CTMC 2021 Webinar Series: Ethical Issues in Acute and Chronic Neurological Conditions

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SPECIAL ARTICLE

AAN position statement: Ethical issues in clinical research in neurology

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- This update to the American Academy of Neurology's 1998 position statement endeavors to provide guidance for the consistent ethical conduct and review of neurologic research involving human participants.

7 principles for the ethical analysis of research on human participants

- social value
- scientific validity
- fair participant selection
- favorable risk–benefit ratio
- independent review
- informed consent
- respect for participants

Addressing all 7 principles is necessary and sufficient for clinical research to be considered ethically permissible.

Table Ethical principles for clinical research

Requirement	Summary	Examples of violations
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Respect for enrolled and potential participants	Potential and enrolled participants must be treated respectfully, with attention to and protection of their privacy and interests throughout the course of the study	A study of a genetic test in which identifiable results can be obtained by employers, law enforcement, or others

Historical concerns

- IRB review
- Equitable research participant inclusion
- Cognitive impairment in research participants

IRB review

- simplifying review of multisite studies under central IRBs
- reducing review of low-risk studies
- giving research participants options for broad consent to future studies
- supports IRBs' use of publicly available ethics checklists
- encourages mechanisms to allow appeals when IRB rulings conflict with the views of independent reviewers

Equitable research participant inclusion

- include both sexes and minority races and ethnicities
- include individuals of all ages
- include enough participants to allow for a valid analysis of whether women or minority participants are affected differently than other participants
- NIH funded trials submit these subgroup analyses to ClinicalTrials.gov
- where possible, participant recruitment should take place at community hospitals as well as academic centers, to promote geographic and socioeconomic diversity

Cognitive impairment in research participants

- temporary or permanent cognitive impairment
- impaired or nonexistent capacity to engage in the informed consent process
- capacity may fluctuate over time
- capacity screening instruments should be used
- results must be confirmed by a qualified clinician

Cognitive impairment in research participants

- The principle of informed consent requires the provision of accurate information about the purpose, methods, risks, benefits, and alternatives to the study and an uncoerced decision by a participant with decision-making capacity.

Cognitive impairment in research participants

Decisional capacity includes 4 abilities:

(1) understanding

(2) appreciation

(3) reasoning

(4) the expression of choice

Cognitive impairment in research participants

Importantly, decisional capacity is recognized to exist on a continuum, depending on the complexity and importance of a decision, and not to be a dichotomous all-or-nothing characteristic.

Cognitive impairment in research participants

- Legally Authorized Representatives (LARs)
- Common Rule specifies that, where state law does not specify rules for surrogate decision-making about research, surrogates for medical decision-making can also be considered surrogates for decisions about clinical research .

Cognitive impairment in research participants

An example of the order of a recognized hierarchy

1) The health care agent, upon proper invocation of the health care proxy

2) Legally appointed guardian or conservator

3) Spouse

4) Adult children – (majority consensus encouraged)

5) The subject's parent – (consensus encouraged)

6) Adult siblings – (majority consensus encouraged).

Cognitive impairment in research participants

Surrogate Consent

The surrogate should use a substituted judgment standard, making the decision based on the participant's historical beliefs and values, as the surrogate believes the participant would, were the participant able to undertake the informed consent process

Cognitive impairment in research participants

Surrogate Consent

IRBs may require additional safeguards, such as independent consent monitors, depending on the degree of cognitive incapacity and the study's risk–benefit ratio and complexity

In developing such safeguards, IRBs should make every effort to fully protect participants with dementia and other cognitive impairments, while minimizing impediments to studies of these important conditions

Conducting emergency research without prospective informed consent

Exception from Informed Consent (EFIC)

Planned Emergency Research

[Code of Federal Regulations]
[Title 21, Volume 1]
[Revised as of April 1, 2019]
[CITE: 21CFR50.24]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A--GENERAL

PART 50 -- PROTECTION OF HUMAN SUBJECTS

Subpart B--Informed Consent of Human Subjects

Sec. 50.24 Exception from informed consent requirements for emergency research.

- Planned Emergency Research subject to HHS regulations 45CFR46 may also be approved with and exception to informed consent per letter number 97-01 from OPRR dated Oct 31, 1996

EFIC Rules FDA and HHS

Conditions for study to be eligible for EFIC

1. Life-threatening situation that necessitates urgent intervention
2. Available treatments are unproven or unsatisfactory
3. Collection of valid scientific evidence is necessary to determine the safety and effectiveness of the intervention
4. Obtaining informed consent is not feasible
5. The intervention must be administered before consent can be obtained from the subject's legally authorized representative.
6. No reasonable way to prospectively identify potential participants
7. Participation holds out the prospect of direct benefit to the subjects
8. Could not practicably be carried out without the waiver

Consent Requirements

50.24(a)(5)—Investigator must commit to attempting to get consent from subject's LAR during the potential therapeutic window before initiating intervention without consent; these contact efforts must be summarized for the IRB at continuing review. *[paraphrased]*

50.24(a)(6) & (7)(v)—If LAR is not available, the investigator must also commit to attempting to contacting a family member to ask if they object to the subject's participation; these efforts likewise must be summarized for the IRB. *[paraphrased]*

Consent Requirements

50.24(b)—Process must be in place to consent the subject, their LAR, or a family member at the earliest feasible opportunity. *[paraphrased]*

50.24(b)—Subject, their LAR, or a family member at the point of being told of the study may discontinue the subject's participation. *[paraphrased]*

50.24(b)—If it was the LAR or family member who was provided the after- intervention consent discussion; when the subject regains capacity they must be informed of the research and given their own opportunity to consent. *[paraphrased]*

Involvement of the Community

50.24(a)(7)—Community Consultation

56.109(g)—Public Disclosure

Another Mechanism for waiver of informed consent.

21st Century Cures Act

- expanded waiving informed consent when there is minimal risk to participants to FDA-regulated studies
- Current FDA regulations only allowed for exceptions from informed consent requirements in life-threatening situations or for emergency research.
- FDA says it plans to revise its regulations on informed consent to allow for waivers or alterations for minimal risk clinical investigations.

FDA says it does not intend to object to an IRB waiving the requirement to obtain informed consent when the IRB finds:

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  - The clinical investigation involves no more than minimal;
  - The waiver or alternation will not adversely affect the rights and welfare of the subjects;
  - The clinical investigation could not practicably be carried out without the waiver or alternation; and
  - Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

FDA says it considers risk to be minimal when

- *"the 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 or routine physical or psychological examinations or tests."*

Randomized, controlled trials as minimal risk: An ethical analysis*

Morris, Marilyn C. MD; Nelson, Robert M. MD, PhD

Critical Care Medicine: March 2007 - Volume 35 - Issue 3 - p 940-944

Participation in a randomized, controlled trial may pose no more than minimal risk when:

1) genuine clinical equipoise exists;
2) all of the treatment options included in the research study fall within the current standard of care;
3) there is no currently available treatment with a more favorable risk-benefit profile than the treatments included in the study;
4) the nontherapeutic components of the research are safely under the minimal risk threshold; and
5) the research protocol provides sufficient latitude for treating physicians to individualize care when appropriate.

Questions/Discussion

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