Inclusion of functional measures and frailty in the development and evaluation of medicines for older adults

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The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E7, the guidance for the conduct of clinical trials in people older than age 65 years, dates from 1994. Since then, the inclusion of older people in clinical trials has hardly improved, particularly for the oldest old age group (individuals older than age 75 years), which is the fastest growing demographic bracket in the EU. Even though most medications are taken by this group, relevant endpoints and safety outcomes for this cohort are rarely included and reported, both in clinical trials and regulatory approval documents. To improve the critical appraisal and the regulatory review of medicines taken by frail older adults, eight recommendations are presented and discussed in this Health Policy. These recommendations are brought together from different perspectives and experience of the treatment of older patients. On one side, the perspective of medical practitioners from various clinical disciplines, with their direct experience of clinical decision making; on the other, the perspective of regulators assessing the data submitted in medicine registration dossiers, their relevance to the risk–benefit balance for older patients, and the communication of the findings in the product information. Efforts to improve the participation of older people in clinical trials have been in place for more than a decade, with little success. The recommendations presented here are relevant for stakeholders, authorities, pharmaceutical companies, and researchers alike, as the implementation of these measures is not under the capacity of a single entity. Improving the inclusion of frail older adults requires awareness, focus, and action on the part of those who can effect a much needed change.

Introduction

The syndrome of frailty has been defined as a state of decreased intrinsic capacity and increased vulnerability to external stressors across multiple organ systems;[1] frailty has been associated with increased risk of negative clinical outcomes, such as mortality or hospital admissions. Frailty can be assessed with various tools focusing on different variables or degree of precision, from a 1-min instrument, such as the pictorial version of the Clinical Frailty Scale to more elaborate instruments, either based on short comprehensive geriatric assessments, such as the Edmonton Frail Scale, that comprise performance-based items, such as the physical frailty scale by Fried and colleagues, or that quantitatively summarise deficits that are mainly morbidity-related, such as the frailty index by Rockwood and colleagues.[2–4] This plethora of assessment tools could make the concept of frailty confusing and decisions on the appropriate assessment instrument difficult.[5] The prevalence of frailty increases with age and can vary within populations—eg, in older adult care home inpatients, prevalence ranges from 48·8% to 80·0%.[6]

However, not all older adults are frail, and frailty can also occur in individuals younger than 65 years with underlying chronic and progressively disabling diseases. In all cases, frailty is associated with an increased risk of negative clinical outcomes, such as mortality, hospital admissions, and clinically significant adverse reactions. Indeed, studies assessing different primary diseases have shown that frailty and multimorbidity are better predictors of relevant primary outcomes than chronological age;[7,8] frailty also outperformed other biological markers, such as DNA-methylation indices.[9] The importance of frailty in predicting outcomes was most recently shown during the COVID-19 pandemic, as it emerged as a clear predictor of mortality.[10,11] In addition to ageing, other mechanisms are responsible for the development of frailty, including the accumulation of morbidities and comorbidities, and psychosocial issues such as sudden changes of the immediate social network and environment (death of family members or friends, caregiving, hospital admissions, or institutionalisation). Unhealthy lifestyles including, but not limited to, physical inactivity, unhealthy diet, and smoking can also contribute to adverse outcomes.

Therefore, frailty is one of the main reasons, in addition to ageing and multimorbidity, why interest groups and stakeholders have been strongly advocating, for more than a decade, to increase the number of older adults in relevant clinical trials and,[12,13] when appropriate, to request post-authorisation studies to further elucidate the risk–benefit balance of drugs under investigation and to establish dosage for real-world clinical practice. In addition, specific trials for the ageing population have been envisaged in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which offers guidance in the development of medicines for special populations,[14] and the US National Institutes of Health has established a clinical research policy to improve inclusion of participants across the entire lifespan.[15]

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However, most investigations have shown that little has changed as a result of these initiatives and important opportunities are still being missed.[16] Examples of these missed opportunities can be found across a broad range of trials, including cardiovascular diseases, oncology, and COVID-19 vaccine development.[17–20] A few studies have shown a positive shift towards an increase in older adults being included in oncology trials and with less arbitrary age limits than previously.[21] More frail older people have been involved in trials of some diseases, such as multiple myeloma.[22] In oncology and haematology, the trend towards personalised medicine has seen the implementation of de-escalation strategies and methods to identify tumours that have an increased risk of recurrence, especially, but not only, for frail older people. Commercially available gene panels, such as MammaPrint or OncotypeDX, accompanied by geriatric assessment, have been used in personalised therapeutics.[23] However, these assays are expensive and might not be required if pathological and immunohistological data are carefully evaluated. The recent American Society of Clinical Oncology guidelines on the management of vulnerabilities in older patients receiving systemic cancer therapy have clearly outlined the need for a systematic approach for older adults, which includes not only frailty screening but also the implementation of at least a pragmatic geriatric assessment.[24,25] A recent initiative that could tackle some of these challenges is the Consolidated Appropriations Act of 2023, which provides the US Food and Drug Administration (FDA) with a legal mandate for additions to the clinical trial requirements to increase trial diversity.[26]

