Clinical Research Ethics in Vulnerable Populations

By Dawn R. Crumel, Vice President and General Counsel, Meritus Medical Center, Hagerstown, MD

People in vulnerable populations, which often include diverse communities, have found themselves subject to inappropriate research over the decades. Several reports both internationally and domestically address research atrocities.[1] The Nuremberg Code[2] addresses research on World War II prisoners who could not consent to the research. In the United States the Tuskegee Experiment described herein exemplifies lack of protection of research subjects. The Belmont Report later codified as the Common Rule provides further guidance and regulatory protection to research subjects in the United States. This article reviews the fundamentals of clinical research ethics in the context of vulnerable populations, including existing protections for human research subjects and implications of the proposed revisions to the Common Rule.

Tuskegee Experiment

From 1932 to 1972 the Public Health Service conducted research on African Americans with syphilis in a protocol entitled "Tuskegee Study of Untreated Syphilis in the Negro Male."[3] While penicillin became a known effective treatment for syphilis in the 1940s, the Public Health Service did not offer treatment to the human subjects and it did not tell the subjects that they had syphilis. The participants were told that free medical care was given in exchange for participation.

Belmont Report

Following the public discovery of the Tuskegee Experiment, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research convened a meeting in 1976 on ethical principles and guidelines for research at the Smithsonian Institution's Belmont Conference Center. In 1979 the Commission issued the Belmont Report[4] considering: (1) the boundaries between research and the accepted and routine practice of medicine; (2) the assessment of risk-benefit in the appropriateness of research involving human subjects; (3) appropriate guidelines for the selection of human subjects for participation in research; and (4) the definition of informed consent.

The Belmont Report applies three principles of biomedical ethics to clinical research: beneficence, respect for persons and justice:

Beneficence—The National Commission defined beneficence in the Belmont report as (a) to do no harm and (b) to maximize possible benefits and minimize the possible harms. Researchers must ensure beneficence by balancing the benefit of the research to the individual to the risk to the individual. By applying the principle of beneficence, researchers balance risk and harm in selecting research participants. The men suffering from syphilis did not receive the benefit of a known treatment to the disease. Accordingly, there was high risk to them and their families without a corresponding benefit, if one existed.

Respect for Persons—The National Commission set forth that respect for persons means to (1) treat individuals as autonomous agents and (2) protect persons with diminished autonomy. Researchers must give weight to the opinions and wishes of subjects and provide them all of the information needed to make an informed decision. For instance, would the men in Alabama have continued to participate in the Tuskegee experiment if they knew that they had a sexually transmitted disease with a known treatment and by not treating it they were putting their loved ones at risk? Researchers show lack of respect for autonomous persons if they do not fully inform them of their options. If a subject would not participate in the research if he knew of a risk that was not revealed, then the principal investigator did not show respect for the subject as an autonomous person. As well, if a person is incapacitated in some manner such as dementia then researchers must ensure adequate protection of the person in respect for that person.

Justice—Justice means to determine who should receive the benefits of research and who should bear the research's burdens. The National Commission defined justice as fair distribution. To determine fairness one examines justice: (a) to each person according to the individual need, (b) to each person according to an equal share, (c) to each person according to individual effort, (d) to each person according to societal contribution, and (e) to each person according to merit. For instance, given that syphilis is not confined to the African American community or to Alabama is there justice to solely test the African American community in Alabama? Is there justice for that particular community to bear the burden for a global society that is subject to syphilis? The men participating in the Tuskegee Experiment bore a burden beyond their own individual need, share, merit or effort.

The Belmont Report concludes with the following statement:[5]

> One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in setting where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

Vulnerable populations may not have other options due to economic status, leaving them in a position on which others may take advantage.

The Common Rule

The Department of Health, Education and Welfare (later renamed the Department of Health and Human Services (HHS)) codified the Belmont Report in the Common Rule,[6] in applying the principles of respect for persons, beneficence and justice in regulations designed to protect people participating in research. For research that presents more than minimal risk, the Common Rule requires that institutional review boards (IRBs) find all of the following elements prior to approving the research:[7]

- the research minimizes the risks to subjects by using procedures which are consistent with sound research and do not unnecessarily expose subjects to risk, and as appropriate use procedures already being performed on the human subjects.
- The risks to the subject are reasonable in relation to anticipated benefits, if any, to the subject. In addition, the benefit and importance of the knowledge to result as reasonably expected.
- The selection of subjects is equitable in relation to the purpose and setting of the research. In particular, the IRB should account for special issues with vulnerable populations.
- Informed consent must be obtained.
- Informed consent must be documented.
- The research plan should require monitoring the data to ensure subject safety.
- Additional safeguards must be in place if the research involves vulnerable populations who are subject to coercion.

