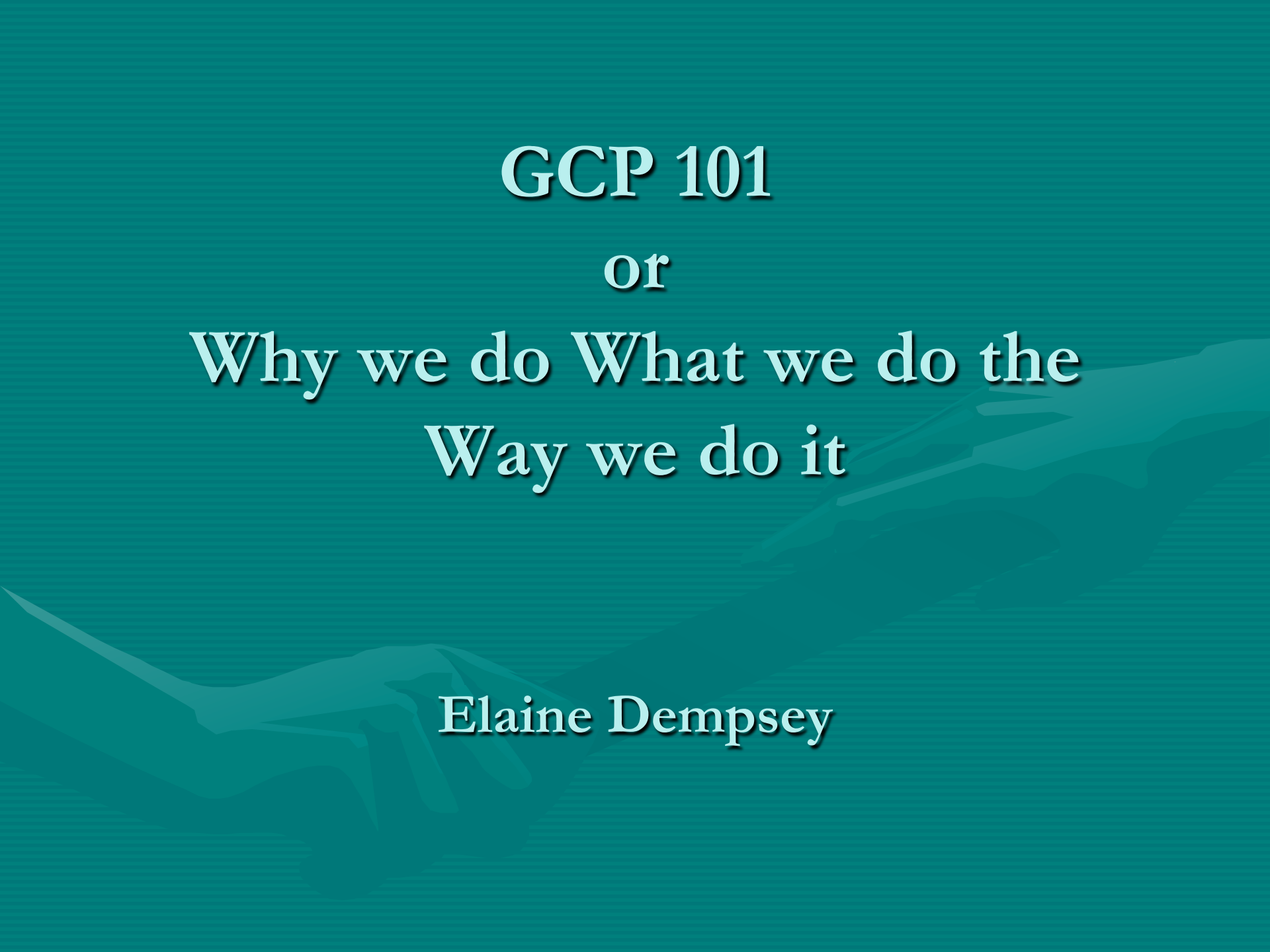




GCP 101

or

Why we do What we do the
Way we do it

Elaine Dempsey

What is a Good Clinical Practice?

Good Clinical Practice is defined as follows by the Institute for the Advancement of Clinical Research:

“Good Clinical Practice (GCP) is an international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials. GCP provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are respected and protected.”