Panel 1: **Ongoing challenges**

Trial design

- When designing a clinical trial, frailty is rarely considered as an inclusion criterion or a population stratification parameter.
- Multimorbidity and related polypharmacy might not be adequately addressed because of numerous and broad exclusion criteria in clinical trials.
- Endpoints relevant to frail older patients, and patient-generated health data, are rarely included or reported, and are even more rarely set as primary or relevant secondary endpoints.
- Measures of physical performance, activities of daily living, social networking, and cognitive function are often missing and not standardised, hampering comparability between trials or conditions.
- Progression of frailty within a trial is almost never measured.

Results

- Data on frail older adults are missing although they represent a large group of patients and major users of medications.
- Compliance and non-adherence to prescribed treatments, related to difficulties in medication use,[27] are not adequately addressed in trials because of the inclusion of older adults with no health complications, or exclusion of frail older adults. Usability studies should provide data from this frail group of older adults to ensure representative cohorts.[28]
- Safety concerns for medicinal products used for common geriatric syndromes (eg, falls, delirium, incontinence), and other symptoms (eg, dizziness, orthostasis, urinary retention, loss of appetite, and cognitive decline) are difficult to measure because of their atypical presentation. These symptoms are also inconsistently recorded by investigators in clinical trials and health-care providers in post-marketing settings. Although safety data from older patients are provided separately for regulatory purposes, the same should apply for data from frail patients.

Communication of findings

- Due to the scarcity of data, the summary of product characteristics and patient leaflet, provided with medications, rarely includes clear information on age-specific or frailty-specific safety concerns.

Ongoing challenges

Despite advances in some areas, important issues and ongoing challenges remain when considering the development of safe and effective medicinal products for older adults (panel 1).

Some of these problems have already been targeted by the European Medicines Agency (EMA) and the FDA in several statements, workshops, and associated literature. Specifically, in 2018, the Committee for Human Medicinal Products (CHMP) adopted scientific guidance on frailty released by the EMA,[29] which recommended the inclusion of baseline physical frailty parameters a priori to allow results to be analysed by subgroup in both clinical trials and in real-world clinical practice (ie, post-authorisation studies and real-world evidence generation). The EMA guidance recommends either the Short Physical Performance Battery or gait speed for a simple screening measurement of physical function.[29] However, ongoing trials, even those designed for older adults, too often do not follow this guidance or implement these measures, thus excluding frail older people.

To avoid harming frail older adults and to clarify which medications have a favourable risk–benefit balance, modern clinical trials of drugs that are expected to be frequently used by older adults or that are likely to be of significant clinical value need to include these patients and to include outcomes that are meaningful to this age group. Not all meaningful outcomes are easy to define or are stable enough to inform the decision-making process of regulatory authorities, such as the EMA or FDA. All approaches, therefore, must meet expectations of good scientific practice and methodology. A recently developed implementation tool that considers the barriers to the implementation of patient-reported outcomes could serve as a crucial component to support inclusion of older people and external validity of outcomes for principal investigators, ethical committees, and authorities alike.[30]

To improve the overall assessment and critical appraisal of drugs taken by frail older adults, we present eight points that must be addressed in future clinical trials (panel 2).

