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Ethical guidance for geriatric clinical research in China

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Abstract

In China, the population is aging rapidly, and the elderly have enormous medical needs. However, the elderly are underrepresented in clinical research, potentially forcing them to use medical devices and treatments that may be not suitable for them. Elderly patients are characterized by multiple comorbidities, concomitant treatments, and high incidence of cognitive impairment, and consequently are at increased risk of participating in clinical research. To reduce the risks involved with the elderly participating in clinical research, guidance on the ethical review of geriatric research is necessary. Based on a literature review and panel discussion, we have developed the *Ethical Guidance for Geriatric Clinical Research*, aiming to provide guidance on the ethical review of geriatric clinical research.

KEYWORDS

clinical research, ethics, geriatrics

1 | INTRODUCTION

The situation of China's aging population is serious. At the end of 2019, the number of elderly people over 60 years old exceeded 253 million.[1] The elderly have a higher incidence of chronic disease, characterized by multiple diseases and the use of multiple medications, and therefore require extensive medical care. However, the current standards for diagnosis and treatment are based mostly on clinical studies of adults aged 18-60 years and are not entirely suitable for the elderly. The continued aging of the elderly leads to the decline of bodily and organ function, comorbidities, and the use of multiple medications. It also leads to an increased risk of adverse drug-related reactions and research-related risks. The elderly also have a higher incidence of cognitive impairment, making it difficult to make independent decisions about whether to participate in clinical research. Therefore, how to apply the basic principles of medical ethics to scientifically and normatively conduct ethical review for geriatric research, to reduce the risk of elderly subjects, and to protect their health and rights are urgent issues in the field of ethical review of the elderly.

Research on the ethical review of geriatrics has been carried out in Europe and North America, resulting in the publication of relevant guidelines.[2-4] However, ethical review is closely related to a country's political, economic, ideological, cultural, legal, and religious beliefs. Therefore, it is necessary to establish ethical guidance for geriatric clinical research suitable for China's national situation.

Lingling Yu and Xiaoling Li contributed equally to this work and they are co-first authors.

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Doing so will better protect the rights and interests of elderly subjects, provide high-quality guidance for ethics committees to review clinical research projects involving elderly subjects, and provide assistance for clinical research in geriatrics.

Under the leadership of the Beijing Municipal Health Commission, the *Ethical Guidance for Geriatric Clinical Research* was written by the National Center of Gerontology, National Clinical Research Center for Geriatric Diseases, Beijing Hospital, and Xuanwu Hospital, Capital Medical University. The Declaration of Helsinki and other domestic and foreign ethical principles, norms, management documents, and ethical guidance for geriatric research and literature were referenced. Experts from 23 institutions, with backgrounds in geriatrics, pharmacy, evidence-based medicine, law, and ethics, were consulted through Delphi expert consultation and discussion. As such, the *Ethical Guidance for Geriatric Clinical Research* is a reference for ethics committees reviewing geriatric clinical research.

This edition of *Ethical Guidance for Geriatric Clinical Research* mainly elaborates the basic points of ethical review for geriatric clinical research. However, the ethical issues of geriatric clinical research for the elderly in places such as nursing care institutions, and under home nursing or palliative care were not covered in this guidance.

2 | DEFINITION OF GERIATRIC CLINICAL RESEARCH

In this guidance, geriatric clinical research refers to research carried out on the population aged 60 years and older. This research focuses on the health and illness of the elderly by studying the physiological, psychological, and pathological phenomena of the elderly, as well as the etiology, pathogenesis, screening, diagnosis, prevention, treatment, rehabilitation, and prognosis of disease. It also includes clinical trials of new medical technologies, therapies, and products for the elderly.[5]

3 | REQUIREMENTS OF RESEARCH INSTITUTIONS AND ETHICS COMMITTEES

Institutions where clinical trials of drugs and medical devices, and stem cell clinical research are carried out must obtain qualifications granted by the State Administration for Regulation. In addition to meeting the requirements of national and local Administration for Regulation, the organizational structure, regulation, standard operating procedures, and review procedures of the ethics committee of a research institution should also meet the following conditions:

3.1 It is recommended to include experts with a professional background in geriatrics in the ethics committee. If this is not possible, it is recommended to hire a geriatric expert as an independent advisor. If possible, general medicine and psychology experts are recommended in research institutions.

