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EDITORIAL ARTICLE

UNDERREPRESENTATION OF OLDER PERSONS IN CLINICAL TRIALS

INTRODUCTION

The older age group physiologically does not have the same characteristics as adults, and generally medications used in the elderly have not been properly evaluated. Clinical trials conducted in the adult population often involve patients between the ages of 18 and 64, so there is insufficient evidence and information about the reactions of geriatric patients to these medications (1).

This is because older people are relatively underrepresented or even absent in most drug studies. The main reason that leads to uncertainty about the risks and benefits of new treatments for the elderly is "age discrimination" in clinical trials. Frail elderly, those with multiple comorbidities and older women are not included in the studies aimed at questioning the validity and safety of most treatments (2).

With aging, physiological changes occur that can affect the pharmacokinetics and pharmacodynamics of the drugs used (For example, the duration of action of the drug may vary). Tolerability and possible negative effects can also be a serious problem. Specific treatment guidelines for the elderly are rare and physicians sometimes have to predict the correct drug dosages for their elder patients. Randomized controlled trials (RCT's) are required to provide evidence of treatment safety and drug benefits in the elderly (3).

A consortium (PREDICT) was formed to study the participation of elderly people in clinical trials and this consortium has checked whether the underrepresentation is real or not. Studies on 6 subjects have been reviewed in the last 10 years: 1-Heart failure, 2-Hypertension, 3- Coronary artery disease, 4-Depression, 5-Alzheimer's disease, 6-Colorectal cancer. The results confirmed that there is a wide deficiency / difference between the patient population in the clinics in real life and the patients included in the studies under all conditions (4).

The clinical research proposals submitted to the Research Ethics Committee covering the educational / teaching hospitals affiliated to Trinity College Dublin were examined. It was noted that patients were

excluded from the studies “based on an arbitrary upper age limit” (5).

In 226 studies that were found suitable for examination 31(13.7%) applied exclusion by setting an age limit only. Those who do not include age-based exclusion are only 22 (9.8%) (by geriatricians) and out of 22 applications, 12 studies are from the field of neurology / psychiatry.

The average upper age cut-off value was recorded as 69.2. Most of the other studies also included exclusion criteria “based on cognitive function”, which further limits the participation of older people in particular. However, according to these results, the participation of older people in research at Trinity College Dublin was found to be higher than in international studies (5).

Recommendations of regulatory authorities in developed countries to researchers and industry are; 1-Avoiding arbitrary upper age limits, 2-Elderly people should not be excluded from clinical trials without a valid reason (1).

EXAMPLES BASED ON ORGAN SYSTEMS AND DISEASES

Cardiovascular Disorders: Cardiovascular diseases are a significant contributor to both mortality and morbidity on a global scale (6). There are notable distinctions between men and women in terms of the pathogenesis, clinical presentations, and consequences of cardiovascular illnesses. To gain evidence-based information on the understanding and management of cardiovascular diseases in elderly individuals and women, it is crucial to incorporate these specific subgroups into RCTs (7). The underrepresentation of elderly adults in RCTs can be attributed to both the diverse distribution of aging and the obstacles faced in patient registration, assessment, and follow-up processes. Indeed, the senior demographic constitutes the predominant consumer base for pharmaceutical products. Consequently, this group is also subject to the

highest incidence of adverse medication responses. The dearth of RCTs including the older population can result in a constraint on the understanding of optimal pharmaceutical usage in terms of safety. Notwithstanding the dissemination of worldwide recommendations aimed at augmenting the involvement of senior individuals and women, the level of their inclusion and consideration in research projects remains inadequate. Due to its status as the primary research funding entity in the United States, the National Institutes of Health (NIH) wields significant influence over the conduct of scientific endeavors inside the nation. The matter of incorporating individuals who are 65 years old and above into research was a subject of deliberation during the “Inclusion Across the Lifespan” Workshop conference held by the National Institutes of Health (NIH) in 2017 (8).

A year subsequent to the implementation of the Inclusion Across the Lifespan policy, persistent difficulties were noted in effectively representing the elderly population in cardiovascular research. During this temporal interval, a significant number of research investigations, specifically one-third, continued to use age restrictions, while a larger proportion, specifically two-thirds, employed exclusionary criteria that disproportionately impacted the senior population (9). In order to enhance the inclusivity of the elderly population and women, particularly in RCTs, it is imperative to critically evaluate and modify ethical regulations and publication policies pertaining to cardiovascular diseases, as well as their associated mortality and morbidity. These revisions are necessary to effectively promote and facilitate the greater involvement of older individuals in such research endeavors.

