2009 Web Seminar Series

Ethical Principles in Clinical Research

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Goals of the Training

- Discussion rather than presentation
- Organized slides to generate questions
- Increase participant awareness of the historical underpinnings of ethics in research
- Acquire knowledge to sustain ethical practice in research studies
- Explore real life ethical dilemmas presented in research studies

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THE HIGH ROAD
ETHICS

Training Outline

- **Topic 1**: Origins of research ethics
- **Topic 2**: Principles governing research
- **Topic 3**: Ethical clinical research components

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Historic Events

Those who do not remember the past are condemned to repeat their mistakes.
(George Santayana, philosopher, essayist, poet and novelist 1905-1906)

- Nuremberg Code (1949)
- Declaration of Helsinki (1964- 2000)
- The Belmont Report (1979)
- CIOMS/WHO International Guidelines (1993, 2002)
- ICH/GCP-International Conference on Harmonization - Good Clinical Practice (1996)

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Guiding Documents

- Nuremberg Code 1947
  - First international conduct standard
- The Declaration of Helsinki 1964 (Amended – 2000)
  - Subject's interest over science
- Belmont Report 1979
  - Human subjects protection
  - Ethical principles
  - Federal regulations

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Ethical Clinical Research Principles

- Valuable scientific question
- Valid scientific methodology
- Fair subject selection
- Favorable risk-benefit evaluation
- Independent review
- Informed consent
- Respect for enrolled participants

Emanuel E, Wendler D, Grady C. What makes clinical research ethical? Journal of the American Medical Association 2000; 283(20):2701-11

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Valuable Scientific Question

- Is there a difference in liver safety between methadone and Bup/Nx (Suboxone®)?
- Does the addition of Motivational Incentives result in better retention and less drug use than treatment as usual (TAU) alone?

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Valid Scientific Methodology

Drug trial

- Adequate number to achieve power
- Equal exposure to medication
- Liver function testing at central laboratories
- Frequent liver testing to watch for problems
- Exposure duration sufficient

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Valid Scientific Methodology

Behavioral trial

- Generalizable
  - Treatment must transfer to real world practice
- Mandated
  - Drug court or Dept. of transportation
  - Intervention and TAU vs. TAU
  - Possibility that randomized participants may achieve lesser outcomes
- Retention / Drug use
  - Design questions must address mandated motivation vs. the incentive
  - Does Mandated status have affect?

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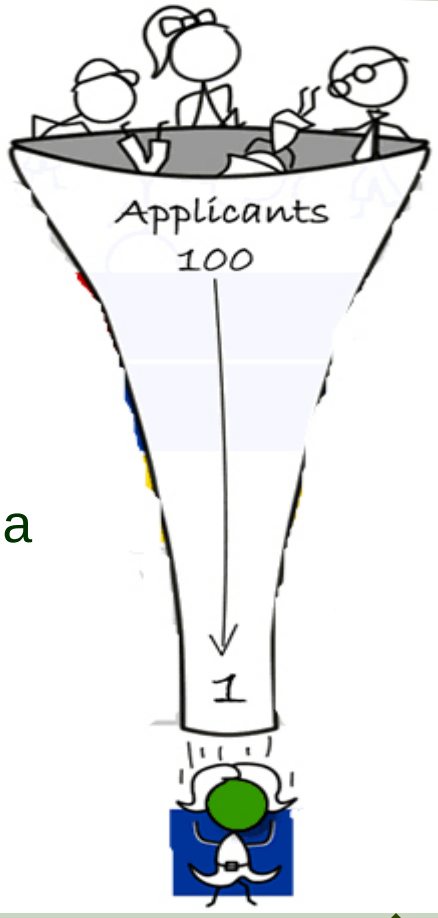
Fair Subject Selection

- Inclusion and Exclusion Criteria
  - Beneficence
    - Experimental arm no worse than (hopefully better than) treatment as usual
  - Do no harm
    - Vulnerable sub-populations
    - Clear and uniform inclusion/exclusion criteria
  - Justice
    - Participant selection free of bias
    - Recruitment free of bias
    - Randomization



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Fair Subject Selection

- **Situation for discussion**
  - Research subjects are compensated for their involvement in clinical trials (e.g., reimbursement for the time spent completing research interviews). Should individuals with substance use disorders be compensated with money for their involvement in research, especially if money can be a cue triggering craving and urges to purchase illicit substances? If so, how much money is reasonable compensation?

