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Unequal Treatment of Human Research Subjects

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Abstract

Unequal treatment of human research subjects is a significant ethical concern, because justice requires that equals be treated equally. If two research subjects are the same in the relevant respects, they should be treated equally. However, not all human subjects are the same in relevant respects: people differ with respect to age, health, gender, race, mental abilities, socioeconomic status, and other characteristics. Disputes sometimes arise concerning the issue of whether subjects are the same in relevant respects and should therefore be treated equally. Allegedly unequal treatment occurs when subjects are treated differently and there is a serious dispute about whether subjects are the same in relevant respects. Patently unequal treatment occurs when there is no significant dispute about whether subjects are the same in relevant respects and they are treated unequally. Research regulations can help to minimize patently unequal treatment by providing rules for investigators, institutional review boards, institutions, and sponsors to follow. However, patently unequal treatment may still occur because the regulations are subject to interpretation. Additional guidance may be necessary to minimize patently unequal treatment of research subjects.

Keywords

human subjects research; justice; equal treatment; ethics; regulation

Introduction

Allegations of unequal treatment of human subjects have taken center stage in some recent ethical controversies. For example, Lurie and Wolfe [1] and Angell [2] argued that perinatal (mother-child) HIV prevention trials conducted in developing countries that included placebo control groups were unethical because they amounted to a double-standard: a higher standard for developed nations and a lower one for developing nations. A treatment regimen known as the 076 protocol had already been proven effective in preventing perinatal HIV transmission in trials conducted in developed nations, and it had become the standard of care there. If the trials had been conducted in developed nations, placebo groups would not have been used because HIV medications would have been available, and it would be considered unethical to deny subjects effective treatment. Defenders of the disputed trials argued that

the social and economic conditions of host countries were morally relevant considerations that justified inclusion of placebo control groups.[3–4] The host nations could not afford to treat patients with about \$800 worth of medications used in the 076 protocol, nor did they have the kind of health care infrastructure necessary to implement it. The goal of the disputed trials was to determine whether a simpler form of treatment, using about \$80 worth of medications, would be effective at preventing perinatal HIV transmission. To perform a rigorous test of this hypothesis, according to the proponents, it was necessary to determine whether this simpler and cheaper form of treatment would be more effective than receiving no treatment (or a placebo), which was the *de facto* standard of care in host nations. Defenders of the perinatal HIV prevention trials argued that subjects in developing nations were not being treated according to a lower ethical standard, but according to one that was appropriate, given their circumstances and the need to develop a therapy they could afford. [3–4]

The Department of Health and Human Services regulations, otherwise known as the Common Rule, allow an institutional review board (IRB) to approve pediatric studies that offer no direct benefits (such as medical treatment) to the subjects if the IRB determines a) that the research involves only a minimal risk to subjects (45 CFR 46.404) or b) that the research involves a minor increase over minimal risk but is likely to yield important knowledge about the child's disorder or condition (45 CFR 46.406).[5] The regulations define minimal risk as "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 of routine physical or psychological examinations or tests (45 CFR 46.102i)." There is an ongoing dispute about whether the risks of "daily life" should be interpreted in absolute terms (i.e. the risks typically encountered by normal, healthy children in their daily lives) or in relative terms (i.e. the risks typically encountered by children recruited in a particular study). Critics of the relative standard have argued that it is unjust because it would permit some pediatric populations to be exposed to higher risks than others, since they face higher daily life risks.[6] For example, children living in a dangerous inner city neighborhood might be permitted to be exposed to higher risks in research studies than children living in the suburbs. Thus, a relative standard would lead to unequal treatment of research subjects.[7] Proponents of a relative standard of minimal risk in pediatric research have argued that it can be justified in some circumstances in order to conduct research, such as an HIV prevention trial in adolescents, which offers important benefits to the population.[8]

What does it mean to treat human research subjects unequally? Is unequal treatment morally wrong? Why does unequal treatment occur and how can it be prevented? This article will investigate these and other issues related to unequal treatment of human research subjects and offer some policy recommendations.

