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Ethical Issues in Investigational Drug Studies

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LEARNING OBJECTIVES

1. Identify important historic events that have influenced ethical issues in investigational studies.
2. Categorize and explain barriers to informed consent.
3. Define incentive, coercion, and persuasion, and the significance of each.
4. Recognize and describe the various risks to patients.
5. Identify and discuss the rationale of using placebo in clinical trials.

ABSTRACT: There has been an incredible advance in the protection of human research subjects since World War II. Unfortunately, the focus of investigators has not always been on the study participants. Protecting the rights, interests, and safety of participants in research is mandatory. Nonetheless,

protecting study participants involves more than ensuring the safety of individual study drugs. Protection of participants involves the patients' understanding of the informed consent information and process, the role and risk of incentives and conflicts of interest, and the general harm that patients may be exposed to as being participants in human studies.

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ETHICAL ISSUES IN INVESTIGATIONAL DRUG STUDIES

INTRODUCTION

The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic, and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility, and quality.^{1,2,3}

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects. In current medical practice and in medical research, most prophylactic, diagnostic, and therapeutic procedures involve risks and burdens. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.^{1,2,3}

A Brief History

To understand where we are today, it is important to discuss key historic events, such as the Nuremberg Code, the Declaration of Helsinki, the Tuskegee Study, and the Willowbrook Affair. These events have shaped the current safeguards for use of human subjects in medical research.

Nuremberg Code

On December 9, 1946, an American military tribunal opened criminal proceedings against 23 leading Nazi physicians and administrators for their willing participation in war crimes and crimes against humanity. In Nazi Germany, physicians planned and enacted the “Euthanasia” Program, the systematic killing of those they deemed unworthy of life. During World War II, Nazi physicians conducted pseudoscientific medical experiments using thousands of concentration camp prisoners without their consent. As a result, most prisoners died or were permanently crippled.^{2,3,4}

Before announcing the guilt or innocence of each defendant, the tribunal

confronted the difficult question of medical experimentation on human beings. Several of the doctors had argued in their own defense that their experiments differed little from previous American or German ones. In addition, they showed that no international law or informal statement differentiated between legal and illegal human experimentation. This argument concerned Andrew Ivy and Leo Alexander, American doctors who had worked with the prosecution during the trial. Dr. Alexander then submitted a memorandum to the United States (U.S.) Counsel for War Crimes, which outlined 6 points defining legitimate research. The tribunal revised this document into 10 points:

1. Voluntary consent by the human subject is essential.
2. The experiment should produce satisfying results for the good of society that cannot be acquired by other methods or means of study, and are not random and unnecessary in nature.
3. The experiment should be designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study, and that the anticipated results will justify the performance of the experiment.
4. The experiment should be conducted to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is a reason to believe that death or disabling injury will occur, except perhaps in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the

humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities should be provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. Only scientifically qualified persons should conduct the experiments. The highest degree of skill and care should be required through all stages of the experiment of those that conduct or engage in the experiment.
9. During the course of the experiment, the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Subsequently, the 10 points became known as the Nuremberg Code. The legal force of the document, however, was not well established. The uncertain use of the Code continued in the half century following the trial but failed to find a place in either the American or German national law codes. Nevertheless, it remains a landmark document on medical ethics and one of the most lasting products of the Doctors' Trial.^{2,3,4}

Declaration of Helsinki

In 1964, the World Medical Association developed the Declaration of Helsinki. It is a statement of ethical principles that provides guidance to physicians and other participants in medical research involving human subjects. The Declaration identified that, in clinical research, a fundamental distinction must be recognized between clinical research in which the aim is essentially therapeutic for a patient and clinical research in which the essential object is purely scientific and without therapeutic value to the person subjected to the research.^{1,2,6}

A demonstration that unethical research was taking place in the U.S. was presented in a 1966 article by Henry Beecher, a physician at Harvard University, in the *New England Journal of Medicine*. This paper described many immoral experiments and challenged several research programs for being obviously unethical. Of the dozens of experiments that Beecher fingered, most were within the mainstream of clinical research, even though they used unknowing human subjects or exposed subjects to extreme risk for the sole purpose of advancing scientific knowledge.^{1,7}

