CRC CERTIFICATION PREPARATION COURSE SESSION 1

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Overview of the Course

- This course consists of 6 sessions from October 2016 – December 2016 at the UCI Medical Center from 11am to 1pm:
  - October 10 and 24
  - November 7 and 21
  - December 5 and 19

  - Each session will provide information on topics that will be on the SOCRA Certification Exam

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SOCRA Certification

- Professional organization that provides internationally recognized certification
- Provides educational tools for clinical research professionals for both industry and academic research
- Annual educational conferences about regulations for clinical research

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ETHICAL PRINCIPLES AND GUIDELINES

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History of Research Ethics

- These guidelines govern the use of human subjects in research
  - Nuremberg Code – In 1947, German physicians conducted deadly or debilitating experiments on concentration camp prisoners.
  - Declaration of Helsinki, an internationally recognized guideline from the World Medical Organization. Adopted in 1964.
  - Belmont Report – Respect for persons, Beneficence, and Justice.
- www.research.uci.edu/compliance/human-research-protections/researchers/ethical-guidelines-fed-regs-and-state-statutes.html

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Nuremberg Code (1947)

- Resulted from "medical experiments" in the Nuremberg Trials where most prisoners died or were permanently crippled as a result of the experiments
- Created the first principles of clinical research:
  - Voluntary Informed Consent is essential
  - Proper formulated scientific experimentation designed and based on animal experiments and knowledge of the history of the disease
  - Beneficence towards participants
  - Freedom to withdraw from trial

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Nuremberg Code (1947)

- Degree of risk should not exceed humanitarian importance
- Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death
- Physician in charge must be prepared to terminate the experiment at any stage, if he/she has probably cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him/her that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject

- www.ushmm.org/information/exhibitions/online-features/special-focus/doctors-trial/nuremberg-code

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Declaration of Helsinki (1964)

- Created by World Medical Association
- Built upon the Nuremberg Code
- Further focus on clinical research
- Gone through 7 revisions, most current 2013
- Considered the cornerstone document of human research ethics and designed from a clearly formulated protocol
- Informed consent must be obtained from subject or legal guardian

Declaration of Helsinki (1964)

- Protocols should be reviewed by an independent committee
- Human subject research should be based on results from laboratory and animal research
- Research should be conducted by a medically qualified person
- Informed consent is a must
- Risk should not exceed the benefits

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Belmont Report

- The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- Ethical Principles and Guidelines for the Protection of Human Subjects Research
- April 18, 1979

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Belmont Report (1979)

- Established three fundamental ethical principles:
  - Respect for Persons
    - Individual autonomy
    - Protection of individual with reduced autonomy
    - Enter into research voluntarily and with adequate information
  - Beneficence
    - Maximize benefits and minimize harm
    - Respecting decisions
    - Securing well-being
  - Justice
    - Equitable distribution of research costs and benefits
    - Participants should be treated equally
    - Selection based on reason related to study

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Belmont Report (1979)

- Expanded and revised regulations that protect human research subjects in the United States
- Led to the establishment of the Office of Human Research Protection (OHRP)
- Led to the creation of the Institutional Review Board (IRB).

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INFORMED CONSENT IN RESEARCH

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General Requirements (from Code of Federal Regulations: Effective 12-13-2001

- No subject can participate in research until legally effective informed consent has been obtained from the subject (or the subject's legally authorized representative) – no study procedures can be initiated
- Sufficient opportunity to consider whether to participate
- No coercion or undue influence
- Use language that is understandable to the subject or their representative

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General Requirements, Cont.

- No exculpatory language through which subject or their representative is made to waive or appear to waive any legal rights, including release of the University or its agents from liability for negligence
- All subjects must receive a copy of any consent document completed by them

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Eight Basic Elements of Informed Consent (45 CFR 46.116)

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental

(2) A description of any reasonably foreseeable risks or discomforts to the subject

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research

- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject

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Elements of Informed Consent, (cont.)

