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Ethical considerations in research. Focus on vulnerable groups

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Ethical considerations in research. Focus on vulnerable groups

The purpose of this paper was to describe the need to protect the rights of human subjects participating in nursing research, and procedures for doing so. The path taken to the task at hand was to approach the topic by discussing the philosophical underpinnings of human subject protection and describing the approach for doing this in all cases where humans are used as research subjects. These underpinnings include specific ethical principles of respect for persons, beneficence, and justice, and the procedures used in the U.S. for protecting the rights of human subjects. Once the process was clarified, the considerations necessary to protect the special groups referred to as "vulnerable" are discussed. Given the author's access to U.S. documents and the fact that U.S. government agencies took early steps to formalize rules and regulations for the protection of human subjects, vulnerable or otherwise, the experience of the United States was selected for presentation. It is recognized that there are now relevant international documents that are exceedingly helpful, and also, that various countries may have their own guidelines for investigators to follow. In such cases researchers can engage in comparative analysis between their own guidance and the processes described here, and decide their path accordingly.

Key words: ethics, research; nursing research; risk groups.

Consideraciones éticas en investigación. Enfoque en grupos vulnerables

El propósito de este artículo fue describir la necesidad de proteger los derechos de los sujetos humanos que participaron en la investigación en enfermería, y los procedimientos que hay para hacerlo. La ruta tomada para realizar esta tarea consistió en el abordaje del tema desde la discusión de los fundamentos filosóficos de la protección de los sujetos humanos y la descripción del enfoque empleado para su participación en la investigación. Estos fundamentos son los principios específicos éticos de respeto por las personas, beneficencia y la justicia, y los procedimientos

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utilizados para la protección de los derechos de los sujetos humanos en los Estados Unidos. Se discuten además las consideraciones a tener en cuenta para proteger a los grupos especiales mencionados como "vulnerables". Se seleccionó la experiencia de Estados Unidos debido a que la autora tenía acceso a los documentos de este país y a que las agencias gubernamentales estadounidenses fueron los primeras que formalizaron normas y reglamentos para la protección de los sujetos humanos, vulnerables o de otro tipo. Se reconoce que ahora hay documentos internacionales pertinentes que son sumamente útiles, y que también varios países disponen de sus propias directrices a seguir, en tales casos, los investigadores pueden realizar análisis comparativos entre su propia orientación y los procesos descritos aquí, y decidir, en consecuencia su camino.

Palabras clave: ética en investigación; investigación en enfermería; grupos vulnerables.

Considerações éticas em pesquisas. Enfoque em grupos vulneráveis

O propósito deste artigo foi descrever a necessidade de proteger os direitos dos sujeitos humanos que participam na pesquisa em enfermagem, e os procedimentos que há para fazê-lo. A rota tomada para realizar esta tarefa consistiu na abordagem do tema desde a discussão dos fundamentos filosóficos da proteção dos sujeitos humanos e a descrição do enfoque empregado para sua participação na investigação. Estes fundamentos são os princípios específicos éticos de respeito pelas pessoas, beneficência e a justiça, e os procedimentos utilizados para a proteção dos direitos dos sujeitos humanos nos Estados Unidos. Discutem-se ademais as considerações a ter em conta para proteger aos grupos especiais mencionados como "vulneráveis". Selecionou-se a experiência de Estados Unidos devido a do que a autora tinha acesso aos documentos deste país e a do que as agências governamentais norte-americanos foram os primeiras que formalizaram normas e regulamentos para a proteção dos sujeitos humanos, vulneráveis ou de outro tipo. Se reconhece que agora há documentos internacionais pertinentes que são sumamente úteis, e que também vários países dispõem de suas próprias diretrizes a seguir, em tais casos, os pesquisadores podem realizar análises comparativas entre sua própria orientação e os processos descritos aqui, e decidir seu caminho em consequência.

Palavras chave: ética em pesquisa; pesquisa em enfermagem; grupos de risco.