Tuskegee Study

This Study involved 600 low-income, African-American males, 400 of which were infected with syphilis for a 40-year period of time from 1932-1972. The Study's original design continued for decades after effective treatment for syphilis became available. In some cases, when other physicians diagnosed subjects as having syphilis researchers intervened to prevent treatment. Throughout the 40 years of the Study,

U.S. Health Service officials periodically reviewed it. In each case, the Study was extended based on the argument that by stopping the Study, while helping these individuals, it would interfere with the benefits to medical science of studying this untreated disease. Ultimately, the U.S. Department of Health, Education, and Welfare stopped the Study only after its existence was leaked to the public and it became a political embarrassment.^{2,3,9}

The Tuskegee Study violated a number of ethical principles that are now applied to human subject research. The Study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. The Study did not minimize risks to human subjects; in fact, it increased their risks. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.⁹

Willowbrook Affair

In 1955, Saul Krugman, a pediatrician at Willowbrook institution in New York, attempted to devise a vaccine against hepatitis. Dr. Krugman had been feeding or injecting mentally disabled children with serum, urine, or fecal filtrate taken from patients with known viral hepatitis. Dr. Krugman argued that the parents had given consent for such work to be carried out, that all children admitted to Willowbrook would get hepatitis if they had not had it already, and that the attack would in any case be mild. He also argued that there was a special unit at the institution to care for them if they developed an overt infection. Others argued that although parents had given consent for the

children to be given the virus, nothing had been said about whether the hazards of the work had been explained to them. It was also argued that no doctor was allowed to do anything that would weaken the physical or mental resistance of a human being, and that no doctor had the right to risk any injury to one person for the benefit of others.^{2,6,10}

The Belmont Report

In 1974, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was formed. The Commission was a multidisciplinary group of scientists, moral theologians, ethicist-philosophers, and policy experts. Its charge was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines that should be followed to assure that such research is conducted in accordance with those principles. In 1979, the Commission publicized the Belmont Report, which describes the 3 fundamental principles of biomedical research ethics: respect for persons, beneficence, and justice.

- Respect for Persons

It incorporates 2 ethical principles: first, individuals should be treated as autonomous agents, and second, individuals with diminished autonomy are entitled to protection.

- Beneficence

In the Belmont Report, beneficence is understood as an obligation. Two general rules have been formulated as expressions of beneficent actions:

(1) do not harm and (2) maximize possible benefits and minimize possible harms.

- Justice

An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed undeservedly. There are several ways to distribute burdens and benefits:

- To each person an equal share
- To each person according to individual need
- To each person according to individual effort
- To each person according to societal contribution
- To each person according to merit

A formal doctrine of informed consent was crafted as an application of these principles. The Belmont Report guidelines were incorporated in the federal regulations. The federal regulations guiding responsible research on human subjects are codified in Title 45, Part 46, of the Code of Federal Regulations; it is known as The Common Rule.^{1,5,6,7}

The Human Subject—Application

The above paragraphs discussed how history changed and developed the regulations we use today in clinical trials. The following paragraphs will discuss how clinical trials are implemented regarding the use of human subjects. We will discuss the process and many of the issues that are involved when study subjects are recruited.