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained

(6) For research involving more than minimal risk, an explanation as to whether any compensation or any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained;

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Elements of Informed Consent, (cont.)

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Additional Elements of Informed Consent (When Appropriate)

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent

(3) Any additional costs to the subject that may result from participation in the research

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Additional Elements of Informed Consent, (Cont.)

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject

(6) The approximate number of subjects involved in the study.

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Documentation Of Informed Consent

- Informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject with a copy given to the subject signing the form.
  - Section 46.117 (45 CFR 46, Subpart A)
  - Section 50.27 (21 CFR 50)
- FDA requires language that the FDA may inspect the records
- ICH requires language that allows regulatory authorities, the sponsor and/or representatives and the IRB representatives to inspect the records

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Short Form Consent

- What is short form consent?
- When is short form consent allowed (per federal regulations?)
- The short form states that the elements of informed consent have been covered with the participant.
- The participant signs only the short form document.
- The presentation using the short form must be witnessed.

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Waiver of Written Documentation of Consent

- HHS regulations permit waiver by the IRB of documentation for purpose of confidentiality (45 CFR 46.117) under defined conditions.
- An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

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Waiver of Written Documentation of Consent

- Does waiver of documentation mean that there is no informed consent necessary for the research?
- The IRB may require that some document be provided to the participants about the research.
- Study information sheet – information, no signature
- **The FDA does not permit waiver of documentation by the IRB.

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Waiver of Informed Consent

- An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

  (1) the research involves no more than minimal risk to the subjects;

  (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;

  (3) the research could not practicably be carried out without the waiver or alteration; and

  (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

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Waiver of Informed Consent

- What is the classic example of the kind of research where the IRB would be willing to completely waive informed consent?

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Emergency Research

- 21CFR 50.24 Emergency Research Regulations
  - Human subjects are in a life-threatening situation, unable to provide consent, but research offers a potential benefit to improve outcome
  - Research must be approved by IRB, including waiver of written consent
  - Research could not practicably be conducted without the waiver
  - Community forum must be assembled to review and agree with the research having potential benefit for the community
  - Investigator still attempts to obtain consent from LAR within a specific time frame, and documents this attempted contact

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Requirements by the State of California

- Under California Health and Safety Code, Section 27172, all persons requested to take part in a "medical experiment" must be given a copy of a specific bill of rights in a language in which the person is fluent.
- Health and Safety Code section 27176 provides for civil and criminal sanctions for researchers who do not comply with section 27172.

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Experimental Subject's Bill of Rights

a. To be told what the study is trying to find out.

b. To be told about what will happen in the study and whether any of the procedures, drugs or devices is different from what would be used in standard medical practice.

c. To be told about the risks, side effects or discomforts of the things that may happen to the subject.

d. To be told if the subject can expect any benefit from participating and, if so, what the benefit might be.

e. To be told what other choices are available and how they may be better or worse than being in the study.

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Experimental Subject's Bill of Rights (con't)

- f. To be allowed to ask any questions concerning the study both before agreeing to be involved and during the course of the study.
- g. To be told what sort of medical treatment is available if any complications arise.
- h. To refuse to participate at all, either before or after the study is started. This decision will not affect any right to receive the standard medical care.
- i. To receive a signed and dated copy of the consent form and the Subject's Bill of Rights.
- j. To be allowed to decide to consent or not to consent to participate without any pressure being exerted by the investigators or others.

State of CA – Witness Signature Requirement

- Signature of a witness on the informed consent document is required for all "medical experiments"
- Signature of a witness may be required by the IRB for any other study

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Obtaining Informed Consent: General Comments

- Informed consent is NOT A PIECE OF PAPER, but rather a multi-step process

- Informed consent is an ongoing process that begins when the participant is first approached to participate in a study. It continues throughout the study via updates and reminders about study procedures / risks, etc.

