BIOMEDICAL RESEARCH INVOLVING ELDERLY SUBJECTS: ETHICAL ASPECTS

Semenova NV ✉

Bekhterev National Research Medical Centre for Psychiatry and Neurology, St. Petersburg, Russia

Due to the aging of the population and growing proportion of the elderly, medicine requires a more active and purposeful approach not only to study theoretical aspects of gerontology, but also to search for new drugs designed specifically for this category of the population. Clinical trials in older people are more in demand than ever. However, researchers must ensure that they conduct their studies ethically. Key ethical issues include prevention of discrimination and violations of the autonomy of older people, as well as special requirements for informing and obtaining voluntary informed consent. When preparing voluntary informed consent for older people, especially for those with cognitive decline, special attention should be paid not only to the information itself, but also to the form of its presentation. The documents should be concise, clear and contain all the key information. In addition, the use of modern multimedia technologies can help the subjects make an informed decision about their participation in the study. For patients with cognitive impairment, it is important to adhere to the principle that the higher the risk for the study participants, the more the patient's cognitive functions and decision-making ability should be preserved. Excluding patients from studies with potential benefit due to age or cognitive impairment is considered unethical and discriminatory. This is taken as an unfair restriction of their access to the achievements of scientific and technological progress in the field of medicine.

Keywords: ethics, old age, vulnerable patients, cognitive impairment, informed consent

✉ **Correspondence should be addressed:** Natalia V Semenova
Bekhtereva Str., 3/1, St. Petersburg, 192019, Russia; nvs@bekhterev.ru

Received: 19.05.2024 **Accepted:** 10.06.2024 **Published online:** 30.06.2024

DOI: 10.24075/medet.2024.012

БИОМЕДИЦИНСКИЕ ИССЛЕДОВАНИЯ С УЧАСТИЕМ ПОЖИЛЫХ ЛЮДЕЙ: ЭТИЧЕСКИЕ АСПЕКТЫ

Н. В. Семенова ✉

Национальный медицинский исследовательский центр психиатрии и неврологии им. В. М. Бехтерева, Санкт-Петербург, Россия

Старение населения и увеличение доли пожилых людей среди населения ставят перед медициной необходимость в более активном и целенаправленном подходе не только к изучению теоретических аспектов геронтологии, но и к поиску новых лекарств, предназначенных специально для этой категории населения. Все более востребованными становятся клинические исследования с участием пожилых людей. Однако проведение таких исследований требует особого внимания к этическим аспектам. Ключевые этические вопросы включают предотвращение дискриминации и нарушений автономии пожилых людей, а также особые требования к информированию и получению добровольного информированного согласия. При подготовке добровольного информированного согласия для пожилых людей, особенно с проявлениями когнитивного снижения, особое внимание следует уделять не только самой информации, но и форме ее представления. Документы должны быть краткими, понятными и содержать всю ключевую информацию. Кроме того, использование современных мультимедийных технологий может помочь испытуемому принять обоснованное решение относительно своего участия в исследовании. Для пациентов с когнитивными нарушениями важно придерживаться принципа, согласно которому чем выше риск для участников исследования, тем в большей степени должны быть сохранены когнитивные функции пациента и способность принимать решения. Исключение пациентов по причине возраста или «когнитивной недостаточности» из исследований, в которых они потенциально могли бы извлечь пользу, считается неэтичным и дискриминационным. Это рассматривается как несправедливое ограничение их доступа к достижениям научно-технического прогресса в области медицины.

Ключевые слова: этика, пожилой возраст, уязвимые пациенты, когнитивные нарушения, информированное согласие

✉ **Для корреспонденции:** Наталия Владимировна Семенова
ул. Бехтерева, д. 3/1, г. Санкт-Петербург, 192019, Россия; nvs@bekhterev.ru

Статья поступила: 19.05.2024 **Статья принята к печати:** 10.06.2024 **Опубликована онлайн:** 30.06.2024

DOI: 10.24075/medet.2024.012

The progressive increase in the proportion of older age groups is an important demographic trend that causes a natural increase in the proportion of specific diseases of late age, especially cognitive disorders. According to Rosstat, the number of people over 65 in the Russian Federation was 16% as of 01.01.2022 (taking into account the results of the All-Russian Population Census in 2020). In the future, the proportion of elderly people in Russia, and especially of those aged 80 and older, will be increasing [1]. As the Russian population ages, the importance of research devoted to the aging process, conditions and diseases that are especially common in older people, is becoming increasingly important. The Ethics Committee (CE) faces a number of questions regarding participation of older people in research. The most important one is as follows: "*Do older people need special protection, and if so, when?*". The CE must maintain a balance between the necessary need for protection and respect for these people [2].

