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ETHICS IN GERIATRIC MEDICINE RESEARCH

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Abstract

This article aims to evaluate the research process in geriatrics from the ethical point of view. The elderly population is increasing rapidly, but there is no parallel in the amount of research concerning this demographic. On the other hand, in the light of research ethics, this group mainly represents vulnerable people and requires more sensitivity. Taking into account all these features, fundamental principles in research ethics are first considered: the soundness of the scientific project, qualifications of the investigators, ethics committee approval, informed consent, confidentiality and privacy, beneficence/nonmaleficence, and justice are evaluated. Special ethical issues in geriatric research such as ageism and research inclusion, paucity of research involving elderly people, vulnerability of elderly subjects, and cognitive impairments are discussed separately.

Keywords

Ethics; Research; Geriatrics

Introduction

The world population aged 65 and older is estimated to be 420 million (1). The increase in the proportion of aged citizens across the globe presents important ethical challenges and obligations in confronting health care needs. The demand for medical services for the elderly is expected to rise exponentially, especially in emerging free-market economies, both in terms of the need for intensive multidisciplinary care and also in terms of the increasing cost of complex and long-term services as a proportion of overall health care. Geriatric medicine will represent an important dimension in the lives of all members of society. This review examines the ethical dimension of research in geriatric medicine in the emerging free market countries. In High Income Countries as a whole, an estimated 73 percent of people aged 65 and over lived in urban areas in 1990, and this figure is projected to reach 80% by 2015. In Low Income Countries over one-third (34%) of people aged 65 and older are estimated to live in urban areas. This proportion is expected to exceed 50% by the year 2015. At the national level for most Low Income Countries, there is a lack of systematic

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research regarding the social, economic, and health status indicators of the elderly population segment (1).

At the outset it needs to be emphasized that geriatrics needs to be examined in a positive framework. Human longevity is a cause of celebration as a result of advances in medical research. There are unique aspects of research in geriatric medicine. A critical issue is that too often research involving the young and even the middle-aged as adult subjects of medical investigations does not necessarily benefit the elderly. In order to address the emerging issues, many programs need to train professionals specialized in research in geriatrics. A number of journals specializing in geriatrics are now flourishing and international funding for reseach on aging is expanding. Parallel to this progress, many important ethical concerns that are emerging involve older subjects as research participants, as well as their families, with respect to the duties and responsibilities of investigators, caregivers, funding agencies, institutions, providers, industry, communities and multisite and multi-disciplinary collaborative relationships (2–4). Conventional research ethics literature and legislation provides guidance for the ethical conduct of research, but clinical realities related to the medical care of older subjects inevitably have a major impact on the actual conduct of research. Some of these aspects can be summarized as follows: compromised health, susceptibility to dangers owing to multiple age-related comorbid conditions, polypharmacy, and difficulties related to reduced mobility, communication, and cognitive functioning (3, 4). Nonetheless it is essential that inclusion of the elderly is promoted in terms of distributive justice. This entails the need for a “new” approach to the establishment of inclusion and exclusion criteria, careful assessment of the benefit-burden ratio, and consideration of issues related to gender disparities, process of informed consent, assessment of competency, and protection of privacy (3). The main theme of this review is the discussion of the research process with the elderly people as a vulnerable group, associated limitations and difficulties, and the effects of ageism in light of the relevant literature. Both fundamental and special geriatric aspects of research ethics are included for guidance.

Fundamental Principles in Research Ethics

Scientifically Sound Research Project

Research designates a set of procedures designed to test a hypothesis and permit conclusions to be drawn; thereby its outcome contributes to generalizable knowledge. A characteristic feature of a research project involves a formal protocol, setting forth an objective and a set of procedures designed to reach the project’s aims. In some cases research and therapeutic practice may be carried out together, especially when research is designed to evaluate the safety and efficacy of a therapy. Invariably, considerations related to the well-being of the human subject take precedence over the interests of science and society (5). Therefore medical research involving human subjects must conform to generally accepted scientific principles, and be based on a thorough knowledge of the scientific literature as well as other relevant sources of information, and on the provision of adequate laboratory facilities. The human subject research considerations should be at the core for achievement of scientific

objectives of any study; participation of human subjects can only be justified if these conditions are ensured (5, 6).

