Received: 2 January 2024 | Revised: 6 March 2024 | Accepted: 14 March 2024

DOI: 10.1111/jgs.18896

COMMENTARY

Journal of the American Geriatrics Society

How to improve drug evaluation in older patients: The perspective of the European Geriatric Medicine Society (EuGMS)

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The European Geriatric Medicine Society (EuGMS) is an umbrella organization including 39 national geriatric societies across Europe (www.eugms.org), which was established in 2000.[1] From the beginning, a major focus of EuGMS has been the advancement of geriatric pharmacotherapy and the advocacy for a better evaluation of drugs in older patients. For older adults, just like for children, the things that matter most can be very different. Particularly with increasing experiences of multimorbidity, frailty, and functional decline, goals and expectations for pharmacotherapy might also change (Figure 1).

The Paediatric Regulation came into force in the European Union (EU) on January 26, 2007. Its objective is to improve the health of children in Europe by facilitating the development and availability of medicines for children aged 0–17 years. Previously, most medicines used in children were approved on the basis of studies performed in adults. At that time, EuGMS wrote a letter to the European Commissioner of Industry to suggest that a similar initiative was also needed for older adults. After this letter, the Commissioner requested the European Medicines Agency (EMA) to assess the adequacy of current guidance on drug evaluation in older people and to contact EuGMS. EuGMS promoted also a dialogue with the American Geriatric Society (AGS) on this topic, which resulted in the organization of a joined symposium with their respective regulatory agencies EMA and the US Food and Drug Administration (FDA) at the 2008 AGS meeting, titled "Fighting age discrimination in clinical trials."[2]

The exclusion of older adults from clinical trials was also addressed by an EU funded research project (Predict).[3] The project developed a Charter for the rights of older people to participate in clinical trials, which was endorsed by several international organizations, including EuGMS and the AGS.[3]

The constant interaction of EuGMS with EMA was one of the factors contributing to the decision of the EMA to develop a geriatric medicines strategy in 2011.[4] The strategy acknowledged that older adults are the main users of medicines and it clearly recognized that the oldest old patients and those with multiple chronic diseases were likely to be excluded from clinical trials. In this document, EMA declared two main goals: first, to ensure that every new medication likely to be used in this population would be properly evaluated to better appreciate the safety and the benefit-risk balance and second, to promote a better availability of information for both patients and prescribers. At the same time, EMA established a Geriatric Expert Group

This article is part of a special collection edited by Janice Schwartz, titled *A changing landscape for evaluation of new therapies for older adults and diverse populations: National and international perspectives*. Once complete, you can explore the rest of the collection here: https://agsjournals.onlinelibrary.wiley.com/hub/journal/15325415/special-collections.