The Formal Principle of Justice

Unequal treatment of individuals is morally wrong, according to many philosophers and political theorists, because it violates the formal principle of justice, which holds that cases that are equal in relevant respects ought to be treated equally.[9] For instance, two people

convicted of the same crime with the same mitigating factors should receive the same punishment, and two people who perform the same kind of work should receive similar pay. The principle has its origins in the writing of Aristotle [10], and has been discussed by many contemporary writers, such as Berlin [11], Rawls [12], Nagel [13], Dworkin [14], and Gosepath [15]. It is referred to as a formal principle because it is a logical requirement that ethical decisions be consistent.[9] Consistency is important for two reasons. First, being consistent is part of what it means to be rational, and many philosophers hold that principles of justice are based on rationality.[12] Inconsistent treatment of cases contravenes the very idea of a just society. Second, inconsistency can erode public support for any system of justice, since people may strongly object to decisions that they view as inconsistent. Individuals may express their displeasure with inconsistent decisions by disobeying the rules, or undermining or manipulating the system.[16]

Justice demands more than mere consistency, however, since decisions can be consistent but unjust.[9] Imposing the death penalty on two people who are convicted of stealing a loaf of bread in similar circumstances would be consistent but unjust, because such punishment would be excessive.[17] Since logical consistency imposes no substantive constraints on decisions, a complete theory of justice must also include material principles that describe how benefits and burdens should be distributed in society.[9] Material principles of justice can play an important role in distinguishing between cases. For example, an influential material principle of criminal justice holds that punishments should be proportional to crimes.[17] One can use this principle to distinguish between different cases of criminal conduct and impose appropriate punishments. Murder is different from stealing a loaf of bread because it causes more harm. Therefore, the punishment for murder should be more severe than the punishment for stealing a loaf of bread.

Though few people question the idea that equal cases should be treated equally, disputes can arise concerning this issue of whether cases are the same or different in relevant respects. For example, controversies pertaining to racial discrimination focus on the question of whether race should ever be a relevant factor in decision making. Proponents of affirmative action in college admissions argue that race can be a relevant factor in decision making, since a school might seek racial diversity in its student body in order to promote the exchange of ideas, experiences, and cultures. Opponents argue that race should not be considered relevant: two prospective students from different races with similar talents and abilities should be treated in the same way when it comes to admissions decisions.[18]

As noted above, disputes concerning unequal treatment have also arisen in research on human subjects. Critics of the perinatal HIV prevention trials that used placebo groups claimed that there were no relevant differences between subjects in developing and developed nations that justified differential treatment. Defenders of the studies argued that there were social and economic differences that justified differential treatment. Another area of controversy is whether to include pregnant women in drug trials. Those in favor of inclusion argue that it is important to understand how drugs affect pregnancy, since women often take medications during pregnancy, and physicians who prescribe drugs to pregnant women need reliable information concerning safety, efficacy, dosing, and so on. Opponents argue that pregnant women should be excluded from drug trials in most cases to protect the

fetus from potential harms of exposure to substances in utero. If the risks of prenatal exposure to a drug are not known, it is better to avoid exposure rather than risk serious birth defects or deleterious effects on development.[19]

Because the issue of whether cases are the same or different is often disputed, it is useful to distinguish between allegedly unequal treatment and patently unequal treatment. Allegedly unequal treatment occurs when there is a genuine dispute about whether there is unequal treatment. A genuine dispute involves disagreement among well-informed parties who offer reasonable arguments for their positions.[20] A dispute may be genuine even when one side is in the minority, provided that the minority position is supported by reasonable arguments. The controversy concerning the perinatal HIV prevention trials in developing nations involves allegedly unequal treatment. Patently unequal treatment occurs when there is not a genuine dispute concerning unequal treatment. For example, most people would agree that two individuals convicted of the same crime with the same mitigating factors (such as prior convictions) should receive the same punishment. Imposing a 10-year prison sentence on one individual and a 5-year sentence on another, when their crimes and mitigating circumstances are the same, would be patently unequal treatment.