Alzheimer’s Disease: The most common cause of dementia is Alzheimer Disease. Not only the memory loss and but other cognitive abilities also interfere with daily life of the older person. The majority of Alzheimer’s patients (72%) are over the age of 80. However, in researches the



representation of patients over the age of 80 is 8%. It is stated that, patients enrolled in clinical trials related to Alzheimer's disease are far from representing the true distribution of patients in the general population (10).

Low Back Pain: Low back pain is one of the health problems that negatively affect the quality of life in old age. Review of the WHO research registration database about exclusion of older adults from ongoing clinical trials related to low back pain was performed. Prospective protocols planning interventions for low back pain were examined. A total of 167 protocols were planned to include participants over the age of 65 as part of the research. Only five entries (2.99%) were designed specifically to target participants over the age of 65. In 93.6% of the protocols, there was no valid excuse for setting an arbitrary upper age limit (11).

THE REASONS OF UNDERREPRESENTATION

A Medline search for all articles that contain the word "elderly" in the title or abstract was performed. Of the 150 articles 89 were excluded because they were not actual RCTs. In the RCTs feature, 50 articles were related to the elderly. Main subjects were hypertension, neuropsychiatry, and cardiology. Reasons why the elderly are not included were summarised as: 1-Simultaneous diseases, multiple pathologies and comorbidities, 2-The fact that symptoms related to other diseases (intercurrent) that occur during the progression of a disease can cause bias, 3-Difficulties in interpreting negative events, 4-Concerns about multidrug use (especially drug interactions and poor compliance) (12).

A literature review was conducted to identify barriers to enrolling elderly people in clinical cancer trials and obstacles were categorized as:

I- Obstacles related to the physician: Tolerance of treatment, metabolism of the drug, lack of evidence for effectiveness, perceptions about age bias.

II- Obstacles related to the patient: Lack of autonomy, quality of life, concerns about the toxic effect, accessibility to clinical trials and logistical and financial difficulties.

III- Obstacles related to research (including eligibility criteria): Performance status, organ dysfunction, presence of comorbidities (13).

Factors that make it difficult for the elderly to participate in research can be summarized as:

A-Complex protocols involving long and laborious result measurements, B-Aggressive treatment protocols with possible toxicity, C-The inclusion criteria of the study can be very limited, D-Lack of expectations of the patient and his/her family for the benefit of the patient from the research (non-therapeutic studies), E-Lack of financial, logistical and social support, F-The patient's poor health condition, G-The presence of anxiety, H-Very advanced age (in some studies).

Reasons are detailed by Shenoy & Harugeri as:
 1- Current difficulties in obtaining informed consent.
 2- Difficulties in the outcome evaluation of multiple comorbid conditions.
 3- Polypharmacy leading to drug-drug interactions.
 4- Difficulties in adapting to procedures of clinical trials.
 5- The need for age-appropriate formulations and packaging.
 6- Fear of failure due to the confusing behavior of medication in the elderly.
 7- Seniors may need supportive care.
 8- Corporate and logistical problems.
 9- Researcher's preferences and perceived difficulties in screening.
 10- Having protocol restrictions with exclusion criteria based on age.
 11- The fact that sponsors may incur higher costs for medical management and compensation (1).

PARTICIPATION OF THE ELDERLY

Methods of involving the elderly in research: Referral from other physicians, one-on-one invitation of the research team to the patient, making presentations and invitations related to working in patient/elderly associations, social

service organizations, nursing homes and meetings are recommended. Establishing communication with nursing homes, universities and health centers distributing advertisements / making announcements to the places where the target individuals can be found and to the centers where meetings or exhibitions are held can be useful.

Factors that facilitate the participation of the elderly in research: Having the approval of family members, the positive attitude of the medical team about the research are important factors. The patient's educational level being high also effects the situation. And if the person who communicates with the patient about research (especially in clinical drug trials) is a physician the participation of the elderly is much more easy.

INFORMED CONSENT

If research involves interaction with participants, or gathering identifiable information, informed consent must be obtained. Validity of informed consent depends on the fulfillment of its fundamental elements. These elements are **competence, disclosure, comprehension of information, voluntariness, and consent**. The process of obtaining consent from elderly individuals is more intricate and involves specific considerations regarding these elements (14).