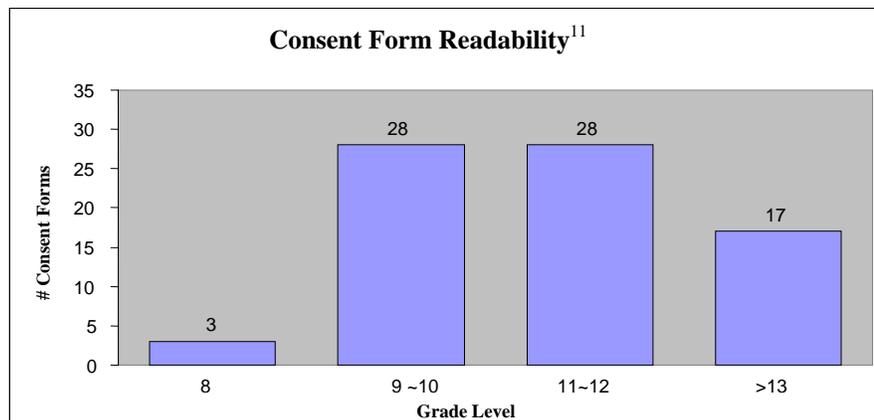
Informed Consent—The Decision-Making Process

Advances in biomedical research, rapid changes in health care systems, and growing legal concerns have fostered a trend toward a more difficult consent process and increasingly complicated consent documents. Fears of litigation have concealed the aim of the consent process, which is to help the potential research participant make an informed decision about participation in a research study. As medical research has become more complex, the emphasis placed on informed consent has increased dramatically. Concurrently, advocates for research participants have increased their concern in the way detailed information is provided.^{3,11,12}

To conduct clinical research in an ethically responsible manner, investigators need to provide potential subjects with a clear and understandable description of what is being proposed and an explanation of their rights as participants. In many cases, however, the information provided in the consent document is more confusing than informative. Even more discouraging is that 90 million Americans are reported to have low literacy skills and 9 million Americans aged 15 years and older cannot read or write a complete sentence. This population cannot read or sufficiently understand business letters, package instructions, or written material given to them by health professionals, not to mention comprehending a consent document that is confusing for the general population. Many of these people, however, are patients in hospitals where clinical trials are being conducted and may be the human subjects taking part in various research protocols.^{3,11,12}

To further exemplify this disparity are the results of a study published in 1995, which suggest that the average person participating in a study would not be able to read and comprehend the informed consent adequately. Within this study, 76 informed consents were evaluated. Of the 76 informed consents, only 3 were found to be in the target 8th

grade range. Ninety-six percent of the informed consents were found to have readability levels higher than an 8th grade level. Of these, 28 scored between grades 9 and 10, 28 scored between grades 11 and 12, and 17 scored above grade 13. The mean readability for the entire group was grade 11.^{11,13}



Investigators are required to solicit the informed consent before enrolling a subject into a research study. Informed consent is based on the ethical principle of respect for persons. Respect for persons is divided into 2 categories. The first category requires that the informed consent process provides the individual with enough information to make an *informed decision*, and that the individual is able to make a *voluntary* decision. The second category requires that if an individual is not competent to make a decision on his or her behalf, then he or she is excluded from participation or someone else is authorized to provide informed consent on his or her behalf. Respect for persons is discussed in the Belmont Report, and the requirements have been incorporated into the federal regulations that govern human subject research.¹³

As demonstrated above, significant barriers to the informed consent process exist. These barriers can be separated into 2 different but related categories: patient-centered and process-centered barriers. Patient-centered and process-centered barriers may co-exist or exist uniquely. If present, they prevent the subjects' consent from being informed.^{13,14}

Patient-Centered Barriers

Age and Education

- Age and level of education predict poor comprehension of information given during the informed consent process.
- A patient's level of education has been shown to predict the ability of a patient to correctly recall the purpose of the study. Almost all patients will report to understanding the information provided to them;

however, only one-third can correctly identify the purpose of the study

- Subjects rely on an incomplete definition of terms during the informed consent process and rarely ask for clarification.

Illness

- Patients who are ill may be less able to provide substantial informed consent.
- Healthy volunteers retain the most information, while patients dealing with illnesses may be less able or not as willing to make an effort to understand the information from the consent process.
- Potential research subjects may pay less attention that they are being asked to enroll in a clinical trial and more that the trial may provide possible treatment for an illness.

Patient-Physician Relationship

- A patient's relationship with the physician may not have an impact on the patient's understanding during the informed consent process, but it may make him or her less likely to refuse enrolling in a clinical trial. A patient may consent half willingly if he or she is afraid of upsetting the physician by declining to participate in a study.

