Research: Ethics, Informed Consent, FDA, Off-Label Use

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Disclosures

• No financial disclosures.
Overview

• Discuss ethics of research
• Define informed consent
• Institutional review board (IRB)
• Food and Drug Administration (FDA), off-label use
Introduction

• Basic ethics of research:
  – Institutional human subjects review board
  – Risk to subjects are minimized and proportional to anticipated benefits and knowledge
  – Data monitoring to ensure safety of subjects
  – Protection of patient confidentiality
  – Determining the need for informed consent
Protection of Human Subjects in Research

• Nuremberg Code
  – Fully informed and voluntary consent of research subjects, minimizing harm and risks to subjects, scientific validity of research design and social value of the research
Ethical principles

• Scientific validity
  – Replicable and statistically significant
• Social value
  – Medical, scientific, and social worth
• Informed consent
• Respect for persons
  – Privacy, dignity and rights of research subjects
• Beneficence
  – Minimize harm and maximize benefit
• Equitable Subject selection
  – Fair and equitable distribution of benefits and harms
• Protection of vulnerable subjects:
  – Pregnant women and fetuses
  – Subordinate populations: e.g. prisoners
• Independent review
Informed Consent

• A statement that the study involves research
• An explanation of the purposes of the research
• The expected duration of the subject's participation
• A description of the procedures to be followed
• Identification of any procedures which are experimental
• A description of any reasonably foreseeable risks or discomforts to the subject
• A description of any benefits to the subject or to others which may reasonably be expected from the research
• A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
• A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
• For research involving more than minimal risk, an explanation as to whether any compensation, and an explanation as to whether any medical treatments are available, if injury occurs and, if so, what they consist of, or where further information may be obtained
• 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
• 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

US Department of Health and Human Services
Principles of Medical Ethics

- **Autonomy**: People have the right to control what happens to their bodies. This principle simply means that an informed, competent adult patient can refuse or accept treatments, drugs, and surgeries according to their wishes.

- **Beneficence**: All healthcare providers must strive to improve their patient’s health, to do the most good for the patient in every situation. But what is good for one patient may not be good for another, so each situation should be considered individually. And other values that might conflict with beneficence may need to be considered.

- **Nonmaleficence**: “First, do no harm” is the bedrock of medical ethics. In every situation, healthcare providers should avoid causing harm to their patients. You should also be aware of the doctrine of *double effect*, where a treatment intended for good unintentionally causes harm. This doctrine helps you make difficult decisions about whether actions with double effects can be undertaken.

- **Justice**: The fourth principle demands that you should try to be as fair as possible when offering treatments to patients and allocating scarce medical resources. You should be able to justify your actions in every situation.
Institutional Review Board (IRB)

• Most IRB’s have 15-25 members who are employees of the research institution with one or two members of the community who are not scientists.
• The IRB ensures that the rights and welfare of human subjects are well protected and to ensure that institutions are complying with regulations.

Responsible Conduct of Research; Shamoo and Resnick.
IRB

• Is this research?
  – Systematic investigation that contributes to generalizable knowledge

• Does it involve human subjects?

• Does it require IRB approval?
  – Exempt review: surveys or educational research; publicly available data

• Does the research need full IRB review?
  – Expedited review: minimal risk. Harm or risk anticipated is no greater than ordinarily encountered during daily life or routine physical/psychological exams.
IRB

• Are risks minimized?
• Are the risks reasonable in relation to benefits?
• Is selection of subjects suitable?
• How will the subjects be recruited?
  – Avoid coercion, deception, and exploitation
• Is confidentiality protected?
• Will informed consent be obtained?
IRB

- Will informed consent be documented?
  - Unless minimal risk
- Is informed consent process adequate?
- Are any safeguards required to protect vulnerable subjects?
  - Adequate informed consent; legally appointed representatives
- Is the protocol scientifically valid?
  - Scientific validity
- Will the data be monitored to protect subjects from risks and ensure validity of results?
- Are there any conflicts of interest?
- Are there any collaborating institutions?
US Food and Drug Administration

• The Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services.

• Consists of the Office of the Commissioner and four directorates overseeing the core functions of the agency:
  – Medical Products and Tobacco
  – Foods and Veterinary Medicine
  – Global Regulatory Operations
  – Policy and Operations
• Medical Device Definitions:
  – Medical devices range from tongue depressors and bedpans to programmable pacemakers with micro-chip technology and laser surgical devices.

• A device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:
  – recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
  – intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
  – intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.
Off-label Use

• Prescribing or using a currently available and marketed medication for an indication that has NOT received FDA approval.
• Overall, 21% of prescriptions are for off-label use.
• 78% of patients discharged from pediatric hospital were taking at least one off-label medication.

• “If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.”

• Use of a marketed product in this manner when the intent is the "practice of medicine" does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by an Institutional Review Board (IRB). However, the institution at which the product will be used may, under its own authority, require IRB review or other institutional oversight.
Off-label Use of Devices

• Biliary stents are approved by the FDA to treat biliary strictures but have been used “off-label” to treat peripheral artery disease.

• Remains controversial:
  – Off label use of drug-eluding stents associated with higher cardiovascular event rates than on-label DES (Brodie et al., JACC Cardiovasc Interv 2008).

• Higher costs for health care system???
Thank you