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Obtaining Informed Consent: First Step

- Explain the study to the prospective subject verbally, providing all pertinent information [purpose, procedures, risks, benefits, alternatives to participation, etc.]
- Allow the prospective subject ample opportunity to ask questions.
- This initial step is sometimes accomplished on the telephone or whenever first contact with prospective participant occurs?
- WHO DOES THIS?

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Obtaining Informed Consent: Second Step

- Provide a written consent form
- Give sufficient time to consider whether or not to participate in the research.
- ["Sufficient time" can range from hours to days, depending on how long it reasonably takes to evaluate risks, potential benefits and alternative treatments.]

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Obtaining Informed Consent: Third Step

- An appropriately qualified investigator [either the Lead Researcher or a co-investigator] must meet with the potential subject
- Review the consent document
- Answer any questions s/he may have.

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Obtaining Informed Consent: Fourth Step

Signing the consent document

- An investigator must sign the consent form
  - assures that the subject meets all study criteria
  - subject was correctly and appropriately consented
  - subject understands the requirements of the study
- Usually, the investigator and subject sign at the same time
- The investigator's signature cannot pre-date the subject's signature
- Usually whomever obtains the participant signature on the final informed consent document, that co-investigator will sign as the investigator on the study.

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Important:

- Simply asking a subject to read and sign a consent form, without an oral presentation and discussion, does not qualify as informed consent.
- Subjects must be given a copy of the IRB reviewed and approved consent and/or assent documents, containing the official IRB approval stamp.
- Failure to use an IRB reviewed and approved consent or assent document constitutes a serious breach of regulatory compliance.

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New Information During Course of Study

- When new information is discovered in the course of the study that may affect the subjects' decision to continue participating in the study [information about adverse events, drug efficacy, or availability of new alternative treatments, etc.] subjects must be asked to consider whether or not to continue their participation in the study, based upon the new information provided.
- If the subject decides to continue participation in the study, s/he may be asked to sign a new informed consent (or a re-consent cover memo).

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Personnel Qualified to Carry Out Informed Consent

- Unless otherwise approved by the IRB, only the Lead Researcher or co-investigators of record [who are intimately familiar with the research protocol and able to effectively discuss with potential subjects the risks, benefits, and alternatives to participation in the study], are to obtain informed consent from subjects.
- Staff, other faculty, residents, medical students and other individuals not listed on the IRB approved consent cannot obtain informed consent from a prospective subject.

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Subjects Who Seem Hesitant About Participating

- If a subject seems hesitant or unsure about whether they wish to participate do not proceed with the study.
  - Encourage the subject to take more time before deciding.
  - Can state that some subjects need additional time before deciding whether to participate or not.
  - Call subject back within a few days if it's okay with the subject to do so.
- For subjects who are still interested, re-schedule an informed consent discussion.
- For subjects who have decided not to participate, record this in their file.
- Do not have any further contact with the subject unless they initiate the contact.

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Summary: General Requirements

- No subject can participate in research until legally effective informed consent has been obtained from the subject.
- Sufficient opportunity must be given to consider whether to participate.
- No coercion or undue influence may be used.
- Use language that is understandable to the subject or their representative.
- No exculpatory language through which subject or their representative is made to waive or appear to waive any legal rights, including release of the University or its agents from liability for negligence.
- All subjects or their authorized representative must receive a copy of any consent document completed by them.

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Informed Consent – What Can Go Wrong?

- What are some of the problems encountered with obtaining effective truly informed consent?

GROUP DISCUSSION

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Informed Consent Video Example

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REGULATIONS AND GOOD CLINICAL PRACTICES

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History of U.S. Laws and Regulations

- 1935: Federal Register Act
  - Daily published record of proposed rules, final rules, meetings
- 1937: Code of Federal Regulations
  - 45CFR 46 Public welfare (HHS)
  - 21CFR 50 & 56 Food and Drug (FDA)
- 1938: Federal Food, Drug & Cosmetics Act
  - Basic food and drug law of the U.S
    - Assures consumers that:
      - Foods are pure and wholesome and safe to eat, sanitary conditions
      - Drugs and devices are safe and effective for their intended use
      - Cosmetics are safe and made from appropriate ingredients
      - All labeling and packaging is truthful, informative and non-deceptive