History

- Ethics in Medicine

- Historically, concerns about the ethics in medicine centered around therapeutics and actual treatment of illness
- It wasn't until the middle of the 20th century (following WWII) that we saw a new emphasis on medical research
- When examples of abuses in medical research were publicized then national and international efforts to protect the rights and welfare of human subjects in research began
- Most of these occurrences were situations where investigators ignored the fundamental rights of human subjects

A Clinical Trial is.....

- Any investigation or study that uses human subjects and
 - is intended to test the clinical effects of an investigational agent and/or
 - to identify any adverse reactions to an investigational agent to assess the safety and efficacy

A Subject is.....A participant in research either as a recipient of the test article or control. A subject may be a healthy human or a patient

The Nuremberg Doctors Trial of 1946

- During WWII medical “experiments” were done on concentration camp internees to obtain information useful for the survival of German military personnel under conditions that would be encountered in war.
- These were mostly survival studies; at high altitudes without oxygen, in frigid water, after wounds of various sorts and severity, after exposures to chemical and biological agents.
- Many died as a result of these “experiments”.
- After a trial of the Nazi leadership by an International Military Tribunal, a trial known as the “Nazi Doctors Trial” was conducted by judges and prosecutors from the U.S. (U.S. vs. Karl Brandt et al.).
- The 23 defendants, including 20 physicians, were charged with murder, torture and other atrocities. 15 were found guilty and 7 were sentenced to death.

Nuremberg Code - 1947

- Informed consent of volunteers must be obtained without coercion in any form
- Human experiments should be based on prior animal studies
- Anticipated scientific results should justify the experiment
- Only qualified scientists should conduct medical research
- Risk to benefit ratio should be commensurate with the problem
- Physical and mental suffering and injury should be avoided
- There should be no expectation of death or disabling injury from the experiment
- Investigator should be prepared to stop the experiment if there is indication of danger
- Subjects should be able to withdraw without penalty

The Declaration of Helsinki - 1964

Written by the World Federation of Physicians and adopted in 1964:

- Incorporated the Nuremberg Code
- Defined therapeutic vs. non-therapeutic research
- Allowed enrollment of certain subjects in therapeutic research without consent so that they might benefit from important medical advances
- Allowed legal guardians to enroll patients in therapeutic and non-therapeutic research trials

Willowbrook 1963-66

- This study enrolled institutionalized mentally retarded children in order to investigate the natural history of viral hepatitis with which they were deliberately infected.
- Willowbrook was overcrowded and only the research wing had room for new patients. Parents had to give permission for their children to be in the study in order for them to be placed at Willowbrook.
- Coercing parents to enroll their children, using a captive and vulnerable subject population for research, and putting minors at risk for no benefit to them violated all of the ethical principles that should guide physicians doing research.

Tuskegee Study of Untreated Syphilis in Negro Males (1932 - 1972)

- A study to determine the course of untreated syphilis was designed by an agency of the USPHS that later became the CDC
- Conducted in Tuskegee, Alabama starting in 1932
- 200-300 black males were to be enrolled
- The study was to end with a non-therapeutic spinal tap in May 1933
- Went on for the next 10 years without review
- Penicillin accepted as the treatment for Syphilis in 1943
- Subjects were continued in the study untreated and exempted from the WWII draft
- By 1951 PCN was widely available but subjects were still not treated because it was realized that the study represented a “never again opportunity”

Tuskegee Study of Untreated Syphilis in Negro Males - contd

- An expose' was published in the Atlanta Constitution (1972)
- Senate hearings led to federal regulations (1973)
- The CDC told survivors that the government would pay their medical bills for the remainder of their lives
- In 1975 medical coverage was extended to wives and children with congenital syphilis
- President Clinton publicly apologized to 8 survivors and their families at a white house ceremony in May 1997
- National Center for Bioethics in Research established at Tuskegee U. in 1999

Protection of Human Subjects in Research Progression

- *Food and Drug Act of 1906*
- *Food, Drug and Cosmetic Act – 1938*
- *The Nuremburg Code – 1947*
- *Kefauver-Harris Amendments – 1962*
- *The Helsinki Declaration – 1964*
- *USPHS IRB / Informed Consent – 1966*
- *The Belmont Report – 1969*
- *Consolidated DHHS/FDA Regulations – 1981*
- *ICH Requirements – 1990*
- *Common Rule – 1991*
- *National Bioethics Advisory Committee – 1995*
- *DSMBs - 1997, 1999*
- *OHRP Established – 2000*
- *ISO – 2001*
- *GCP Document of the Americas – 2005*
- *WHO Handbook for Good Clinical Practices - 2006*

The process will continue to evolve and refine!