Overestimation of Benefit

- Despite the uncertainty of benefit stated in the consent form, almost half of patients report that they were

sure they would receive some therapeutic benefit.

Process-Centered Barriers

Time Allocated to Decision Making and Questions

- Half of investigators report spending less than 15 minutes on the consent process.
- Patients who spent more time with researchers reviewing the protocol and the consent form were more likely to retain information shared during the consent process.
- A majority of patients report not having enough time to ask questions.

Readability of Consent Form

- The average consent form is written at a level that requires at least a high school education.
- The average person reads at an 8th grade reading level.

Content of Consent Form

- Subjects have been found to incorrectly interpret statements 26% to 54% of the time.
- A patient who has no questions is not an indication that the patient has understood all of the information discussed.

To address and overcome some of these barriers, individuals involved in requesting and acquiring human subject informed consent should follow the key points below:

Twenty Key Points to Improve Understanding of the Informed Consent Process¹⁵

- Consider principles of teaching, learning, and communication when crafting and delivering informed consent communications.
- Build alliances with patient: get in touch with patient's attitudes, knowledge, and perceptions about study participation.
- Recognize that many factors influence comprehension, especially low educational, literacy, and vocabulary levels.
- Screen literacy skills using informal and formal measures.
- Present information according to the patient's preference; gauge preference by asking patient about his or her perception of the quality and quantity of the information being conveyed.
- Obtain patient input and feedback throughout the informed consent process.
- Include a family member or friend in the informed consent interaction.
- Enhance the reading ease of the informed consent document by using a variety of design techniques.
- Simplify verbiage, be clear and concise, use plain language, and relate medical terminology to everyday situations from the patient's viewpoint.
- Provide time for patient to digest the information.
- Provide multiple opportunities for interaction both in the document itself and during the informed consent process
- Summarize often; ask the patient to speak or write about the elements in the informed consent document.
- Probe and verify understanding: ask patient to repeat what he or she has heard in his or her own words.
- Assess understanding using reliable and valid measures.
- Use a combination of printed and electronic methods to reinforce the informed consent message.
- Encourage and provide take-home consents and/or aids.
- Enhance the communication of the required elements of the informed consent customized to a subject's demographics, psychographics, or behavioral characteristics.
- Evaluate your interactions.
- Improve your communication skills through continuing education.
- Conduct systematic investigations to advance science.

An additional requirement for informed consent is the disclosure by a health care professional to a patient or research subject all information about his or her medical condition, recommended interventions or proposed protocols, and the identity and qualifications of those who will be participating in the interventions or protocol. An informed

consent demands that whoever is making decisions is free from any coercion or other form of unjustified influence that would prevent the consent from being free and voluntary. To truly understand this, a discussion of the following concepts is warranted: incentives, coercion, and conflict of interest.^{15,16}

Incentives and Coercion

An incentive is something that urges a person on. It is a cause of action or effort, motive, or stimulus. Offering an incentive is a usual recruitment and retention practice in studies. Subjects may be offered regular health checkups, access to health care for those typically unable to afford such care, or access to treatments that are unavailable except through participation in the clinical trial. Coercion is an extreme form of influence by another person that completely controls a person's decision or deprives the person of autonomous choice. Coercion is possible only if one person or group intentionally and successfully influences another person's decision by using threats so as to make it impossible to resist the person's or group's desires. Persuasion is the successful and intentional use of reason to convince a person to willingly accept the beliefs, choices, or decisions favored by the persuader.¹⁷

Not all incentives that researchers offer to study participants are viewed as coercive. Subjects have the option to accept or refuse an incentive that is offered. How great an influence the incentive creates depends on the socioeconomic situation of the patient. The potential research subject who has fewer financial resources may view the incentive quite differently. Incentives, whether coercive or not, can cause particular groups within society to bear an unfair share of the burdens of research without reaping the same level of benefits. Incentives have the potential to convince vulnerable persons to subject themselves to significant, unnecessary risks that they would not otherwise consider. Incentives that convince people to do something that

they ordinarily would not do may exploit these persons even though the incentives are not coercive. Keep in mind that incentives can be morally suspect even when they do not meet the criteria for coercion.¹⁷

