Colgate Palmolive

Clinical Research Training Program

Module 4

Ethical Research Practices

developed in conjunction with:

AAL™
ACADEMY FOR ACADEMIC LEADERSHIP

Content Creator and Trainer:
Bruce Pihlstrom, D.D.S., M.S.

Professor Emeritus, University of Minnesota
Associate Editor for Research, Journal of the American Dental Association (JADA)
Independent Oral Health Research Consultant
Former Director of Extramural Clinical Research, National Institute of Dental and Craniofacial Research (NIDCR), National Institutes of Health (NIH)

Disclosure (May 1, 2016): Dr. Pihlstrom currently receives financial compensation as a research consultant to AAL and several universities. He currently receives financial compensation as the Associate Editor for Research of JADA and as an author of the bimonthly JSCAN article that is published by JADA. He has received financial compensation as a consultant to the Colgate Palmolive Company in the past. He has received support from several corporations for research conducted while he was an active faculty member at the University of Minnesota (1974-2002) and as an independent research consultant. He currently receives no financial compensation from any company that markets professional or consumer dental products.

This educational material was created by Dr. Pihlstrom and should not be construed as reflecting policies or practices of the University of Minnesota, the Journal of the American Dental Association, the NIDCR, or any other organization or body.

Colgate®

Module 4 Goal

Provide an overview of ethical research practice in terms of its history, standards and mechanisms for review and approval of research involving human subjects

Overall References for this module:

Ripley EBD, Macrina FI. Ethics in oral health research. *In:* Giannobile WV, Burt BA, Genco RJ. *Clinical Research in Oral Health.* (2010) Hoboken NJ: Wiley Blackwell, pp.13-36.

Grady C. Ethical Principles in Clinical Research. *In:* Gallin JI, Ognibene FP. (2012) *Principles and Practice of Clinical Research*, 3rd ed., London: Academic Press, pp.19-30.

Learning Objectives:

- Understand major historical events in the development of ethical research practices
- Learn about standards for ethical conduct of human subjects research
- Learn about ethical review and approval of research involving human subjects

Major Historical Events in the Development of Ethical Human Subjects Research

Human Experimentation in Nazi Germany

- In Nazi Germany, German physicians planned and enacted the "Euthanasia" Program, the systematic killing of those they deemed "unworthy of life."
- The victims included the mentally retarded, the institutionalized mentally ill, and the physically impaired
- During World War II, German physicians conducted meaningless, pseudoscientific medical experiments utilizing thousands of concentration camp prisoners without their consent. Most died or were permanently crippled as a result.

https://www.ushmm.org/information/exhibitions/online-features/special-focus/doctors-trial

WWII: Subsequent Nuremberg Trials

- Doctors' Trials: USA versus Karl Brandt et al.
- Dec 9th 1946 to August 20th 1947
- Held before US military court
- 20 of 23 defendants were medical doctors
- All accused of Nazi human experimentation
- 7 acquitted, 7 death sentences, 9 prison sentences (10+ years to life in prison)

https://www.ushmm.org/information/exhibitions/online-features/special-focus/doctors-trial

Nuremberg Code (1947)

1. Voluntary consent of human subjects is absolutely essential
2. Experiment results must aim to be beneficial for society and cannot be obtained in another other way
3. Experiment should be based on previous knowledge (such as animal experiments) to justify the experiment
4. The experiment should avoid unnecessary physical and mental suffering and injury
5. Experiment should not be conducted when there is any reason to believe that it implies a risk of death or disabling injury

http://www.hhs.gov/ohrp/archive/nurcode.html

Nuremberg Code (1947)

6. Risk of experiment should not exceed humanitarian importance of problem solved by the experiment
7. Subjects must be protected from even remote possible injury, disability or death
8. Experiment must be conducted by scientifically qualified persons
9. Subjects must be at liberty to withdraw from study
10. Scientist in charge of experiment must be prepared to terminate experiment at any stage if continuation is likely to result in injury, disability or death of the subject

http://www.hhs.gov/ohrp/archive/nurcode.html

Two Prominent Examples of Unethical and Harmful Human Experimentation in the United States