Introduction

Many countries are developing guidance for nurse researchers and others who conduct nursing or health research or other scientific studies involving human subjects. The purpose of these efforts is to assure that research is scientifically sound while being respectful toward human beings who participate in such studies, recognizes human dignity and does not jeopardize their health in any way. Development of such guidance has become urgent in recent years, especially with respect to the protection of vulnerable groups/individuals who are least able to speak on their own behalf or take steps to protect themselves. Thus, greater vigilance is indicated on the part of investigators, human subject review committees (HSR), also known as Institutional Review Boards (IRB) and institutions where research is conducted, to make sure that appropriate oversight and precautions are in place to protect vulnerable individuals. In order to address the special case of vulnerable persons involved in research, it is important to first discuss the ethical principles that underlie human subject research, considerations in informed consent, and procedures for informed consent that apply for all research participants, and subsequently, consider the special case of vulnerable groups.

Background

The subject of human protections in research became an issue in the U.S. and worldwide, when Nazi regime's experiments with humans during the Second World War came to light, and eventually led to the Nuremberg Code.[1] Subsequently, the World Medical Association[2] developed the Declaration of Helsinki in 1964, revised periodically, with the latest version being in 2008. Similarly, within the United States (U.S.) several research projects came to light where human rights and dignity were violated. Ironically, these studies were funded by agencies of the U.S. government, such as the Public Health Service. One of these studies had begun in the 1930's, known as the Tuskegee syphilis studies, and continued for many years without the public being aware of the circumstances involved. In order to study the progression of the disease, the investigators did not treat the patients with the new drug penicillin, which had been discovered during the war, and concealed this information from the research participants. Other projects closer to modern times were revealed with infirm patients or adolescents with mental illness; together, these disclosures shocked the conscience of the citizenry, and moved the government to take action. The guidelines and the steps required since then have been formalized and are impressive; they are now required of all institutions in the U.S. where research with humans is conducted, and of all investigators as well at *any* level. Thus, due to the clarity and general availability of the steps that were taken to protect humans participating in research the discussion provided here will be based on the experience of the U.S. It needs to be recognized that many countries, but by no means all, have developed guidance for investigators' use when conducting research with humans. There are some similarities across the different guidelines that are meant to be country-specific, but they are all guided by shared concerns for the welfare of research subjects.

Ethical principles

The guideline development began in the 1970s when the U.S. Congress created a commission to articulate the philosophical and ethical foundations that should underlie and guide any rules to protect human subjects of research. The document that resulted from the initial deliberations was known as the *Belmont Report*;[3] it influenced all work in this area and continues to do so to this day. Any and all agencies of the Department of Health and Human Services (DHHS), that is the largest funder of health research, and other US government departments supporting research with humans, are expected to comply with the same governmental guidelines. Various entities can posit additional guidance specific to their domain. For example, the Food and Drug Administration (FDA) uses the basic guidelines of the DHHS, and in addition, has specific expectations that govern drug trials at different phases.

There are a number of ethical principles that can be found in ethics texts, although not all of them are applicable to human subject research. The focus of existing guidelines is to protect research participants from harm, whether physical, mental or social in nature. Other resources that come into play are the codes of ethics that most professional associations have, including the International Council of Nurses (ICN), and in the U.S., the American Nurses Association.[4] We will briefly present three principles that are central in the Belmont Report; they are: *respect for persons, beneficence, and justice.*

Respect for person. This concept assumes that individuals are autonomous beings and respect is due to them because of that fact. They have self-determination, and can make judgments as to what will be done to their persons. Under certain circumstances the autonomy of some individuals may be diminished; when that occurs, they are considered vulnerable and entitled to certain protections. These vulnerabilities may be due to age, health condition, or other circumstances.

Beneficience. This concept means doing good, and incorporates an implied sense that there is an obligation to do good, that is, to benefit the subjects of research. Some philosophers discuss the principle of non-maleficence, meaning do

no harm, as a separate principle, although the *Belmont Report* does not deal with this as a separate principle, but rather, as having the opposite meaning from beneficence. In the ordering of various principles, philosophers and codes of ethics place non-maleficence prior to beneficence; this is to say if unable to do good, it is important to choose the option of doing no harm.[5] While beneficence can be seen in relation to obligation to individual participants, the principle can also apply to the obligation of a profession as a whole toward society, which entails the obligation to conduct research in order to enhance the quality of its care to the public. Investigators may be inclined to list the potential benefits of their research when discussing their work with prospective participants; however, in the real world, results of no single study are ready to be applied to patients immediately, without replications or meta-analytic studies; thus, it is most likely that any benefits to patients are likely to accrue, if at all, years in the future rather than immediately, to those who participate in the research. This point is important to bear in mind so that in our zeal to get consent from individuals we stay truthful to potential subjects.

