Received: 16 January 2019 | Revised: 17 May 2019 | Accepted: 17 June 2019

DOI: 10.1111/bcp.14044

COMMENTARY-THEMED SECTION

New harmonized considerations on the evaluation instruments for baseline characterization of frailty in the European Union

Francesca Cerreta | European Medicines Agency Geriatric Expert Group

European Medicines Agency, Amsterdam, The Netherlands

Correspondence
Francesca Cerreta, MSc, European Medicines Agency, Domenico Scarlattilaan 6, 1083 HS. Amsterdam, The Netherlands.
Email: francesca.cerreta@ema.europa.eu

KEYWORDS

clinical trial [MeSH], drug development [MeSH], European Medicines Agency, frail elderly [MeSH], guideline, International Conference for Harmonization

As the world population ages, and as the older-old (≥85 years) are representing the fastest growing age group, it is increasingly evident that chronological age is a suboptimal indicator of the true health status and susceptibility of an individual to adverse drug outcomes, and its perspective to healthy ageing. The variability of homeostatic reserves, the general fitness status, and the clinical history of present and past morbidities create a picture of individual variability, of which age by itself is a poor surrogate.[1-3]

The International Conference for Harmonization (ICH), includes, among its clinical efficacy guidelines, the ICH E7 guideline *Studies in support of Special Populations: Geriatrics*.[4] At the time of adoption in 1993, the E7 guideline advocated 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". The guideline did not include definition for either a geriatric patient or an elderly person. However, the term geriatric was clearly associated with biological rather than chronological age and the term elderly was clearly meant to indicate patients aged ≥65 years.

Within a decade, it became clear that the guidance needed further consideration, as the world population aged rapidly and as older, multimorbid patients were increasingly frequent in clinical practice i.e. patients aged ≥65 years were becoming the norm rather than the exception.[1] However, older patients can respond differently from younger patients to drug therapy and such differences can be greater in patients aged ≥75 years.[3,5] Moreover, not all potential differences in pharmacokinetics, pharmacodynamics, disease–drug and drug–drug interactions, and clinical response that can occur in the older populations can be predicted from younger populations. Older patients are far more likely to have multiple illnesses, to be receiving multiple drugs, and to present pharmacokinetic differences due to altered renal and hepatic function and changes in body composition.[1,5]

Therefore, the ICH E7 guideline was supplemented with a questions and answers (Q&A) document. The Q&A indicated that, rather than a minimum of 100 patients aged 65 years, an *appropriate representation* of older patients in the clinical trials for new drug registration should be included. Also, data should be presented for the various subsets of the older population (<65, 65–74, 75–84 and ≥85 years), the distribution of patients enrolled in the clinical study should be appropriately assessed, and the benefit/risk balance of a treatment in each of the different subgroups should be evaluated separately.[4] While recognising the existence of the concept of frailty, and the challenges it poses to the clinical development plans for medicines (Quote: "There may exist a reluctance to include vulnerable geriatric patients at high risk of adverse outcomes (so-called *frail* geriatric patients). However, care in randomization should allow the appropriate attribution of findings either to the investigational drug or to other factors.") the ICH E7 guideline and Q&A did stop short of considering frailty as a viable clinical trial population baseline stratification parameter. In addition, a clear definition on the term *frailty* and how this would relate to the term *geriatric* was missing. There was also not any associated ICH guidance on the formulation characteristics that would ensure the practical use of drug products in old, geriatric and/or frail patients.[6]

Since then, the concept of frailty has been extensively studied. The term *frailty* is now commonly used to identify older adults who have reduced resistance to stressors and are consequently at increased risk of poor clinical outcomes, such as incident disability, cognitive decline, falls, hospitalization, institutionalization or increased mortality. Frail older persons are also more vulnerable to clinically important adverse drug reactions. Hospital admissions related to medicines are especially seen in these patients and are often preventable. Cross-sectional studies suggest that about 7% of persons older than 65 years are frail,

and that the prevalence of frailty increases with age and may exceed 45% after age 85 years.[5]

In addition to these research advances, a gradual regulatory shift is taking place. The European Clinical trials regulation advocates in recital 15 that "in order to improve treatments available for vulnerable groups such as frail or older people, people suffering from multiple chronic conditions, … medicinal products that are likely to be of significant clinical value should be fully and appropriately studied for their effects in these specific groups".[7] This encouraged the European Medicines Agency to attempt to identify instruments that could be used to characterize the frailty status of a population enrolled in a clinical trial, to support a better understanding of the benefit/risk balance of a medication in a population where data are often limited at the time of marketing authorization application.