Panel 2: **Recommendations to improve the critical appraisal of drugs taken by frail older adults**

1 Promote the inclusion of older adults (particularly individuals >70 years) in all clinical trials of drugs that could be administered to individuals in this age group to increase the representation of patients who will be treated in clinical practice. This goal has already been stated in several papers issued by the Committee for Human Medicinal Products,[29] in a roadmap of the US Food and Drug Administration (FDA)[31] and by both the European Medicines Agency (EMA) and the FDA.[32]

2 Involve more frail and functionally impaired older adults in clinical trials[33] to ensure registration trial enrolment is representative of the target treatment population.[34] Although representativeness cannot always be fully realised and varies between regions, trial enrolment should involve some kind of pre-screening and stratification by age and functional frailty level to increase the number of older adults with relatively lower functional status in clinical trials. Because this consideration is not applicable to all scenarios, involvement could be implemented as follows:
- If the drug will be taken mostly by people aged 70 years and older, relevant enrolment strategies should be implemented to enrol a more representative sample of this population to increase external validity of study results. Monitoring physical frailty, as per several reflection papers, can be used and adapted to the individual trial setting (Short Physical Performance Battery [SPPB], gait speed, clinical frailty scale, and others).[29,34]
- Alternatively, sub-study approaches within the pivotal trial can be taken, which should also include specialised Comprehensive Geriatric Assessment (CGA) and pharmacological assessments (pharmacokinetic, pharmacodynamic, and comparative safety and efficacy). The increasing prevalence and growing recognition of the complexity of the geriatric population, including concomitant (and ever more aggressive) therapies and comorbidities, calls for inclusion of a relevant number of older patients in phase 2 and phase 3 studies across the frailty spectrum to detect clinically important differences.[32]
- Post-authorisation randomised trials in older adults, as part of the post-marketing commitments.

3 Increase programmes that support funding of trials for products that have a potentially favourable risk–benefit ratio in older adults, which need further characterisation, such as:
- Time-to-benefit approaches as prespecified secondary analyses, especially for primary prevention approaches, such as antidiabetic, antihypertensive, anticoagulant, platelet regulatory, proton-pump inhibitory, or lipid-lowering drugs.[35,36]
- De-prescribing trials in frail older people to provide sound evidence to guide appropriate withdrawal of drugs in this vulnerable population: these trials would support appropriate prescription and medication review guidance.
- De-escalation trials, especially in geriatric oncology and haematology.[37]
- Studies that use goal attainment outcomes as secondary outcomes, which put patients' wishes first (what matters most to a frail older adult).[38] Given that these scales are very specific, not only to age and frailty but also to the disease studied, they need to be validated.
- Trials with sufficiently long duration to allow long-term safety and effectiveness assessment, so that better information on optimal treatment length or beneficial treatment time can become available.

4 Include baseline functional parameters, such as SPPB or gait speed and, in addition, an overall clinical measure of biological ageing and physical frailty, such as the Clinical Frailty Scale and a measure of cognitive function.[29] Ideally, after identification of a prevalent frailty, the evaluation should be completed by means of a more complex CGA.[39,40]
- Use deficit-accumulation indices, generally database-driven and constructed post hoc from morbidity data (diseases, laboratory values, etc) and anthropometric data (age, weight loss, etc). These rarely include functional items and might therefore not represent the same population as compared with a validated physical frailty instrument, such indices have mostly been evaluated and used in real-world studies.[28,41] Specific deficit-accumulation indices have also been developed for some trials, such as the Zoster Vaccine trials.[42] The EMA is exploring this approach in the Data Analysis and Real-World Interrogation Network (DARWIN) project, investigating the real-world frailty status of patients at the point of diagnosis for a number of conditions.
- Both approaches (frailty scales and deficit-accumulation indices) must be considered. Although functional frailty scales should be especially used for screening and recruitment of frail older adults, both approaches can inform further subgroup analyses of the trial, ideally as prespecified secondary analyses.[43] Ideally, these functional parameters should be measured throughout the study and included in final analyses and reporting.

5 Design patient-centric medicinal products to meet the needs, capabilities, and limitations of the patients for whom they are intended, considering age, chronic disease, and physical ability. The pharmaceutical development of medicines should consider the aspects described in the EMA's guidance on the pharmaceutical development of medicines for use in older people.[27]

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(Panel 2 continued from previous page)

6 Use of modern pharmacological approaches, such as physiologically based pharmacokinetic modelling, quantitative systems pharmacology, and population pharmacokinetics and pharmacodynamics in early development.[44,45]

7 Real-world evidence studies, registries, and post-authorisation safety and efficacy measures to:
- Assess the extent to which randomised controlled trials are representative of the target population actively being prescribed the medication in clinical practice. The EMA is exploring this aspect within the DARWIN initiative.
- Identify frailty prevalence (measured by physical phenotype approaches and deficit-accumulation indices) in the population taking the specific medicinal product and understand how the natural history of disease could differ.
- Conduct comparative safety and effectiveness studies in frail older adults to investigate whether safety concerns are the same (or weighted the same) for older patients who are frail and those who are not; comparisons should be made during pragmatic clinical trials or randomised registry trials in early phases of drug availability, without changing routine clinical practice and maintaining the strength of randomisation.[46]
- Study multimorbidity-related potential interactions among commonly prescribed drugs.

