical Practices

A Simple Guide

James D. Campbell, MD, MS
University of Maryland School of Medicine
Overview of Rounds
What are Good Clinical Practices?

In human subject research, GCPs are the ethical and scientific guidelines we use to enhance quality.

- Design
- Conduct
- Reporting and recording
- Monitoring
- Auditing
- Analysis
What are Good Clinical Practices?

*Here is something most people don’t tell you and most people don’t figure out for a long time...*

There is no one ultimate resource or guide or rule or SOP or universally accepted set of simple instructions.

However, most differences sponsor to sponsor and guideline to guideline are variations on a theme.
Components of GCPs at UMB

• 45 CFR 46
  – OHRP
• 21 CFR 11, 50, 54, 56, and 312
  – FDA
• FDA Form 1572
  – ‘contract’ signed by investigator
• International Conference on Harmonization (ICH)
• UMB HRPP Policies and Procedures
• Also, sponsors and departments and divisions
Good Clinical Practice
Principles of ICH GCP

UMB HRPO mantra—

Culture of conscience
Culture of compliance
Good Clinical Practice
Principles of ICH GCP

The International Conference on Harmonization (ICH) 1996

Objectives:
• Provide a unified standard for conducting trials that would provide data for submission to regulatory agencies
• EU, US, and Japan
• To facilitate mutual acceptance of clinical data

The guidelines were developed in accordance with existing standards in the US, EU, Japan, Australia, Canada, Nordic countries, and WHO.
Good Clinical Practice
Principles of ICH GCP

- Research should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and the applicable regulatory requirements.
  
  - Read the Belmont Report
  - Read the new Declaration of Helsinki (2013)
  - Use the CFR to your advantage
  - GCP principles to guide your SOPs
DoH Clause 27. “When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.”
Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual subject and society. A trial should be initiated and continued only if the anticipated benefits justify risks.

- IRB (and subjects) care most about risks and benefits
- Honestly provide all of them
  - Easy to distort overtly or unknowingly
- Think about how you are minimizing risks by design and procedures
- When new information comes along- think about it in terms of the volunteer risk/benefit calculus
Good Clinical Practice
Principles of ICH GCP- New Info and Risk

• At trial start, only evidence HIV PrEP works is in monkeys and in theory or extrapolation
• You explain this to all enrollees
• 6 months later, it shown that HIV PrEP works for gay men, but you are working with straight mostly married couples.
• Options
  – Do nothing
  – Give Grand Rounds on how your trial will probably succeed
  – Tell your IRB
  – Discuss the issue with participants
  – Reconsent
  – Stop the trial because the question is answered.
Good Clinical Practice
Principles of ICH GCP

• The rights, safety, and well-being of the trial participants are the most important considerations and should prevail over interests of science and society.
  – We are dealing with people and their specimens/data. Their interests trump.
  – What someone consents to is what they consent to
  – Be kind, gracious, and respectful
  – Get alternate contact means
  – Know what the rules are for safety reporting
  – Provide a safety monitoring plan and then follow it, whether simple or complex
  – Read and report global safety reports- summarize them for the IRB and your team
Good Clinical Practice
Principles of ICH GCP- New IBs

- You are doing 10 industry sponsored trials.
- Products you study are perfectonib, imawondadrugumab, optimab, superbonib, and topdogamab.
- Sponsor sends you a new IB for one product

You should?
- File IB in your essential documents with all the other study related sponsor emails that are too long and detailed to review
- Read the IB changes and make sure nothing needs to be done
- Send to IRB as RNI with reason for RNI as “sponsor requires we submit this stuff to you”
- Review; make sure there are no new risks or other info pertinent to your study and especially to your participants; submit to IRB with explanation of new items and why you are choosing to inform or not inform participants
Good Clinical Practice
Principles of ICH GCP

• The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

  – If you work with investigational products or licensed products, be an expert on them
  – Don’t be convinced by web links, news reports, sponsor propaganda, government pressure—do you think the info supports the trial?
  – Read the IB or PI; when new versions come along, read and decide, don’t merely submit
  – Know what is going on in the field
Good Clinical Practice
Principles of ICH GCP

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

  – Protocol in template format assures all items are included
  – Every detail in the protocol should be known by investigator and coordinator
  – Overzealous on SOPs
  – Be type A organized
  – Don’t assume anything- ask. There are no dumb questions.
Good Clinical Practice
Principles of ICH GCP

• A trial should be conducted in compliance with a protocol that has received prior IRB/IEC approval/favorable opinion.

  – Full detailed protocol is best
  – Protocol is not a guideline or suggestion
  – Try to avoid modifications- make them before submission, when possible
  – No deviations at all, even if you think what you are doing fits the “spirit” of the protocol- example: exclusion criteria
  – Follow versions and note when draft amendments are approved and in force.
  – Learn Cicero; ask questions; understand details of the process
Good Clinical Practice
Principles of ICH GCP- Eligibility

• The protocol states that the serum creatinine must be within the gender-specific normal range for your lab.
• The (unstated) reason for including this criterion is to exclude those with renal insufficiency.
• Lab norm is 0.76 to 1.27 mg/dL for men.
• A potential male subject has a creatinine of 0.72 mg/dL.

– May you enroll him?
– What options do you have?
Good Clinical Practice

Principles of ICH GCP

• The medical care given to, and medical decisions made on behalf of, participants should always be the responsibility of a qualified physician or, when appropriate, a qualified dentist.

  – Do not allow assistants without adequate training, licensure, etc. to make clinical decisions. Especially difficult with that very intelligent research assistant.
  – Document that you (investigator) made the decisions-eligibility, treatment of AEs, intercurrent illness, determining how to follow up a lab abnormality
Good Clinical Practice
Principles of ICH GCP

• Each individual involved in conducting a clinical trial should be qualified by education, training, and experience to perform his or her respective tasks.

