Received: 22 December 2023 | Accepted: 27 December 2023

DOI: 10.1111/jgs.18826

SPECIAL ARTICLE

Journal of the American Geriatrics Society

Addressing the gaps in evaluation of new drugs for older adults: Strategies from the International Union of Basic and Clinical Pharmacology (IUPHAR) Geriatric Committee

Sarah N. Hilmer MBBS, PhD[1,2] | **Janice Schwartz MD**[2,3] | **Mirko Petrovic MD, PhD**[2,4] | **Lauren E. Walker MBChB (Hons), PhD**[2,5] | **Petra Thürmann MD**[2,6] | **David G. Le Couteur MBBS, PhD**[2,7]

[1]Kolling Institute, The University of Sydney and Northern Sydney Local Health District, St Leonards, New South Wales, Australia

[2]International Union of Basic and Clinical Pharmacology (IUPHAR) Geriatric Committee, Brentwood, Tennessee, USA

[3]Divisions of Geriatrics and Clinical Pharmacology, Department of Medicine, University of California San Francisco, San Francisco, California, USA

[4]Section of Geriatrics, Department of Internal Medicine and Paediatrics, Ghent University, Ghent, Belgium

[5]Institute of Systems, Molecular and Integrative Biology (ISMIB), University of Liverpool, Liverpool, UK

[6]Helios University Hospital Wuppertal, Chair of Clinical Pharmacology, University Witten/Herdecke, Witten, Germany

[7]Centre for Education and Research on Ageing, University of Sydney and Concord RG Hospital, Concord, New South Wales, Australia

Correspondence
Sarah N. Hilmer, Kolling Institute, The University of Sydney and Northern Sydney Local Health District, St Leonards, NSW, Australia.
Email: sarah.hilmer@sydney.edu.au

Abstract

The International Union of Basic and Clinical Pharmacology (IUPHAR) Geriatric Committee aims to improve the use of drugs in older adults and develop new therapeutic approaches for the syndromes and diseases of old age through advocacy, education, and research. In the present paper, we propose strategies relevant to drug development and evaluation, spanning preclinical and the full range of clinical studies. Drugs for older adults need to consider not only age, but also other characteristics common in geriatric patients, such as multimorbidity, polypharmacy, falls, cognitive impairment, and frailty. The IUPHAR Geriatric Committee's position statement on 'Measurement of Frailty in Drug Development and Evaluation' is included, highlighting 12 key principles that cover the spectrum of translational research. We propose that where older adults are likely to be major users of a drug, that frailty is measured at baseline and as an outcome. Preclinical models that replicate the age, frailty, duration of exposure, comorbidities, and co-medications of the proposed patients may improve translation. We highlight the potential application of recent technologies, such as physiologically based pharmacokinetic–pharmacodynamic modeling informed by frailty biology,

This paper is part of a special collection edited by Janice Schwartz MD, 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.

and Artificial Intelligence, to inform personalized medicine for older patients. Considerations for the rapidly aging populations in low- and middle-income countries related to health-care and clinical trials are outlined. Involving older adults, their caregivers and health-care providers in all phases of research should improve drug development, evaluation, and outcomes for older adults internationally.

KEYWORDS

drug development, frail, geriatric, pharmacology, polypharmacy

IUPHAR GERIATRIC SUBCOMMITTEE

The International Union of Basic and Clinical Pharmacology (IUPHAR) is a voluntary, nonprofit association representing the interests of scientists in pharmacology-related fields to facilitate Better Medicines through Global Education and Research around the world. The Geriatric Committee aims to improve the use of drugs in older people and develop new therapeutic approaches for the syndromes and diseases of old age. It was initially established as the Geriatric Subcommittee of the Clinical Division of IUPHAR by Dr Darrell Abernethy (USA) in 2008. In 2022, it became a full committee of the Clinical and Translational Division of IUPHAR, with the restructure of IUPHAR. Current members are Dr Sarah Hilmer (Australia, Chair), Dr David Le Couteur (Australia), Dr Mirko Petrovic (Belgium), Dr Janice Schwartz (USA), Dr Petra Thürmann (Germany), and Dr Lauren Walker (UK). The Geriatric Committee's actions span advocacy, education, and research. These are outlined in Table 1, with examples of how these actions relate to drug evaluation for older adults.

The contributions of the IUPHAR Geriatric Committee to evaluation of new drugs in older adults include position statements bringing together key principles for international application. These can inform advocacy, education, and future research.