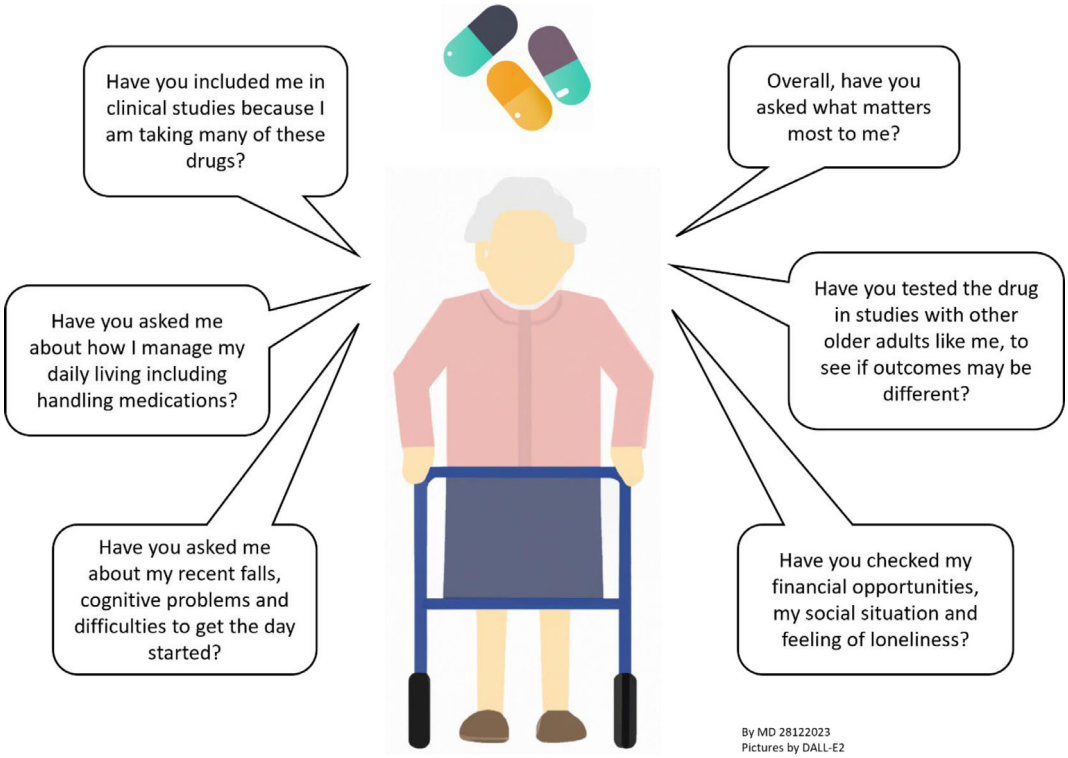

FIGURE 1 Questions related to the evaluation process of new drugs as seen by a frail older woman.

(GEG) to provide scientific advice for the implementation of its geriatric medicine strategy. During the following years, however, the GEG was seldom consulted.

The major request was to identify points to consider on frailty and propose evaluation instruments for baseline characterization of clinical trial populations. These points to consider were intended to provide guidance only for the evaluation of the baseline frailty status of patients (typically, but not exclusively aged >65 years) enrolled in a clinical trial or other clinical investigation (e.g., registry) and to supplement the requirements of ICH E7 Questions and Answers.[5]

The short physical performance battery, with gait speed as an alternative, were identified as the most suitable tools.[6] After 2019, following the withdrawal of the United Kingdom from the European Union, there was a complete interruption of the activity of the GEG. The COVID-19 pandemic was a strong reminder of the vulnerability of older adults and highlighted the need for appropriate testing of therapeutic interventions. An expert group convened by EuGMS carried out a systematic review demonstrating that older subjects, particularly those older than 75 years, were clearly underrepresented in clinical trials evaluating the efficacy and safety of COVID-19 vaccines.[7] The presence of a large representation gap between the clinical trial participants and the real-world patient population was also confirmed by Lau et al., who evaluated clinical trials published between 2010 and 2019 concerning drugs used in seven important therapeutic areas for geriatric patients. The most important finding was the large underrepresentation of subjects older than 75 years, whereas adults 60–74 years old were adequately represented.[8]

"...to fully appreciate the efficacy and safety of drugs, it is necessary to promote the inclusion of participants who are reasonably representative of those who will be treated in clinical practice. In this respect, the heterogeneity of older subjects represents a major challenge which is important to recognize in the evaluation process of medicines."

Therefore, it is necessary not only to take into account age, but also to consider sex and gender, as well as the prevalence of geriatric characteristics, such as frailty, multimorbidity, and functional limitations.

Because the older population in Europe is primarily composed of individuals of European descent, that is, White individuals, neither race nor ethnicity as variables are discussed in this commentary.

One of the most common elements overlooked in clinical trials is the differences between men and women across age groups. The overall underrepresentation of women in clinical trials is particularly concerning in the older population, where women significantly outnumber men. Sex and gender differences have an important role in affecting patient's health, risk for chronic illnesses, functional decline, and vulnerability to adverse effects of drugs.[9]

Although sex is always registered in clinical trials but rarely considered as an effect modifier, frailty, functional impairment, and multimorbidity are often not considered nor measured. Frailty has a stronger association with risk of adverse events than age.[10] Moreover, frailty is associated with a higher risk of adverse drug reactions[11] and is important to be considered during treatment decisions, for example, concerning the treatment of malignancies, arterial hypertension, or atrial fibrillation.[12–14] Functional status is a key indicator of health status in older patients, because functional impairment and even more overt disability are associated with worse clinical outcomes.[15,16] Finally, multimorbidity, that is, the presence of multiple chronic diseases, is common in older subjects and causes a higher probability of polypharmacy and adverse clinical outcomes. Because the exclusion criteria set in clinical trials often concern chronic diseases or drugs used to treat them, multimorbid older subjects are underrepresented in clinical research.[17]

The lack of structured measurement of these domains leads to their retrospective evaluation, considering the available information. In the case of frailty, this can induce the use of heterogeneous versions of the frailty index. However, this measure often is mainly based on chronic diseases or established disabilities, lacking measures of early functional impairment. This approach limits the possibility to detect the early stages of the frailty process, which are better identified by performance deficits. Therefore, it is important to assure that frailty, multimorbidity, and functional impairment measures are assessed in clinical studies already at the baseline evaluation as well as during follow-up. Of course, and when feasible, other domains commonly evaluated with comprehensive geriatric assessment such as cognition, mood, socioeconomic situation, sensory impairment, and falls history can be extremely informative to further characterize the clinical trial population.