In addition to the requirements for providing special protection to vulnerable segments of society [3], which are guided by the CE, there are no special standards or Russian laws for conducting research on the elderly. According to the general opinion, the elderly represent a heterogeneous population, which, as a rule, does not require any special protection, except for two cases:

- people with cognitive impairments;
- persons located in specialized medical institutions.

In these cases, the approach to these study participants will be the same as to others under the same circumstances.

There is no specific age starting from which elderly patients are considered unsuitable for research. Some of them may not have clinically pronounced cognitive impairments and related disorders of daily functioning. However, some researchers try to avoid involving the elderly in research due to certain difficulties in their selection. Older people tend to avoid participating in the research that disrupts their normal daily routine, is inconvenient or does not directly benefit them. Also, conducting a study involving elderly patients may be more difficult and expensive.

Older people may have problems with vision, hearing and speech. Thus, it may take more time to explain to them the tasks of participating in the study. They interrupt their participation in research more often than young people, so it is necessary to initially screen more participants.

Despite these difficulties, it is necessary to include older people in research. If they are excluded or treated with special methods, the doctor must make sure that they are protected and not treated in a contemptuous, stereotypical or patronizing manner. The tasks of the CE are to conduct an ethical examination and recommend conducting a study for this category of patients, taking into account all possible risks both for the studied drug and for the procedures.

Screening and diagnostic procedures, as well as therapies, are becoming more complex and diverse. So, the question of adequate and accessible information for patients about the methods used, adverse events and all other diverse aspects included in the procedures of clinical research is becoming more acute. Thus, obtaining the informed consent of an elderly patient, especially if there are problems with cognitive functioning, becomes not just a discrete procedure carried out before the start of any research procedures, not just a legal and ethical requirement, but an ongoing process based on the relationship between the researcher and the patient. Owing to the informed consent, the patient obtains an optimal opportunity to take an autonomous decision that best suits his beliefs and preferences.

The CE should treat the cognitive impairments of older people in the same way as it treats any other potential research participants. Elderly people with cognitive impairments can be involved in research only under the following circumstances:

- when other groups of people are not suitable for research;
- if the study is related to the problem seen only among patients with similar disorders;
- if the study entails a minimal risk only.

Using age as a criterion for the ability to give consent and thus participate in the study is unjustified. And although it is recognized that memory impairment can be a problem for some older people (thus, their ability to constantly express their willingness to participate in the study is being questioned), the task of the CE is to determine *if older people can make informed choices*

Numerous experimental and psychological studies are consistent with household observations that elderly people are worse at learning new information compared to young people. In older patients, memory impairment is combined with a number of other changes in cognitive functions. The latter relate primarily to reaction time, which tends to increase with age. As a result, older people need more time to do a similar amount of mental work as compared to younger people. In older age, fatigue during mental exercises also develops somewhat faster than in younger people. The main causes of cognitive impairment in older age are various neurodegenerative (primarily Alzheimer's disease), cerebrovascular diseases and dysmetabolic disorders [4, 5]. The prevalence of moderate cognitive impairment among people aged 60 years and older ranges from 5.0 to 36.7% [6].

There are four types of impaired decision-making ability that are taken into account when planning and conducting scientific research in patients with cognitive disorders:

1) the fluctuating is seen in some conditions, when painful symptoms periodically increase and decrease;
2) the prospective is found at the early stages of Alzheimer's disease, when the symptoms are steadily increasing and, despite the existing ability to make decisions at this time, there are compelling reasons to expect violations in the future;
3) the limited relates to more advanced stages of Alzheimer's disease, when the ability to express informed consent is impaired, but the subject is still able to express "less qualitative" consent (assent) or refuse to participate in the study;
4) the complete is about the final stages of Alzheimer's disease, deep dementia, when almost any ability to make decisions based on any significant reflection is lost [7, 8].