3.2 In addition to receiving regular medical ethics training, ethics committee members should also take the initiative to learn about geriatrics, geriatric research, and geriatric medical ethics, as well as International Committee of Harmonisation-Good Clinical Practice E7, "Studies in Support of Special Populations: Geriatrics."6

3.3 It is recommended that ethics committee members with professional backgrounds in geriatrics participate in the entire review process from the initial review to the continuing review.4 When it comes to pharmacokinetic studies and drug-drug interaction studies in the elderly, it is recommended to seek expert advice from a clinical pharmacologist as the primary reviewer or as an independent advisor.

4 | PRINCIPAL INVESTIGATOR AND RESEARCH TEAM

In addition to meeting the requirement of relevant local and national regulations and guidelines, the principal investigators and research team members of the study should meet the following conditions:

1. Principal investigators of intervention studies should have senior professional titles and extensive experience in the field of geriatrics. Principal investigators and research team members should receive training on good clinical practice and have sufficient time and energy to devote to research.
2. Research team members should include geriatric expertise[7] and experts in clinical research methodology. Also, it is important to understand the common cognitive and mental health challenges in the elderly.
3. Research team members should have good communication skills and be effective at communicating with the elderly.
4. The elderly are prone to suffering from multiple diseases, and are therefore more likely to be using multiple medications and adverse drug reactions. For studies with high expected risks, research team members should be trained in emergency and first-aid capabilities.

5 | RESEARCH PROTOCOL REVIEW

5.1 | Research background and preliminary work

The research protocol should elaborate current research progress and status and the scientific value, to avoid conducting meaningless and repetitive research.

Prior to the initiation of intervention studies, adequate preliminary research basis should be provided, such as in vitro studies, and experiments on cell and on aging animal models. If necessary, data from other studies of adults or healthy older adults should be obtained first.

5.2 | Objectives

When the research involves older people, it is set to diseases or health problems specific to the elderly population, or the target population of diseases contains a significant number of elderly patients.[6]

5.3 | Study design

5.3.1 | Inclusion and exclusion criteria

Study participants should represent the target population according to the clinical and epidemiological data of the targeted disease. The following criteria are critical for a successful study:

1. Age: The definition of geriatric population is those aged 60 years and above.

If the study sets upper age cut-offs, sufficient and reasonable evidence should be provided.[6,8] The age of participants should match the disease population. The older the target population, the more important it is to include very old people.[6] There should be data representing different age groups when the study aims to evaluate the consistency of efficacy and safety characteristics in elderly patients with non-elderly patients.

2. The number and proportion of participants of each biological sex should be representative of the geriatric population, unless a disease is sex-specific.

3. To ensure the principle of justice, the study participants should be representative of the population who suffer from the disease. If a study is focused on a disease generally associated with aging, such as Alzheimer's disease, it is expected that geriatric participants will constitute the major portion of the study participants.[6] Elderly persons with special living conditions, such as living alone or in long-term care or nursing institutions, should not be excluded from clinical studies.

4. Concomitant Illnesses: It is important not to unnecessarily exclude patients with concomitant illnesses. Drug-disease and drug-drug interactions can be detected only by observing such patients.[6]

5. Participants with cognitive impairment: If participants with cognitive impairment are enrolled, the research should generally provide potential individual benefit. If the research does not offer any potential individual benefit, the risks must be minimized to be no more than minimal, and the research must have social value.[9]

5.3.2 | Sample size

Sample size should be based on the research type, primary outcomes, and other factors. Sample size calculation should consider the following factors:

a. The minimal sample size that can achieve the research purpose, such as physiological process of disease, affecting factors, and so on. Large sample design must have sufficient theoretical basis and preliminary research basis.
b. High dropouts and heterogeneity, such as comorbidity, concomitant treatments. If necessary, stratified design can be adopted according to relevant factors.
c. The health status and bodily function of the elderly in different age groups are different and change with time, so the differences between age groups should be taken into account when estimating the sample size.

5.3.3 | Study design notes

1. Protocol should maximize the potential individual benefit and minimize individual risk.
2. The study design and analysis should be appropriate to the purpose of the study, and the outcome assessment indicators should correspond to the stage at which the disease is being assessed.
3. The following conditions should be taken into account: the combined disease, drug combination, and differences between elderly and younger participants, especially the changes in pharmacokinetics, liver and kidney dysfunction, and multiple drugs leading to drug-drug interactions.[6] These conditions may lead to an increased reaction to drug toxicity, so we need to adjust the dosage according to the elderly and the subjects.
4. Comprehensive geriatric assessment is recommended in the suitable field, such as frailty, cognitive status, nutritional status, balance function, falls, and urinary incontinence, to assist in judging the tolerance to intervention and long-term survival of the subjects.[3]

5.3.4 | Choice of control and placebo control

A positive control should be a standard or an established effective preventive, diagnostic, or therapeutic measure. Placebo controls need to be carefully selected in geriatric studies. Placebo controls must comply with principles that minimize the risk and placebo may be used as a comparator only if[10]:

1. There is no established effective intervention;
2. The placebo is added on to an established effective intervention;
3. An established effective intervention is not known to be safe and effective in a particular context;
4. There are compelling scientific reasons for using placebo, such as the clinical response to the established effective intervention is highly variable, the symptoms are inconsistent and there is a high rate of spontaneous remission, or the condition is known to have a high response to placebos.

