# Regulatory Considerations on the Enrollment of Older Adults in Oncology Clinical Trials

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## Introduction

The International Conference of Harmonisation (ICH) E7 efficacy guideline "Studies in support of special populations: geriatrics" was adopted in 1993 by the regulatory bodies of Europe, USA and Japan, stating that *"a minimum of 100 patients would usually allow detection of clinically important differences"* and that "*it is also important not to exclude unnecessarily patients with concomitant illness".*[1] Since then, the world's population has been aging rapidly: in the United States, the percentages of patients with cancer who are older than 65, 70 and 75 years are, respectively, 60%, 46% and 31%. [2]. Cancer incidence in the over 65 years category is expected to increase dramatically by 67% from 2010 to 2030. [3] Restrictive eligibility criteria such as arbitrary upper age limits or exclusion criteria based on comorbidities, polypharmacy or reduced life expectancy, have resulted in the exclusion of older people from clinical trials.[4]

In 2006, the European Commission requested the European Medicines Agency (EMA) to provide their opinion on the 'adequacy of guidance on the elderly regarding medicinal products for human use':[5] 56 drug development guidelines were reviewed and analyzed together with 10 recently approved medicine dossiers in indications relevant to older patients. Recommendations in the report included an update of ICH E7 for better representation of the target population. [5]

This resulted in the adoption in 2010 of the addendum to ICH E7 in the form of a questions and answers (Q&A) document underlining that the number of geriatric patients to be included in a marketing application should be influenced by the target patient population and expected use: [6] "… *it is very important to ensure, to the extent possible, that the population included in the clinical development program is representative of the target patient population and that in the marketing application, depending on the numbers of patients, data should be presented*

*for various age groups ( i.e.<65, 65-74, 75-84 and > 85) to assess the consistency of the treatment effect and safety profile in these patients with the non-geriatric patient population."* However, recruiting in a Phase 3 trial a patient sample whose age structure is similar to the target population can be challenging, and even so, the resulting smaller number of older patients would not necessarily guarantee sufficient power to show significant efficacy in that subgroup: this is compounded by the greater variability inherent to the older population.

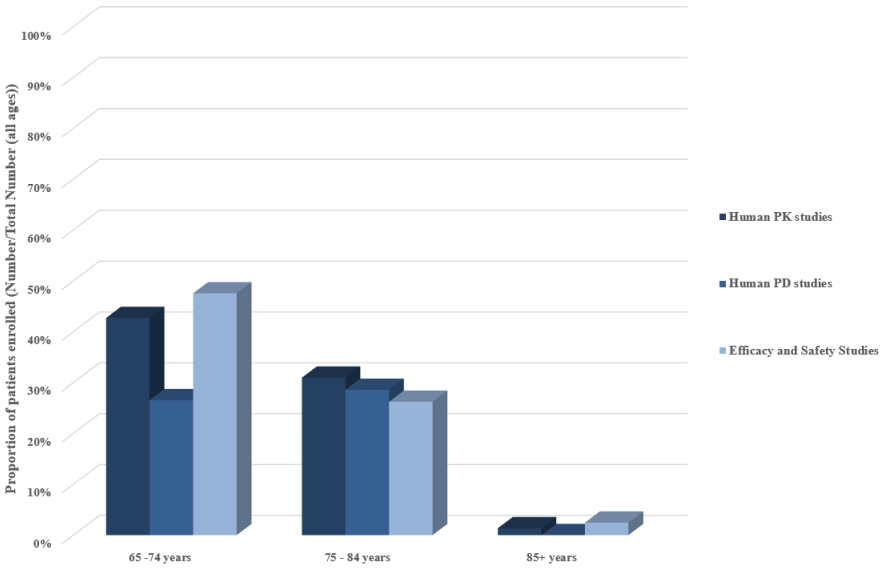
Therefore in 2011 the EMA adopted its Geriatric Medicines Strategy, [7] which aims, when granting a marketing authorization for a new medicine, to consider its benefit/risk balance in relation to the expected use, and to clearly communicate the conclusions (in terms of findings and/or request for post-authorization data) in the EMA approval documents.

As the world's population is aging, the relevance of this approach has been underlined in a recent paper [8] where survival gains demonstrated in a clinical trial setting have not been verified in an older real-world population with more comorbidities.