For patients with cognitive impairment, it is important to adhere to the principle that the higher the risk for the study participants, the more the patient's cognitive functions and decision-making ability should be preserved. In other words, patients with more pronounced cognitive disorders may be included in studies where the risk is no more than minimal. Patients with cognitive impairment, even if they are legally capable, should not be involved in the same studies where the possible risk is high and where confidence is required that, by agreeing to participate in the study, an elderly patient understands all the features of the study associated with a possible risk.

Though in the second half of the 20th century bioethics focused on the balance of risk and benefit in research, in the beginning of the 21st century, increasing attention is being paid to ethical aspects such as providing access to new, advanced medical technologies and medicines to vulnerable patients in particular need. Therefore, excluding patients from studies where they may receive potential health benefits due to a certain age or cognitive insufficiency seems unethical. Today, their exclusion from research is considered as discrimination and unfair restriction of their access to scientific and technological progress in the field of medicine [2, 3].

When preparing informed consent for older people, especially those with cognitive decline, the following fundamental points should be taken into account. Special attention should be paid not only to the information contained in the consent form, but also to how this information is submitted. Researchers should create concise and understandable documents with the key information that causes no different interpretations of its content. This can help the subject to make the right decision about the possible participation in the study [9]. Often, improvements of informed consent forms are associated with the use of modern multimedia technologies (for example, slide shows, short video presentations, questionnaires, audio recordings of the key information, etc.). It helps to present the content of the document in a more concise and visual manner and to improve the understanding of specific medical information by potential research participants.

In cases where an elderly patient cannot read the text of the informed consent form himself, the researcher must read this information in full and answer all questions that arise. During the procedure of informing and obtaining informed consent, the presence of an impartial witness is required. The witness must not be the researcher's subordinate or relative. The witness confirms that the informed consent form was fully read to the patient and understood by him in the witness presence, and that the patient had the opportunity to ask any questions and get answers. The impartial witness, along with the patient and the researcher, must also sign and date the informed consent form.

Some of the features associated with obtaining consent from older people include methods of providing information, written or oral. A quite high level of reading skills is required to understand the informed consent form. As far as discussion of the consent form goes, a clear and understandable explanation should contain simple terms, lack of professional and other jargon, and willingness to answer any questions, regardless of whether the patient has a cognitive impairment or not.

If necessary, it is recommended to use additional methods to help the subject better understand information about

the nature of scientific research and the consequences of their participation herein. They include repeated provision of information, use of educational videos, group discussion with patients who previously participated in similar studies, etc.

Structured procedures prevail among the methods that contribute to a better understanding of the consent form. They are as follows: specially designated question-and-answer sections, interactive presentations with the possibility of preview, and questionnaires regarding the consent form. Often, improvements in the field of informed consent forms are associated with the use of modern multimedia technologies (for example, slide shows, short video presentations, questionnaires, audio recordings of the consent process, etc.), which helps to present the content of the document in a more concise and visual manner and to improve the understanding of specific medical information by potential research participants.

As soon as the question of decision — making ability arises, the clinician's task is to determine this ability as accurately as possible. It should be taken into account that a universal tool for evaluating this function has not yet been created. Therefore, if there are certain doubts, a consultation with colleagues may be a good idea.

Elderly patients, including those with cognitive impairments, can participate in the "caregiver" study. The caregiver (accompanying person) may be a family member or other relative, neighbor, friend, or close person who will help the patient cope with the research procedures, come to the research center for visits and provide the researcher with the necessary information about changes in the patient's condition. Before being included into the study, the caregiver must sign and put a date on a special, separate informed consent form for the caregiver, which provides information about the essence of the study, its procedures, as well as describes the responsibilities of the caregiver and, if necessary, compensation for his expenses (for transport, food, etc.). Just like the main participant in the study, the caregiver can withdraw from further participation in the study at any time. In such a situation, however, there may be a risk that the patient will not be able to continue participating in the study without an accompanying person. Therefore, when considering candidates for caregivers, the researcher needs to make sure that the person will be able to perform quite long-term duties of accompanying the patient in the study based on the physical and psychological condition. At the same time, it must be clearly understood that the caregiver cannot be the legal representative of the patient and make any decisions regarding participation or non-participation in the study and its procedures for the patient.