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History of U.S. Laws and Regulations

- 1976: Medical Device Amendments to FD&C Act
  - First major amendment specifically for devices
- 1987: Treatment Use of IND
- 1989: ICH – International Conference on Harmonization
- 1997: Food and Drug Modernization Act

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Regulatory Agencies & Functions

- International: ICH (guidelines are based on Declaration of Helsinki)
- Federal DHHS: Department of Health and Human Services (regulations are based on principles of Belmont report)
- Federal FDA: Food and Drug Administration (regulations from FD&C Act)
  - FDA Guidance documents
- State: California
- Local regulation: UCI IRB, UC policy

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FDA Guidance Documents

- As defined by the FDA:
  - FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word “should” in agency guidances means that something is suggested or recommended, but not required.

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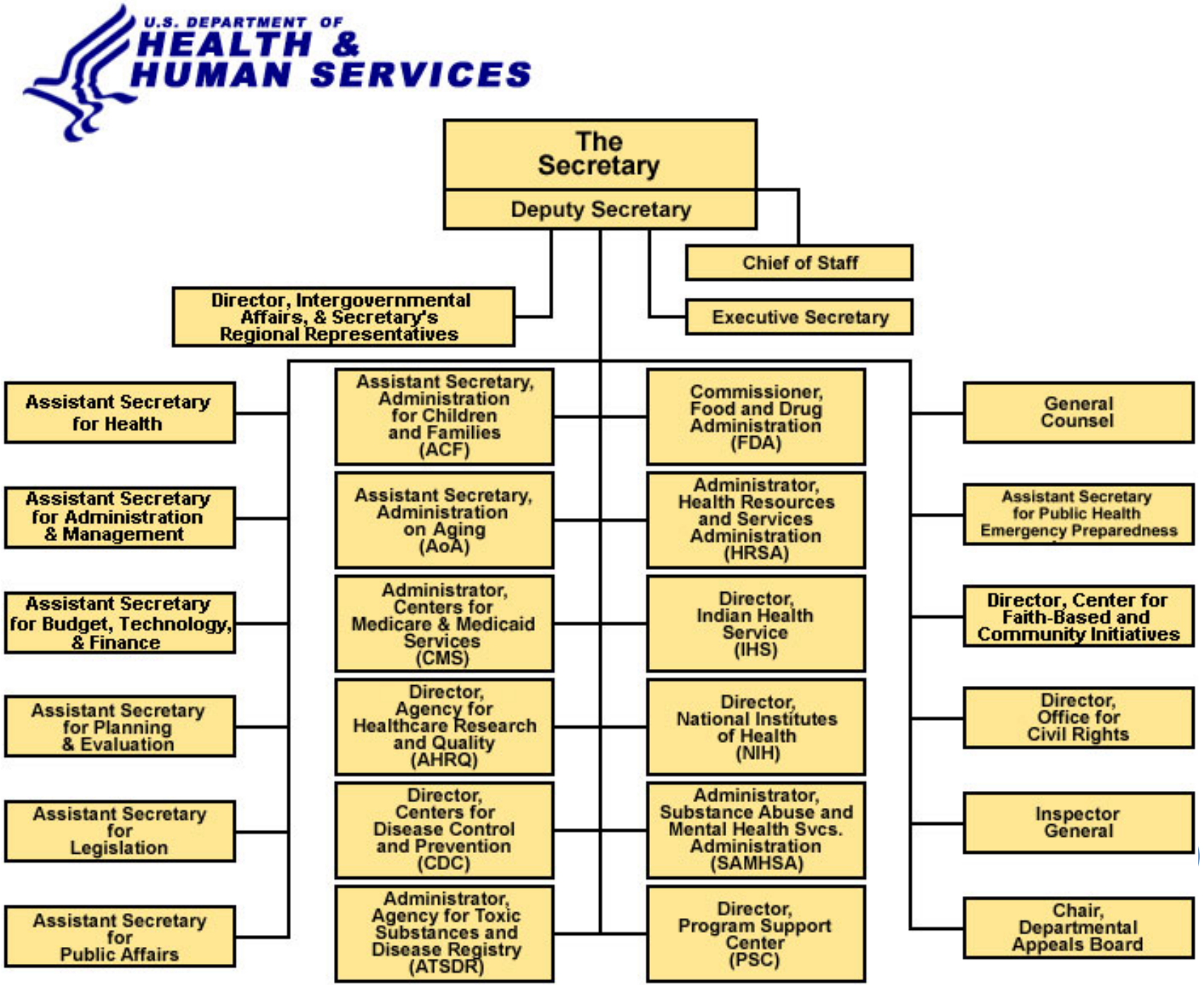
U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
The Secretary
Deputy Secretary
Chief of Staff
Executive Secretary
Director, Intergovernmental Affairs, & Secretary's Regional Representatives
Assistant Secretary for Health
Assistant Secretary for Administration & Management
Assistant Secretary for Budget, Technology, & Finance
Assistant Secretary for Planning & Evaluation
Assistant Secretary for Legislation
Assistant Secretary for Public Affairs
Assistant Secretary, Administration for Children and Families (ACF)
Assistant Secretary, Administration on Aging (AoA)
Administrator, Centers for Medicare & Medicaid Services (CMS)
Director, Agency for Healthcare Research and Quality (AHRQ)
Director, Centers for Disease Control and Prevention (CDC)
Administrator, Agency for Toxic Substances and Disease Registry (ATSDR)
Commissioner, Food and Drug Administration (FDA)
Administrator, Health Resources and Services Administration (HRSA)
Director, Indian Health Service (IHS)
Director, National Institutes of Health (NIH)
Administrator, Substance Abuse and Mental Health Svcs. Administration (SAMHSA)
Director, Program Support Center (PSC)
General Counsel
Assistant Secretary for Public Health Emergency Preparedness
Director, Center for Faith-Based and Community Initiatives
Director, Office for Civil Rights
Inspector General
Chair, Departmental Appeals Board