- Experiments involving surgery
  - 1913 to 1951 Dr. Leo Stanley “San Quentin Prison Experiments” “Rejuvenation” experiments involving testicular transplantation from deceased persons and animals
- Clinical study involving disease
  - 1932 to 1972 Tuskegee Syphilis study

http://ahrp.org/1913-1951-dr-leo-stanley/

U. S. Tuskegee Syphilis Study 1932-1972

- United States Public Health Service began study in 1932
- Prospective cohort study involving 600 poor black men in Mississippi
  - 399 had syphilis
  - 201 did not have syphilis
- Purpose: Study natural history of syphilis

Jones, JH. Bad Blood: The Tuskegee Syphilis Eperiment. Simon & Schuster, NY. 1993, pp302.

U. S. Tuskegee Syphilis Study 1932-1972

- Men given free medical care, meals and burial insurance for participating in study

- Even after funding was discontinued, study continued
  - Men not informed that they had syphilis – only that they had “bad blood”
  - None were treated with penicillin even after it was shown to be an effective treatment for the disease

Jones, JH. Bad Blood: The Tuskegee Syphilis Experiment. Simon & Schuster, NY. 1993, pp302.

Colgate®

The Belmont Report 1979

Summarizes Basic Ethical Principles for the Protection of Human Subjects of Research

- Boundaries between research and practice
- Basic ethical principles
  - Respect for persons
  - Beneficence
  - Justice

http://www.hhs.gov/ohrp/policy/belmont.html#

The Belmont Report 1979

- Respect for persons - Key points
  - Individuals should be treated as being autonomous
  - Participation in research must be voluntary
  - People must have adequate information about the research to make informed decisions about their participation
  - Persons with diminished autonomy are entitled to protection

Belmont Report defined an autonomous person as “an individual capable of deliberation about personal goals and of acting under the direction of such deliberation.”

http://www.hhs.gov/ohrp/policy/belmont.html#

The Belmont Report 1979

- Beneficence - Key points

  - Maximize benefits of participation in research
  - Minimize potential harm or risks participation in research

http://www.hhs.gov/ohrp/policy/belmont.html#

The Belmont Report 1979

- Justice - Key points

  - There must be fair selection of subjects for participation in research

    - ✓ Must not offer potentially beneficial research only to those who might benefit from it

    - ✓ Must not offer potentially risky research only to certain persons who may be viewed as “undesirable” (i.e., prisoners)

http://www.hhs.gov/ohrp/policy/belmont.html#

The Belmont Report 1979

- Justice - Key points (cont.)
  - Some people may be dependent and/or may have a compromised capacity for free consent
  - People must be protected against being involved in research solely because:
    - ✓ It is convenient to include them in research
    - ✓ They are readily available
    - ✓ They are easy to manipulate as a result of an illness or socioeconomic condition

Examples: Racial minorities, the economically disadvantaged, the very sick, and people who are institutionalized

http://www.hhs.gov/ohrp/policy/belmont.html#

Declaration of Helsinki (1964)

World Medical Association (WMA) established recommendations, first in 1964, then revisions in 1975, 1983, 1989, 1996, 2000, 2008 and 2013 followed

Some Key Points:

- Minimize risks and maximize benefits for participant
- Obtain informed consent from participant, preferably in writing
- Safeguard personal integrity of participants
- Participants free to withdraw from research
- Research considered to be harmful should be discontinued

http://www.wma.net/en/30publications/10policies/b3/index.html

Declaration of Helsinki

Some Key Points (cont.):

- Vulnerable populations must be protected
- Clinical trials must have post-trial provisions for care
- Ethical committees must have right to monitor ongoing studies
- Studies must be registered in publicly available registry before subject enrollment is begun
- Use of a placebo or any treatment that is less effective than a proven treatment must not result in any serious or irreversible harm

http://www.wma.net/en/30publications/10policies/b3/index.html

Research Standards

- **International**
  - Good Clinical Practice E6 Guidance - ICH guidelines on design, conduct, safety and reporting of clinical trials
  - International Ethical Guidelines for Biomedical Research Involving Human Subjects - Council for International Organizations of Medical Sciences (CIOMS)
    - ✓ Addresses the conditions and the needs of low-resource countries, and implications for multinational or transnational research in which they may be partners