Unequal Treatment of Human Research Subjects

Equal treatment of human subjects is essential for the ethical conduct of research for the same reason that it is important in other areas of life: to promote consistency. The authors of the *Belmont Report*, an influential document concerning research ethics, describe three principles for research with human subjects: respect for persons, beneficence, and justice. They recognized that justice requires that equals be treated equally, but they also understood that this formal principle needs to be supplemented by material principles that can distinguish between cases.[21] One of those principles, which is described in the *Belmont Report* and codified in federal research regulations, is that the selection of research subjects should be fair or equitable (45 CFR 46.111a3). This principle implies that certain categories of subjects should not be included in or excluded from research without a legitimate scientific or ethical justification.[22–23] The authors of the *Belmont Report* were especially concerned that certain populations, such as prisoners, children, or mentally disabled or socioeconomically disadvantaged people, had been enrolled in studies because of their availability or manipulability and not because the research was relevant to their disease or condition. They argued that these and other vulnerable subjects should be included in research only under certain conditions.[21]

One implication of equitable subject selection is that exclusion of certain categories of potential participants is not unequal treatment if there is legitimate scientific or ethical reason for exclusion. A scientific reason for excluding a certain category of subjects would be that they are not relevant to the scientific question being addressed.[22] For example, women can be excluded from clinical trials of prostate cancer treatments because they do not have prostates, and adults can be excluded from observational studies of the effect of exposure to lead in household paint on brain development because they have already completed their development. Caucasians and Asians could be excluded from a study of

heart disease in African Americans, and individuals with advanced lung cancer could be excluded from a study of early stage lung cancer.

There are a number of ethical reasons for excluding subjects from research. Perhaps the most important one is the inability to provide informed consent. Most commentators agree that subjects who have a compromised ability to provide consent, due to age, institutionalization, or mental disability, should not be included in risky studies that offer them no direct benefits, such as Phase I trials of new drugs. A subject who is capable of providing informed consent can be exposed to greater risks in research that offers no direct benefits than a subject who lacks the ability to provide consent, because the consenting subject can make an autonomous to take risks.[24–26] The federal research regulations limit the risks that subjects who have a compromised ability to provide consent, such as children, neonates, fetuses, and prisoners, can be exposed to in research (45 CFR 46, Subparts B, C, D).[5] Another important ethical reason for exclusion is to protect subjects from harm. Many Phase II and Phase III clinical trials have exclusion criteria that limit the population to individuals who have the disease being studied and who are well enough to respond to the treatment. Individuals who are too sick may be excluded for their own good and to avoid biasing the results.[22]

The federal research regulations¹ help to minimize patently unequal treatment of research subjects by providing investigators, IRBs, institutions, and sponsors with a system of rules for the conduct of research. The rules include criteria for approving studies, requirements for obtaining and documenting informed consent, and procedures for reviewing, approving, and overseeing research.[5] Patently unequal treatment of human subjects still occurs, however, because the regulations may be interpreted differently by IRB members and investigators, due to their diverse expertise, backgrounds, experience, and values. The Office of Human Subjects Protections (OHRP) [27] and the Food and Drug Administration [28] issue interpretative guidance on certain aspects of the regulations, but this guidance does not eliminate divergent interpretations of the rules.

