

Underrepresentation of the elderly in clinical trials, time for action

In the general population, the use of prescription drugs increases with age. European data show that 46% of the European population in the age group 45–54 years use prescribed medicines. This number increases to 87.1% in those aged ≥ 75 years.¹

Due to pharmacokinetic and pharmacodynamic changes with aging, the presence of multimorbidity, and an increased prevalence of drug–drug and drug–disease interactions, this high drug consumption in older people is accompanied by an increased susceptibility to adverse drug events (ADEs).^{2,3} This is particularly the case for the subgroup of elderly drug users considered frail, a clinically recognizable state in which the ability of the elderly population to cope with every day or acute stressors is compromised by an increased vulnerability brought by an age-associated decline in physiological reserve and function across multiple organ systems.⁴ Around 10% of people aged over 65 years are considered frail, rising to between a quarter and a half of those aged over 85.⁵ Frailty is more prevalent in elderly patients with polypharmacy and especially hyperpolypharmacy (>10 drugs used).⁶ In the frail elderly population, even small changes in health can have life-changing consequences. An increased susceptibility to hypotensive or sedative effects of drugs may lead to falls, fractures, and a loss of independence, forcing the patient to leave home and move to a nursing home. The same serious consequences can be found in cases of drug induced cognitive deterioration/delirium and incontinence.³ The presence of so-called competing risks challenges the efficacy figures found in standard drug trials.⁷

Assessing whether a drug is safe and effective for use by elderly persons requires that a sufficient number of elderly persons be included in clinical drug trials. When elderly people are excluded the safety concerns and effectiveness outcomes unique to this population will not be detected making risk: benefit difficult to gauge. In 1993, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) published the ICH-E7 guideline: “Studies in Support of Special Populations: Geriatrics.”⁸ This guideline, which was adopted by the European Medicines Agency (EMA), the US Food and Drug Administration (FDA) and pharmaceutical companies, states that, as a general principle “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.” It also states that “It is important not to exclude unnecessarily patients with concomitant illnesses; it is only by observing such patients that drug–disease interactions can be detected.” The guideline defines the geriatric population as comprising patients aged 65 years or more. Regarding the proportion of older persons, it states that “for drugs used in diseases not unique to, but present in, the elderly, a minimum of 100 patients would usually allow detection of clinically important differences.” Given the fact that the ICH-E7 guideline was published in 1993, one would expect that randomised controlled drug trials nowadays are designed in accordance with this guideline. However, this is not the case.

In 2014, Beers et al. studied the inclusion of older people in clinical trials for recently registered drugs.⁹ They found that in trials involving diseases characteristically associated with ageing, 57% of the included patients were aged 65 and older and 22% were aged 75 and older. In trials involving diseases not unique to old age, 9% were aged 65 and older, and 1% were aged 75 and older.

Last year, Ruiter et al. published a structured review of approval documents of FDA-approved drugs.¹⁰ This review included the 10 most frequently on-label prescribed drug classes, drugs with known pharmacokinetic differences in the elderly or drugs that are relatively contraindicated in elderly patients. Over time, the availability of information regarding the elderly population in these approval documents increased from 0% in the period 1970–1979 to 76% for the period 2010–2018. For most of the drugs (62%), the initial approval documents in the database showed information on pharmacokinetics in an elderly subpopulation. Information on safety and efficacy was less frequently present, that is, 42% and 45%, respectively, and did not improve over time.

Major reasons for the underrepresentation of elderly patients in drug trials are the use of arbitrary age limits and exclusion criteria for conditions highly prevalent in the elderly.

Cruz-Jentoft et al. studied the World Health Organization (WHO) Clinical Trials Registry Platform for ongoing clinical trials about type 2 diabetes mellitus.¹¹ Of 440 eligible trials, 65.7% excluded individuals using an arbitrary upper age limit. Exclusion for comorbidity was present in 76.8%. Exclusion for polypharmacy (29.5% of trials),

cognitive impairment (18.4%), short life expectancy (8.9%), and other poorly justified exclusion criteria that could limit the inclusion of older individuals was also present.

In 2019, Lockett et al. studied 623 phase III clinical trials from 1965 to 2015 that addressed major causes for hospitalization and/or disability-adjusted life years in older persons.¹² They found that 33% of studies had arbitrary upper age limits with approximately one-quarter of those studies not allowing people age 65 and older to participate. Beyond explicit exclusion by age, older adults were often implicitly excluded based on various comorbid conditions such as polypharmacy/concomitant medication (37%) or cardiac issues (30%).

Bourgeois et al. evaluated the exclusion of elderly adults from 839 randomized trials studying drug interventions for ischemic heart disease.¹³ From these trials, 446 (53%) explicitly excluded elderly adults. The estimated proportion of participants aged 65 and older was 42.5% and the estimated proportion aged 75 and older was 12.3%.

But, in some fields of research a gradual improvement in the recruitment of older persons can be seen. Last year, Ludmir et al.¹⁴ published a paper studying 742 oncologic randomized controlled trials.¹⁵ Upper age restriction enrolment criteria were identified for 10.1% of RCTs. As a positive finding, they found a decreasing incidence of age restriction criteria over time, at a rate of -1.1% annually; trials initiating enrolment in 2002–2005 had a 16.1% rate of age-restrictive eligibility criteria, compared with 7.6% for trials initiating enrolment in 2010–2014.

These are just a few of the many studies showing that, despite the ICH-E7 guideline, elderly patients are still underrepresented in drug trials, and data on efficacy and harms are often missing in approval documents. Of course, the inclusion of patients with multimorbidity and polypharmacy can be seen as inconvenient since it challenges the principle of standardisation. In a more heterogenic population, the number of risk modifiers builds-up which will increase variation in outcomes and thus the sample size needed to detect significant relevant outcomes.