Informed consent is one element of human research protection designed to protect autonomy and free will. A person cannot choose to participate in research without fully understanding the implications to such participation.

People in vulnerable populations, which often include diverse communities, have found themselves subject to inappropriate research over the decades.

Proposed Changes to the Common Rule—Implications to Vulnerable Populations

In its Advanced Notice of Proposed Rulemaking (ANPRM),[8] HHS proposed changes to the specifics of informed consent. HHS has expressed concerns that the length of the informed consent form commonly may be 15-30 pages and well above an 8th grade reading level. A form that is too long and not easily understood may be a barrier to informed consent by discouraging human subjects from thoroughly reading and understanding what they are signing.[9]

To accomplish informed consent, HHS considers changes to the consent form such as:[10]

- prescribing appropriate content that must be included in consent forms with greater specificity than is provided in the current regulations;
- restricting consent that would be inappropriate in consent forms;
- limiting the acceptable length of various sections of consent forms;
- prescribing how information should be presented in consent forms, such as information that should be included upfront, or types of information that should be included in appendices and not in the main body of the consent form;
- reducing institutional "boilerplate" in consent forms (that is, standard language that does little to genuinely inform subjects, and often is intended to primarily protect institutions from lawsuits); and
- making available standardized consent form templates which could satisfy applicable regulatory provisions.

To evaluate these proposed changes, HHS poses several questions such as whether investigators must assess how well potential research subjects comprehend the information provided to them before they are allowed to sign the consent form. What additions or deletions to the requirements of informed consent would be appropriate? Ensuring a person has the capacity to consent is quintessential to obtaining informed consent. On the clinical side, academic medical

center providers must evaluate a patient's appreciation of the benefits and risks of proposed treatment. Similarly, in research a potential human subject needs to appreciate the benefits and risks of participating in research to provide knowing consent.

In general, commenters to the ANPRM were not proponents of a required standardized consent form.[11] "Because research procedures vary greatly, the amount of information necessary to inform subjects should also be expected to vary. Limiting consent form length would invariably result in the proliferation of additional forms that subjects would be required to read and/or sign,"[12] according to Dr. Janet Weisenberger, Senior Associate Vice President for Research, The Ohio State University. Dr. Lo of the University of California, San Francisco and Mr. Mark Barnes of Harvard University addressed the mechanisms to protect vulnerable populations:

> To strengthen the consent process, the registration procedures and IRBs need to identify studies that should be exceptions to any presumption in favor of "template" consent forms. Researchers can develop innovative ways to educate participants about the disease being studied, clinical research generally, and the specific research project. *They can also assess participants' comprehension of key aspects of the study, shifting ethical focus away from consent forms.*
>
> Challenges to consent are compounded if some participants are vulnerable in the context of the specific study because of compromised ability to make informed, voluntary choices or significantly higher risk for adverse events than other participants. Such vulnerability should trigger proportionate IRB oversight. For example, the registration process for excused protocols should include a checklist to assess whether significantly vulnerable participants are targeted and might suffer serious risks. If so, investigators should describe what measures will ensure that consent is appropriate and risks minimized. Measures to protect vulnerable participants should not exclude them from studies of health needs and conditions in underserved communities and should not discourage such studies. To minimize barriers and delays, IRBs and HHS should post and regularly update guidance and best practices for protecting vulnerable participants. Community advisory boards can identify risks that are salient at a site, strengthen the informed consent process, and suggest how to build community support for the study and recruit participants.[13]

Informed consent is the application of ethics in the selection of research participants. Therefore, informed consent forms should document that the principal investigator evaluated the ethical principles of the Belmont Report in selecting the research participants. Tools to ensure participants understand the risks of research as referenced by the comments above are useful to ensure an autonomous person participates in research, while at the same time that the informed consent form adequately documents such consent. In other words, there must be an appropriate balance between a complex form setting forth all of the liabilities of the research institution and ensuring that the principal investigator achieves the purpose of the consent: justice, respect for persons and beneficence.

Vulnerable populations may not have other options due to economic status, leaving them in a position on which others may take advantage.

What Makes Clinical Research Ethical?

Drs. Ezekiel J. Emanuel, David Wendler and Christine Grady argue that there are seven requirements for clinical research to be ethical.[14] These requirements are: Value, Scientific Validity, Fair Subject Selection, Favorable Risk-Benefit Ratio, Independent Review, Informed Consent and Respect for Potential and Enrolled Subjects. They argue that the principles in the Nuremberg Code and the Belmont Report are responses to specific research atrocities and that their seven requirements are more universal. Their analysis of what makes research ethical provides a systematic framework for protecting human subjects in research. Many of these requirements are in the Common Rule[15] and may be utilized by an IRB in approving research for initial or continuing review. For instance in approving research as defined by the Common Rule,[16] IRBs should assess whether there is value to conducting the research and if there is scientific validity to the methodology. The Common Rule does not require independent review, although it does occur with some research. HHS should consider requiring such review with vulnerable populations.