Another important point concerns the choice of outcomes. Traditional outcomes, such as mortality or healthcare service use is still important for older subjects, but those who are frail or have limited life expectancy might value more other aspects, such as preservation of cognitive and physical function and quality of life. Outcomes that matter most to older people should be carefully selected and implemented[18] not only as secondary outcomes but possibly also as primary outcomes for some indications, provided that a thorough development and validation have been performed. This certainly includes patient reported outcomes (PROMS) or experiences (PREMS).

Many of the abovementioned aspects have been discussed in more detail in a recent publication by the EuGMS pharmacology special interest group together with representatives of other scientific organizations and EMA.[19] Besides the points raised above, this article also summarizes several other measures that EuGMS considers important and achievable to improve a better appraisal of drugs for older people. This includes the promotion of studies that advance geriatric approaches for patients and health systems alike such as trials with longer duration, trials that evaluate time to benefit, pragmatic clinical trials, and deprescribing/de-escalation studies.

In view of the limited generalizability of randomized clinical trials in the older population, post-marketing studies might have an important role in generating useful evidence, provided that they are carefully designed, collecting all the relevant data that allow a proper adjustment for relevant geriatric variables and confounders that might influence the response to drug treatments and adverse events.[20] In this respect it is important to take into account the indications provided by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), an organization that brings together regulators and drug developers from Europe, Japan, and the United States with the aim of achieving international harmonization for the development and approval of safe, effective, and high-quality medicines. In the update of the guideline devoted to the evaluation of drugs in geriatric patients,[5] originally released in 1994,[21] the ICH stated that "Every effort should be made to include geriatric patients using concomitant therapies and with co-morbidities in the premarketing clinical development program. In some cases, enrollment of these patients can be challenging and it could be appropriate to collect data post-marketing. However, the adequacy of, and the need for, data in these patients should be considered during

drug development and discussed in the marketing application submission. Where enrollment of geriatric patients has been insufficient despite the efforts of the applicant, a specific plan to collect data post-marketing should be discussed during development and presented in the marketing application." Therefore, post-marketing studies should be carefully justified and planned, being complementary rather than substitutive to a proper premarketing evaluation.

Furthermore, the opportunity of acquiring relevant scientific information concerning the effects of drugs in older people using real-world data that are produced in clinical practice is being increasingly appreciated. However, studies with real-world data should be carefully selected, because many studies have important methodological biases.[22] The main EuGMS recommendations are summarized in Table 1.

EuGMS will continue to advocate a better evaluation of drugs in older subjects in order to maximize the clinical benefits while minimizing harms, providing the necessary information to tailor the treatment to specific subgroups of the older population. To achieve this goal, EuGMS not only aims to continue the collaboration with other scientific societies, including AGS, but also to reactivate the discussion with regulatory agencies and stakeholders to promote a new revision of the international regulatory guideline concerning clinical trials in older subjects.[5,21]

TABLE 1 What is needed to improve the evaluation of drugs in older adults: A six-step plan.

1. Inclusion of participants into randomized controlled trials and clinical studies who are representatives of the real-world population affected by the condition of interest in terms of age, sex, and gender, at least within pivotal sub-study approaches
2. Appropriate assessment of geriatric domains to characterize the heterogeneity of older patients, such as functional status, multimorbidity, and frailty, both at baseline and as an outcome. Ideally, assessment of other dimensions evaluated by means of comprehensive geriatric assessment, such as cognition, mood, socioeconomic factors, history of falls, and sensory impairment
3. Implementation and funding of studies with sufficient duration and evaluation of time needed to benefit
4. Use person-reported outcomes and experiences and other suitable measures which reflect what matters to older adults
5. Implementation of deprescribing and de-escalation trials, especially in very frail and disabled older adults, with limited life expectancy (e.g., nursing home residents)
6. Post-marketing studies that are carefully designed and properly implemented and use of high quality real-world evidence studies

AUTHOR CONTRIBUTIONS

All authors contributed to the writing of this commentary.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

SPONSOR'S ROLE

None.

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How to cite this article: Cherubini A, Denkinger M, Knol W, Gudmundsson A. How to improve drug evaluation in older patients: The perspective of the European Geriatric Medicine Society (EuGMS). *J Am Geriatr Soc*. 2024;72(9):2928-2932. doi:10.1111/jgs.18896