- http://www.fda.gov/downloads/drugs/.../Guidances/ucm073122.pdf
- http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html
- http://www.cioms.ch/publications/guidelines/guidelines_nov_2002_blurb.htm

Colgate®

Good Clinical Practice (GCP) E6

- International unified ethical and scientific quality standards for conducting, recording, and reporting trials involving human subjects

- Developed with consideration of the current good clinical practices of the European Union, Japan, the United States, Australia, Canada, the Nordic countries, and the World Health Organization (WHO)

http://www.fda.gov/downloads/drugs/.../Guidances/ucm073122.pdf

Good Clinical Practice (GCP) E6

- Provides a unified international standard to facilitate mutual acceptance of clinical data by regulatory authorities in these jurisdictions

- Compliance assures that the rights, safety, and well-being of trial subjects are protected, consistent with the Declaration of Helsinki and that clinical trial data are credible

http://www.fda.gov/downloads/drugs/.../Guidances/ucm073122.pdf

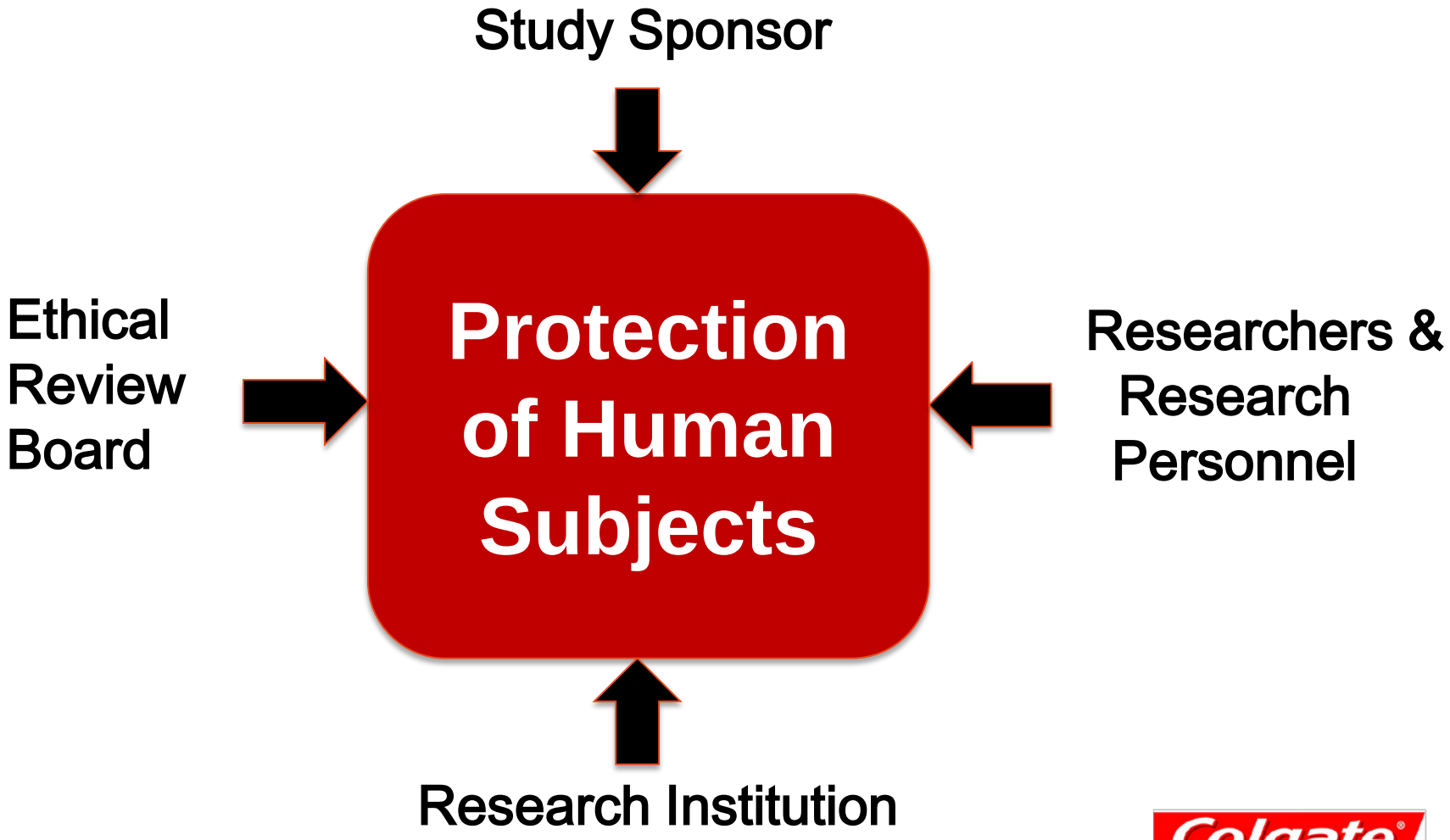
Research Standards

- **United States**
  - Code of Federal Regulations (CFR)
- **Canada:**
  - Tri-Council Policy Statement: Ethical Conduct for Research Involving Human Subjects
- **India:**
  - Indian Council of Medical Research: Ethical Guidelines for Biomedical Research on Human Participants

Research Standards

- **Europe**
  - European Commission - Clinical Trials Regulation No 536/2014

Human Subject Protection is a Shared Responsibility



Review and Approval of Research Involving Human Subjects

Ethical Review of Research

- Institutional/Ethical Review Boards
- Data and Safety Monitoring

Wichman, A. Institutional Review Boards. *In:* Gallin JI, Ognibene, F.P. (2012) *Principles and Practice of Clinical Research*, 3rd ed., London: Academic Press, pp. 53-65.

Friedman LM, Dixon DO. Data and Safety Monitoring. *In:* Gallin JI, Ognibene FP. (2012) *Principles and Practice of Clinical Research*, 3rd ed., London: Academic Press, pp.101-108.

Institutional/Ethical Review Boards or Committees

- Overall goal is to protect subjects enrolled in research
- Provide an independent, objective review of human subject research based on established ethical principles and country standards
