

Elderly Representation in Clinical Trials: Not a Gray Area

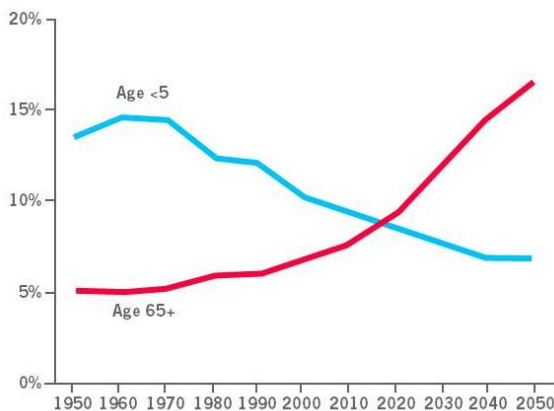
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Typically, clinical trials conducted in adult populations include patients between the ages of 18 and 65. This is a broad range, but arguably no longer broad enough. In most therapeutic categories, this upper age cutoff is too low, given that:

- Trial participants should be representative of the patient population receiving the therapy in daily medical practice.
- People over age 65 make up the majority of patients for many medications treating chronic conditions.
- The over-65 segment is the fastest growing segment of the world's population. By 2050, the number of people ages 65+ will be 16 percent of the global total, up from 5 percent in 1950¹ (see Figure 1).

Regulators have, in fact, offered guidance on the subject, stating that study participants should be representative of the patient population and that protocols should not set an arbitrary upper age limit. Only when the current "age barrier" is overcome in clinical trials will medical decisions for those over age 65 be evidence based. Here, we discuss the issue and offer suggestions for sponsor companies wishing to address the changing world demographics in their clinical research.

Figure 1: Young Children and Older People as a Percent of Global Population: 1950-2050



Source: United Nations. *World Population Prospects: The 2010 Revision*. Available at: <http://esa.un.org/unpd/wpp>.

A New Definition of Elderly: 75 Is the New 65

According to the World Health Organization (WHO), most developed nations have adopted the definition of old age as beginning at age 65. "While this definition is somewhat arbitrary, it is many times associated with the age at which one can begin to receive pension benefits."^{*}

That, however, doesn't necessarily correlate with a person's ability to participate in a clinical trial, or his or her overall health. Chronological age, per se, is not a valid exclusion criterion for participation in clinical trials. Indeed, an article published by the U.S. National Institutes of Health has noted that since 1992, "... the physical activity of healthy elderly (over 65) has been more youthful by 7.5 years in men and 10 years in women" and "... the current definition of elderly (65 years and over) should be changed to those over 75 years."[†]

Many demographers, sociologists, economists, and policymakers recognize a need to adjust the definition of elderly to reflect the aging of society. A strong argument could also be made for adjusting the exclusion criteria for clinical trials to 75 as well.

^{*}World Health Organization. "Definition of an older or elderly person." www.who.int/healthinfo/survey/ageingdefolder/en/.

[†]Zasshi, Nikon Ronen Igakkai. *PubMed.gov*. 2006 Jan;43(1):27-34

THE NEED FOR REPRESENTATION

A full 20 years ago, the International Conference on Harmonisation (ICH) laid out a compelling case for including geriatric patients in all clinical trials for therapies targeted to adults. The bottom line is that "not all potential differences in pharmacokinetics, pharmacodynamics, disease-drug interactions, drug-drug interactions, and clinical response that can occur in the geriatric population can be predicted from non-geriatric populations."² In

other words, conclusions reached in studies of adults cannot be extrapolated to the elderly.

Yet this is exactly what is happening in daily medical practice: Medical decisions for the elderly are routinely based on medical data derived from studies of younger adults. In these situations, practitioners are left to treat the elderly without adequate knowledge of older adults' response to medication, dosing ranges in acute and long-term use, side effect profiles, potential for accumulation in the body, and drug-drug interactions.

Consider, for example, the difficulties in treating patients over age 80 for thrombolysis in stroke within the EU, for which only one agent, recombinant tissue plasminogen activator, is approved for use. Because only 42 of the 4,000 patients on whom the drug was tested were over 80 years old, the European Medicines Agency (EMA) approved the drug only for patients 80 and under. So, older patients can only receive the medication off label, and the chances of that happening depend on the hospital and country of treatment.

The medical community recognizes that trial practices are creating an issue in treating patients. A survey of medical professionals in nine EU countries conducted by the PREDICT³ group found that:

- Over 70 percent agree that not having enough older people in clinical trials resulted in difficulties for older patients.
- Eighty-seven percent believe that excluding people on age grounds alone was unjustified.

There is clearly a need to be able to treat elderly patients from a basis of evidence; people are living longer and have an expectation that treatments will produce cures and improve their quality of life. To deny them this opportunity runs counter to the precepts of medical practice and could even be considered unethical.