8 Inclusion and thorough implementation of patient-reported outcomes and patient-centred outcomes.[30,47] These outcomes would be mostly used as secondary outcomes, due to known difficulties with validity, sensitivity, and precision. For some drugs, validated patient-reported outcomes could best reflect the primary goal of a specific medicinal product and, therefore, could also be considered for primary analysis if validated. Possible other relevant outcomes include:[48–50]
- Functionally relevant endpoints, such as physical activity, gait speed, cognition, and falls.
- Institutionalisation or admission to hospital.
- Living independently.
- Physical frailty and frailty index, as measured by a deficit-accumulation index.

Search strategy and selection criteria

For the development of the paper, a non-systematic search was conducted in the MEDLINE and PubMed databases from March 1 to March 31, 2022 for publications in English and German. The initial broad search string with "clinical trials" OR "clinical studies" OR "intervention studies" OR "intervention trials" AND "older adults" OR "elderly" OR "geriatric population" was refined by adding specific terms related to inclusion criteria and representation: ("inclusion criteria" OR "eligibility criteria") AND ("older adults" OR "elderly") AND ("representative" OR "representation"). Exclusion criteria were not defined before the search was made. Because of the narrative and non-systematic approach, inclusion criteria were all articles that related directly to the main topic of the manuscript: inclusion of older people in clinical trials. MD screened the abstracts and wrote a first draft of the recommendation paper. This draft was then circulated to all authors for feedback. After feedback was received, a virtual meeting was conducted to explain and clarify statements and to establish a consensus. This draft was then shared with the European Medicines Agency (EMA) Healthcare Professionals' Working Party and the EMA Patients' and Consumers' Working Party for written consultation. Comments received via these iterative processes were implemented by the authors. An updated draft was generated and subsequently shared with EMA authorities and again commented on and discussed in a virtual meeting. The final consensus was incorporated by the authors to develop the final version of the manuscript.

Conclusion

Although the inclusion of older people in clinical trials has improved, albeit variably and inconsistently, since the inception of the EMA geriatric medicines strategy in 2013, the inclusion of functionally impaired or frail older adults has not. In addition, despite medications being extensively and perhaps excessively used by this vulnerable group, specific data on benefits and risks are often missing and relevant outcomes are not always measured. The inclusion of functional parameters in clinical studies and in real-world evidence studies that focus on frail older people is strongly encouraged. Additionally, to increase involvement of the health-care professional community and to supplement regulatory expertise, the EMA has launched a public call for experts in geriatric medicine. These experts can provide support to the EMA committees with input on the design of clinical trials, the evaluation of new medicines approvals, and the drafting of guidelines, which are the areas where we aim to increase our focus.

To summarise the different options and to facilitate medicine development and evaluation for frail older people, we suggest eight important measures (panel 2). Due to the global effect of ageing on health service and medicine use, these points should be brought to the attention of stakeholders, authorities, pharmaceutical companies, and researchers alike, including regulatory authorities and health technology assessment bodies, irrespective of their geographical jurisdiction.

Contributors

MD contributed to the conceptualisation, data curation, analyses, methodology, visualisation, writing the original draft, and reviewing and editing the manuscript. WK, AnC, AS, CL, DL, EP, MM, PO, PVK, and

PS contributed to the conceptualisation and reviewing of the manuscript. AmC, AL, AK, BS, CT, ER, E B-I, MTH, MMR, MT, NMS, SM, and MB contributed to reviewing of the manuscript. IS contributed to the conceptualisation, reviewing, and editing of the manuscript. FC contributed to the data curation, discussion, and reviewing and editing of the manuscript. FC and MD had final responsibility for the decision to submit for publication.

Declaration of interests

CL reports research support from Pfizer and Gilead Sciences, is one of the inventors and patent owners of Creatan Iama Olvos Science, has received payment for expert testimonies from WHO and the European Commission, and has served on advisory boards for MSD, Pfizer Hellas, and Vianex. PS has received honoraria for lectures at educational events from Novartis and Polpharma. MD has received honoraria for lectures at educational events from Amgen, Daiichi Sankyo, Pfizer, and Heel, which were transferred to Agaplesion Bethesda Ulm hospital. All other authors declare no competing interests.

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