The aim was to identify a simple yet informative scale that could work alongside demographic data collection to decide on the characteristics of older patients to be enrolled in a clinical trial for the development of a new medicine. In this way, a better informed decision could be made on the presence of data to support the benefit risk balance of a medicine in the frail older population, or on the appropriateness (or not) to extrapolate the data collected in younger adults.

In February 2018, the European Medicines Agency published its *Reflection paper Physical frailty: instruments for baseline characterisation of older populations enrolled in clinical trials*.[8,9] This guidance is the first attempt, from the regulatory viewpoint, to characterize, and possibly stratify, the population enrolled in a clinical trial on the basis of their frailty status rather than chronological age alone.

In principle, several aspects of frailty could be considered to categorize patients, and may assume different relevance depending on the indication and the pharmacodynamics profile of the drug under investigation: physical frailty, cognitive dysfunction, malnutrition and multimorbidity. In the draft guideline released for public consultation in 2016, all four domains were considered. However, from the public consultation, two elements emerged: the body of evidence to support the predictive value for adverse outcomes of the four domains was much stronger for physical frailty (and, to a lesser extent, multimorbidity); and the inclusion of so many different aspects was making the aim of the guideline confusing to the public.

For this reason, the guideline was simplified to encompass only physical frailty. The parameters considered in the choice of instrument included validation status, predictive value and ease of use, and represented expert opinion by consensus. The scope was to identify a valid instrument of simple, wide applicability across therapeutic areas and

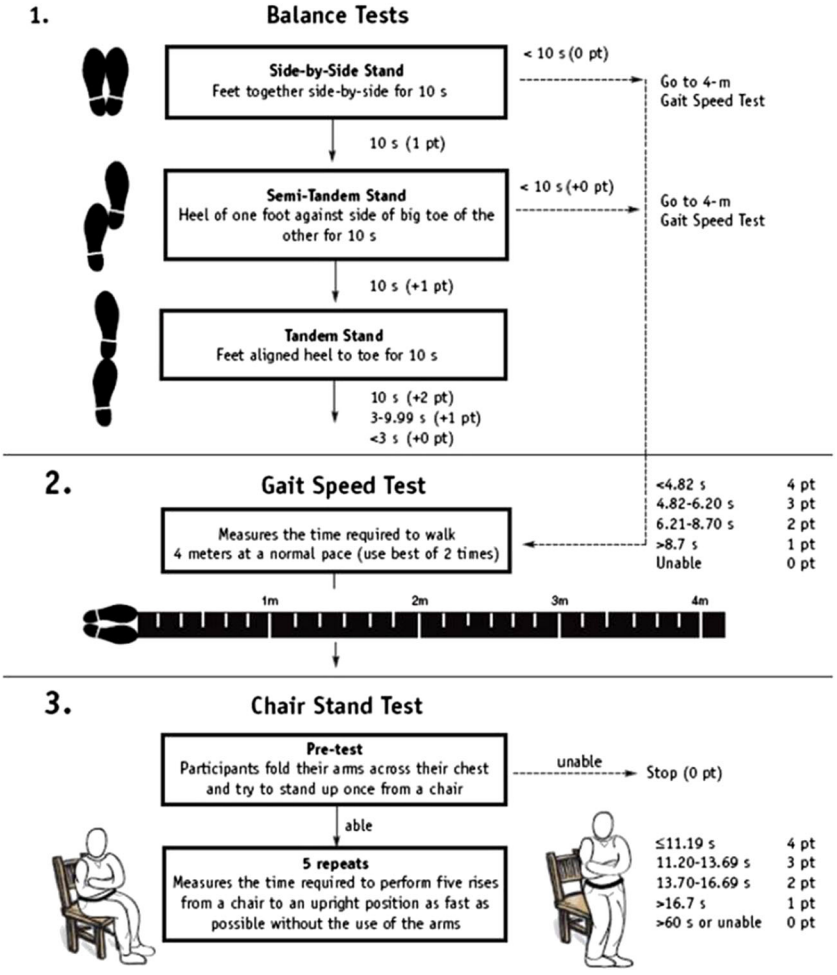

FIGURE 1 Short Physical Performance Battery

conditions, which could be administered without extensive training. The intent was not to provide a full clinical characterization of the frailty status of a patient, for which specialized and more comprehensive instruments exist, but to offer the opportunity to better elucidate the type of patients to be enrolled in clinical trials, or to enrich the population of a trial if specific data in frail patients were to be required.