The IUPHAR Geriatric Committee identified the measurement of key characteristics of geriatric patients in clinical trials as an important gap to fill. These characteristics include frailty, multimorbidity, polypharmacy, falls, physical function, and cognition. There has been recent progress in development and use of validated measures of these characteristics in cohort studies of geriatric patients and in clinical trials focusing on geriatric patients, and core outcome sets have been published.[7] However, there remains a lack of consistency in measures used between studies, making it difficult to synthesize research findings. In some cases, this lack of consistency is unavoidable, because the measure needs to be tailored to the study population to detect change without floor or ceiling effects. In other cases, the lack of consistency reflects the lack of evidence to inform which is the most appropriate measure, or variation in the feasibility of measurement in different trials or populations.[8]

It is essential to understand the prevalence of these geriatric characteristics at baseline to ensure that the clinical trial population is representative of the people using medications. Furthermore, these factors are clinically meaningful outcomes. Although there is some overlap between these geriatric characteristics, each has different relationships with clinical pharmacology. For example, multimorbidity results in drug-disease interactions, polypharmacy results in drug–drug interactions, and specific drug classes

Key points

- The IUPHAR Geriatric Committee, which aims to facilitate better medicines for older adults through global advocacy, education and research, identified the measurement of key characteristics of geriatric patients in research as an important gap to fill.
- Key principles and practical issues for consideration of frailty in all phases of drug development and evaluation are presented.
- These have broad international application, including to low and middle income countries, where populations are aging, non-communicable diseases are rising and clinical trials are increasingly conducted.

Why does this paper matter?

Inclusion of frailty in all phases of drug evaluation internationally will stimulate generation of relevant data for drugs commonly used in this population as well as development of new therapeutics for the syndromes and diseases of old age, with data applicable to geriatric patients, improving drug use and outcomes in older adults.

TABLE 1 Actions of the International Union of Basic and Clinical Pharmacology (IUPHAR) Geriatric Committee: relevance to drug evaluation for older adults.

Action	Relevance to drug evaluation for older adults
Advocacy	
Engage with regulatory agencies to improve safety, efficacy, and access to pharmacologic therapies for older patients	Engagement through membership of expert advisory committees, submissions in response to reviews of regulatory systems, promotion of relevant issues and guidance, e.g., contribution to FDA Roadmap to 2030 for Drug Evaluation in Older Adults.[1]
Visit governmental agencies/offices to advocate for pharmacologic sciences relevant to geriatrics	Local advocacy for investment in relevant sciences, including infrastructure and skilled workforce for preclinical studies in aging animals, clinical trials in frail older people, and pharmacometrics.
Education	
Develop webinars and seminars at relevant conferences to promote geriatric pharmacology	Education on the importance of considering geriatric pharmacology for scientists, clinicians, and regulators; at conferences focused on geriatrics, gerontology, basic and clinical pharmacology, pharmacy, drug regulation, any specialty medicine treating older adults.
Inform international education in geriatric pharmacology	Ensure next generation of health professionals understand and apply geriatric pharmacology, e.g., IUPHAR International geriatric clinical pharmacology curriculum for medical students.[2]
Research	
Synthesize guiding principles to guide research in geriatric pharmacology	Identify key topic areas and publish rapid synthesis and position statements, e.g., Development, evaluation, and use of COVID-19 vaccines in older adults: Preliminary principles for the pandemic and beyond.[3]
Engage with basic research applicable to translational geriatric pharmacology	Application of recent innovations in preclinical gerontology to preclinical geriatric pharmacology, e.g., health span outcomes,[4] frail mouse models,[5] polypharmacy mouse model.[6]

increase risk of falls or cognitive impairment. Furthermore, whereas these factors are usually considered separately, they often lead to complex sequences in older patients, such as drug-disease-drug interactions, where prescribing of one condition, leads to deterioration of another, leading to more prescribing, including prescribing cascades.

The Geriatric Pharmacology committee determined that consideration of frailty in drug development and evaluation is a key priority and subsequently developed the position statement presented in the following section. Simultaneously, an astute European statement on 'Inclusion of functional measures and frailty in the development and evaluation of medicines for older adults' was developed,[9] building on the foundational European Medicines Agency 'Reflection paper on physical frailty: instruments for baseline characterization of older populations in clinical trials' (EMA/CHMP/778709/2015). Although many of the principles in the European publications align with those identified by the IUPHAR Geriatric Committee, our scope is broader, covering both preclinical and clinical drug development and evaluation, with an international focus. In addition, our position statement provides deeper consideration of the pragmatic issues for measuring frailty in pharmacology research.

MEASUREMENT OF FRAILTY IN DRUG DEVELOPMENT AND EVALUATION: POSITION STATEMENT OF THE IUPHAR GERIATRIC PHARMACOLOGY COMMITTEE

What is frailty?

Frailty has been defined as a state of increased vulnerability to adverse health outcomes secondary to multiple deficits in physiological, physical, and mental function.[10] Whether frailty represents advanced biological aging or is a separate condition has not yet been established, but many of the biological Hallmarks of Aging occur in frailty. Frailty has become a major focus of gerontological research mostly because it has a strong association with and is often a predictor of poor health related outcomes. Although there is overlap between frailty, multimorbidity, and disability, they are separate constructs.

There has been substantial advocacy to introduce frailty screening in research and practice,[11] based on the possibility that there are potential specific treatments and opportunities to prevent poor outcomes.[12] However, to

date, Comprehensive Geriatric Assessment (CGA) with particular focus on medications, nutrition, and physical activity is the main evidence-based intervention that can be offered.[13] Although frailty screening has potential to inform treatment to optimize outcomes for older adults, there is a risk that potentially useful treatments such as surgery or chemotherapy are withheld based on frailty, because of concerns about poorer outcomes including increased severity of adverse events.