Potential research subjects ought to be made aware of any risks or unfavorable circumstances, especially from proposals advocating trivial but commercially motivated research. These include post-licensing drug comparisons that have more to do with marketing than with useful clinical comparisons (7). Recruiting human subjects for such clinical trials represents an unnecessary and potentially exploitative use of their trust and altruism (2).

Qualifications of the Investigators

The highest degree of skill and care is required through all stages of research, and procedures should be conducted only by scientifically qualified professionals and under the supervision of medical personnel according to good clinical practice (5, 8).

Research Ethics Committee Approval

Research activities should undergo a thorough review process with the objective of protection of human subjects (6). Research protocols should be submitted for consideration and comment as well as guidance, and approved by an independent ethical review committee. Protocols should include information regarding sources of funding, sponsorships, institutional affiliations and compensation-incentives. As it is stated in the Helsinki Declaration, research ethics committees should have the responsibility to monitor ongoing trials. The researchers should be obligated to provide monitoring information to the committee, with clearly defined guidelines with respect to reporting occurrence of any adverse events (5, 6).

Informed Consent

The Nuremberg Code dictates that the consent of human subjects be voluntary. A central premise of this is the legal capacity of a subject to give informed consent without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion. In order to exercise this right, a subject needs to possess sufficient knowledge and comprehension of the elements of the research: its risks and benefits, nature, duration, and purpose, as well as possible conflicts of interest and institutional affiliations of the researchers. Whenever therapies are involved, the subjects need to be offered alternative procedures (5, 8). It is necessary to adapt the presentation of information to the subject’s intellectual and mental capacities (6). To avoid misunderstanding, subjects should be provided with the opportunity to ask questions and to contact the researchers if additional questions arise or if they change their decision at any time. After ensuring that the subject has understood the information, the researcher should then document the subject’s freely-given consent. If the consent cannot be obtained in written form, non-written consent must be elicited and again formally documented and witnessed. During the whole process, the professionals should be particularly cautious if the subject is in a dependent relationship or may consent under duress (5).

For elderly subjects who are legally incompetent, physically or mentally unable to give consent, the investigators must obtain informed consent from their legally authorized representatives in accordance with applicable law. The subjects should not be included in research unless the research is necessary to promote the health of the population represented, and cannot otherwise be performed on legally competent persons. When the subject is deemed to be legally incompetent but nonetheless is able to give assent to the decision for research participation, the investigator must obtain their assent in addition to the consent of the legally authorized representative. The refusal of a patient to participate in a study must never interfere with the patient–physician therapeutic relationship (5). Eventually the subjects should be informed of the right to withdraw consent to participate at any time without reprisal (6).

Confidentiality and Privacy

Investigators should establish adequate protections to respect and safeguard the privacy, confidentiality and integrity of the research subjects during the study procedures and to ensure that any information that can potentially identify a person is kept in secure and restricted files and away from unmonitored and unauthorized access (2, 5).

Beneficence/Nonmaleficence

All research proposals should be preceded by careful assessment of any predictable risks and burdens, in comparison with foreseeable benefits to the participants (5). This perspective for protection of human subjects has absolute priority over social and scientific aspects. Furthermore, the benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebos, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists (5). At this time the local standard of treatment with respect to the best available current treatment option continues to be under debate. Nevertheless, the argument recognized by the FDA for resource poor countries does not apply to the US, or to all other highly developed countries. At this time the US regulations stand alone on this issue.