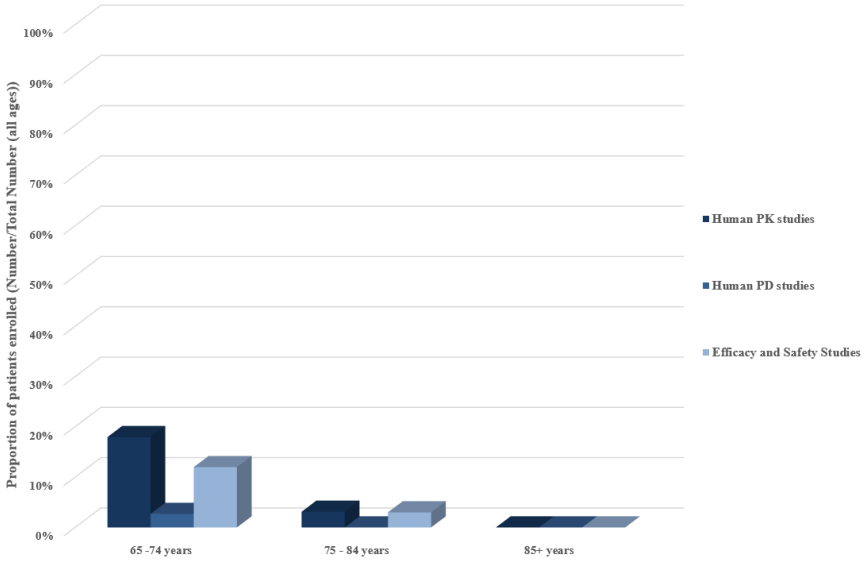
**Representation of older patients in clinical trials: two recently approved drugs**

We have considered the proportion of older people included in clinical trials for two recently approved oncology medicines in indications highly prevalent in the older population: Xofigo® (radium-223 dichloride) for prostate cancer, and Perjeta® (pertuzumab) for breast cancer. Both drugs were approved in 2013 by the EMA. In terms of age groups, there was good representation of older patients with lower representation only of patients older than 85 years. This appears reasonable for the clinical trial population of a Phase 3 trial, where the aim is to characterize the benefit/risk of a medicine without exposing potentially frailer patients in the initial phase of development. [9] These data satisfy the requirements of ICH E7 Q&A. A more in depth-look at the characteristics of these older patients shows that the protocol of Xofigo®

pivotal study specified ECOG PS ≥3 as exclusion criterion (i.e. "capable of only limited self-care, confined to bed, more than 50% of walking hours"), while the Perjeta® pivotal study excluded patients with ECOG PS≥ 2 (i.e. "ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours") [10]: this might have contributed to the fact that for Perjeta® enrolment in the oldest age bracket was lower, reflecting a known enrolment trend for older-old women in breast cancer trials. [9]




a)




b)

**Figure 1.** a) Prostate cancer and b) breast cancer drug % (1dp) of elderly patients (i.e. 65 to 85+ years) in PK, PD, efficacy and safety studies.

An analysis of the exclusion criteria in 25 phase II and III clinical trials for breast cancer (i.e Perjeta®, Halaven®, Tyverb®, Kadcyla®, Afinitor®, Herceptin®, Avastin®, Abraxane®) showed that age limits are, however, still present as an exclusion criterion in many protocols, and only one of these pivotal clinical trials considered patients with ECOG PS 3 to be eligible.

It is important that the information on frailty or ECOG status of the studied population is clearly communicated: achieving "real evidence based medicine" for the ageing population will constitute the challenge for the coming years.[8, 10]

**Who can help?**

Companies should take into account the recommendations in ICH E7 Q&A when designing clinical trials. While every effort should be made to include geriatric patients using concomitant therapies and with co-morbidities in the premarketing clinical development program, it is recognized that enrolment of these patients can be challenging, particularly in the initial phases of drug development: if this is the case, a specific plan to collect data post-marketing should be discussed with the regulators during development, and presented in the marketing application. To assist characterization of these patients beyond chronological age, the EMA is developing guidance on frailty assessment tools which can be used as demographic stratification parameters for older patients included in clinical trials. [11]

Patient preferences play an increasingly important part in drug development, and the relevance of additional trial endpoints, such as QoL, could be considered for the older population. [12]

Lastly, to support physicians and patients in their therapeutic decisions, there should be clear communication of the available evidence, on the conclusions of the benefit risk in the population of expected use, and of any post-authorization data collection required.

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**Disclaimer**

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