Conflict of Interest

Concerns have grown that financial conflicts of interest in research may affect the rights and welfare of human subjects in research. In May 2000, The U.S. Department of Health and Human Services (HHS) announced 5 initiatives to strengthen human subject protection in clinical research. One of these initiatives was to develop guidance on financial conflict of interest that would serve to further protect research participants. On May 12, 2004, HHS released the final guidance document, "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection." This document applies to all human subjects' research conducted or supported by HHS agencies or regulated by the Food and Drug Administration.¹⁸

In the Guidance document, HHS raises points to consider in determining whether specific financial interests in research affect the rights and welfare of human subjects and, if so, what actions could be considered to protect those subjects. Institutions, institutional review boards (IRBs), researchers, and other responsible parties are encouraged to use this information to help ensure that any potential conflicts of interest stemming from financial relationships are identified and eliminated or managed with the subjects' best interests in mind.¹⁸

As institutions, IRBs, and researchers consider potential financial conflicts of interest, they can refer to the Guidance document for possible mechanisms to manage such conflicts. These mechanisms include but are not limited to:¹⁸

- Separating institutional responsibility for research activities from management of the institution's financial interests;
- Establishing conflict of interest committees (COICs) or identifying other bodies or persons and procedures to address financial interests in research;
- Using independent organizations to hold or administer the institution's financial interest;
- Determining whether current methods for managing conflicts of interest are adequate for protecting the rights and welfare of human subjects and whether other actions are needed to minimize risks to subjects;
- Determining the kind, amount, and level of detail of information to be provided to research subjects regarding funding and financial interests; and
- Using special measures to modify the informed consent process when a potential or actual financial conflict exists.

Having completed the discussion on informed consent, an additional ethical dilemma warrants discussion. This dilemma is similar to one of the ethical issues raised in the Tuskegee Study: not providing effective treatment when treatment was available. The 'use of placebo' study design echoes this concern. 'Use of Placebo' or 'no treatment when effective treatment is

available' speaks to the possibility that patient harm or lack of benefit would occur if placebo is given.

Use of Placebo

The scientific rationale for including a placebo control in a randomized, double-blind, controlled clinical trial is well established. There is general agreement that placebo should not be used if delayed treatment causes irreversible morbidity or mortality; some contend that it is not ethical to use a placebo control if there is an effective standard. Others maintain, however, that placebo controls can serve an indispensable role, even when effective medications are available.¹⁹

It may seem ironic that clinical trials with active comparators have more nonresponders than those clinical trials with placebo controls, but this may be attributable to an aspect of statistical power analysis. There is an inverse relationship between the sample size requirement and the detectable population effect size. More participants are needed to detect smaller differences between groups. Consequently, a larger sample size is needed to detect the relatively smaller group differences of an active-controlled trial compared with that of a placebo-controlled trial keeping power and Type I error constant. The appeal of a greater, overall, expected response rate in an active-controlled trial is offset by a substantially larger sample size requirement compared with that of a placebo-controlled trial. As a result of the larger sample size, there are actually more nonresponders.^{19,20}

Suppose the response rate to a placebo is 10%, while an active comparator has a 60% response rate and the

investigational agent has a 70% response rate. In a placebo-controlled trial, only 12 subjects are required in each arm, with about 4 nonresponders expected in the investigational group and about 11 in the placebo group, there is a total of only

15 nonresponders. On the contrary, with an active comparator, the required sample size per group is 376, with about 150 nonresponders in the active control arm, 113 in the experimental arm, for a total of about 263 nonresponders.²⁰