Incompetency issues: Regarding the elderly, situations such as cognitive impairment, psychiatric problems, hearing and / or vision problems that affect perception, may decrease the ability to make decisions or incompetency occurs. Refraining from all forms of discrimination, especially age discrimination, every individual should be treated as competent unless the opposite is determined after careful assessment. Competence signifies the cognitive abilities of the individual and it may vary in time according to the health status of the individual. Therefore, the competence assessment conducted is specific to the moment of evaluation. According to

the course of health of the individual reassessment may be required later. The evaluation of an individual's decision-making capacity is typically carried out by medical professionals; in difficult, uncertain cases, appeal to a specialist from psychiatry or other fields of medicine is common practice (14).

Scales such as Mini-Mental State Examination (MMSE), Clinical Dementia Rating and MacArthur Competence Assessment Tool for Treatment (MacCAT-T) are also used, which are complementary to the evaluations made by physicians and support the objectivity of the evaluation, without being a stand-alone determinant (15-18).

Concerning non-competent individuals, consent is obtained from a "legal representative" generally a family member based upon the assumption to be the one who knows the subject best and is most likely to make a decision that would be in keeping with the subject's values. Assent, the expression of willingness to agree to go along with research protocol or refusal, should be obtained from the elderly who cannot provide informed consent and should be taken into consideration as in the case of adolescents. Even with impaired people with dementia, assent may support the ability to reveal the subjects' values and preferences (19, 20).

Disclosure: Regarding disclosure to elder participants, the complexity, content, and presentation format of the information that will be conveyed, should be evaluated. Mainly content is comprised of: a statement that the proposal is on participating research, voluntary nature of participation, the objectives, the approximate number of participants, the amount of time that will be spent in research, description of the procedures participants will be engaged, foreseeable risks and discomforts, potential benefits, statement on the protection of confidentiality and privacy, if relevant compensations and insurances, statement affirming that declining to participate will not result in any losses or penalties and they may leave the study any time without facing any adverse consequences.



Communication information of a contact person from the study should be shared. The format of the provided information should be as simple and clear as possible. Large fonts should be used, and decision aids such as audio or visual elements may be utilized. Elder participants may require more time to comprehend information, allocation of additional time and well-trained, empathic staff are needed. To avoid misunderstanding, subjects should be provided with the opportunity to ask questions (19).

Frail older people who are invited to participate in research accommodating in nursing homes or being hospitalized, or with dementia, may not be able to say “no” to the researchers’ recommendations. At this point, extra caution, and protection on the voluntariness of the consent obtained is needed. Research staff should have awareness of the potential risk of therapeutic misconception and comply with preventive measures.

The distribution of burdens and benefits of research should be considered carefully by the researchers and ethics committees that will review the protocols. Excluding older people from research without appropriate reasons violates the ethical principle of “justice”. Considering distributive justice, more efforts are needed by researchers, institutions, and research sponsors to involve older people in research (19).

Additionally, in accordance with non-maleficence and beneficence principles an elderly person can be taken into research that will provide real and direct benefits to her / him. It may not be appropriate to be taken into research that does not have a therapeutic effect (20).

THE RESEARCH PROCESS

General precautions for drug research on the elderly: Study protocols should be designed taking into account comorbidities and polypharmacy. There should be no “upper age limit” for participation in the study unless there is appropriate justification

(within the framework of the ethical rules). More education and observation / communication are required to increase compliance in elderly individuals (e.g. telephone calls, home visits). The ideas of patient organizations and elderly individuals should also be taken.

Study design for the elderly: There is no “standardized methodology” for including older patients with comorbidities and disabilities in clinical trials. A carefully prepared and adequately resourced protocol design is important, but many clinical trial designs fall short.

Study participation: The development of clinical trials in the elderly poses a number of challenges related to study participation, data retention and data analysis. Often, the elderly patient is not alone at the decision stage, and family members or caregivers also need to be convinced by the researcher with a “friendly approach” (21).

Adaptation to research: Protocols should be made appropriate for the reception of the elderly as well. It should not include complex and difficult applications. Research should not impose an economic burden on the patient and if necessary, transportation of patients should be provided. Participating in the research should not make it difficult for the patient physically, spiritually and socially. In pharmaceutical studies, the drugs should be in an easily accessible form, blister packaged and labeled. It is also recommended to provide telephone connection with patients and rewards can be given during control visits (22).

Post-research period: The approach to elderly patients in the post-research period is very important. This approach to be applied after the research should be designed “at the very beginning” of the study and approved by the “ethics committee”. At the end of the study, elderly patients should be informed about the research results. They should be monitored for unwanted side effects for a while longer and should be referred for medically necessary treatments.

