Ethical Issues to Consider in Clinical Trials in Neuroscience

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Federal Food, Drug and Cosmetic Act – revised in 1938
Required that drugs are proven safe before marketing
Resulted in a need for clinical trials
1962-Kefauver-Harris amendment
- First US law requiring informed consent
National Institutes of Health (NIH) traces its roots to 1887 within the Marine Hospital Service – predecessor to US Public Health Service

1891 – Hygienic Laboratory moved to DC

1930- Randsell Act changed the name of the Hygienic Laboratory to the National Institute (singular) of Health
Historical Perspective

- National Institute of Health - 1930
- National Cancer Institute – 1937
- National Institutes of Health – 1948
- *National Institute of Neurological Disorders and Stroke (NINDS)* - 1950
- 1970 – 15 Institutes
- 1998 – 27 Institutes and Centers (capped by Congress)
- 2011 – National Center for Advancing Translational Sciences (NCATS) replaced National Center for Research Resources (NCRR)
1947 - The Nuremberg Code
- Developed by International Military Tribunal
- Nazi physician experiments on concentration camp inmates
- First internationally recognized code of research ethics
The Nuremberg Code

- Voluntary consent is absolutely essential
- Study should yield fruitful results for good of society
- Anticipated results should justify conducting the study
- Study should be conducted to avoid unnecessary physical/mental injury
- No a priori reason to suspect death/injury
The Nuremberg Code

- Risk should not exceed importance of question being answered
- Subjects protected from even remote possibility of injury
- Study conducted by qualified persons
- Subject free to end participation in study
- Scientist must stop subject’s participation if continuing likely to result in injury
Question?

- How many Institutes/Centers are there within the National Institutes of Health?
  - A. 25
  - B. 27
  - C. 32
  - D. 35
The Immortal Life of Henrietta Lacks by Rebecca Skloot

- Best seller book in 2010
- Cervical cancer cells taken in 1951
- Development of the first living cell line – HeLa cells
- Bought and sold by the billions
- No informed consent
- Family has made no financial gains
Willowbrook State School for mentally disabled children open from 1930s until 1987

1963-1966: Otherwise healthy children were intentionally inoculated orally and by injection with hepatitis virus then treated with gamma globulin to monitor the effects

Parents were told that subjects would receive “vaccinations”
1964 – Declaration of Helsinki

- 18\textsuperscript{th} World Medical Assembly
- Established 12 Basic Principles to Guide Physicians in Conducting Biomedical Research Involving Human Subjects
Beecher article in NEJM

- Article by Henry K. Beecher in New England Journal of Medicine in 1966
- 22 examples of published clinical research placing subjects at risk without consent
- Pointed out that competition for funding and recognition contributed to the problem
- Recommended evaluation for compliance to ethical standards prior to publication
Office for Protection for Research Risks (OPRR)

- 1966
  - Establishment of the Office for Protection for Research Risks (OPRR)
  - Department of Health and Human Services (DHHS) adopts “Policies for the Protection of Human Subjects” issued by OPRR
  - Establishment of Institutional Review Boards (IRBs)
1972 - “Syphilis Victims in US Study Went Untreated for 40 Years” - NY Times headline
- “Tuskegee Study of Untreated Syphilis in the Negro Male”
- Initiated in 1932, planned for 6-8 months
- Public Health Service investigators
- Penicillin available 1950s, subjects not told
National Research Act - 1974

- DHHS “Policies for...” become “Regulations for...”
- Establishment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- Commission met over four years and developed the Belmont Report
The Belmont Report

- Respect for Persons
  - Recognition of personal dignity and autonomy
  - Special protection of those with diminished autonomy
  - Informed Consent
    - Information
    - Comprehension
    - Voluntariness
The Belmont Report

- **Beneficence**
  - Obligation to protect persons from harm
  - Maximize anticipated benefit, minimize possible harm
  - Risk/benefit ratio
    - Risk – probability, magnitude
    - Benefit – subject, society
The Belmont Report

- Justice
  - Fair distribution of research benefits and burdens
  - Inclusion/exclusion on scientific basis rather than convenience, availability
  - Two levels of justice
    - Social
    - Individual
Code of Federal Regulations

- 1983 - 45 CFR 46 revised for special classes of subjects
- 1991 - 45 CFR 46 incorporated into the “Common Rule”
  - Codified separate regulations by 15 Federal departments and agencies
Which of the following is NOT one of the founding principles of the Belmont Report?