Department of Health and Human Services (HHS)

- 45CFR Part 46 “Common Rule”:

“The Common Rule”: Federal Policy for the Protection of Human Subjects

- Subpart A: Basic HHS policy
- Subpart B: Pregnant women, Fetuses and Neonates
- Subpart C: Prisoners
- Subpart D: Minors

Who enforces this regulation?

OHRP – Office for Human Research Protections

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Food and Drug Administration (FDA)

- 21CFR Parts 50 and 56
  - INDs- New Drugs/ Biologics (21CFR 312)
  - IDEs- New Devices (21CFR 812)
  - Emergency Use of Test Article

Who enforces this regulation?

FDA does their own enforcement

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Dual Reporting

- Do we have to abide by both OHRP and FDA requirements?
- If so, when?
- What is their span of authority?
- Can we be monitored / audited by both?

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HHS and FDA Regulatory Differences

- HHS and FDA do not have complete harmony between their regulations.
- Some examples:
- HHS allows for waiver of written consent in minimal risk research; FDA does not recognize waiver of consent
- FDA clinical investigation = research; HHS definition of research is very detailed and specific
- Scope of responsibility
  - FDA – all food, drug, biologic and device research
  - HHS – research funded by Federal govt, or all research as per FWA

Office of GCP in FDA-Regulated Clinical Trials

- Coordinates FDA policies
- Provides leadership and direction through the administration of FDA's Human Subject Protection/Good Clinical Practice Steering Committee
- Coordinates FDA's Bioresearch Monitoring program with respect to clinical trials, working together with FDA's Office of Regulatory Affairs (ORA)
- Contributes to international Good Clinical Practice harmonization activities
- Plans and conducts training and outreach programs
- Serves as a liaison with the HHS Office of Human Research Protection (OHRP) and other federal agencies and external stakeholders committed to the protection of human research participants.

