Respecting Vulnerable Persons

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Regulatory and ethical guidelines for human research emphasize protection of research subjects. The Nuremberg Code, Helsinki Accord, and CIOMS guidelines consistently insist that each person enrolled as a subject in research give informed consent. Based on a free and informed choice to participate, the consent document describes the clinical trial in detail. Principal investigators make efforts to disclose all risks and benefits, and ethical oversight committees seek to ensure that subjects have access to all relevant information. Using principles of autonomy, beneficence, and justice, ethical oversight members work in corporation with clinical trial personnel to ensure that the subjects enrolled in the research are respected as moral agents who freely choose to participate.

The autonomy principle applied in the consent process and validated by the informed consent document assumes that the individual subjects are fully competent to assess the value and validity of the research; that they understand the risks and benefits, and all persons in the geographical location of the trial have fair and equal access to participation. By contrast, persons without the attributes necessary to satisfy ethical norms are considered vulnerable and due extra protection. Prisoners, because of their limited freedom, as well as persons with limited capacity, are examples of vulnerable persons. Protecting subjects becomes all the more imperative when their capacities are limited or compromised. Such protection requires a degree of paternalism that is unavoidable in human research ethics while respect for persons emphasizes autonomy.

In the doctor-patient relationship, the physician has skill and knowledge needed by the patient making the relationship inherently unequal. The doctor offers treatment options and the patient agrees to the recommendation or rejects it. Accepting or rejecting the recommendation is an exercise of autonomy by the patient whether or not it is in the best interest of the patient. If a child needed medical care and parents refused to allow the child treatment, legal recourse is an option. In clinical research, researchers function as physician and scientist. The best interest of the patient can putatively be at odds with the research goals. Research ethics review boards are charged with protecting human subjects from unnecessary risk while allowing some freedom and autonomy of the individual subject in the process of informed consent. Necessarily then research ethical oversight functions in adialectic of autonomy and paternalism.

Autonomy vs. Paternalism

Freedom and competent reasoning provide the foundation for autonomy. A moral agent chooses an action consistent with his/her normative values in a process of self-governance. Autonomy implies and expects reason to empower individual choice, to define life goals and to give priority to values, without specifying to what extent the context and circumstances of an individual situation may affect a person's exercise of moral choice. Respect for Persons posits that moral law (autonomy of the will) requires freedom. What a moral agent determines to do according to reason is autonomy of the will, which equates with the dignity of persons (1). Kant asserts that moral agents are subject to the moral law, which can be discovered by pure reason (2). Kant's "Categorical Imperative" posited: "Act only on that maxim which you can at the same time will to be a universal law" (2). Maxims are rules the moral agent crafts by way of a thought experiment, testing alternatives to discover whether one can act in a way that would seem prudent for any other person, without defeating one's own intention. The goal, end, objective and intention of the act proposed by the moral agent are important because the moral agent has a duty to self and others.

The presumption is that people should be free to do what they desire, to choose relationships, and to act as they determine morally right and best. Nevertheless, we regulate liberty when a person chooses to act in ways harmful to self and or others. Legal statutes prohibit injurious acts e.g. unwarranted violence, or to prevent harm, e.g. seat belt laws. A person's freedom can be limited for the individual and communal good. In extreme cases, such as attempted suicide the individual's freedom takes second place to protective actions. Paternalism in this sense is protective and for the intent of prevention of harm. If a persons' freedom is limited in a protective sense, it is what Joel Feinberg calls "soft paternalism" where the limitation of freedom is necessary because the individual's decision-making ability is impaired, or nonautonomous (3). In contrast, "hard paternalism" limits freedom of autonomous persons to protect them "against their will from harmful consequences even of their fully voluntary choices and undertakings" (3).

Circumstances may well limit the autonomous choice of a person. In cancer patients, a clinical trial may seem like the hidden therapeutic cure, in which the potential subject suffers from "therapeutic misconception." Because of a strong desire to live and failure to achieve help through standard therapies, a cancer patient may seek out a clinical trial as a last hope. Such patients enter phase I clinical trials where there is no "therapeutic benefit" and the consent document clearly states that "you will not benefit from this study" and yet patients assert that their hope is to benefit (4).

Accepting the justification that such patients intend to advance the research toward a more effective therapy is fairly common for ethical review boards. Interviewing individual patients in the consenting process is not one of the routine practices of the ethical review board members. A bystander, free of cancer or any other serious disease, might well question if the patients are cognitively impaired by the cancer, fear of dying, or other social and familial concerns. Minimally, individuals with terminal disease may suffer distortions of judgment in exercising autonomy.