5.3.5 | Study duration and follow-up

According to the study objectives, unnecessary extension of the study period and the number of follow-up visits should be avoided. For follow-ups with elderly participants, especially those with

motor impairments, appropriate transportation compensation and, if necessary, escort assistance should be provided. Remote follow-ups (phone, Internet, etc) or home visits may be used if the study permits.[11]

5.3.6 | Observational indicators of intervention studies

Observational indicators of intervention studies include:

1. Validity indicators related to the purpose of the study and safety indicators related to the intervention;
2. The monitoring indicators of adverse reactions caused by multiple diseases and drug interactions caused by multiple drugs may be added based on the characteristics of the enrolled elderly subjects;
3. For large intervention studies, health economics evaluation indicators may be considered.

5.3.7 | Missing data

Dropouts and missing data are inevitable in long-term studies involving the elderly. There needs to be a clear plan to deal with participant dropout and missing data before the study begins.

5.3.8 | Risk management

The study should develop risk control and management strategies based on the age of the subjects, the level of coexisting diseases, and other identifiable risks. For a study above the minimal risk, the risk identification, assessment, and management strategies should be formulated.

5.4 | Risk-benefit assessments

a. For studies with potential individual benefit, the expected benefits of the study need to outweigh the risks of the study.
b. For studies with no potential individual benefit, the research risks should be kept to a minimum, and the risks should be comparable to the social and scientific value of the acquired knowledge.
c. For subjects with impaired informed consent: for studies with potential individual benefit, the study risks should be minimized and not be greater than the expected potential individual benefit; for studies with no individual benefit, the study risk must not exceed the minimum risk; for studies that do not benefit individuals but have appreciable social value, and cannot be conducted on subjects with informed consent ability, the risk of the study can be increased to slightly more than the minimum risk value.[10]

5.5 | Additional special protections for subjects

Vulnerable groups among the elderly include patients suffering from a variety of chronic diseases, mental diseases and cognitive disorders, as well as elderly individuals who have been living in nursing or long-term care institutions, and elderly patients with end-stage diseases.[4] Although only a subset of the elderly subjects belong to the vulnerable group, all elderly subjects should be provided special protections in the course of the clinical study due to the physiological and pathological changes caused by aging.

In the study design, the inherent lifestyle of the elderly population should be considered (including rest, meal and sleep habits) and more care should be provided during the course of the clinical study. For elderly subjects who need to be accompanied, accompanying staff should avoid being separated from the subjects. The study design should consider the physiological characteristics and living habits of their elderly subjects, so as to reduce or eliminate any unfamiliar and distressing emotions caused by participation in the clinical study. According to the purpose and risk of the study, the number of examinations, degree, and invasiveness of operations and sample collection during the study should be reduced as much as possible. If the study allows, remote follow-up or door-to-door follow-up can be used.[10]

5.6 | Compensation

In addition to the regular compensation for things such as transportation, nutrition, and accommodation during the course of the study, compensation for cab expenses of elderly subjects and transportation of accompanying personnel for follow-up visits should also be provided, if necessary. For intervention studies, it is recommended to purchase insurance for the study to cover the cost of treatment and compensation for research-related harm.

6 | REVIEW POINTS OF INFORMED CONSENT

6.1 | Principle

Informed consent should be given to elderly subjects.[12] The informed consent form should have sufficient information, and the informed consent process should meet the requirements of complete notification, full understanding, and independent choice. Elderly subjects with cognitive impairment should receive the same respect as cognitively healthy subjects.[12]

6.2 | Informed consent form

a. The writing of the informed consent form: The informed consent form should be written based on the comprehension ability

of the elderly subjects, using the native language with an explanation in terms that the elderly subjects can understand. As such, the writing should be clear, and a large number of medical terms should be avoided. In order to facilitate comprehension, the written typeface of the informed consent form can be enlarged, and the information can be transferred vividly and completely with the help of illustrations, audiovisual aids, and examples of typical cases.[12] Metaphors can also be used to explain technical terms, such as comparing placement into the test group or the control group as the likelihood of selecting a side when tossing a coin, when explaining "random" grouping. International multicenter clinical research involving elderly subjects should consider the subjects' national conditions and language habits, and avoid direct translation from foreign languages.