To determine whether clinical research involving vulnerable populations is ethical requires close consideration of the framework discussed in this article. The application of the principles of justice, beneficence and respect may require a different analysis in this context. For example, paying a recruiter is often an IRB-approved methodology of recruitment given certain conditions. Yet, the selection of someone with seemingly little option to improve his socioeconomic condition may show a lack of justice in the research, i.e., an unequal burden of participation on a vulnerable population that will disproportionately face harm for the benefit of the organization conducting the research and society as a whole.

The application of the principle of beneficence may not be as clear cut where subjects derive some benefit from the research. In all cases, however, researchers should be readily available to minimize harm to subjects.

Regarding respect for a person's autonomy, recruiters and researchers must ensure the individual has the capacity to consent and fully appreciates the risks and harm. This process may include setting up tests to determine capacity to consent or ensuring a legal representative is available to consent on the person's behalf.

A more simplified informed consent form as suggested in the ANPRM also may help to ensure clinical research involving vulnerable populations is ethical. A test on the capacity to consent as suggested in the ANPRM through an innovative presentation may assist individuals and their caretakers in understanding fully what it would be like to participate in the research. A checklist on targeting vulnerable populations, as suggested by Dr. Lo and Mr. Barnes in the ANPRM commentary, also could aid in identifying whether a vulnerable population may unjustly bear the burden of the research.

Recognizing these bedrock principles and utilizing some of the innovations suggested by Dr. Lo and Mr. Barnes could go a long way in helping to ensure that clinical research involving vulnerable populations is conducted ethically. C

About the Author

Dawn R. Crumel (Dawn.Crumel@MeritusHealth.com) is Vice President and General Counsel at Meritus Medical Center in Hagerstown, MD. She also has been in-house counsel for Children's National Medical Center, Howard University Medical Center, and the University of Pennsylvania Health System. In addition, Ms. Crumel clerked for the New Jersey Supreme Court and was a health care associate with the law firm, Buchanan Ingersoll. She is the Chair of AHLA's Teaching Hospitals and Academic Medical Centers Practice Group and serves on AHLA's Advisory Council on Diversity.

Endnotes

1 Nuremberg Code, Nuremberg Military Tribunal decision in United States v. Brandt, 1947; Declaration of Helsinki, World Medical Association, 1964, 1975, 1983, 1989, 1996; International Ethical Guidelines for Biomedical Research involving Human Subjects, Council for International Organizations of Medical Sciences in collaboration with World Health Organization, proposed in 1982, revised 1993.

2 *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10*, Vol. 2, pp. 181-182. Washington, D.C.: U.S. Government Printing Office, 1949.

3 *See* http://ori.hhs.gov/education/products/mass_cphs/training_staff/RCReng/RCRRecruiting1a.htm; http://www.cdc.gov/tuskegee/timeline.htm.

4 44 Fed .Reg. 23192 (1979).

5 *Id.* at 23192, 23197.

6 45 C.F.R. § 46 (2009).

7 *Id.* § 46.111 (2009).

8 76 Fed. Reg. 44512 (2011).

9 *Id.* at 44512, 44522-44523.

10 *Id.*

11 American Society for Investigative Pathology, Letter to Jerry Menikoff, MD, JD, Office of Human Research Protections, October 18, 2011; Betsy A. Kohler, Executive Director NAACAR, Letter dated October 26, 2011; David Lavallee, Executive Vice Chancellor for Academic Affairs and Provost, State University of New York and Bonny Boice, Executive Vice President, The Research Foundation of State University of New York, Letter dated October 25, 2011.

12 Janet Weisenberger, PhD, Senior Associate Vice President for Research, The Ohio State University, Letter to Jerry Menikoff, MD, JD, Director, Office for Human Research Protections, October 24, 2011.

13 Dr. Lo of the University of California, San Francisco and Mr. Mark Barnes of Harvard University, Comments to Jerry Menikoff, MD, JD, Director, Office for Human Research Protections, October 26 , 2011 (emphasis added).

14 Ezekiel J. Emanuel, Md, PhD, David Wendler, PhD, Christine Grady, PhD, *What Makes Clinical Research Ethical?*, JAMA Vol. 283, no. 20 (2000).

15 45 C.F.R. § 46.111, § 46.116.

16 45 C.F.R § 46.102(d).

The opinions expressed herein are solely of the author and do not reflect the opinion or position of Meritus Medical Center and its affiliates or the American Health Lawyers Association. This article was originally presented at AHLA's Annual Meeting in San Diego, CA (July 1–3, 2013).