Justice. Justice has several meanings; there is the meaning of retribution (also known as just deserts). Another meaning is justice as fairness, questions that concern the participants of research are, who need the benefits of the research the most?, who carry the heaviest burden?, and who benefit the most?; these are pertinent to justice as fairness. Concerns about how the benefits and burdens in society are distributed, gets at the third meaning of justice, which is distributive justice; in the latter case, several rules can be used for distribution: to each an equal share, to each according to need, to each based on her/his contributions.

Some have advocated that justice would require that when therapies become available as a result of research, those who participated in the research and took the most risk, should be given priority in receiving and benefiting from the outcome of research. To my knowledge, there are no policies at national levels mandating such action. However, these discussions have occurred between communities and investigators/funders in instances of international research, especially in cases involving drugs to treat HIV-AIDS. Some international foundations have developed agreements with pharmaceutical companies to sell drugs at much lower prices than can be had on the open market, and thus, entire communities have received new treatments due to such agreements.

Informed consent: What is it based on?

In considering informed consent we will need to go back to the principles described earlier. What does respect for persons mean? It means providing accurate and truthful information (that is at the same time understandable to the subject); it means allowing the person to make decisions as to participation without any explicit or implicit pressure; and it means keeping patient information confidential. There are occasions where confidentiality may not be feasible; in those instances anonymity might serve as a reasonable substitute. What is the difference between anonymity and confidentiality? Anonymity means that data cannot be linked to a specific participant; with confidentiality, on the other hand, data can be separated from subjects' information, although the researcher can still link the data with an individual; in promising confidentiality, the investigator may be able to link data with a specific person, but s/he takes steps to keep critical identifying information under lock and key, with no one else having access. There are occasions when data cannot be linked to a person when the research does not require this. In such instances both confidentiality and anonymity can be promised.

Justice requires that participants be treated fairly and all members of the relevant pool have an equal chance of being represented, that selection is free of bias. As well, participants should be protected from discomfort and harm; if there is the possibility of any discomfort occurring, participants should be informed of the possibility in advance. Investigators as well as IRB committees need to assess the benefits and risks, and to the extent possible, maximize benefits and minimize

risks. The question has arisen as to whether IRBs should review the quality of proposals, or limit themselves to areas of human subject protection. It is now well accepted that both features of proposals should be considered during IRB reviews and monitoring. While these bodies were created as a result of governmental and subsequently, institutional mandates, specifically to protect humans involved in research, it has come to be accepted that human participants are rare, critical resources, and should not be squandered on investigating problems that are insignificant, or proposals that are poorly conceived.

A word needs to be said about investigator qualification and training. All individuals planning to conduct research with human subjects need to be qualified; if not fully credentialed as investigators, they need to be supervised by authorized and qualified individuals, such as in the case students. In addition, all investigators need to take and pass a test such as CITI,[6] that will demonstrate their understanding of elements crucial to human subject research. Some institutions have developed their own test, which is equivalent to CITI. See for example the University of Michigan test known as PEERRS.[7]

Elements of informed consent. All health care agencies/employers in the U.S. that receive funding from the U.S. government have templates for applications to human subject review [HSR] committees, and they are based on the federally promulgated requirements. They cover the same points which we will briefly describe here. From a philosophical perspective, the function of informed consent and the justification for it have been prominent. Beauchamp and Childress[5] describe two justifications: protection of participant from harm, and protection of person's autonomy, with the latter also serving as a primary function for these authors. However, in a more practical vein, we will present the elements of informed consent that are embedded in rules and regulations that are applied on a day to day basis.[8]

Providing relevant information. This includes the nature of the research, expected discomforts if any, the type of intervention to be done and what alternatives might be available, if confidentiality and anonymity can be promised and if not, what precautions can be taken; if compensation is being offered, the option to withdraw at any time should be given; if some information is being withheld for research purposes, debrief the person following the intervention, and offer to answer any questions.

