Editorial Review:

Trials in Elderly Patients – What Are We Missing On?

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Abstract:
A clinical trial is a research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions. Clinical trials generate safety and efficacy as well as pharmacokinetic data for health interventions. The geriatric age group may be under-represented in clinical trials for a number of reasons. There are many factors that affect participation of older adults in clinical trials. The most important factors are - health literacy, communication, and social service needs. A general criticism of pharmacokinetic studies is that the subjects employed do not represent the population of patients to be treated. Advances in modern medicine have led to increase in average age of the population resulting in a greater proportion of the population being comprised of geriatric age. The need for information on the clinical pharmacology of drugs in the elderly can hence no longer be ignored. Studies should specially be designed to answer the research question pertinent to ailments and include only elderly population with the relevant disease in order to avoid heterogeneity. This would render a better understanding of drug kinetics and dynamics in the elderly and will lead to improved care and quality of life of the elderly patient.

Keywords: Clinical trial, Research study, Heath literacy

Background: A clinical trial is a research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions. Clinical trials generate safety and efficacy as well as pharmacokinetic data for health interventions (e.g., drugs, diagnostics, devices, treatment protocols). It is now widely acknowledged that aging is a major cause of variation in response to drugs in man. This is due to a variety of important changes in body physiology and homeostatic responses, which occur in the elderly and render them more susceptible to adverse effects of drugs. Physiological changes with aging occur in all organ systems. Several of these factors are involved in variation in drug response in elderly. Some examples include changes in gastrointestinal tract leading to decrease in absorption, and decrease in renal and hepatic functions leading to decreased drug elimination. Changes also occur in body composition, with an increase in body fat and relative decrease in total body water. Furthermore, pharmacodynamic changes like decrease in receptor population and

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sensitivity also occur with increasing age. [1, 2,3, 4] In addition to these general factors, drug response in elderly is also affected by co-morbidities and polypharmacy [1, 2].

This recognition of variations in drug kinetics and response with advancing age has led to marked changes in the attitudes to clinical research in the elderly, and in the requirements of some licensing authorities for special studies of new drugs in old age [2]. Caird has very appropriately stated the present situation. He says, 'For drugs likely to be a risk for the elderly, there are stringent requirements for testing in old age and close monitoring. Thus, a facet of clinical trial that has for years been immoral and unethical has suddenly become compulsory' [5]. This is particularly true in case of drugs with a narrow therapeutic range (narrow safety margin), those whose clearance is likely to be reduced in elderly, where interactions are likely with other drugs commonly used in elderly, and where pharmacokinetic or pharmacodynamic differences can occur with increasing age, and newer drugs.

The geriatric age group may be under-represented in clinical trials for a number of reasons. To start, patients, family members and/or physicians often have negative notions concerning the benefits to older patients enrolling in clinical drug trials (CDTs). The under-representation of this vulnerable population is often an outcome of exclusion criteria that are most likely to make exclusions of subjects who have multiple diseases and take multiple medications. Two other common barriers to participation of the elderly are cost and transportation. Many older adults may have a difficult time plying to and from the study site and are therefore may be unable to participate [6, 7, 8].

The literature review in the PREDICT study on participation of elderly in clinical trials indicated that due to non inclusion of older people, the possibility of testing the potentially beneficial treatments for the elderly is significantly reduced. Consequently, older people may be receiving treatment without being tested in appropriate clinical trials or they may not be treated due to lack of trials in elderly. Future clinical trials can be improved if views of patients and clinicians are taken into consideration [9].

By not including older adults in drug trials, the full potential impact of new drugs on this population cannot be fully understood and may have serious and unexpected repercussions for the health of this population when they are administered the medication directly following marketing approval. This is troubling in terms of the impact on the health of older adults.

There are many factors that affect participation of older adults in clinical trials. The most important factors are - health literacy, communication, and social service needs.