Number of Nonresponders, Active and Placebo Comparator²⁰

<i>Comparator</i>	<i>Arm</i>	<i>Response Rate</i>	<i>Number Enrolled</i>	<i>Nonresponders</i>	<i>Total Nonresponders</i>
Placebo	Placebo	0.1	12	11	15
	Investigational Drug	0.7	12	4	
Active	Standard Drug	0.6	376	150	263
	Investigational Drug	0.7	376	113	

The use of placebo control, however, ignores those patients who may be considered nonresponders because they did not have the opportunity to participate in the study. Minimizing the number of nonresponders in clinical trials is not by itself an adequate reason to justify withholding effective treatment. The decision needs to be based on the individual characteristics, objectives, and theoretical outcomes associated with each study.^{19,20,21}

Risks to Patients

Protecting the rights, interests, and safety of participants in research is required. Risk is inevitable in clinical research, but it is essential that the risk be minimized. There are 5 potential risks to research participants:

1. Anxiety and distress
2. Exploitation
3. Misrepresentation
4. Identification of the participant by themselves or others
5. Misunderstanding²²

Anxiety and Distress

Interviews are the most common method of collecting information in health services research and are used for the collection of data on sensitive topics. Many interview questions may lead to or provoke anxiety or distress in a patient. Questions that lead to anxiety and distress depend on the personal history and experience of individual participants and cannot always be predicted accurately.^{22,23}

Exploitation

Even when researchers have a commitment to the people being studied there is inevitably a power imbalance between the investigator and participant. The participant may feel pressured to participate in research because of a sense of duty. Participants may also be exploited during the interview if the researcher attempts to ask inappropriate and sensitive questions urging participants to divulge more information

than they had anticipated when consenting to the study.^{22,23}

Misrepresentation

The researcher's commitments, characteristics, and preconceptions influence analysis of data. Interpretation of research almost always guarantees that the published results are a version of the truth. The validity of findings must be judged in relation to the care taken to analyze the data. Participants have noted that when a study is socially constructed, they feel their views are more likely to be misrepresented or taken out of context. Personal narratives are often interpreted and generalized, and patients worry about losing control over self-identity. Most research is designed to answer specific questions about the patients' perceptions and behavior, and can be influenced by preconceived notions. Sampling strategies are often determined by preconceived theories and participant characteristics are built into the study design and can be affected by the background of the researcher.^{22,23}

Identification of Participant by Self or Others

Research studies collect large amounts of information about participants' health and illness, lifestyles, and views about health care, as well as information about members of their families and social groups. If identification occurs, it may potentially lead to harm. It is impossible to keep all data anonymous throughout the interview stage and analysis. Even if all precautions to keep data anonymous are applied, speech mannerisms and context may provide enough information for participants to be identified by themselves or others.^{22,23}

Misunderstanding^{24,25,26}

- Misconception is when the research subject combines research with clinical care. Most often, patients confuse research with clinical care. Misconception is rarely tolerable because understanding the nature of research is necessary for an autonomous decision when participating in research.
- Misestimation is when the research subject underestimates risk, overestimates benefit, or both. Patients usually overestimate the probability that they would receive benefit in the trial and would downplay the risks of the experimental agent. Misestimation is somewhat tolerable because understanding the exact probability of harm and benefit may not be necessary for an autonomous decision when participating in research.
- Optimism is the research subject hoping for a personal outcome. Optimism is always tolerable because hope does not compromise an autonomous decision when participating in research. An optimistic outlook makes a positive contribution to the healing process; if participants understand, they can hope for the best medical outcome.

Conclusion

The demand for knowledge and new technology is constantly increasing. As this demand increases, the science and design of research become inherently more complex. Since the consolidation of the human subject protection regulations in 1981, new data and recent technology have dramatically increased the diversity and number of human study subjects in clinical trials today, and,

therefore, the need to ethically respect and treat human subjects has never been greater.

Research Investigators should be aware of the ethical, legal, and regulatory requirements for research on human

subjects in their own countries, as well as applicable international requirements. Not any national, ethical, legal or regulatory body or requirement should be allowed to reduce or eliminate the well-earned protections for human subjects.¹

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