The ethics of medical research in humans

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Brief background

- The Declaration of Geneva (1948), World Medical Association
  - "The health of my patient will be my first consideration,“
- The International Code of Medical Ethics
  - "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

Brief background

- The Purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.
- In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.
- Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

Brief background

- In the field of biomedical research a fundamental distinction must be recognized between
  - medical research in which the aim is essentially diagnostic or therapeutic for a patient, and
  - medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Basic principles
(Declaration of Helsinki)

- Biomedical research involving human subjects
  - must conform to generally accepted scientific principles
  - should be based on adequately performed laboratory and animal experimentation, and
  - on a thorough knowledge of the scientific literature.

Basic principles
(Declaration of Helsinki)

- Experimental procedures involving human subjects should be clearly formulated in an experimental protocol
  - The protocol should be transmitted for consideration, comment and guidance to a specially appointed committee* independent of the investigator and the sponsor
    - *Research Ethics Committee
- This independent committee must act in conformity with the laws and regulations of the country in which the research experiment is performed.

Basic principles
(Declaration of Helsinki)

- Biomedical research involving human subjects
  - should be conducted only by scientifically qualified persons, and
  - under the supervision of a clinically competent medical person.
  - The responsibility for the human subject must always rest with a medically qualified person
    - Never rest on the subject of the research, even though the subject has given his or her consent.

Basic principles
(Declaration of Helsinki)

- Biomedical research involving human subjects
  - cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject
  - Therefore, every biomedical research project involving human subjects
    - should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others.
    - Concern for the interests of the subject must always prevail over the interests of science and society.

Basic principles
(Declaration of Helsinki)

- The right of the research subject to safeguard his or her integrity must always be respected.
  - (Rights of the individual vs society)
- Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject

Basic principles
(Declaration of Helsinki)

- Physicians should
  - abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable.
  - cease any investigation if the hazards are found to outweigh the potential benefits.

Basic principles
(Declaration of Helsinki)

- Right to information
  - In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail.
- Participation must be voluntary
  - He or she should be informed that he or she is at liberty to abstain from participation in the study
  - He or she is free to withdraw his or her consent to participation at any time.

Basic principles
(Declaration of Helsinki)

- No study without consent
  - The physician must obtain the subject's freely-given informed consent, preferably in writing.
  - The Nuremburg code (1947): ”The voluntary consent of the human subject is absolutely vital”
- Is ”voluntary” truly voluntary?
  - When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress.
  - In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

Basic principles
(Declaration of Helsinki)

- Consent when the study subject is not competent
  - In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation.
  - Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.
  - Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

Some problems with consent

- When the subject is truly and permanently incompetent (dementia, mental retardation)
  - Extreme caution is required
    - If the subject able to understand even just a little, attempts should be made to communicate
    - What are the motives of the legal guardian for giving consent?
      - Financial incentives which benefit then guardian should never be permitted!
    - The ratio of risk-to-benefit should be very low

Some problems with consent

- When the subject is transiently incompetent (unconsciousness, victims of severe trauma, transient mental illness)
  - Extreme caution is required
  - The research protocol must be reviewed very critically by a research ethics committee
    - Consider having representatives of the general public review the protocol
  - The risk-to-benefit ratio must be low
  - Remember that next-of-kin/relatives may be in a state of shock
    - May not be capable of understanding what is being asked

Some problems with consent

- When the subject is a child
  - The younger children cannot give consent
    - Parents must consent on their behalf
  - Older children will need to be consulted according to their level of understanding
    - Children older than 12 years of age should perhaps be asked to assent to their parents' consent
    - Children older than 16 years of age may (in Norway) consent without their parents
      - The need to involve the parents will then very much depend on what the study involves

Some problems with consent

- When the subject is a child
  - Studies in children need to be weighed very carefully for the risk-benefit ratio
    - Any study involving more than minimal risk should offer a substantial potential benefit
  - The mental and emotional state of the parents must be considered carefully
    - Consent may not be truly valid if the parents are in emotional turmoil

Some problems with consent

- When the subject is a child
  - BUT, children should not be deprived of the benefits of medical progress just because they are children!
    - Too little research has been done in pediatric pharmaco-therapy because the pharmaceutical industry has been afraid
    - Very few drugs have been developed specifically for the needs of children
  - Therefore, research in and for children is necessary

Medical research and clinical care

- In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.
  - The ”compassionate care” principle
- The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

Medical research and clinical care

- In any medical study, every patient--including those of a control group, if any--should be assured of the best proven diagnostic and therapeutic method.
- The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
- If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (Research Ethics Committee)

Medical research and clinical care

- The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

Non-Clinical Biomedical Research Involving Humans

- In the purely scientific application of medical research carried out on a human being
  - it is the duty of the physician to remain the protector of the life and health of the person on whom biomedical research is being carried out.
- The subjects should be volunteers
  - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

Non-Clinical Biomedical Research Involving Humans

- The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

- In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

A proposed study may not be acceptable if....

- Solid knowledge is already available on the subject and nothing new could be learned from the study
- The design of the study is flawed and the results would not be valid
  - Inadeguate number of study subjects
  - Wrong target population
- Basic studies have not been performed in animals
  - But could be done and might yield results that could modify the design of the proposed study

A proposed study may not be acceptable if....

- The risk to the patient outweighs any potential benefit
- The patient (or family) is offered financial rewards for participation
  - Which constitute enough of a financial incentive to override any misgivings the patient (or family) may have had
    - Covering the expenses the patient (or family) may have in connection with the study is permissible

A proposed study may not be acceptable if....

- the consent form does not make it absolutely clear to the patient that she/he may withdraw from the study at any time without needing to explain their reasons

Do children benefit from participation in research studies?

- Yes
  - If they are in the intervention arm and the intervention turns out to be beneficial
    - Example: Surfactant treatment of respiratory distress syndrome
- Yes
  - Studies have shown that even children in the control arm may have better outcomes than historical controls
    - Study subjects are likely to receive more meticulous attention from doctors and nurses

Research ethics in Norway

- Each health care region has its own research ethics committee (REC)
- Above these, there is a national committee
  - All proposals for studies in human subjects which are of a prospective nature must be submitted to the REC for approval
    - No study can be initiated without REC approval
  - All collection/storage of material (blood, tissue,data) requires ”biobank” approval

Research ethics in Norway

- The Data Directorate
  - Requires an application for collection and storage of data
    - Storage of data must be secure
      - Locked storage
      - Secure data net

Research ethics in Norway

- The ”ombudsmann” for patient protection
  - Many hospitals have a designated person who advices researchers on study protocols
    - She/he may have some privileges as far as approving study protocols locally
      - Protocols that do not active intervention
      - Retrospective chart reviews
        - » Can be performed without consent if done by the hospital’s own staff as part of a ”quality control” study
        - » Will require consent is one of the researchers comes from outside the hospital
        - » For example a visiting student doing an elective term

Thank you for your attention!