• Health literacy is the ability to read and comprehend basic health-related materials, such as prescription bottles and hospital forms [10]. In developed countries like The Americas, where individuals get healthcare after enrolling in a national managed care organization, low health literacy is very common [11]. The problem is more severe in developing countries. It is observed that overall functional health literacy in older groups is very bad even after due consideration of factors such as vision, chronic ailments, and

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general condition of health. [12] Much higher proportion of older adults has inadequate health literacy than the younger ones. Low health literacy is also found to be associated with lower socioeconomic strata. [11]

• Impaired hearing or vision, are barriers for many older adults as these create difficulties in communication like telephone interviews or written surveys respectively. [12, 13]

• Enrollment of elderly can also be adversely affected by issues like transportation or mobility of the individual. [14, 15, 16, 17]

Criticism: A general criticism of pharmacokinetic studies is that the subjects employed do not represent the population of patients to be treated. Very often they are healthy young ambulant volunteers rather than the older, sick, infirm patients who may need the drug for treatment. This same problem must, therefore, be addressed in considering studies in the elderly. The following groups of patients must be included in such studies [2, 7,8]:

- 'Normal' elderly subjects, aged 65 or above, who are drug-free and show no evidence of systemic disease on clinical examination, electrocardiography and routine tests of haematological, liver and renal function.
- Because there is an inevitable association of (and often multiple) chronic diseases with increasing age, there is a strong case against excluding patients with such conditions from the study, provided that they are clearly recognized as a well-defined cohort of patients, separate from the 'normal' group already defined. However, critically ill patients should be excluded from such studies considering the risk / benefit ratio in the light of hitherto available information.
- Many elderly patients take drugs chronically may be lifelong, either regularly or intermittently particularly non-steroidal anti-inflammatory drugs / purgatives / other gastrointestinal agents, and it is desirable that kinetic or AND dynamic interactions which might occur in the elderly should be recognized as early as possible. Patients who are stabilized on such long-term treatment with other drugs may, therefore, be considered for inclusion in studies, provided that they are clearly defined as a subgroup distinct from those groups of subjects discussed in groups 1 and 2 above.
- Finally, the drug should be examined in detail in patients suffering from the condition for which it is indicated. This group may be relatively heterogeneous when compared with the other groups above, but nevertheless the effects of the disease process, both on presentation and during its response to treatment, on the drug's kinetics and actions must be determined.

The following considerations though regarded as self-evident, should nevertheless be stated:[2, 4, 8]

- All clinical trials, including those in the elderly, should be subjected to scrutiny and approval by an independent, impartial, properly constituted ethics committee (IEC /IRB) before commencement. Where elderly subjects may be used, the committee should

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include a geriatrician /gerontologist or clinician with a special interest in, and experience of geriatric medicine.

- A badly designed experiment is unethical in itself. Because of the heterogeneity of the elderly patient population, it is essential that studies designed to investigate them should have appropriate advice in their preparation from a statistician experienced in clinical trial design and data analysis. Too many studies in the literature involve small and inadequate numbers of patients, so that their conclusions are invalid.
- It is important for the public perception of clinical research, as well as for the assured well-being of the subjects, that investigations in the elderly should be supervised by a geriatrician / gerontologist or clinician with a special interest in, and experience of geriatric medicine.
- Another factor which is important for public acceptance of the need for research in elderly subjects is the assurance that 'informed consent' will be freely obtained before inclusion in a study. The prior approval of an ethics committee and involvement of immediate / legally acceptable relative/s and / or a suitable LAR / witness in the informed consent procedure will also help to safeguard the interests of the volunteers.
- It is desirable that the results of all prospective clinical trials in the elderly should be published and become part of the public domain. This principle applies, of course, ideally to all well conducted human investigations, but particularly to studies in the elderly because of the relative paucity of good information on the factors influencing drug kinetics / response and adversity in them.

Abellan et al reported that investigators from 33 leading Research Centres in Europe proposed a 25-item data set (Geriatric minimum data set-GMDS) as the minimum set of information which should be obtained for older subjects in any clinical trial.

Seven different domains covered by these 25 items are as follows:

- General information including data on clinical diagnosis and medication use (5 items),
- Functional performance (5 items),
- Cognitive and emotional status (4 items),
- Cardiovascular risk profile (3 items),
- Nutritional status (3 items),
- Biochemical parameters (1 set and 1 item), and
- Social status (3 items).

The authors claim GMDS-25 will be very useful for comparison of data, meta-analyses, and help tailor GMDS-25 clinical trials to the needs and outcomes relevant for the elderly [18].

Advances in modern medicine have led to increase in average age of the population resulting in a greater proportion of the population being comprised of geriatric age. The need for information on the clinical pharmacology of drugs in the elderly can hence no longer be ignored. Studies should specially be

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designed to answer the research question pertinent to ailments and include only elderly population with the relevant disease in order to avoid heterogeneity. This would render a better understanding of drug kinetics and dynamics in the elderly and will lead to improved care and quality of life of the elderly patient.

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