The Short Physical Performance Battery (SPPB) emerged as the instrument of choice, together with gait speed (Figure 1) as a possible alternative instrument, although not as well validated and as multifaceted as SPPB. These tools can identify the increased vulnerability that is the hallmark of physical frailty, prognostic of disability and mortality in older subjects, and have been extensively used across a variety of clinical settings. The SPPB assesses lower-extremity function by measures of three separate tests: standing balance, gait speed, and ability to rise from a chair. Summary score cut-offs have been defined based on subsequent risk of disability and mortality.

Currently, there is increasing evidence that older, and especially frail people are not yet well represented in clinical trials.[10] It is hoped and encouraged that the currently developed instruments for frailty will be used in pre- and postauthorization studies for medicines registration across all therapeutic areas. The standardized characterization of frailty proposed in the *Reflection paper* for new drug applications may also be useful to enrich the frail population in postauthorization studies that might be required in a risk management plan, or that may otherwise be conducted as part of the product life cycle management.[6] It is also hoped that the increased focus on the aging population and frailty will encourage industry and other parties to enrol increasing numbers of older old patients, to elucidate the benefit/risk profile of new medicines in this population. Ultimately, the available evidence should be reported in the SmPC (Summary of Product Characteristics), which form the backbone of the Compendia. In this way, physicians will gain better access to data to support evidence-based treatment of their patients.

ACKNOWLEDGEMENTS

The European Medicines Agency Geriatric Expert Drafting Group; A Cherubini, A. Cruz-Jentoft, A. Gudmundson, M. Haberkamp, P. Jansen, N. Marchionni, S. Morgan, A. Pilotto, M.-M. Rosa, E. Rönnemaa and H. Wildiers.

COMPETING INTERESTS

There are no competing interests to declare.

ORCID

Francesca Cerreta https://orcid.org/0000-0001-9316-7800

REFERENCES

1. Beard JR, Officer A, de Carvalho IA, et al. The world report on ageing and health: a policy framework for healthy ageing. *Lancet (London, England)*. 2016;387(10033):2145-2154.
2. Cerreta F, Eichler HG, Rasi G. Drug policy for an aging population--the European medicines Agency's geriatric medicines strategy. *N Engl J Med*. 2012;367(21):1972-1974.
3. Lattanzio F, Landi F, Bustacchini S, et al. Geriatric conditions and the risk of adverse drug reactions in older adults: a review. *Drug Saf*. 2012;35(Suppl 1):55-61.
4. International Conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. Studies in support of special populations: geriatrics E7. 1993. Available at: https://wwwichorg/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E7/Step4/E7_Guidelinepdf. Accessed December 24, 2018.
5. Buchman AS, Wilson RS, Bienias JL, Bennett DA. Change in frailty and risk of death in older persons. *Exp Aging Res*. 2009;35(1):61-82. https://doi.org/10.1080/03610730802545051
6. van Riet-Nales DA, Hussain N, Sundberg KA, et al. Regulatory incentives to ensure better medicines for older people: from ICH E7 to the EMA reflection paper on quality aspects. *Int J Pharm*. 2016;512(2):343-351.
7. European Union. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. 2014. Available at: https://eceuropaeu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_enpdf. Accessed December 24, 2018.
8. Products. EMACoHM. Reflection paper on physical frailty: instruments for baseline characterisation of older populations in clinical trials. 2018. Available at: https://wwwemaeuropaeu/documents/scientific-guideline/reflection-paper-physical-frailty-instruments-baseline-characterisation-older-populations-clinical_enpdf. Accessed December 24, 2018.
9. Cerreta F, Ankri J, Bowen D, et al. Baseline frailty evaluation in drug development. *J Frailty Aging*. 2016;5(3):139-140.
10. 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;62(10):1883-1890.

How to cite this article: Cerreta F. New harmonized considerations on the evaluation instruments for baseline characterization of frailty in the European Union. *Br J Clin Pharmacol*. 2020;86:2017–2019. https://doi.org/10.1111/bcp.14044