Ascertain that consent information is clearly understood. Some consent documents are prepared in simplified form to assure that they are easily understood; while this assures that individuals at a variety of levels will understand what the research plan is, we need to guard against oversimplification, and otherwise, we risk missing crucial information.

Competency for consent. Determination of competency for consent needs to be made, whether it is a function of age, illness or special circumstance. Where indicated, permission may need to be taken from a guardian or family member. This will be covered in the next section of this paper.

Ascertain that consent is given voluntarily. The concept of voluntariness is critical to the informed consent process; thus, no coercion should be exerted, whether it is explicit or implicit.

Informed consent and special populations

Populations or groups that require special attention are variously defined; although these groups are defined in the literature, there may be circumstances when groups that normally may not be deemed vulnerable, become so under specific circumstances, making them eligible for special considerations. For example, the federal regulations include pregnant women, fetuses, neonates, even giving special attention, after delivery, to the placenta or fetal materials if these are being considered for research; prisoners are another vulnerable group, as are children or individuals of any age who have been rendered cognitively impaired. These are illustrative; additional categories are provided later in this

paper.[9] In addition to the informed consent rules that apply in all cases, vulnerable groups require some additional conditions or protections. Until several decades ago, most researchers avoided using groups that now fall under the rubric of "vulnerable groups," since they were either difficult to access, or too easy to access, or we were lacking in guidelines; thus, they were either ignored altogether, or treated with disregard when included. The result was that most frequently men were chosen as research subjects, and it was believed that what was learned in studies will be equally applicable to other groups. This state of affairs was untenable from a societal perspective, since frequently it was these very groups who needed research done to improve their care, whether the groups were women, minorities, or the elderly. About 20 years ago, however, the National Institutes of Health began developing guidelines for inclusion of women and culturally/ethnically different groups, and required that such groups be included in studies, or provide rationale as to why they would not be included. This opened up the door to include a wide spectrum of populations, as the realization occurred that findings of research with male subjects did not necessarily apply to other groups and that diseases behave differently in various groups.

The following are considered vulnerable groups within the DHHS guidelines: pregnant women and fetuses, children and minors, cognitively impaired persons, prisoners, traumatized and comatose patients, terminally ill patients, elderly/aged persons, minorities, students and normal volunteers, and subjects in international settings, when research is conducted by U.S. investigators under the sponsorship of the U.S. government or a U.S. institution. The DHHS has developed detailed guidance for vulnerable groups, and each of the groups mentioned is carefully considered. These are on the website and we summarize the highlights here.[8,9]

Each of the considerations identified applies to one or more of the vulnerable groups mentioned, and the IRB has the responsibility to weigh relevant factors in approving, modifying or rejecting the research protocol. Space constraints do not allow us to include a thorough presentation of the circumstances and issues relevant for each group; as well, it is of note that there are many similarities in the underlying principles; thus, we hope that the highlights provided will enable readers to appreciate the commonalities and differences across the different groups deemed vulnerable, and their application to other vulnerable groups not mentioned here.

Children/Minors, (Pregnant) Women, Fetuses

1. IRBs would want to know that, where relevant, prior studies have been conducted with animals or healthy groups to provide some basis for determining the risk to the vulnerable individuals/groups to be included;
2. The risk to the subject is weighed against any direct benefit to same; or, if no such benefit is expected, the risk is minimal and the research promises to yield important knowledge that cannot be had in any other way;
3. In the case of pregnant women, the amount of risk to the woman and the fetus are weighed against the knowledge yield, and circumstances under which the father is asked to provide consent along with the woman;
4. Under all circumstances the investigator must avoid conflict of interest, or even the appearance of conflict. For example, the researcher should not take part in any discussions to terminate a pregnancy or regarding the viability of the fetus, if either the fetus or placenta are the subjects of research;
5. In the case of neonates, both parents should give approval;
6. Research that has more than minimal risk that promises a direct benefit to the subject is approvable if the IRB has determined that the risk is justified by the expected benefit to the subject, and the risk-benefit ratio favors the research subject and is comparable to existing alternatives, and provisions are made

for obtaining the agreement of the child., and permission of the parents or guardian;

7. In unusual circumstances, research that is not typically approvable, may be undertaken following consultation by a group of multidisciplinary experts, and where the research promises to address serious health problems in children;
8. In some cases where a child is a ward of the state an advocate may be appointed to represent the interests of the child.