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Audience Interactions

- Any examples related to Fair Subject Selection

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Favorable risk-benefit evaluation

- Risk benefit ratio must benefit the patient
- Cannot risk participant welfare to achieve research goals
- Research design and procedures must be scientifically sound
  - Reduce risk and maximize benefit to the degree possible
- Clear regarding direct or secondary benefit

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Independent review

- The Two Protections
  - Independent Review Board (IRB)
    - What is being reviewed by IRB
      - Protecting participants through independent review
      - Must approve prior to starting and annually thereafter
  - Data Safety Monitoring Board (DSMB)
    - What is being presented at DSMB
      - Make sure the study is being conducted appropriately and safely

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Independent review

- **Situation for Discussion**
  - The Nov. 12, 2009 article in New Eng J of Med has a good example learning ethical principles in clinical research. Researchers from Johns Hopkins University published an article today and found Pfizer sponsored clinical trials of off-label use of gabapentin has been skewed to emphasize favorable results. The researchers compared internal company documents with published data from 12 clinical trials and found inconsistencies between data that made it into the medical journals and findings from the original trials. Discrepancies included reports of positive results from trials that were initially found to be negative, and primary study goals reported as secondary study goals. Trials that presented findings that were not significant for the protocol-defined primary outcome in the internal documents either were not reported in full or were reported with a changed primary outcome.
  - If the evidence is enough, it would suggest Pfizer attempted to mislead the medical community about the effectiveness of gabapentin for certain off-label conditions. This would be a serious misconduct against ethical principles in clinical research and practice.

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Informed Consent

- Fundamental to assuring Research is Ethical
- A person becomes a participant
- Respect for persons
  - Information
    - 8 requirements
  - Comprehensibility (understandable)
  - Voluntary Participation
- Right to choose
- An opportunity to build trust and a rapport with participants
  - Also used as a guide for verbal study explanation
- Provides all information needed for the participant to make and informed decision
- Provides time for the participant to ask questions
- Ensures participant comprehension
  - Therapeutic misconception

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Audience Interactions

- Any examples related to informed consent

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Respect for Enrolled Participants

- Therapeutic misconception
  - It is research not treatment
- Continual information sharing
- Respect right to withdrawal
- Confidentiality
  - 42 CFR
  - Certificate of Confidentiality
- Implicit and explicit pressure – Autonomy
- Monitoring participant welfare

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Respect for Enrolled Participants

- **Situations for discussion**
  - Your client has a positive drug test for the research study but a negative one for the clinic. The clinician is talking to you about how well the client is doing but you know that they have been using. The clinician asks you how all of their tests are coming back for the study. You know that they have been positive but can't tell them.

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Respect for Enrolled Participants

- **Situations for discussion**
- A client's mother calls you asking if they have come in today for their appointment. You tell them at first that you can't confirm or deny whether they have been at the clinic. The mother is really worried & is asking for your help. You do not have permission to give any information on this client to her.

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Respect for Enrolled Participants

- **Situations for discussion**
  - You accidentally skipped a question on one of the assessments. You think that you know how the client would respond & are tempted to complete the question on the CRF. You know that your site will have data queries if it is left blank & you don't want to mark your really good data record. Do you fill it in with the information that you think is correct?

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Respect for Enrolled Participants

- **Situations for discussion**
  - You have a husband & wife that are both participating in the study. You have developed a great rapport with both of them during all of their study visits thus far. They just received their test results last week but the husband has not told the wife about his results. She starts asking you about it during her appointment. You have let her know that you can't share the information but she is getting very upset.