Both clinicians and researchers should be aware of the ethical issues associated with decision-making by elderly patients. It is necessary to take into account the possible violations of cognitive functions responsible for the quality of decision-making. When elderly patients are included in the study, it is important to make sure that their decision-making is autonomous, has no outside influence and coercion, which in its turn can increase the confidence of this group in biomedical research. The possibility of further progress in the treatment of elderly diseases largely depends on the willingness of this cohort to participate in clinical trials.

References

1. Kuzin S. The aging of the population: socio-economic aspect. Vestnik Universiteta. 2018; (3): 137–143. DOI: 10.26425/1816-4277-2018-3-137-143 Russian.
2. E`ticheskaya e`kspertiza biomedicinskix issledovanij: rukovodstvo dlya komitetov po e`tike. Pod obshhej red. Xoxlova AL. 3-e izd., pererab. i dop. M.: Izd-vo OKI. 2021. Russian.
3. Semenova NV. The informed consent and borders of autonomy in clinical trials with participation of vulnerable groups of patients. Medicinskaja etika. 2018; 1: 63–65. Russian.
4. World Alzheimer Report 2018. The state of the art of dementia research: New frontiers. London: ADI. 2018.
5. Levin OS. Diagnostika i lechenie kognitivnyh narushenij i demencii v klinicheskoj praktike. M.: MEDpress-inform. 2019; 448 s. Russian.
6. Sachdev PS, Lipnicki DM, Kochan NA, et al. The Prevalence of Mild Cognitive Impairment in Diverse Geographical and Ethnocultural Regions: The COSMIC Collaboration. PLoS One. 2015; 10(11): e0142388 c. 1–19. Available from URL: https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0142388&type=printable (accessed 10.05.2024)
7. Research Involving Persons with Mental Disorders that May Affect Decision Making Capacity. Report and Recommendations of the National Bioethics Advisory Commission. Rockville. MD: NBAC. 1998; 1:176
8. Research Involving Persons with Mental Disorders that May Affect Decisionmaking Capacity. Commissioned Papers by the National Bioethics Advisory Commission. Rockville, MD: National Bioethics Advisory Commission (NBAC). 1999; 2:79
9. Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators. Department of Health and Human Services, Office of Secretary 2011, FR Doc No: 2011–18792, July 26.

Литература

1. Кузин С. И. Старение населения: социально-экономический аспект. Вестник университета. 2018; (3): 137–143. DOI: 10.26425/1816-4277-2018-3-137-143
2. Этическая экспертиза биомедицинских исследований: руководство для комитетов по этике. Под общей ред. А. Л. Хохлова. 3-е изд., перераб. и доп. М.: Изд-во ОКИ. 2021.
3. Семенова Н. В. Информированное согласие и границы автономии в клинических исследованиях с участием уязвимых групп пациентов. Медицинская этика. 2018;1: 63–65.
4. World Alzheimer Report 2018. The state of the art of dementia research: New frontiers. London: ADI. 2018.
5. Левин О. С. Диагностика и лечение когнитивных нарушений и деменции в клинической практике. М.: МЕДпресс-информ. 2019; 448 с.
6. Sachdev PS, Lipnicki DM, Kochan NA, et al. The Prevalence of Mild Cognitive Impairment in Diverse Geographical and Ethnocultural Regions: The COSMIC Collaboration. PLoS One. 2015; 10(11): e0142388 c. 1–19. Режим доступа: [Электронный ресурс]. URL: https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0142388&type=printable (дата обращения 10.05.2024).
7. Research Involving Persons with Mental Disorders that May Affect Decision Making Capacity, Report and Recommendations of the National Bioethics Advisory Commission. Rockville, MD: NBAC. 1998; 1:176
8. Research Involving Persons with Mental Disorders that May Affect Decisionmaking Capacity, Commissioned Papers by the National Bioethics Advisory Commission. Rockville, MD: National Bioethics Advisory Commission (NBAC). 1999; 2:79
9. Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators. Department of Health and Human Services, Office of Secretary. 2011, FR Doc No: 2011–18792, July 26.