The content of the informed consent form should follow the principle of complete elements, and the information presented in the informed consent form must be formulated with reference to relevant national regulations and guidelines.

6.3 | The process of informed consent

1. The communication principle of informed consent of elderly subjects: Based on the physical and psychological particularities of the elderly, in the process of obtaining informed consent, the researcher should follow the contents of the informed consent form and explain the facts to the elderly subjects item by item, with detailed explanations and full notification. If necessary, the number and time of conversations should be increased, and the conversation language and style should be understood and accepted by the elderly subjects. Researchers should actively communicate with their family members and/or those accompanying them to obtain support and understanding.
2. It is recommended to use the guide list for elderly subjects as an auxiliary document of the informed consent form to reduce the complexity of the content of the informed consent form to improve the understanding of the informed consent form by the elderly subjects. The content of the guide list mainly includes matters that require the cooperation of subjects, such as treatment methods, diet control, and visit arrangements. It also includes basic information, such as an introduction to the research project and research contacts.[3]
3. Avoid influencing the decision-making autonomy of elderly subjects: Due to their health-care needs, some elderly patients are prone to becoming dependent on their physicians, resulting in helplessness and forced participation in research, especially if the research protocol contains treatment options. When the physician recruits subjects as a researcher, elderly patients may be worried that they will be unfairly treated by medical personnel if they refuse to participate in the research, and may feel forced to agree to participation in the research study. In order to avoid possible undue influence, it is recommended that researchers other than the subject's physician obtain the informed consent. Before obtaining informed consent, researchers should strive to strengthen psychological counseling for elderly subjects and increase objective cognition of disease treatment and clinical research to make independent decisions to participate in the study.
4. Informed consent for geriatric psychology research: Informed consent may affect the subjects' answers to questionnaire items in non-interventional psychology research for the elderly, so the informed consent can be obtained after the research is completed.[5] Such form of informed consent should be approved by the ethics committee before the study is implemented.
5. Evaluation of the informed consent ability of elderly subjects: For subjects who may have impaired informed consent, the researcher should conduct an informed consent ability assessment before obtaining the subject's informed consent. The evaluation of the informed consent ability of elderly subjects should use a comprehensive evaluation method, including the subject's cognitive function and other factors that may affect their decision-making ability, such as emotional state, physical function, psychological status, economic level, and living conditions.[13,14] Researchers should receive training in the assessment of informed consent ability before evaluating subjects.
6. Pay attention to the consistency of the interests of the guardian and the elderly subjects[12]: In the case where the guardian's informed consent is required, the researcher should assess the consistency of the interests of the guardian and the elderly subjects in order to protect the rights of the elderly subjects from being coerced to participate in the study for various reasons (such as economic incentives). At the same time, the researcher needs to observe whether there is a possibility of abuse.

6.4 | Signing of the informed consent form

For elderly subjects with full capacity, the informed consent form should be signed by themselves. For elderly subjects who are incapacitated, their guardians must decide on whether to agree to participate in the study and sign a guardian informed consent form. For elderly subjects with limited capacity, the consent of the subjects themselves and their guardians must be obtained, and the signatures of both of them must be obtained. The disagreement of the subject should be respected. When the guardian of the elderly subject decides on behalf of the subject, it should be based on the subject's previous wishes and long-term beliefs, and consider the subject's current wishes.[13] If the subject's previous wishes and long-term beliefs are not clear, the guardian should follow the principle of maximizing the interests of the elderly subject and minimizing the risks in making a decision for their elderly dependent.

6.5 | Informed consent of elderly subjects suffering from cognitive impairment-related diseases

Cognitive impairment-related diseases affect the ability of elderly subjects to agree to informed consent. As the disease progresses,

the decision-making power of the subject is gradually replaced by the guardian. During the research process, the researcher should promptly and accurately assess the remaining cognitive and decision-making abilities of the subjects.[15] Researchers should fully respect the wishes expressed by elderly subjects with cognitive impairment when they are able to express their personal wishes. The research data can be released only when permission is provided by the cognitively impaired elderly subjects and their guardians, and this should be informed in the informed consent process.[12]

CONFLICTS OF INTEREST

Nothing to disclose.

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