For greater detail on rules, the reader is advised to consult the *Code of Federal Regulations* and the *Institutional Review Board Guidebook* referenced.[8] As well, there are likely to be additional requirements depending on the level of risk being undertaken, the seriousness of the condition of participants in the case of medical research testing the efficacy of certain new drugs or procedures and other unique circumstances. Similarly, IRBs are called upon to provide ongoing monitoring of the research to assure that the research continues to be conducted in accordance with the approved protocol, the closeness of the oversight/monitoring depending on the level of risk and the potential of harm to the subjects.

All other Groups

In the case of each vulnerable group the major concern should be clearly highlighted and understood by the investigators; for example, in the case of those who are cognitively impaired, their capacity to understand information is compromised, thus, they are unable to make rational decisions about their involvement in research. This could similarly apply to comatose patients, some terminally ill patients, some elderly persons, or individuals who are under the influence of alcohol or drugs. The sections below were extracted from the *Institutional Review Board Guidebook*, Chapter VI, ["Special classes of subjects"].[9] Below we list the major concerns or principles at stake in the various circumstances of potential research subjects:

1. Research should be done with subjects if they are the only appropriate group to answer the research question, the research question is unique to the group sought, and the risk is minimal.
2. In emergency cases, informed consent is waived when risk is minimal, when life-threatening situations arise and where there is no known therapy to save a patient's life.
3. If alternative populations exist very sick patients should not be asked to participate in research.
4. Alternatively to the point above, terminally ill patients should not be excluded from research if they are interested in participating, as some of these patients may have the desire, out of altruism, to do what they can to contribute to scientific knowledge development, using their difficult circumstance benefit humanity.
5. Elderly individuals with no known handicaps do not need special protections, as they are a diverse group, except under conditions of cognitive impairment and while under institutional care.
6. The National Institutes of Health (NIH) has taken the position that women and minorities must be included in studies so that study results can be generalized to all groups or to groups who are at risk of contracting a certain disease. If there are reasons why these groups are to be excluded, the proposal to the IRB should present justification. Thus, attention should be paid in the subject selection process considering fairness, strengths and weaknesses of volunteer groups.
7. In the case of normal volunteers, employees and students who are typically healthy groups, beneficence and respect are applicable principles: do no harm, maximize benefits, minimize harms, and allow the exercise of autonomous action in the informed consent process. The possibility that there may be implied coercion, such as can occur in the case of a professor vis-à-vis students, would suggest that investigators broadly advertise for

volunteers rather than approach individuals specifically, and ensure that the approach is not done by the person who is currently or was recently, in a position of authority vis-a-vis the subjects.

8. Prisons present convenient locations and can be found in many locations in the U.S. Yet, due to their condition of incarceration, it is questionable if prisoners are able to exercise self-determination, thus, the principle of autonomy is a relevant concern. In the case of this population the risks prisoners are asked to undertake should be comparable to what a non-prisoner population is asked to undertake.
9. In the case of international research supported by the DHHS, all procedures must collectively be designed to protect human subjects. Although there may be differences in local procedures and policies, the IRB can evaluate the equivalence of the procedures with that of the US requirements, and give its approval accordingly. As well, some settings might use the World Health Organization[10] standards and operational guidance, which can also be evaluated for equivalence.

By way of ending, we need to point out that some institutions have developed their own documents in these and related areas which are specific to the needs of the settings while adhering to the DHHS requirements. See for example several such documents from the University of Michigan.[7,11,12] As well, the DHHS website contains additional information related to the matters discussed in this paper that readers may find useful. Two examples are listed in the references by DHHS.[13,14] Another related resource specific to nursing is the scientific integrity guidelines developed by the Midwest Nursing Research Society[15] which is the largest regional research organization. While this does not relate specifically to vulnerable groups, it considers a range of issues that researchers need to consider in the process of conducting research and in the publication process.

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