- Members include researchers, non-researchers, members of the local community and others with specific expertise relevant to the study under review
- Membership should be diverse in terms of gender, ethnicity, and include members who are familiar with vulnerable subjects if they are involved in the research

Institutional/Ethical Review Boards or Committees

- Review and approval provides assurance to each of the following that the research adheres to applicable regulations and that the welfare and safety of human subjects are protected:
  - Research subjects
  - Public
  - Government
  - Investigators
  - Research institutions
  - Sponsors
  - Journals

Institutional/Ethical Review Boards or Committees

- Are often standing committees appointed by an institution for the purpose of protecting human subjects involved in research at the institution
- May be independent of a research institution and may charge a fee for reviewing studies
- Members may not vote on their own research projects

Examples of Ethical Board Review Criteria

- Is the research design scientifically sound?
- Is consent to participate truly voluntary?
- Are people coerced in any way to participate in the study?
- Can subjects withdraw from study at any time?
- Are subjects exposed to unnecessary risks?
- Are risks reasonable in relation to benefits?

Examples of Ethical Board Review Criteria

- Are risks to subjects minimized?
- Is subject selection equitable and fair?
- Does subject selection take into account such things as gender, age, ethnicity of people who are at risk for the disease or condition being studied?
- Does the study select for vulnerable people such as those who are institutionalized or disadvantaged?
- Is subject privacy and confidentiality maximized?

Examples of Ethical Board Review Criteria

- Have sample size estimates been calculated and is there sufficient statistical power to answer the research question?
  - Using insufficient sample size would be unethical because the study could not answer the research question and would be futile
  - Using excessive sample size would be unethical because it may expose people to unnecessary harm or inconvenience
- If study is a clinical trial, have *a priori* stopping rules been developed?