Justice

The distribution of burdens and benefits of research should be considered carefully by the researchers and the relevant ethics committees. Medical research is only justified if there is a reasonable likelihood that the populations within which the research is carried out stand to benefit from the results of the research (5). The selection of research subjects needs to be scrutinized in order to determine whether some classes of vulnerable subjects are being systematically selected simply because of convenience, cost, easy of availability, compromised status, or their manipulability, rather than for reasons directly related to the problem being studied (6). These subjects include not only women, children, and racial and ethnic minorities, but the elderly, persons with disabilities, those confined to institutions, and patients on public assistance. A further issue under debate is the premise that at the conclusion of the study, every subject entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study (5). Again, this principle has been linked by the FDA to the concept of locally available best

standard of treatment, only applicable in resource poor countries, but not necessarily applicable in the context of resource poor settings within developed countries. Some have argued that such an adjustment of the principle of distributive justice would set a double standard, and that at least for the purposes of research involving human subjects such an exemption ought not to be applied.

Collection and Dissemination of Data

Investigators should ensure that they have no conflict of commitment with undue incentives to complete the research rapidly, without adequate regard for the validity and value of research results (2). Valid results, regardless of both positive and negative outcomes, represent valuable knowledge to the medical community, patients, and caregivers. All parts have a legitimate interest in receiving relevant information as soon as possible. In recognition of this, both researchers and journal editors should be committed to disseminating knowledge generated by studies in a timely manner consistent with the best scientific and ethical standards (2, 5).

Investigators should adhere to accepted standards for publication and keep clear of scientific misconduct, fraud, sloppy research, fabrication, falsification and plagiarism (2, 9). Roots of research misconduct related to individuals include lack of education and scientific discipline, excessive desire for institutional and academic promotions, desire for money, reputation (Hollywood syndrome), disproportionate institutional pressure, “publish or perish” perception and psychiatric disorders (10). Although there are several guidelines governing the responsible conduct of research, the ethical responsibilities primarily lie with the principal investigators (with institutional oversight) who design and carry out the research and publicize their findings (7).

Special Issues Concerning Ethics in Geriatric Research

Ageism and Research Inclusion

Until the 1980s, people over age 65 were excluded from clinical trials. Bugeja et al. examined all original research papers in four leading medical journals and found that of the 490 papers involving older subjects, 170 studies (35%) excluded those aged 75 years and above without any meaningful scientific justification (10). By 2005, the situation was noted by the authors to have improved, with 15% of the studies still excluding older subjects without due justification (11). Comorbidity, reduced life expectancy, polypharmacy and specific drug use, cognitive and physical impairment examined as main exclusion criteria in two recent studies and results supported the poor justification claims (12, 13).

A parallel finding in 2000 involving a study of research ethics committee decisions revealed that review processes had not identified the non-inclusion of older people as an ethical issue (14).

A study conducted by Crome et al. in nine European countries over 540 subjects and six categories of professionals (geriatricians, general practitioners, nurses, clinical researchers, ethicists and pharmacists) revealed that 84% of the respondents believed that older people

were underrepresented in clinical trials and that such underrepresentation caused difficulties for clinicians (79%), thus disadvantaging older people as a result (73%) (11).

Paucity of Research Involving Older Persons

Older people receive a disproportionately lesser share of the burdens and benefits of clinical research compared to young and middle aged adult subjects (4). There are multiple factors that limit research involving older subjects. These involve practical difficulties in conducting geriatric research, difficulties in the implementation of specific research procedures, social and cultural barriers to access, impaired capacity to provide informed consent, inconvenience, cost, and the likelihood of higher incidence of adverse events. Finally, since many elderly persons may have more limited means to access new treatments, they may be deemed a less attractive market with respect to clinical trials (4).