  – Develop or use a good form for delegated responsibilities
  – Carefully track training, licenses, certificates, etc.
  – Form FDA 1572 for IND studies (similar principles if not)
  – Know what persons are permitted to do on your protocol and in your region
Good Clinical Practice
Principles of ICH GCP- Personnel qualifications

• Can a smart person with a bachelor’s degree in history take vital signs?
• If you train a person who is not a nurse, medical assistant, EMT, etc. to draw blood, is that ok?
• Can a nurse do physical exams? What if the only thing is to check for axillary lymph nodes?
• Your study has lots of screening labs. Can a nurse coordinator interpret the results?
PI Responsibilities
Investigational New Drugs

FDA Form 1572

- Conduct study per protocol
- Personally conduct or supervise investigation
- Inform volunteers that drugs are investigational
- Obtain proper informed consent
- Obtain proper IRB approval
- Report adverse experiences to the sponsor
- Read and understand Investigator’s Brochure
- Ensure staff are informed of their obligations
- Maintain adequate and accurate records
- Make records available for inspection
- Ensure IRB complies with requirements
- Promptly report to IRB all changes, unanticipated problems involving risks
Good Clinical Practice
Principles of ICH GCP

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

  – Prior to any and all study related activities (except description of study so that participant can decide)
  – Revise with any new pertinent information and decide if reconsenting is needed
  – Many ways to exert undue influence
  – Illiteracy, translated consent, impartial witness
  – Need all the elements of informed consent
Good Clinical Practice
Principles of ICH GCP- Consenting

• You really want to meet your enrollment targets
• You are the main one consenting/explaining the study
• The consent form says you may be protected against Ebola if you get the vaccine; you may not. It also lists a number of possible side effects.

• Do you?
  – Talk slowly and passionately about the great protection in non-human primates, that other similar vaccines have been completely safe?
  – Gloss over and seem dismissive of the risks?
  – Use the trust and white coat to convince the participant all will be okay?
Good Clinical Practice
Principles of ICH GCP

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

  – Notes to file
  – Real time everything- charting
  – Make reports
  – Ask questions exactly as written
  – Prepare fully for all visits- no surprises
  – Document per sponsor guidelines, exactly
  – Pilot your CRFs; sometimes “clear” fields are not clear
  – Essential documents
Good Clinical Practice
Principles of ICH GCP- trial information

• A data field has a date and 4 check boxes below: exact date, unknown year, unknown month, unknown day.

• A 40 year-old participant says he was diagnosed with myopia at age 5, probably in 1969 or 1970, and he remembers getting glasses just before starting kindergarten.

• **What do you write in the date field and which box do you check?**
  – Check exact date and come to an agreed upon exact date: 12 Aug 1970
  – Check unknown day and guess on month
  – Check unknown month and put 01 Sep 1969 as a guess
  – Check all the unknown boxes and do not enter a date
  – Other thoughts?
Good Clinical Practice
Principles of ICH GCP

• The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements.

  – Separate codes from coded records
  – Prevent hard copy and electronic loss of confidentiality
  – Confidentiality often confused with privacy
  – Let participants know how you will protect but that you cannot assure 100%
  – The greater the potential risk of loss of confidentiality the greater the burden for protections
Good Clinical Practice
Principles of ICH GCP

• Investigational products should be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice (GMP) standards and they should be used in accordance with an approved protocol.

  – Careful records for all product handling
  – 24/7/365 storage oversight
  – How will product be destroyed?
You are investigating the efficacy of antiretrovirals (HIV medications) to prevent HIV acquisition, in rural Uganda.

These drugs are used clinically and stored in boxes on shelves at whatever ambient temperature it is.

The sponsor and manufacturer require controlled storage with low humidity and cool temperatures.

- How do you go about arranging this?
- How do you assure it stays in range?
- If it goes 1 degree out of range, now what?
Good Clinical Practice
Principles of ICH GCP

• Systems with procedures that ensure the quality of every aspect of the trial should be implemented (QA & QC).

  – Monitor early
  – Pilot CRFs
  – Whole team has improvement input
  – Stakeholders input in development and throughout
  – Adequate resources: population, time, staff
  – Consider windows for all visits
Good Clinical Practice
Principles of ICH GCP- Quality

• You expect an FDA inspection is possible when the trial ends. Which preparation may be helpful?
  – An internal quality management plan
  – Frequent, tough-as-nails monitoring visits
  – Review of common FDA 483s
  – Notification of HRPO of expectation of FDA visit
  – A mock inspection
  – Reviewing with your team all known “sticky points” and refreshing your memory on approach
Source Documents & Records

“ALCOA”

Apply **ALCOA** to achieve data quality:

- **Attributable**: Is it obvious who wrote it?
- **Legible**: Can it be read?
- **Contemporaneous**: Information current and in the correct time frame?
- **Original**: Is it a copy? Has it been altered?
- **Accurate**: Are conflicting data recorded elsewhere?

**Other Documentation Guidelines:**

- Sign and date all entries
- All document users listed on signature/initials/responsibilities log
- Do not obliterate
  - Correct errors with single line, initial, date.
- If serial evaluations or entries in a note, write the time.
- Label all documents with volunteer identifier.
“The interest of science should never take precedence over the well-being of the subject.”

“It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.”

Declaration of Helsinki
Thank You.

Acknowledgments
HRPO
IRB
CVD colleagues
Dr. Bob Rosenthal
Dr. Bruce Jarrell
Dr. Bob Edelman
Participants