For example, a survey of U.S. IRB chairpersons conducted by Shah and colleagues [29] found that they often interpret minimal risk in pediatric research differently. 53% of respondents said that an electromyogram was minimal risk but 41% said it was a minor increase over minimal risk. 23% of respondents classified allergy skin testing to be minimal risk, while 43% said it was a minor increase over minimal risk and 27% said it was more than a minor increase over minimal risk. The study suggests that unequal treatment of children involved in research occurs in the U.S. as a result of different interpretations of minimal risk, since some IRBs might approve a risky study that others do not approve.[29]

Additional evidence for patently unequal treatment of human subjects comes from studies that document inconsistent IRB review of multisite research.[33] Green and colleagues examined how 43 different IRBs evaluated the same protocol.[34] 31 gave the protocol full board review, 10 gave it expedited review, 1 determined that it was exempt from IRB review, and 1 decided that the study was too risky.² McWilliams and colleagues reported the

¹This article focuses on the Common Rule. The Food and Drug Administration [30–31] and other countries [32] have similar rules.

results of a genetic epidemiology research protocol submitted to 31 IRBs. 15 required the study to have more than one type of consent document and 10 did not require a child's assent.[35] Mansbach and colleagues looked at how 34 IRBs evaluated a pediatric research protocol. 13 approved it with no changes, 18 approved it with minor revisions, and 3 deferred the approval, pending substantive revisions.[36] Stark and colleagues examined how 18 IRBs reviewed a study of vitamin A supplementation in low birth-weight infants. Their study found that there was considerable variability in IRB review, due to difficulties with assessing the appropriateness of the study design.[37] Inconsistent IRB review of multisite research may lead to patently unequal treatment of human subjects when differences in how IRBs deal with risks and benefits or consent process affect the rights or welfare of subjects.

Other studies have demonstrated significant variation in IRB policies and practices. For example, Resnik and colleagues found significant variation in how IRBs define "minor changes" to previously approved research protocols.[38] The federal regulations allow IRBs to approve minor changes to previously approved research through an expedited review procedure instead of full board review, but do not define "minor changes" (45 CFR 46.110). As a result, some institutions may require full board review of amendments that other review on an expedited basis. Since the full IRB may detect some ethical and scientific problems with research that are not caught by expedited review, variability in the definition of "minor changes" may lead to patently unequal protections of human subjects.[38]

Grady and colleagues documented widespread variation in payment for participation in research. Dollar amounts ranged from \$5 to \$2000, depending on the amount of time involved and the risks and discomforts of research. Different sites in multisite studies offered differing amounts of payment, and studies at the same institution offered different amounts for studies involving similar procedures.[39] Payment for research participation can lead to patently unequal treatment of human subjects if the amount of money offered affects how participants weigh benefits and risks.[40] The federal research regulations do not cover the topic of payment to research participants.[5]

Glickman and colleagues found significant variation in institutional policies for including subjects with limited English proficiency in clinical research. 84% of required that the main consent document be translated while 16% did not. 70% specified when a shorter version of the consent form may be used, while 30% did not. 32% stated fluency requirements for the person obtaining consent, while 68% did not.[41] Variations in policies for including subjects with limited English proficiency in research can results in unequal treatment of human participants when they lead to differences in the consent process.

Resnik and colleagues conducted a survey that demonstrated significant variation in institutional compensation for injury policies. They found that 51.2% of 169 responding institutions offered no compensation; 8.1% offered compensation at the discretion of the institution or sponsor; 36.9% offered compensation if certain conditions are met (such as

²Under the Common Rule, certain kinds of studies, such as some types of research involving surveys or the analysis of existing de-identified samples or data, are deemed to be exempt from IRB review (45 CFR 46.101). The Common Rule allows IRBs to forego full board review and use an expedited procedure to review new studies deemed to be minimal risk (45 CFR 46.110).[5]

there is an agreement with the sponsor to provide compensation); and 3.8% offered compensation without discretion or conditions.[42] Their study suggests that participants in the same multisite study could receive compensation or no compensation, depending on the site's policy. The federal research regulations do not require institutions, sponsors, or investigators to compensate subjects for research related injuries, although they do require subjects in more than minimal risk studies to be informed about the compensation for injury that is available, if any (45 CFR 45.116a6). Variation in compensation for research-related injury policies also can lead to patently unequal treatment of human subjects because compensation impacts the risks and benefits that subjects receive as a result of their participation.[40] Subjects who receive no compensation for their injuries may have to pay for their own medical care if their insurer does not cover research-related injuries. Subjects who receive no compensation may suffer additional harms if they cannot pay for their medical treatment.[42–43]