Research Interests

Oversight committee members rely on the validation of autonomy by the process of informed consent. Trusting that subjects are exercising autonomy in research trials with substantial risks respects autonomy. The review board also weighs beneficence in assessing the risks in the protocol and the benefits to the individual subject as well as for general increase in knowledge anticipated by the study.

The basic values inherent in national and international guidelines for research with human subjects began with the Nuremberg Code requiring that the scientific merit of the study be likely to benefit humanity and that each and every subject give informed consent to participate. Within a decade it became obvious that research was done without obtaining informed consent (5) and as a correction, the Declaration of Helsinki of 1964 required independent ethical review of all research enrolling human subjects. The Belmont Report, grounded ethical review in the principles of autonomy, beneficence and justice (6). Codified in law, "the Common Rule" set a legal framework around the ethical review of research with human subjects. By adhering to the "Rule" and evaluating the research proposal with respect to the guiding principles, the review members accepted a necessary degree of paternalism. Absent

any paternalism, the risk limit would be set only by what the "volunteer" was willing to accept.

All clinical research is designed to answer scientific questions that have predictable value but unknown answers. Any subject in clinical research is at some degree of risk, hopefully counterbalanced by some benefit to the individual or community. Benefit to the individual may lie in the desire to see the trial through and to be part of some larger project that advances medicine. Volunteers in HIV/AIDS vaccine trials face the possibility that the vaccine will not be protective. No such vaccine is known at present (7). Vaccine testing of human volunteers in populations with high prevalence of HIV infection is required in order to evaluate the protective effect of a vaccine. If absolute protection were mandated to the extent that no subject in the study could become infected post-vaccination, the study would have no scientific merit. Thus, placebo controls although risky, are one way to determine efficacy of an experimental product. It would be unconscionable to put persons at risk of HIV infection without educating them about protective and preventative strategies. Thus the balance is delicate: education for preventing infection balanced against the need to evaluate the protective nature of the vaccine.

In international trials collaboration requires adherence to the guidelines of ethical oversight of human subject research and requires sensitive, active listening to review board members in the host country along side their counterparts from the sponsor. There are moral and rational reasons for conducting clinical trials in regions of the world with the highest prevalence of disease, HIV, malaria, so that efficacy can be determined. Critics have called attention to ethical challenges in this type of research, e.g. whether placebo controlled studies can be justified. Rather than impose sponsoring country rules or standards in international contexts, there is merit in a consideration of respecting the host's ethical reviews in their own context.

The U.S. Department of Health and Human Services (DHHS) commissioned a Working Group to examine how to implement 45 CFR 46.302 (8). The DHHS study was clear in the message to other countries that U.S. regulators are willing to compromise with respect to how, but not if, research participants are protected. Such evolving policies need to express sensitivity to multinational collaborative research.

Prisoners, a case in point

Generally, researchers often exclude prisoners as subjects because such persons are believed to lack sufficient freedom to satisfy the autonomy principle of informed consent. Regulations within 45CFR46 subpart C allows research with prisoners under tight controls, designed to protect their vulnerability. If interpreted too strictly, prisoners risk being denied the opportunity to participate and any putative benefits inherent in the research.

Imagine that a large clinical trial with an AIDS vaccine enrolled thousands of people. After completing the vaccination phase of the trial, and during the follow-up phase, individuals became prisoners. On the basis of the assumption that prisoners cannot be subjects, such individuals would be withdrawn from the study. Indeed ethical review might require such an action. In a recent international trial being conducted in Thailand this situation occurred and the Thailand Ethics Review Committee along with U.S. collaborators faced the decision to require withdrawal of persons while incarcerated or to allow individuals the freedom to choose to remain in the trial with a process of re-consent.

I served on the review team that visited two Thai prisons as part of the process of evaluation that is required to reach context sensitive decisions. As we drove into the parking lot near the first prison, we noted clean grounds; well-tended gardens of tropical plants surrounded the entrance, and construction that was modern and well maintained. The entry process included surrender of cell phones, cameras, and any sharp instruments. The guards were sharply dressed in uniforms, had pleasant demeanors, and carried no weapons. No guns were seen anywhere in the prison. Inside the grounds, the prisoners were employed at various jobs, some tended the plants lining the walks, others prepared food for the noon meal, others studied in classrooms, while others worked at metal or wood crafts. Prisoners were not sitting idle in cells but were actively engaged in activities useful for the prison community and simultaneously were acquiring useful skills for their future re-entry into society. The sleeping facilities were dorm style with clean showers and toilets, open to the tropical air, enclosed by gated bared doors. These conditions could not be staged for the benefit of outside visitors.