ICH - International Conference on Harmonisation

- Designed to streamline the process for developing and marketing new drugs internationally
- Composed of representatives for the pharma industry and the regulatory bodies of the US, Japan, and the European Union
- Observers include Canada, the European Free Trade Area and WHO

ICH

- Established several international standards of good clinical practice (GCP)
- Many countries adopted the guidance as “law”
- The U.S. (FDA), however, only adopted the ICH as guidance
 - Not regulation
 - Does not have the force of law
 - Compliance is voluntary

The Belmont Report (1979)

- Based on a comprehensive federally-commissioned review which explored the ethical and human rights considerations of human biomedical and behavioral experimentation
- Resulted in more strenuous protection for human research subjects based on three ethical principles that form the basis for informed consent:
 - Respect for Persons
 - Beneficence
 - Justice

Respect for Persons

- Autonomous agents
 - individuals able to make their own *informed* decisions
- Persons with diminished capacity are entitled to increased protection.
 - includes children, mentally disabled, prisoners, and pregnant women

Beneficence

- Do no harm.
- Assess the risk benefit ratio
 - maximize benefits and minimize risks
- Although there is a need to protect subjects from risk, there is also a need to compare the substantial benefits that may be gained from research

Justice

- Should not involve persons not likely to benefit from research
- Requires fairness in selection of subjects
- Should not systemically draw subjects from certain groups simply because of availability
 - Welfare patients/economically disadvantaged, racial or ethnic minorities, institutionalized individuals, very sick patients, or prisoners

Informed Consent

- Form vs process
- Freely given consent to participate in a clinical research study
 - No coercion
 - Emphasis on “informed”
 - Obtained prior to enrolling the subject

Requirements:

- Lay language
- Participant must have sufficient time to consider consenting
- Reading level
- Adequate presentation of the facts to the subject and/or representative

Protocol

- A document that describes the objective(s), design, methodology, statistical considerations, and organization of a clinical trial
- Usually gives the background and reason the trial is being conducted, but these could be provided in other documents referenced in the protocol (Investigator's Brochure)
- A study plan on which the clinical trial is based
- Describes, among other things, what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study

Investigational New Drug (IND)

- Federal law requires that a drug must have an approved marketing application prior to being transported or distributed across state lines
- When a sponsor screens a new molecule for pharmacological activity and toxicity in animals and wants to test the drugs diagnostic or therapeutic potential on humans
 - At this point, the molecule changes in legal status
 - Under Federal Food, Drug, and Cosmetic Act, it becomes a new drug subject to regulation

Serious Adverse Event (SAE)

- Death
- Life-threatening (risk of death)
- Hospitalization
- Disability
- Requires further intervention to prevent additional impairment or disability

Randomization

- Random assignment of subjects to either the experimental group or the control group
- Used to control the imbalance of risk factors within the treatment groups
- Control of the randomization should rest with a neutral party, if possible
 - Sealed envelopes
 - Randomization center
- Various ways of randomizing
 - SS #
 - Random number generator

Pre-clinical Studies

- Usually used to test drugs and toxicology on animals
- Used to evaluate a compound
- Pre-human testing
- During this phase, the “IND” may be submitted to the FDA

Phase I Trials

- Used to evaluate and test the pharmacology of the investigational drug and/or the dosing range
 - toxicity
- Usually uses healthy subjects to determine **safety** issues
- N = usually <100 subjects (20 – 80 is optimal)

Phase II Trials

- Occurs after the safety of the drug has been determined in a Phase I trial
- Primarily used to collect data on the safety and efficacy of the drug in subjects with the disease the drug is intended to treat
- Usually, about 100-300 subjects
- Subjects must fit the inclusion/exclusion criteria