Although an obvious rationale for excluding cognitively impaired elderly subjects in research is the application of the first ethical principle in the Belmont report (respect for persons), excluding them violates the third ethical principle in the report (justice), especially if the research questions at hand cannot otherwise be addressed to help sustain research benefits that may accrue specifically to the elderly. In other words individuals, irrespective of their age or other vulnerable circumstances, ought not to be systematically excluded if they are unlikely to benefit when the research is conducted without their participation (15).

While there are problems associated with the inclusion of the elderly in clinical trials, their exclusion altogether poses greater problems. Excuses in protocols related to such exclusions based on ageism (often ages 70 and above) include: need for patients to be reliable/fully competent; able to follow instructions; and higher rates of poor compliance and dropping out (16). The work of Crome and colleagues (involving data from the Czech Republic, Lithuania, Italy, Israel, Netherlands, Poland, Romania, Spain and UK) agrees that exclusion from clinical trials on age grounds is unjustified (87%) and that under-representation of the elderly in trials causes difficulties for physicians (79%) and patients (73%) alike (11).

The poor representation of older patients in clinical trials leaves clinicians in a dilemma. If they prescribe treatments untested in older people, they do so in the absence of solid evidence of efficacy and toxicity for that age group. Alternatively, if they do not prescribe such treatments they may be denying them worthwhile benefits (11).

Vulnerable Elderly Subjects

Members of vulnerable subgroups of elderly include those with multiplex and chronic medical and mental conditions, cognitive impairments/dementia, those in nursing home or long-term care institutional settings, and those terminally ill and dying (16). An argument is that research involving the elderly subjects in each and every one of these sub-categories can and ought to be justified if indeed such research can benefit them. Elderly persons living in nursing homes have been thought of as particularly vulnerable, but with appropriate protections can participate in scientific research (16). Older people may experience conditions such as dementia or live in long-term care facilities that impair their ability to express their rights and interests (2). Nevertheless, by virtue of their burden they also deserve attention by the researchers, and protections need to be in place to ensure their

inclusion. In this respect it may be important to appreciate that vulnerability can indeed arise through the under-researching of a group's particular condition or from not exposing them to the research process (16).

Particular attention ought to be paid to providing protections to ensure their participation. These include their deference to authority, obeisance, submissive dependence on others which may lead to a higher likelihood of manipulation or coercion, and/or lack of respect by others for the concept of their own lives and interests (16). There is a high level of gratitude from patients towards hospice staff. Because of this, patients may feel that they should not refuse to take part in research and consent may not necessarily be "freely given" (16).

Elderly Subjects with Cognitive Impairments

Some authors use cognitive impairment interchangeably with dementia. This is not necessarily correct, as elderly subjects experience varying degrees of cognitive impairments ranging from borderline to very severe (15); nevertheless, dementia in the elderly remains an overarching concern. Even subjects with Mini-Mental State exam scores as low as the 10–20 range may be able to give valid consent for projects. More complex information and more complicated decisions require greater degrees of cognitive function. Vulnerable elderly subjects of most concern in geriatric research remain those with dementia, and especially those who reside in long term care facilities. They are at particular risk of not gaining access to the fruits of the research endeavor, such as new and expensive medications or the latest diagnostic testing and surgical procedures (4).

Issues Related to the Process of Informed Consent—Informed consent means that the subject understands the relevant information and that the decision is made voluntarily. The cognitive and sensorineural deficits of some older persons may mean that they require more time to comprehend information. In practical terms, this extra time requires the commitment of empathic and well-trained staff and may need to include people who are responsible for the patient's health care. These research staff are as important to a well-designed protocol as the provision of adequate equipment and technical expertise (2). There are degrees of cognitive impairment and elderly patients with mild dementia generally have the capacity to consent (16). Incorporating the consent form questions into an information sheet so that questions follow relevant paragraphs that can be walked through in the consent process is helpful. Information sheets need to have a lower reading level and larger typeface (16). In addition, family will need to be involved in the consent process and the consenting subjects should have the right to express their point of view even if it is different from that of their relatives (16). Impaired decision making capacity and an inability to give informed consent may be a temporary condition or it may be permanent. Geriatric researchers often know patients or potential subjects before their loss of decision making capacity. There may be opportunities for advanced consent and proxy consent. Helping the subject to understand as fully as possible, and ascertaining how well the subject understands, is critical in geriatric research. A lot of authors have emphasized the importance of visual and hearing aids, such as pictures, vignettes, storybooks and audio- or videotapes. However, some of them showed that these aids proved a distraction rather than an aid for elderly subjects. Educational training was also suggested as a method of enhancing decision-making capacity.