Although there have been no systematic studies of international variation in review and oversight of human subjects research, anecdotal evidence suggests that it occurs. For example, numerous authors have written about variations in consent practices in different countries.[44] According to the Western model, consent should be obtained from the individual who is participating in research or from that individual's legal representative if he or she is unable to consent. Consent should be documented using a form that describes various aspects of the research. The form should be signed by the participant or the participant's representative.[5] In some African and Asian countries, the usual practice is to involve tribal leaders, the family, or the community in the consent process.[44–45] In some Islamic societies, the spouse or other family members may consent for a woman.[44–46]. In some countries there is usually no documentation of the consent process because most people are illiterate or the society follows an oral tradition.[45] These cultural aspects of consent raise the issue of whether the Western model should always be followed.[47] One might argue that there should be some local variations in consent that take into account cultural differences.[45] If these cultural differences are viewed as ethically relevant, they would justify differential treatment of human research subjects, which would not be considered patently unequal treatment of human research subjects. These differences might be viewed as allegedly unequal treatment if there is a serious dispute concerning the general applicability of the Western model of consent. International guidelines may help to resolve such disagreements.[48–49]

Conclusion

Unequal treatment of human research subjects is a significant ethical concern, because justice requires that equals be treated equally. If two research subjects are the same in relevant respects, they should receive equal treatment. However, disputes sometimes arise concerning the issue of whether subjects are the same in relevant respects and should be treated equally. Allegedly unequal treatment occurs when subjects are treated differently and there is a serious dispute about whether subjects are the same in relevant respects. Patently unequal treatment occurs when there is no significant dispute about whether subjects are the same in relevant respects and they are treated unequally. Research regulations can help to minimize patently unequal treatment by providing rules for investigators, IRBs, institutions,

and sponsors to follow. However, patently unequal treatment can still occur because the regulations are subject to interpretation. Federal agencies have provided guidance on how to interpret the regulations that can help promote consistent review and oversight of human subjects research. Additional direction may be needed on topics that are not adequately covered by current guidance or regulations, such as research risks, payments, compensation for injury, and changes to approved protocols. International ethics guidelines can help promote equal treatment of human research subjects around the globe.

Some commentators have argued that one way of promoting consistency in human research protections would be to centralize IRB review.[33,50] OHRP announced in 2011 an Advanced Notice of Proposed Rulemaking that would change the Common Rule to require a single IRB to take responsibility for reviewing U.S. multisite research.[51] For example, if a clinical trial is conducted at 25 sites, one institution could handle the IRB review and the other institutions would rely on that institution's review. While centralizing the IRB review process can play a crucial role in promoting equal treatment of human research subjects, it is still important to obtain input from institutions concerning the local context of research (e.g. social, cultural, or economic considerations), since this may impact recruitment, consent, and other aspects of a study. Institutions could provide information concerning the local context to a central IRB, which it could take into account in its decision making.[52] Taking local context into account is especially important in international human studies, since cultural, social or other factors unique to the population may impact the conduct of research.

While it is important to promote equal treatment of human research subjects, it is unrealistic and unwise to expect research review and oversight to be uniform. Because investigators and IRB members have different understandings of regulations and guidelines, some variation in the review and oversight of human subjects research is inevitable. Local context (e.g. cultural, economic, or social factors) may also lead to variations. While minor variations in the treatment of research subjects should be tolerated and even welcomed, major ones (i.e. those that significantly impact human rights or welfare) should be avoided to promote justice in research.

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