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Audience Interactions

- Challenges with Respect for Enrolled Participants

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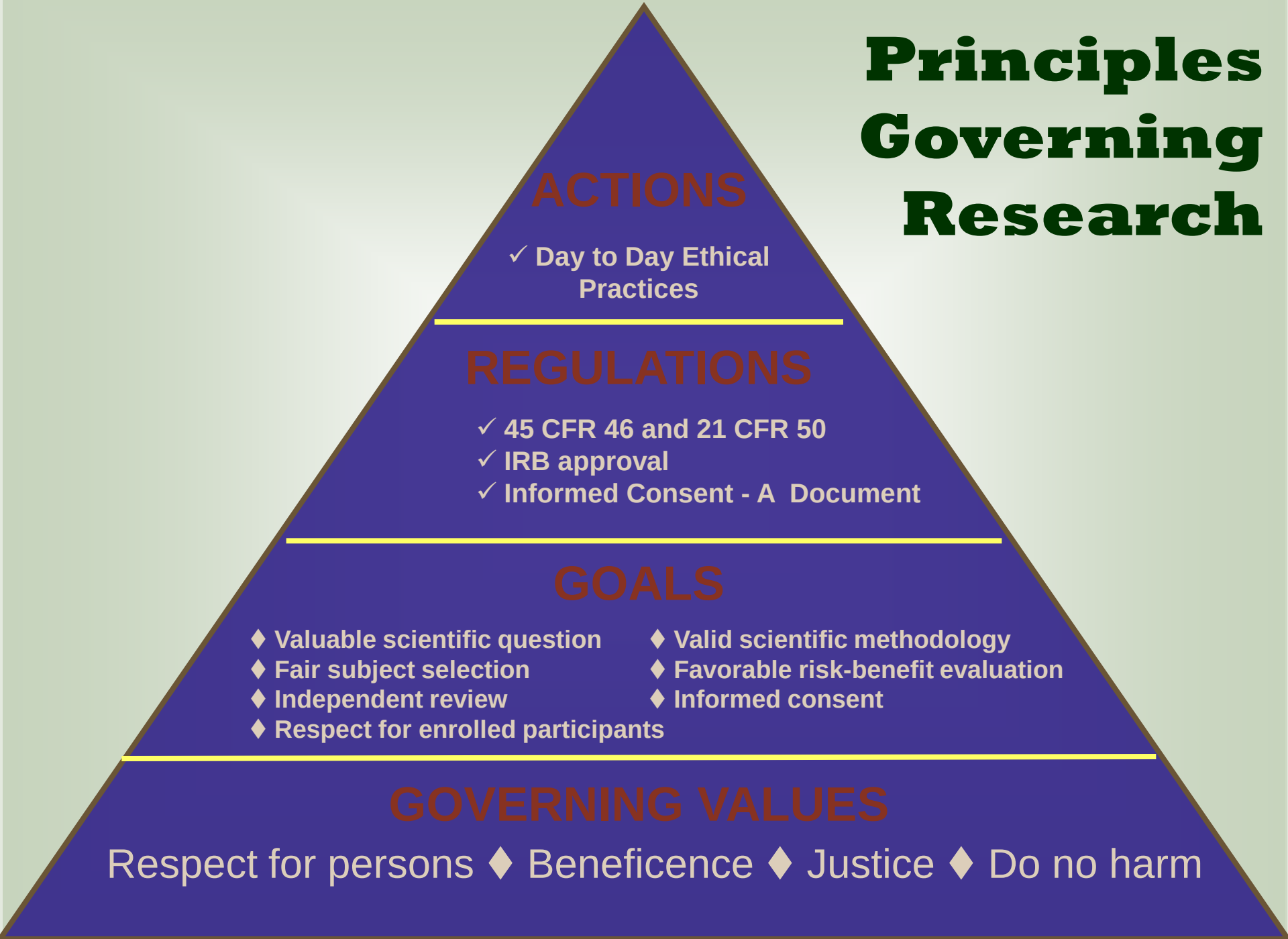
Principles Governing Research



Questions

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Handouts & Resources

- **Handouts**
  - **Presentation handouts**
  - **A Primer to Ethical Analysis**
    - *www.uq.edu.au/oppe/PDFS/Ethics_**primer**.pdf*
      - Source: Beauchamp, T. & Childress, J. (2001) Principles of Biomedical Ethics, 5th Ed, Oxford University Press, Oxford.
- **Resources**
  - **NIH Research Ethics online**
    - http://researchethics.od.nih.gov/
      - NIH online training course Introduction to the Responsible Conduct of Research

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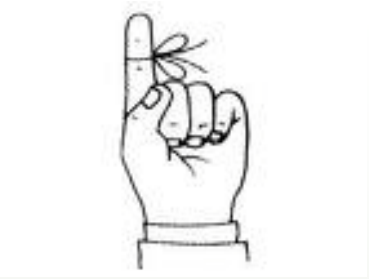

- **Continuing Education (CEU)**
  - The Society of Clinical Research Associates (SoCRA) accepts participation documentation for recertification if the program is applicable to clinical research regulations, operations or management, or to the candidate's clinical research therapeutic area.
  - **The CTN web seminar series courses qualify as appropriate sources of continuing education credits.**
    - Please use the following conversion formula. 1 hour = 1 CME or 0.1 CEU or 60 minutes.

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