The clinic was well stocked with medicine, equipment and staffed with competent professionals. The interactions between prisoners and guards were polite, respectful and courteous. The impression was more like a college campus than a prison. Speaking with the warden, our questions revealed an impressive reform system. The recidivism rate had dropped to less than10% with the current emphasis on human dignity and a commitment to help each prisoner return as a productive member of society.

Respect for persons should allow individuals to exercise autonomy even while vulnerable. Study officials asserted that the prisoners already enrolled in the protocol prior to incarceration have a right to remain in the study. It was evident that being a prisoner in the two prisons we visited was a vastly different context than the conditions associated with being in prison in many other places. Given the communitarian ethos of Thai society, individuals in these prisons are not deprived of human interaction, not restricted to endless hours of boredom but have a communal role within the prison community. Nevertheless, they were in prison.

Recognizing that such research volunteers are vulnerable while incarcerated, their willingness to continue in the research would need additional safeguards, to protect their rights, safety, and welfare. Privacy and confidentiality issues were addressed by limiting knowledge of who was in the study to the prison physician and warden. Records for the research protocol were kept by the study team at a separate location from the prison medical records. At one site, research personnel made visits in the same way and at the same place as family members. At the other site, study participant visits followed the same procedures as for prisoners visiting the clinic for other reasons. Research visits were conducted in a private room. Further, each volunteer was given the opportunity to re-consent with each follow-up visit during incarceration and to withdraw if they desire.

Respecting vulnerable persons

Universally, autonomy is the principle underscoring informed consent. Plurality of interpretation in different contexts respects autonomy of human diversity. Gerald Dworkin noted that autonomy means, "liberty (positive or negative), dignity, integrity, individuality, independence, responsibility and self-knowledge … self assertion … critical reflection … freedom from obligation … absence of external causation … and knowledge of one's own interests." (9, 10) This partial list reveals how far contemporary conceptions of autonomy are from their Kantian origins. Rather than aligning autonomy with respect of persons as Kant did, current practice within the process of obtaining informed consent come closer to a form of individual independence. Given the more individualistic freedom model of autonomy, it is understandable why concern and policy would proscribe withdrawing any research subject during incarceration. From the view inside the Thai prison we visited, the greater praxis of respect for prisoners as persons, autonomy takes on a more Kantian connotation.

Research ethics committees have a responsibility to protect subjects from violations of their rights and welfare. It is clear that doing so means getting inside the context of the situation in view of the regulatory requirements. The process requires avoiding any stereotypic understanding of a persons' status be they prisoner or free. The experience reported here exposes how diverse the context and circumstances can be for "prisoners." Norms such as autonomy in clinical trial research are expected to transcend cultural differences. For a principle or moral standard to hold universal appeal and relevance, the particular context of the individual and group must be taken into account. Rules, principles, and research ethics guidelines are foundations from which we weigh particular situations using reason, interpretation and judgment (9).

Informed Consent is a process, not merely a document. Knowing prisoners are vulnerable subjects should not lead to an absolute application of exclusion; rather such knowledge should lead us to learn more about their specific circumstances. In situations where the prisoner has the other protections afforded human subjects, it is possible that sufficient autonomy is present to warrant their continued participation in a clinical trial for follow-up purposes. To deny that "right" simply by application of a protective rule could add unjustified burdens. Rather than ruling out such subjects, site visits and investigation into the circumstances of the trial participants offers the opportunity to determine how best to protect and simultaneously respect enrolled subjects. Soft paternalism may lead research review board members to assume that risk of harm to enrolled subjects while incarcerated justify removal of such persons from the study, but it is also possible that sensitivity and awareness of context would lead to a decision to allow subjects to remain in the study. We should not assume that subjects are incapable of protecting their own interests. We should strive to enable subjects to make autonomous decisions rather than rely on regulations to protect them.

Communitarian cultures such as that in Thailand remind us that one does not live alone, that persons are social beings, that an individual needs interaction with others, and that our values and goals are influenced by our society and friends. One person takes from the social construct what is good and refines his/her values according to reason. This process is the complex matrix in which a person is autonomous. Allowing a person to use their reason and act according to their values is a dynamic process.

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