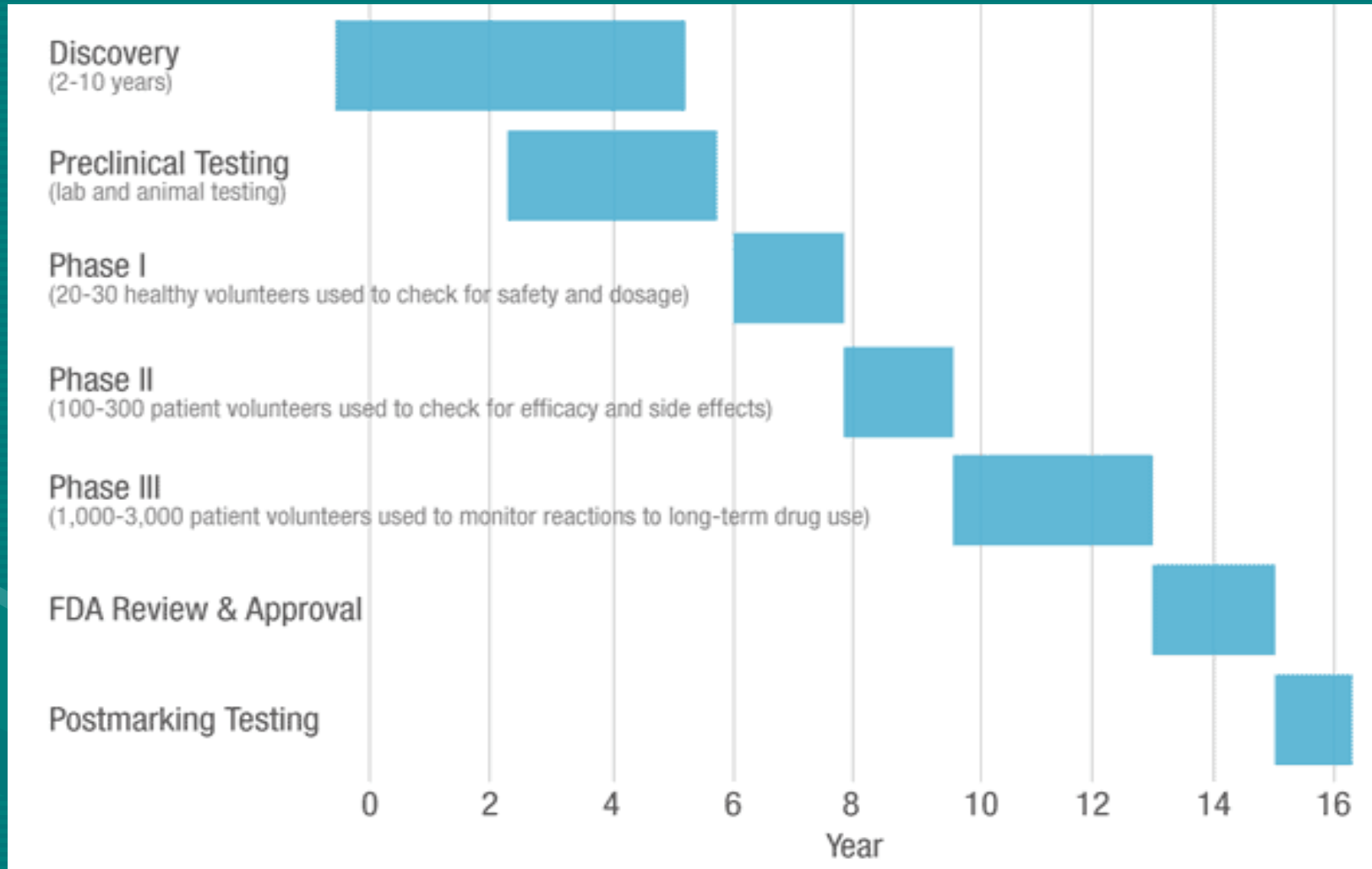
Phase III Trials

- Designed to collect data on the side effects, idiosyncrasies, and the effectiveness of the drug
- Usually >1,000 subjects, multi-centered
- Usually randomized, blinded and placebo controlled

Phase IV Trials

- Designed to expand the indications for the drug. Takes place after IND is approved and the drug is available
- Used to re-document the safety of the drug and to gather more information regarding drug interactions
- To study the drug on additional populations

Clinical Trials Timeline



Are Statisticians and Programmers responsible for upholding Good Clinical Practices?

YES!

The data and subsequent analysis must be accurate. This requires strenuous quality control and validation of results as well as documentation of statistical methods. Good Clinical Practices apply because it is our responsibility to ensure the quality of the data and to perform the analysis in the proper way.