Inclusion of the elderly may also require different outcomes. In a geriatric population scales measuring feelings of autonomy, levels of psychological, social, and physical functioning may be more relevant than using outcomes such as survival or time to event.

But even if exclusion criteria are limited and chosen outcomes are relevant, inclusion of elderly patients will be difficult. Driven by doubts about the usefulness of studies for their clinical situation or the expectation of logistic problems, the elderly often show less motivation to participate in clinical trials. Investigations demanded by the study protocol can be physically and mentally to exhausting for frail older persons. Inclusion of the elderly in clinical trials demands an approach different from the approach needed to include younger persons.

Clearly, the goals of the ICH-E7 guideline are still valid today, but some parts seem outdated; the EMA came to this conclusion in 2006.¹⁶ The definition of geriatric patients should be narrowed. Most persons aged 65–70 years nowadays are relatively healthy and socially active and should not be seen as representative of the

population of the more frail, older patients. The statement that for drugs used in diseases not unique to, but present in, the elderly, a minimum of 100 patients will suffice should be revisited and revised since it is in conflict with the advice that patients entering clinical trials should be reasonably representative of the population that will be later treated by the drug.

However, even without a revision, pharmaceutical companies and regulatory authorities should take full responsibility for their implicit mandate: bringing effective and safe drugs to those who are in need of such therapy. This accountability to the millions of elderly drug users for whom efficacy and safety data are lacking requires that pharma should not wait until new guidelines are developed but that stakeholders use the current ICH-E7 guideline as intended. Pharmaceutical companies should stop using debatable inclusion and exclusion criteria. Furthermore, they should design trials in a way so that elderly persons are more inclined to participate. Moreover, regulatory authorities should be stricter in their evaluation of registration dossiers and should make more efforts to ensure the needs of the older population are met in the evaluation and registration of new medicines.

COMPETING INTERESTS

There are no competing interests to declare.

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REFERENCES

1. European Union. Eurostat statistics explained. Medicine use statistics 2014 https://ec.europa.eu/eurostat/statistics-explained/index.php/Medicine_use_statistics#Prescribed_medicines
2. Drenth-van Maanen AC, Wilting I, Jansen PAF. Prescribing medicines to older people—how to consider the impact of ageing on human organ and body functions. *Br J Clin Pharmacol*. 2019 Aug 19.
3. Davies EA, O'Mahony MS. Adverse drug reactions in special populations—the elderly. *Br J Clin Pharmacol*. 2015 Oct;80(4):796-807.
4. WHO Clinical Consortium on Healthy Ageing. Topic focus: frailty and intrinsic capacity. Report of consortium meeting 1–2 December 2016

- in Geneva, Switzerland. <https://apps.who.int/iris/bitstream/handle/10665/272437/WHO-FWC-ALC-17.2-eng.pdf>
5. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. *J am Geriatr Soc.* 2012 Aug;60(8):1487-1492.
 6. Palmer K, Villani ER, Vetrano DL, et al. Association of polypharmacy and hyperpolypharmacy with frailty states: a systematic review and meta-analysis. *Eur Geriatr Med.* 2019;10(1):9-36.
 7. Kleipool EE, Dorresteijn JA, Smulders YM, Visseren FL, Peters MJ, Muller M. Treatment of hypercholesterolaemia in older adults calls for a patient-centred approach. *Heart.* 2020 Feb;106(4):261-266.
 8. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH guideline E7: 'Studies in Support of Special Populations: Geriatrics' https://database.ich.org/sites/default/files/E7_Guideline.pdf
 9. Beers E, Moerkerken DC, Leufkens HG, Egberts TC, Jansen PA. Participation of older people in preauthorization trials of recently approved medicines. *J am Geriatr Soc.* 2014 Oct;62(10):1883-1890.
 10. Ruiter R, Burggraaf J, Rissmann R. Under-representation of elderly in clinical trials: an analysis of the initial approval documents in the Food and Drug Administration database. *Br J Clin Pharmacol.* 2019 Apr;85(4):838-844.
 11. Cruz-Jentoft AJ, Carpena-Ruiz M, Montero-Errasquín B, Sánchez-Castellano C, Sánchez-García E. Exclusion of older adults from ongoing clinical trials about type 2 diabetes mellitus. *J am Geriatr Soc.* 2013 May;61(5):734-738.
 12. Lockett J, Sauma S, Radziszewska B, Bernard MA. Adequacy of inclusion of older adults in NIH-funded phase III clinical trials. *J am Geriatr Soc.* 2019 Feb;67(2):218-222.
 13. Bourgeois FT, Orenstein L, Ballakur S, Mandl KD, Ioannidis JPA. Exclusion of elderly people from randomized clinical trials of drugs for ischemic heart disease. *J am Geriatr Soc.* 2017 Nov;65(11):2354-2361.
 14. Ludmir EB, Subbiah IM, Mainwaring W, et al. Decreasing incidence of upper age restriction enrollment criteria among cancer clinical trials. *J Geriatr Oncol.* 2020 April;11(3):451-454.
 15. European Medicines Agency. Adequacy of guidance on the elderly regarding medicinal products for human use. 2006. https://www.ema.europa.eu/en/documents/scientific-guideline/adequacy-guidance-elderly-regarding-medicinal-products-human-use_en.pdf
 16. European Medicines Agency. EMA geriatric medicines strategy. 17 February 2011 https://www.ema.europa.eu/en/documents/other/geriatric-medicines-strategy_en.pdf