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State of California - CA Health and Safety Code: 24170-24179.5

- Protection of Human Subjects in Medical Experimentation Act
- Requires "experimental subject's bill of rights"
- Defines Legally Authorized Representative
- Section 24178 – surrogate consent for research
- Consent for minors – if ≥7, assent required
- Use of death records for research – requires IRB

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Local Control

- UCOP
- Local IRBs
- SOM Policies and Procedures
  - Financial review

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ICH GUIDELINES

- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) – first met in 1991
- Joins efforts of Western Europe, U.S., Japan
- Primary purpose is to coordinate the drug regulatory process to prevent redundancy in research
- GCP Guidelines issued, based on Declaration of Helsinki, attempt to provide a unified standard for the protection of human subjects

Definition of GCP

- 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 wellbeing of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible (ICH, 1996).
- Be familiar with the E6 ICH document

ICH PRINCIPLES FOR GCP

- Clinical trials 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 requirement(s).
- Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

ICH PRINCIPLES FOR GCP

- The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
- The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

ICH PRINCIPLES FOR GCP

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

ICH PRINCIPLES FOR GCP

- Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
- Freely given informed consent should be obtained from every subject prior to clinical trial participation.
- All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

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ICH PRINCIPLES FOR GCP

- 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).
- 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.

ICH PRINCIPLES FOR GCP

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

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Vulnerable Populations (45CFR46)

- Pregnant women: (Subpart B)
- Prisoners: (Subpart C)
- Children: (Subpart D)
- Handicapped or mentally disabled persons

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45 CFR 46: Subpart B:
Pregnant Women and Human Fetuses

- Applies to all research involving pregnant women or human fetuses, and to research involving the in vitro fertilization of human ova
- Allowable research if:
  - Previous research (pre-clinical, animal, non-pregnant women) has assessed potential risks for pregnant women and fetuses
  - Risk to fetus is minimal, or if greater than minimal also holds out prospect of direct benefit for the woman or the fetus
  - Risk is the least possible for achieving the objectives of the research

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Subpart B

- The woman's consent has been obtained with usual provisions
- The woman is fully informed of reasonably foreseeable impact of the research on the fetus
- No inducements are offered to terminate the pregnancy
- Researchers will have no involvement in termination of the pregnancy
- Researchers will have no involvement in determination of viability of the fetus

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Decision Chart for Subpart B

	Benefit to mother only	Benefit to mother & fetus	Benefit to fetus only	No direct benefit or benefit to society only
Risk is greater than minimal	Mother's consent only 46.204 (d)	Mother's consent only 46.204 (d)	Mother and father's consent 46.204 (e)	Not approvable unless* 46.204 (d)
Risk is no more than minimal	Mother's consent only 46.204 (d)	Mother's consent only 46.204 (d)	Mother and father's consent 46.204 (e)	Mother's consent only 46.204 (d)

* The risk to fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means. Only Mother's consent is required.

45 CFR 46: Subpart C: Prisoners

- Applicable to all biomedical and behavioral research involving prisoners as subjects
- Additional safeguards are necessary since incarceration could affect their ability to make a truly voluntary and uncoerced decision about whether to participate as subjects in research

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Subpart C

- Research involving prisoners shall also meet additional specific requirements:
  - Majority of members will have no association with the prisons involved
  - At least one member of the review board will be a prisoner or prisoner representative with appropriate background and experience to serve in that capacity

Subpart C: IRB Duties

- Research may involve prisoners when:
  - Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, or
  - Study of prisons as institutional structures or of prisoners as incarcerated persons,
    - provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.
  - Other types of research involving prisoners must have approval of the Secretary, DHHS

Subpart C: IRB Duties

- Advantages of participation in the research are not of such a magnitude that subject's evaluation of risk/benefit is impaired
- Risks involved are commensurate with risks accepted by non-prisoners
- Subject selection within prison is fair
- Parole boards will not take into account research participation in making parole decisions
- Necessary follow-up has been provided

