What is Good Clinical Practice?

- “International ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials.”
- Aim is to protect the rights, integrity and confidentiality of trial subjects
- Results in credible data

History

• Prior to development of guidelines – no standards lead to clinical studies that were potentially dangerous and unethical
  ▫ Experiments conducted by Nazi doctors and scientists on concentration camp visitors in WWII
  ▫ Tuskegee Study – “Tuskegee Study of Untreated Syphilis in the Negro Male”
• Nuremberg Code 1947 – 10 points for conducting ethical research in human subjects
• Declaration of Helsinki 1964 – World Medical Association – recommendations guiding medical research involving humans
History

• Belmont Report Ethical Principles (1979) – Respect for persons → informed consent, protection of vulnerable populations; Beneficence → non-malfeasance; Justice → fairness

• International Conference on Harmonisation (IHC) – consolidate guidance on GCP – 1990s US, EU and Japan → www.ihc.org → 1997 endorsed by FDA

13 principals of ICH-GCP

• Ethics
  1. Ethical conduct of clinical trials
  2. The benefits of the trial justify the risks
  3. The rights, safety and wellbeing of the subjects prevail

• Protocol and Science
  4. There is non-clinical and clinical information that support the trial
  5. The clinical trial should be scientifically sound with a clear detailed protocol.
13 principals of ICH-GCP

• Responsibilities
  6. There should be IRB/IEC approval prior to initiation of study
  7. Medical care and decisions should be performed by qualified physician or dentist
  8. Each individual involved in the trial is qualified (education, training and experience) to perform trial tasks

• Informed Consent
  9. Informed consent should be obtained from every subject prior to participation
13 principals of ICH-GCP

• Data Quality and Integrity
  10. Accurate reporting, interpretation and verification
  11. Protection of confidentiality of records.

• Investigational products (IPs)
  12. IPs should be manufactured, handled and stored in accordance with Good Manufacturing Practice (GMP)

• Quality Control/Quality Assurance
  13. There should be systems in place to ensure the quality every aspect of the trial
Who is responsible for GCP compliance? (Or why to we have to keep taking training on GCP)

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Everyone
Case 1

• You have noticed that in the rural part of your state that there seems to be an excessive amount of Crohn’s disease among Latino farm workers.
• You suspect that an exposure to the mycobacteriosaurus which is found in the crops in your state is responsible for this “outbreak” of Crohn’s disease.
• You develop an antibiotic regiment that is highly effective for mycobacteriosaurus and now want to conduct a placebo controlled trial to treat these patients.
Case 1

Consentimiento Informado

- You develop an informed consent in Spanish that has been approved by the IRB
- You hire a Spanish interpreter to help with the informed consent
- Enrollment starts and you are amazed that everyone asked to enroll is agreeable. There is 100% enrollment
- There is an interim analysis done at 6 months into the trial and the results are not what was expected.
Case 1

• While walking through one of the migrant farm worker housing units you noted a box with 100 vials of your carefully labeled study medication — none of the seals have been broken on the vials.
• You find that the study subjects all signed onto the study because they thought their job was in jeopardy if they did not participate. The interpreter did not explain what the trial was about and to your dismay the subjects did not read the informed consent due to literacy issues.
GCP

- **What was good?**
  - There appeared to be sound scientific reasoning for the trial.
  - IRB approval was obtained prior to initiation.
  - Informed consent was translated into Spanish and there was an interpreter.

- **What went wrong? How did this case deviate from GCP?**
  - Informed consent was not informed.
  - Vulnerable population – potential for coercion
  - Translator not qualified to perform his/her tasks.
Case 2

• Caribou Pharma has developed a promising new growth factor enema preparation for the treatment of ulcerative colitis. They embark on a clinical trial comparing the growth factor to a placebo enema preparation.
• The physician in charge of the trial at Deer University noted that when the enemas were mixed, one set of study medication was slightly tinted.
Case 2 Continued

• The physician thought that the tinted enemas were most likely the active medication.
• As patients were randomized into the study he worked with pharmacist to make sure that the tinted enemas went to the patients with the highest disease activity index thinking that they needed the active medication more than the patients who had less active disease.
Case 2 Continued

• Deer University enrolled the largest number of patients into this clinical trial from among the study sites.
• The overall study results showed that the enema therapy was ineffective
• At Deer University there was a 20% response to active therapy and a 30% response to placebo
• At the other sites combined, there was a 70% response to active drug and a 30% response to placebo
GCP

• What happened in this case?
• How does it deviate from GCP?
• How can randomization blind be ensured in a study – to comply with GCP?
• How can study sites ensure that this type of event will not occur?
• Is there a problem in trial design?
GCP

• **Ethics**
  - Physician was concerned about patients but if there was a worry about the severity of disease in a group of patients – the benefits of the trial may not justify the risks.

• **Protocol and science**
  - Non-compliant with protocol however there are design flaws that allowed this to happen. Treating physician should be blinded to investigational product. Randomization should be independent and fixed. Bias was introduced into the trial.
Case 3

• You have been asked to participate in a trial of a new monoclonal antibody treatment for ulcerative colitis.
• One of the endpoints of the trial is mucosal healing. A sigmoidoscopy is performed at screening and then after 12 weeks of study medication. If there is improvement the patient continues in the trial.
• The patient has returned for the 12 week sigmoidoscopy and the recording equipment fails.
Case 3

- You do the sigmoidoscopy and you think things are better and the patient is begging to stay in the trial. You score the endoscopic findings as being slightly better so that the patient has a chance to stay in the trial and take pictures.
- Due to the technology failure you do not have video documentation of the sigmoidoscopy but you do have pictures.
GCP

• Should the patient remain in the trial?
• What are your responsibilities to GCP in this trial?
• What is the sponsors responsibility?
• What is the responsibility of the CRO?
GCP

• **Data quality and integrity**
  - In this case the failure of the equipment is leading to problems with reporting and interpretation and verification of results.
  - You want there to be an improvement so the patient can remain in the trial – placing bias into the decision if you make that decision.

• **Quality Control/Quality Assurance**
  - Critical technology for should be have consistent quality checks to try to prevent failure.
  - There must be systems in place to deal with technology failure – this is the responsibility of the sponsor/CRO