- A. Respect for persons
- B. Scientific integrity
- C. Beneficence
- D. Justice
Good Clinical Practices (GCP)

- International Conference on Harmonisation (ICH) Guideline E6 on Good Clinical Practices - 1996
- Established international standards for clinical research
19-year old healthy volunteer in bronchoscopy research protocol
Administered up to 4 times the amount of recommended lidocaine
Died on March 31, 1996 of acute lidocaine toxicity
Failure to follow protocol
Failure to inform of risks
18-year old who suffered from ornithine transcarbamylase (OCT) deficiency
Controlled with low-protein diet and drugs
Gene therapy – infusion of corrective genes transported by an adenovirus
Within 24 hours, multiple organ system failure
Died 9/17/1999
Ineligible subject, failure to follow protocol - Investigators sanctioned
Healthy 24-year old volunteer
- Asthma study – inhaled hexamethonium
- Became ill within 24 hours
- Died of respiratory and renal failure one month after the study in June of 2001
- Compensation $365
- Failure to disclose experimental nature of the study and failure to properly research the risks of hexamethonium
May 1999 – human subjects research halted at Duke

July 2000 - human subjects research halted at University of Oklahoma

November 2000 – human subjects research halted at University of Colorado Health Sciences Center
Office for Human Research Protections

- Established in 2000
- Growing public and Congressional concern over the effectiveness of a 30-year old system
- OHRP issued 78 determination letters in 2000
- Issued a peak of 126 letters in 2001 and 146 in 2002
- ~35 determination letters/year in 2007-2010
What does GCP mean?

- A. Great Cleveland Partnership
- B. Good Clinical Practices
- C. Global Consciousness Project
- D. Global Citizenship Project
Regulations

- DHHS
  - Title 45 CFR Part 46
- FDA
  - Title 21 CFR Part 50, Protection of Human Subjects
  - Title 21 CFR Part 56, Institutional Review Boards
Research
- Systematic investigation designed to develop or contribute to generalizable knowledge

Human Subject
- Living individual about whom an investigator conducting research obtains (a) data through intervention or interaction with the individual or (b) identifiable private information
Minimal Risk

- Probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those *ordinarily encountered in daily life* or during the performance of routine physical or psychological examinations or tests.
- Does not apply to IND/IDE studies (investigational new drugs and devices)
Risks to subjects minimized
Risks to subjects reasonable in relation to
  - anticipated direct benefit
  - knowledge to be gained
Selection of subjects equitable
Informed consent sought and documented
Appropriate provisions for monitoring safety
Provisions for confidentiality
Additional safeguards for vulnerable populations
Subpart B – Pregnant Women, Human Fetuses, and Neonates
Subpart C – Prisoners
Subpart D – Children
- Note: No specific regulations for cognitive impairment
45 CFR 46 - Elements of Consent

Mandatory Elements

- Statement that study involves research
  - Purposes
  - Duration of subject’s participation
  - Procedures, are any experimental
- Risks
  - Reasonably foreseeable
  - Risks or “discomforts”
- Benefits
  - To subject or others
  - Reasonably expected from the research
- Alternative procedures/treatments, if any
45 CFR 46 - Elements of Consent
Mandatory Elements

- Extent of confidentiality of records
- If questions, who to call
  - About research itself
  - About subject rights
- Voluntary participation
  - Okay to refuse - no penalty or loss of benefits
  - May discontinue at any time
- For research involving more than minimal risk
  - Is compensation available
  - Research related injury – where treatment is available, who to contact if injury occurs
Unforeseeable risks of treatment/procedure
Circumstances where investigator may terminate subject’s participation
Additional costs to subject
Consequences of subject’s decision to withdraw
New findings affecting willingness to participate will be provided to subject
Number of subjects in study
Informed Consent - Purpose

- Informed consent – primary ethical principle governing human subjects research
- Empowers subjects to make their own determination about whether to participate
- Ensures subjects understand nature of research and knowledgeably and voluntarily make a decision

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Informed Consent – A Process

- Not an isolated event or a single document
- Rather, an educational interaction between investigator and prospective participant
- Begins with initial contact – recruitment ads
- In studies involving multiple visits
  - confirm willingness to continue
  - opportunity for additional interaction and questions about the research
Consent – A Legal Concept

- Only legally competent adults can give consent
- Incompetent adults cannot give legal consent
  - Cognitively impaired, unconscious, developmentally disabled
  - Evaluation of competence on case by case basis
- Minors cannot give legal consent

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Assent

- Minors and incompetent adults should be asked to “assent” – knowledgeable agreement
- Objection of minor or incompetent adult is a “veto” of the consent of legally authorized representative unless IRB stipulates otherwise
- Documentation of Assent/Consent
  - Assent Document + Informed Consent Document for younger children and parent/guardian
  - Informed Consent Document alone if at appropriate reading level for teenager
Consent process must be documented
  - Using consent document approved by IRB
  - With signature of subject or legally authorized representative

Copy of consent document must be given to person signing the form

Consent and its documentation may be waived in certain circumstances
Which of the following is not a mandatory element of consent?

- A. Statement that the study involves research
- B. Risks
- C. Payment
- D. Alternative therapies
Impaired decision-making capacity
Impaired decision-making capacity is not limited to individuals with neurological, psychiatric or substance abuse problems.