PROTECTION OF THE ELDERLY

There are some specific recommendations for protecting the elderly in clinical trials. These are: 1-Ensure the safety of the drug in the systems of organs of concern (such as kidneys, liver and cardiovascular) in the elderly. 2-Exclude the elderly population with clinical study-specific anxiety. 3-Only patients with round-the-clock caregivers at home should be included in the study. 4-Make sure that emergency medical assistance is available near the patient's residence. 5-Elder friendly clinical trial support materials and patient diaries should be kept ready. 6-Ensure that the caregiver is also present and testifies during the approval process. 7-Intensive counseling should be given by the researcher to both the patient and the caregiver. 8-Patients should be called regularly and frequent phone follow-up should be performed (1).

According to Skolnick & Alexander, registration systems should be established at the National Institutes of Health, a standard model should be developed for enrollment plans involving older adults in clinical trials. Research on new drug or device applications should include plans to ensure that older adults are adequately registered. There is no advisory board or a special department to supervise or advocate for the representation of older adults in research. A department can be created to review dosing, registration and data collection protocols in elderly populations. This department can also monitor progress in the inclusion of elderly people in important trials. There are also statements aimed at drug manufacturers for the protection of individuals at the far end of the age spectrum; 1-Providing an appropriate patent extension for conducting research for the elderly and conducting geriatric labeling studies, 2-Mandatory maintenance of post-marketing safety records in the treated elderly, 3-It should be noted that medicines can be approved after the accumulation of safety data (23).

AGAINST ELDER DISCRIMINATION

Participants of the roundtable discussion on reviewing the participation of the elderly in clinical trials were; 1-American Geriatrics Society, 2-European Union Geriatric Medicine Society-EUGMS, 3-US Food and Drug Administration-FDA, 4-European Medicines Agency-EMA. Cherubini A et al stated that, in the battle against age discrimination in clinical trials; there are delays, prejudices and reservations are still ongoing. Regulatory agencies should work together to propose 1-New definitions, 2-Study designs, 3-Technologies aiming at improving the evaluation of drugs in elderly people with multiple comorbidities and polypharmacy (24).

It is well documented that, elderly individuals have been disproportionately affected by the COVID-19 pandemic. There were disruptions in the provision of clinical services and there have been profound effects on the research. Research on COVID-19 and similar issues should be carried out with an inclusive approach especially the fragile elderly, elderly people with cognitive impairment or multimorbidity, and those who live in nursing homes. From the point of view of the elderly, research not related to COVID-19 is of "critical" importance and should not be hastily neglected (25).

ARTIFICIAL INTELLIGENCE

Artificial intelligence is a technology that offers new tools aimed at making clinical trials safer, faster and cheaper. In order to evaluate how drugs react at the molecular level, it is aimed to create a system that produces more drug candidates in less time and with fewer experiments by combining artificial intelligence, quantum physics, cloud computing algorithms.

As it is known; insufficient research design is a difficulty that can be encountered in clinical trials. More qualified literature review can be conducted, appropriate endpoints can be addressed, the appropriate sample size / statistical analysis method



can be determined, the possibilities of changes that may occur during the study can be reduced and inconsistencies in the protocol can be prevented by artificial intelligence technologies (26).

In research on the elderly, the use of artificial intelligence may be practical both at the design and protocol stage and also at the stage of determining appropriate endpoints. It is reported that artificial intelligence systems are developed using data that reflect the implicit and explicit biases of society, and therefore there are significant concerns about how predictive models in artificial intelligence systems increase inequality, privilege and power in society.

However, the opinion that age discrimination does not exist to a large extent prevails in the artificial intelligence bias literature, but given the aging population globally and the increase in artificial intelligence applications, it is reported that there is a need to critically examine and monitor the existence of age-related bias in artificial intelligence systems, and its ethical and legal dimensions should definitely be taken into account (27).

CONCLUSION

The most important consumers of health resources and medicines are the elderly. The use of drugs that have not been included in the elderly studies may be risky and dangerous. In drug research where the elderly are not included in the scope of the study, the reasons for "not including the elderly" should be clearly explained to readers when "the results are written as an article" (22).

Research patients who have tried medical treatments and interventions do not represent patients who are seen in daily routine practical applications in clinics. This creates problems for physicians. It is necessary to consider whether the positive or negative results obtained from the studies apply to elderly patients especially the frail ones.

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