Experienced consent seems a promising tool to optimize informed consent in frail elderly subjects (17).

Advance Directives—In general, the legal status of research advance directives is not clear. As an example, most of the state laws in the US creating advance directives focus on clinical decisions, especially those pertaining to the use of life-sustaining treatments. Promoting the use of advance directives for research might create the impression that they are required to do research on dementia. Only a small group of adults complete advance directives in daily clinical medicine; it is possible to assume that even fewer would be relevant to research, and one can envision a scenario in which research advance directives actually end up inhibiting rather than promoting dementia research (4).

Proxy Consent—A family member is most suitable for proxy consent because he or she knows the potential subject best and is most likely to make a decision that would be keeping with the subject's values. The proxy has the best interest of the subject at heart and will make the best decision. As a closely involved family member, the proxy is the person most likely to be affected by the decision. A negative aspect of proxy consent includes potential conflicts of interest. Data from clinical decision making studies demonstrate significant discord (4). Declaring someone unable to make decisions or to give consent should not be based on diagnostic labels. There is lack of legal clarity in using proxies. There is a need to ensure the proxy's independence from the research team and to overrule any possibility of conflict of interest. A key problem is how to ensure dispassionate proxy consent (16).

A role for assent—The ability of a research subject to express his or her willingness to agree to go along with a research protocol, even if the subject cannot provide informed consent, involves the process of assent that is often used in research involving adolescents. When given information about specific research protocols, even with very impaired people with dementia, it is possible to see that assent supports the ability to reveal the subjects' values and preferences (4).

Challenges Involving Subjects with Serious Cognitive Impairments

There are many ethical and legal challenges central to research subjects with cognitive impairments. These include: (1) determining capacity; (2) surrogate decision making; (3) assessment of risk; (4) potential benefits; and (5) measures to increase study understanding (15). Grisso and Appelbaum (1998) note four factors relevant to assessing capacity. These include the ability to: (i) communicate a choice; (ii) understand relevant information; (iii) appreciate alternatives/consequences; and (iv) think rationally about issues involved (16).

These factors need to be considered in a purely cognitive sense, but at the same time there may be a lack of emotional appreciation. In particular, in subjects with dementia or pseudodementia there may be comorbidity with depression that is unrecognized and untreated.

Challenges in Rrecruitment and Specialized Research Settings

Recruitment—Challenges in the recruitment phase of a research project are highly important in that this phase is directly linked to representative sampling frame, study validity and generalizability, as well as ethical principles with respect to the promotion of diverse and just participation, and consideration of feasibility and retention of participants (3).

Homebound Elderly Subjects—One challenge involving research with homebound elderly adults is that they may not closely monitored by health professionals. Furthermore, they often remain socially isolated. Conducting studies with homebound older adults involves additional vulnerabilities, especially in terms of the separation of researcher and therapeutic roles. The venue of the research also provides greater access to participants' otherwise private home lives and thereby presents further ethical challenges. Care must be taken to describe the course of action that will be taken if specific risks are observed during the course of investigation. Researchers will need to be in close contact with the primary physician or home health nurse. Researchers will need to further inform potential participants that if any sign of abuse or neglect is observed, they will notify adult protective services. Furthermore, if a threatening situation is observed, this will be notified to the research ethics committee as an adverse event (18).