A DISPARITY BETWEEN RESEARCH AND MARKET NEED

Broadly speaking, patients 65 and over are underrepresented in all phases of clinical trials, even though in many therapeutic categories, they are the primary drug users. Older adults suffer the greatest health burden in the Western world, enduring disproportional high rates of cancer, cardiovascular disease, dementia, arthritis, and Parkinson's disease.⁴

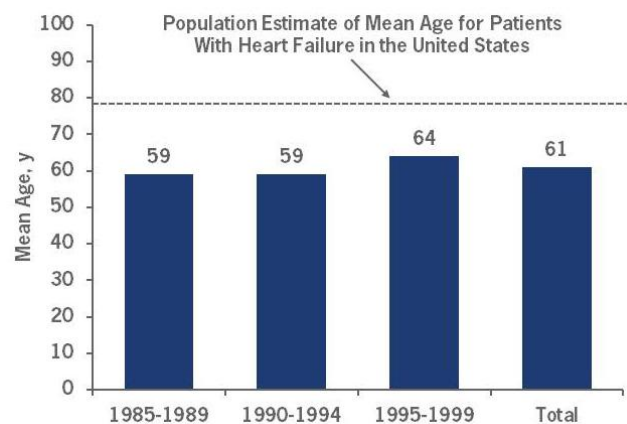
Several literature reviews have examined the disparity between older patients' trial participation and disease burden and drug usage as reported in research papers, revealing that:

- Thirty-five percent of research efforts published in one year (1996-97) excluded the elderly for no justifiable scientific reason, while only four percent were specific to patients 75 or older.⁵

- The elderly account for 60 percent of all new cancer cases, but only 36 percent of patients over 65 participate in cancer trials.⁶
- In heart failure, only two out of 59 trials conducted between 1985 and 1999 reflected the general presentation of community patients with respect to both age and sex⁷ (see Figure 2).
- In trials for Alzheimer's disease, the mean age of subjects was less than 75, but the incidence of the disease rises substantially over that age.⁸
- In antidepressant treatment trials, only 9–11 percent included older adults, despite the fact that prevalence of depression is highest in the elderly.⁸

These findings highlight the fact that older adults have been systematically excluded from participating in clinical trials — even for medications developed to treat conditions that primarily afflict them. While some of these studies were completed within a few years of the ICH guidance being published, others were done as many as 16 years later.

Figure 2: Mean Age of Patients in Heart Failure Trials Compared to Mean Age of Disease



Source: Asefeh Heiat. *Arch Intern Med* 2002.

EXISTING GUIDANCE

In 1994, the ICH developed guidelines on “Studies in Support of Special Populations: Geriatrics,”⁹ setting forth several important principles:

- Drugs should be studied in all age groups, including the elderly, for which they will have significant utility. Patients entering clinical trials should be reasonably representative of the population that will be later treated by the drug.
- Protocols should not ordinarily include arbitrary upper age cutoffs. It is also important not to exclude unnecessarily patients with concomitant illnesses; it is only by observing such patients that drug-disease interactions can be

detected. The older the population likely to use the drug, the more important it is to include the very old.

- Geriatric patients should be included in the Phase 3 database (and in Phase 2, at the sponsor's option) in meaningful numbers. The geriatric subpopulation should be represented sufficiently to permit the comparison of drug response in them to that of younger patients.

The EMA subsequently published a supporting document in 2011, stating, "The EMA will ensure that the assessment process gives adequate consideration to the information available to ensure safety and effective use of products in the elderly."¹⁰ As a follow-on exercise, the Geriatric Medicine Working Party of the European Forum for Good Clinical Practice published recommendations of the ethical aspects of clinical trials in older people, in February 2013.¹¹

In turn, the US Food and Drug Administration (FDA) issued a question and answer document in 2012 to expand upon the ICH guidance. The FDA thus asserted, "An appropriate representation of the geriatric population should be enrolled in the clinical development program to adequately characterize efficacy and safety in the geriatric population and allow for comparisons with the non-geriatric population."¹²

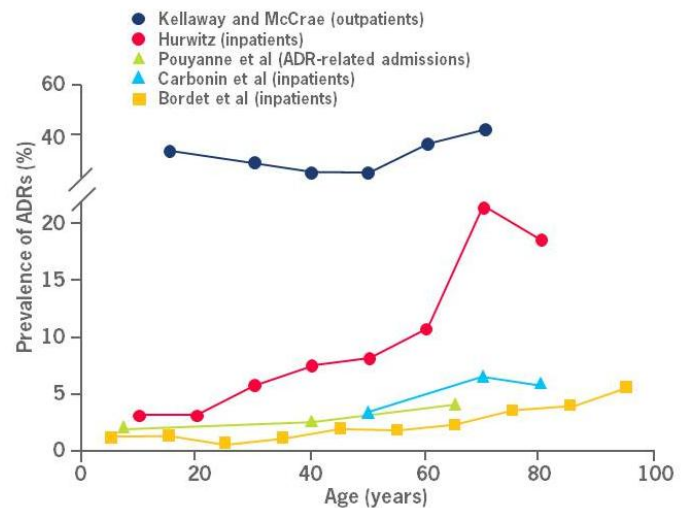
So, given the clarity of guidance from regulators on the issue, why has the industry been slow to change the exclusion criteria of clinical studies so as to capture data on patients beyond age 65?