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45 CFR 46: Subpart D: Children

- Applies to children (have not attained the legal age for consent to treatments or procedures) as subjects
- No greater than minimal risk (category I)
  - Assent of child is necessary
  - Permission of parents or guardians is sought
  - Permission of one parent is adequate

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Risk / Benefit Analysis for Research Involving Children

	Minimal Risk	> Minimal Risk
Direct Benefit	I	II
Indirect Benefit	I	III

HHS 45CFR Part 46 Subpart D

45 CFR 46: Subpart D: Children

- > minimal risk; prospect of direct benefit (category II)
  - Risk is justified by anticipated benefit
  - Anticipated benefit/risk is comparable to available alternative approaches
  - Assent of child is necessary
  - Permission of parents or guardians is sought
  - Permission of one parent is adequate

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Subpart D

- > minimal risk; no prospect of direct benefit, but likely to yield generalizable knowledge about subject's disorder or condition (category III)
  - Risk represents a minor increase over minimal risk
  - Intervention or procedures are reasonably commensurate with those inherent actual or expected situations
  - Intervention or procedures are likely to yield generalizable knowledge that is of vital importance for understanding and/or ameliorating subject's disorder or condition
  - Assent of child is necessary
  - Permission of parents or guardians is sought
  - Permission of **both parents** is required, except…

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Permission of Both Parents

- Under certain conditions, permission is required from both parents, except when:
  - One parent is deceased, unknown, incompetent, or not reasonably available, **or**
  - One parent has legal responsibility for the care and custody of the child

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Risk Category I for Children

- Minimal risk
- IRB Duties
  - Confirm provisions for child assent
  - Confirm provisions for parental consent

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Risk Category II for Children

- > Minimal risk, but direct benefit
- IRB Duties
  - Determine that risk is justified by benefit
  - Benefit/risk relationship is at least as favorable as alternative approaches
  - Confirm adequate provisions for child's assent and parental consent (one or both parents)

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Risk Category III for Children

- > Minimal risk, no direct benefit, but likely to yield generalizable knowledge about the subject's disorder or condition
- IRB Duties
  - Determination of minor increase over minimal risk; project will yield knowledge of vital importance to the subject's disorder
  - Determination that intervention presents experiences relatively commensurate with alternative medical, dental, psychological, or educational interventions
  - Confirm provisions for child assent and parental consent (both parents)

Subpart D

- Research **not otherwise approvable** which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children (category IV)
  - Can be approved by DHHS after
    - IRB review
    - DHHS Consultation with an expert panel, and opportunity for public review and comment
    - Local IRB cannot approve this research

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Subpart D

- Assent of children should be solicited when in the judgment of the IRB the children are capable of providing assent (based on age, maturity and psychological state)
  - State regulation (Health and Safety Code) mandates consent of child who is seven years of age or older

Financial Disclosure

- FDA requires form 3454 and 3455
  - Submitted with IND or IDE applications/updates for "covered clinical studies"
  - Form 3455 – certification of no financial interest
  - Form 3455 – disclosure of interests and steps to minimize bias
- Definition of covered clinical trial
  - any study of a drug or device in humans submitted in a marketing application or reclassification petition that the applicant or FDA relies on to establish that the product is effective, or to demonstrate safety.

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Financial Disclosure

- Significant equity interest
  - Any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in a nonpublicly traded corporation), or any equity interest in a publicly traded corporation that exceeds $50,000 during the time the clinical investigator is carrying out the study and for 1 year following completion of the study.
- Record maintenance
  - Complete records of financial interests or payments made/received must be maintained for a minimum of 2 years following approval of the drug/device application.

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Question

- Codes / Guidelines vs. Regulations / Guidance
  - Nuremberg Code and Declaration of Helsinki are codes/guidelines
  - Belmont Report is an ethical guideline
  - 45CFR 46 and 21CFR 50, 56, 54, etc. are regulations
  - FDA issues guidance documents
    - What is the difference between these?

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