Stopping Rules for a Clinical Trial

- Stopping rules are established before or shortly after the trial begins recruiting patients
- Specifies the limit for the difference between test and control subjects for the primary outcome
- If limits are exceeded, results in termination of the test or control treatment – depending on direction of the observed difference

Meinert, CL. (2012) Clinical Trials: Design, Conduct and Analysis, 2nd ed., Oxford University Press,NY.

Stopping a Clinical Trial: Example 1

- Interim statistical analysis (masked to study investigators) of an ongoing trial shows that a new drug being tested for treatment of oral cancer is not as effective as the control treatment (according to pre-specified stopping rule)
- The trial must be stopped so that the control treatment can be given to test subjects

Stopping a Clinical Trial: Example 2

- Interim statistical analysis (masked to study investigators) of an ongoing trial shows that a new drug for treatment of oral cancer is more effective than the control treatment (according to pre-specified stopping rule)
- The trial must be stopped so that the new drug treatment can be given to control subjects and be made available for treatment of patients who have oral cancer

Stopping a Clinical Trial: Example 3 & 4

- Interim statistical analysis (masked to study investigators) shows that the new treatment is harmful and that the trial must be stopped to prevent further harm to subjects

- Interim statistical analysis (masked to study investigators) shows that continuing the trial is futile because enrolling more subjects will not change the outcome of the trial

Data and Safety Monitoring of Clinical Research

- Data and safety monitoring is usually the responsibility of Data and Safety Monitoring Board (DSMB) - an oversight committee that monitors research that exposes subjects to more than minimal risk

- The primary objective of a DSMB is to ensure safety of human subjects who participate in clinical research

Data and Safety Monitoring

- Enhances scientific integrity of the study because there is oversight of study progress, data collection and analysis

- Provides an independent mechanism for recommending stopping a study because:
  - Safety of participants is being compromised
  - Continuing the study is futile because of insufficient enrollment or other reasons
  - The study shows a clear benefit of an intervention that must be given to all participants in the study regardless of the group to which they have been randomized

Data and Safety Monitoring

- Randomized clinical trials generally require data and safety monitoring
- A principal investigator may establish a DSMB to monitor a study
- The ethics review committee (IRB) may require a DSMB as a condition of approval of a clinical trial
- The study sponsor may require that a DSMB monitor the progress of a clinical trial

Data and Safety Monitoring

- DSMBs may typically include:
  - Biostatistician with experience in clinical research and clinical trials
  - Experts (MD, DDS) in the field(s) of the study – one expert usually chairs meetings
  - An medical ethicist
  - A medical monitor who checks data regularly and notifies DSMB quickly as needed – not a member but is present at meetings

Data and Safety Monitoring

- DSMBs responsibilities
  - Prior to evaluation, DSMB members agree on guidelines for stopping rules before study is initiated
  - Review study masked and unmasked study results and data
  - Review records and interventions by race, ethnicity, gender, age, and severity of disease at regular intervals

Data and Safety Monitoring

- DSMBs responsibilities (cont.)
  - Assesses adverse events and safety
  - Assesses study and enrollment progress
  - Monitors data collection and management
  - Makes recommendations to:
    - ✓ Stop the study
    - ✓ Continue the study
    - ✓ Modify the study

Data and Safety Monitoring

- DSMB does not directly make decisions for stopping, continuing or modifying a trial
- DSMB makes recommendations to ethical review committee (IRB) and study sponsor
- Study sponsor has responsibility for implementing recommendations of DSMB

Module 4 Key Points

- Clinical investigators must understand the major historical events that led to current ethical principles and standards that protect human research subjects.

- Clinical investigators must understand the ethical principles for human subject research as stated in the U.S. Belmont Report and the Declaration of Helsinki.

Module 4 Key Points

- Clinical investigators must understand that their research must comply with research standards for human subject research that have been established by their governments. These include Good Clinical Practice (GCP) guidelines, international ethical guidelines, as well as research standards of the countries in which the clinical research is conducted.
- Clinical researchers must understand the need ethical review and ongoing monitoring of clinical research.
- Clinical investigators must understand the role of researchers, sponsors, ethical review boards, data and safety monitoring boards, and the institution where the research is conducted in assuring that human subjects are protected.

End of Module 4