Palliative Care—Palliative care is "the active, total care of patients whose disease is not responsive to curative treatment. Control of pain, other symptoms and psychological, social and spiritual problems are paramount. The goal of palliative care is the achievement of the best quality of life for patients and families" (16). Direct therapeutic benefits of research for palliative care patients can be seen, like better pain and symptom control, fine tuning of sedation, and better understanding of nutrition and hydration. Attention, understanding, worth, hope, being altruistic and being valued are indirect benefits. There are costs to be borne by palliative care patients involved in research. It seems important to engage the whole multi-professional team in defining hospice research priorities. Hospice staff should be involved in early discussions and designing of research and in the progress of studies through ethical approval (16).

Recommendations for Training in Responsible Conduct of Research and Service on Research Ethics Committees

Training in Responsible Conduct of Research—Investigator training in Responsible Conduct of Research (RCR) is currently implemented in the USA as a requirement in all federally sponsored research training. The model is also increasingly disseminated in Europe as well as by many major funding agencies promoting research in Low and Middle Income countries. This needs to be coupled with good research management and work of the research ethics committees in the institutional context (9).

Service on Research Ethics Committees—Geriatrics healthcare professionals should serve on these committees to provide input about the experiences of care and research in the elderly (2). Investigators should cultivate relationships with patient organizations to include expertise derived from the direct experience of aging and disease. Patient groups can assist

the research team in the evaluation of risks and benefits and the value assessment at consensus conferences and workshops. This kind of participation will help researchers to decide whether to pursue particularly risky or innovative research (2).

Conclusions

As generally accepted, the ethical principles of beneficence and nonmaleficence were first mentioned in biomedical research, the respect for autonomy subsequently following in due course. The process of “informed consent” has become the respected beacon for the application of these ethical principles in research practice. There are now various levels of safeguards for ethical research practice: international codes and guidelines, national legislations and the ensuing work of research ethics committees. Maintaining the rights of participants and preventing probable injury or harm to human subjects continue to be the overarching aim in the conduct of biomedical research involving human subjects worldwide.

In geriatric medicine, and also in pediatrics, child psychiatry and psychiatry, there are common concerns for the application of these ethical principles, especially with respect to the difficulties relevant to the process of obtaining informed consent. Special difficulties mentioned concerning research on geriatric populations include less willingness or fewer opportunties available to them to participate in research. There are myriad reasons for the exclusion of elderly human subjects from biomedical research, the least of which ought to involve their higher likelihood to suffer from multiple ailments (including their greater probability of suffering from hearing and visual losses, and limitations in cognitive abilities including onset of dementia), or the probability of their being subjected to a multitude of procedures and/or polypharmacy. In fact, one would imagine that these factors ought to be grounds for their inclusion in research, as it would entail benefits to them if they are indeed to be implictly included rather than excluded. Nor would one exclude the elderly because they reside in environments in which their individual rights may be constrained by virtue of isolation, or living in long term care settings. Ironically, a major barrier to the elicitation of informed consent is also implicit as a barrier to applying the principle of distributive justice. Protecting the rights of elderly participants and preventing them from the risk of exposure to harm or injury during research, although an overarching aim, ought therefore not to be a criterion for exclusion. Inclusion implies respect for a better life with all the potential benefits and fruits of research.

In this paper we argue that greater attention ought to be paid to the principle of distributive justice, with emphasis on the expenditure of the needed time and effort to ensure that researchers, institutions and funding agencies appreciate the inclusion of elderly subjects. The era of excessive protections as a rationale for exclusion of the elderly from research can no longer be a convenient excuse for not resolving challenging informed consent problems. Protections per se are not an adequate solution to ensuring beneficence, or detering malficence, since benefits cannot accrue without inclusion. This is an essential fact. The approaches to resolve these concerns that we argue herein are likely to strenghten the enterprise of geriatric research in the future, especially in the context of evolving demographics worldwide.

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