EXCLUSION DRIVERS

The historical exclusion of the elderly from clinical trials has not been without basis. There are, admittedly, a number of challenges to including older adults in trials, ranging from:

- *Medical factors*
 - Older patients have a higher risk of experiencing adverse events,¹³ as seen in Figure 3, due to pharmacokinetic and pharmacodynamics changes associated with aging.
 - Multiple comorbid conditions can complicate trials, and more than half of older adults have three or more chronic conditions.¹⁴
 - Reduced life expectancy could be a factor in trials spanning several years.

Figure 3: Relationship Between Age and Prevalence of Adverse Drug Reactions



Source: McLean, LeCouteur. "Aging biology and geriatric clinical pharmacology." *Pharmacol Rev* 2004 Jun;56(2):163-84.

- *Scientific factors*
 - These could include the need to manage withdrawal from a trial drug due to deterioration of cognitive functions.
- *Socioeconomic factors*
 - Elderly patients may lack the needed social/home care support to remain compliant with the protocol.
 - They may also have difficulties with transportation and access to clinics and hospitals.
- *Ethical challenges*
 - Investigators must take extra care in ensuring that informed consent is obtained from frail and vulnerable patients; in some cases, it is appropriate to involve family members and caregivers in the decision to participate in a trial.

Thus, including geriatric patients complicates study design and recruitment in ways that many sponsors have chosen to avoid. These challenges are far from insurmountable, however, and the right partner can help companies broaden their trials to include the elderly successfully.

RECOMMENDATIONS

Older adults are not the only sub-group within the general population to have been underrepresented in clinical trials. Prior to the enactment of the EU Paediatric Regulation of 2007, children were considered an “orphan population” in the EU. Similarly, the U.S. has “evolved from a view that we must protect children from research to a view that we must protect children through research,”¹⁵ said Robert Nelson, MD, PhD, pediatric ethicist for the FDA.

Indeed, both children and the elderly share many similarities with respect to research in that they react differently to medication from the 18–64 age group, present challenges in gaining informed consent, are subject to specific diseases, and need age-relevant formulations. Researchers may do well, then, to pursue research in the elderly, much as they have done with children.

Given the world’s changing demographics, it is time for sponsors to move the standard upper age limit for clinical trials from age 65 to 75. Beyond this, for sponsors to comply with regulators’ guidance and to adjust to new market realities, they should begin, in all phases of development, to:

- Ensure that the ages of trial participants reflect the age strata in the consuming patient population. In many therapeutic areas, this suggests that the representation of those over 65 in trials should be significant.
- Design their studies to accommodate elderly subgroups, breaking out those with comorbidities and concomitant medications and adding appropriate laboratory evaluations as needed.
- Be prepared to justify age-related exclusion criteria.
- Tailor their outcome measures to the population under study; outcome measures for the elderly should include quality of life and may need to include effects on cognition, balance and falls, urinary incontinence, and weight loss.¹⁶
- Assume that all adults are capable of providing informed consent, unless proven otherwise. Informed consent procedures should be adapted to the needs of the elderly, taking into account their level of literacy, sensory or cognitive deficits, and the possible need to involve family or caregivers. Should there be any doubt that the older patient understands the trial process, the sponsor should seek the assent of a proxy or legal representative.

A Shining Example

Despite the overwhelming number of cases to the contrary, there are examples of trials designed to test a drug in an elderly population. One is in hypertension, where age is the most power risk factor.** The Hypertension in the Very Elderly Trial (HYVET) produced encouraging data supporting aggressive management of people over 80 years old, most notably:

- A significant (64 percent) reduction in the rate of heart failure.
- A significant (30 percent) reduction in stroke.

Interestingly, the median duration of the study follow-up was 1.8 years.

** Elliott WJ. "Management of hypertension in the very elderly patient." *Hypertension*. 2004 Dec;44(6):800-4.

In turn, it may be necessary for sponsors’ Clinical Research Organization (CRO) partners to:

- Develop specific cultural competence training for principal investigators so that they are better prepared to conduct trials with patients who may have communication, sensory, mobility, and cognitive problems.
- Provide sites with specially designed communication aids for use in explaining the protocol to older patients. These may include easy-to-understand information sheets and participation guides; easy-to-see pictures, videos, and animations; and hearing aids, for example.
- Use a special diagnostic tool to ascertain the degree to which a patient understands the trial purpose, protocol, and expectation prior to seeking informed consent.
- Build in extra time for patient recruitment so that all appropriate age brackets can be properly filled.
- Develop a program of reminders geared toward older patients to help them improve compliance with the protocol.
- For new compounds in development, suggest the formulations most relevant to elderly populations.

CONCLUSION

At this point, sponsors should not shy away from including elderly patients in clinical trials for either practical or ethical reasons. Regulatory guidance quite clearly promotes their regular inclusion, and ethical guidance now exists to help companies with their legitimate concerns in dealing with a potentially vulnerable population. As the demographics of the world population are changing, sponsors have a responsibility to provide a base of evidence on the use of their products in patients over 65 years of age. Doing so has become a regulatory recommendation, an ethical imperative, and a business opportunity.

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