Conversely, individuals with neurological, psychiatric or substance abuse problems should not be presumed to be decisionally-impaired.

Limiting research to least-impaired individuals impacts on subject autonomy (Belmont principle) and hampers research for potential therapies for many disorders.
Informed Consent with Cognitive Impairment

- Unlike children, prisoners and pregnant women and fetuses, there are no additional DHHS regulations that specifically govern research involving persons who are cognitively impaired.
- It is important for clinical investigators to interact with potential subjects and assess their ability to consent and decision making abilities.
Points to Consider for Informed Consent in Cognitive Impairment

- Conflicting Roles and Potential Conflicts of Interest
  - Subjects may have difficulty understanding the difference between research and treatment leading to “therapeutic misconceptions”
  - The consent process must clearly differentiate between individualized treatments for the disease and the research process as well as between the clinician and the clinical investigator
Assessing Capacity to Consent

- Researchers need to be sensitive to differing levels of capacity and use assessment methods tailored to the specific situation.
- Simply answering a number of factual questions about a protocol may not be an adequate assessment.
- Decision making capacity may fluctuate over time involved in the clinical trial – requires ongoing assessment during the course of research.
- Consent process is ongoing – IRB may require an outside witness to observe the consent process.
Assessing Capacity to Consent

- There are no generally accepted criteria or tools for determining competence
- Important for investigators to consider the population encountered and describe methods and tools used to assess decision making abilities to assure continuing informed consent
Points to Consider for Informed Consent in Cognitive Impairment

- Comprehension
  - The clinician/investigator is in the ideal position to evaluate the subjects ability to understand the implications of research and whether the subject is making a rationale decision to participate
  - Also in the position to make the best judgment of the subject’s ability to understand and follow the protocol
  - The investigator is obligated to incorporate any special accommodations necessary to assure the subject populations or their surrogates comprehend the nature and purpose of the study
Points to Consider for Informed Consent in Cognitive Impairment

- Voluntary Agreement
  - Ensure that subjects’ participation is completely voluntary
  - Can be evidenced by written consent or their assent
  - Desperation of subjects AND caregivers may impact decision to consent (ALS and GBM)

- Second Signature on Consent Document
  - Many situations where subjects should be encouraged to authorize the involvement of family members
Legally authorized representative

Investigators need to understand the laws and regulations of their state

Investigators need to describe the need for surrogate consent to the IRB
In Iowa, the LAR for cognitively impaired adults is designated (in this order):

- The designated proxy (Durable Power of Attorney for Health Care)
- Court appointed guardian
- Spouse
- Adult Child
- Parent
- Adult Sibling
Special Issues in Human Subjects Protection in Neurological Clinical Trials

- Inability to comprehend during informed consent
  - IRB application must have requested that cognitively impaired subjects will be enrolled
  - Legally authorized representative must sign for consent for the subject.
  - Subject should be given the opportunity to assent, if able
Inability to speak during informed consent

- Investigators need to be able to assess that the subject has an understanding of the trial, the risks/benefits, etc.

- Query with yes/no questions

- Do not simply ask “do you understand?”
Inability to write (sign ICF document)

- Investigator needs to assess comprehension
- Investigator needs to recognize state laws and describe in IRB application
- Most states recognize a mark or an “X” as proof of identity and intent
FDA and DHHS regulations allow for some types of emergency research to be conducted without prior consent of subject or LAR (i.e. Emergency research consent waiver)

The exception for consent applies to a limited class of research activities involving human subjects who are in need of emergency medical intervention but cannot give consent because of their life-threatening condition
Emergency Research Consent Waiver

- Used in acute stroke or TBI trials
- IRB must make several determinations about the proposed research:
  - Life-threatening
  - Obtaining informed consent is not feasible
  - Participation holds the prospect of direct benefit to the subjects
  - The research could not practicably be carried out without the waiver
  - Proposal describes attempts to contact LAR within therapeutic window, if feasible
  - IRB has reviewed and approved the ICF and consent procedures to be used when feasible
Additional protections of the rights and welfare of subjects are provided, including:

- Consultation with representatives of the community
- Public disclosure to the community of plans for the research – is there the ability to opt out?
- Public disclosure of the results to the community following completion
- Establishment of an independent Data and Safety Monitoring Committee or Board
- Plans to contact LAR for consent if feasible within therapeutic window
- Plans to inform subject or LAR as soon as feasible of participation in research
Special Issues in Human Subjects Protection in Neurological Clinical Trials

- Desperation can lead to undue coercion
- Subjects may have comprehension difficulties
- Difficult to properly explain certain nuances of neurological clinical trials
  - Biomarkers
  - Adaptive randomization or adaptive dose assignments
Final Considerations

- Informed Consent is the cornerstone of protection of human subjects
- Investigators must take into consideration the abilities of potential subjects in order to properly execute informed consent
- We need more clinical trials in neurological disorders!
Questions?