When applying frailty to clinical practice and research, it is important to consider different etiologies and manifestations of frailty. Factors that contribute to frailty include the aging process itself, a single disease, multimorbidity, treatment, social, and psychological factors. Frailty can manifest as predominantly physical, cognitive, social, or as a combination. These subtleties have important implications for response to treatment. For example, a person whose frailty is predominantly attributable to a single disease may derive more benefit from intensive management of that disease, along with support to optimize overall function, than a frail person with the same disease who has multiple other causes of frailty.[14]

Several biomarkers of aging are associated with frailty.[15] These include markers of inflammaging, mitochondrial dysfunction, and neurodegeneration. Interpretation of biomarkers of frailty needs to consider the complexity of acute illness and multi-morbidity, which can affect their generation and clearance. Current biomarkers do not have adequate sensitivity or specificity to be useful surrogate outcomes in clinical trials but could provide insights into mechanisms of responses.

How is frailty diagnosed?

There are numerous tools that have been published for the diagnosis of frailty. These fall into three groups:

1. Based on the phenotypic and bioenergetic characteristics: The main example is the Fried Frailty Phenotype,[16] which requires specific measurements of unintentional weight loss, exhaustion, slow walking speed, reduced grip strength, and low physical activity.
2. Based on accumulation of deficits: These scales of which the Rockwood Frailty Index is the most established,[17] originated as a patient questionnaire. This has evolved to items that can be extracted from medical diagnoses within medical records and sums multiple measurements collected for routine healthcare or research purposes, which could include a wide range of clinically measured parameters, blood tests, or data collected electronically.
3. Based on overall appearance or clinician impression: The main example is the Rockwood Clinical Frailty Scale (CFS). The Clinical Frailty Scale (CFS) is a judgment-based frailty tool that assesses the person's illnesses, function, and cognition to generate a frailty score ranging from 1 (very fit) to 9 (terminally ill).

These tools do not always identify the same people as frail, respond variably to interventions, and differ in their predictive capacity in different situations. It is also unknown which (if any) measure is best related to pharmacokinetic and pharmacodynamic factors that influence medication related outcomes. The lack of a single accepted tool for diagnosing frailty has hampered the scientific endeavor to understand frailty, its impact on clinical pharmacology and to operationalize its diagnosis in research and practice. There is a need for a standard multi-domain measure of frailty that can be used consistently in drug development and evaluation, and more broadly in research and practice. Application of different frailty tools to drug evaluation clinical trials is outlined in Table 2.

How does frailty influence pharmacokinetics and pharmacodynamics?

The changes in pharmacokinetics in frailty overlap with those seen in any individual in old age. It is difficult to reach a conclusion on the effects of frailty based on the current literature as existing studies were mostly small, did not use consistent definitions of frailty, and did not consider or adjust for other patient characteristics.[18] Nonetheless, the main reported change attributed to frailty is a reduction in hepatic clearance of about 20%. The few studies of renal clearance did not demonstrate a change of over 20% in drug clearance between frail and non-frail older adults. The sarcopenia of frailty confounds the interpretation of studies that use serum creatinine to estimate renal function. It is likely that drug volumes of distribution decrease with weight loss and sarcopenia, which are common in frailty.

The larger and perhaps more important issue is whether frailty alters pharmacodynamic effects. Theoretically, the reduced homeostatic reserve in frailty is likely to affect the dose–response curve, as well as broader resilience to tolerate drug-induced changes. There are hardly any objective interventional data on pharmacodynamic changes in frailty.[19] The emerging research on the physiology of frailty and geroscience[15] provides opportunities to include this in physiologically based pharmacokinetic and pharmacodynamic modeling studies.

Frailty is associated with multimorbidity and a shortened life expectancy. This might in turn reduce potential

TABLE 2 Characteristics of common frailty assessments relvant to their use in drug evaluation.

Tool	Description	Data required	Assessment in clinical trials
Frailty Phenotype	Physical frailty syndrome	Weight loss, self-reported exhaustion and physical activity, objective measures of walking speed and grip strength	Assess in clinical trial center or home (space for walking speed, dynamometer). Strongly influenced by acute illness.
Frailty Index	Cumulative health deficits	At least 30 health deficits across multiple domains including direct observations, patient (or proxy) reported, laboratory results, routine records	Analysis of data collected from clinical trial, health records or questionnaires in any setting. Deficits in the Frailty Index should be consistent within trials but can differ between trials.
Clinical Frailty Scale	Overall clinical impression	Person's, function, and cognition, based on direct observations, patient (or proxy) reported, routine records	Comprehensive clinical assessment in any setting, requires clinical judgment.

effects of any drug for primary and/or secondary prevention, due to competing causes of morbidity and mortality and lack of time to benefit from the preventative drug. It is therefore particularly relevant to measure frailty in a standardized manner in clinical trials of preventative drugs and to analyze any drug effect in the light of multimorbidity and frailty.

Relationship between polypharmacy and frailty

Polypharmacy has now been shown in numerous cohort studies to be associated with frailty and to predict the onset of frailty. Causation is unclear[20] and this finding may reflect the association of multimorbidity with frailty, as well as adverse drug effects. The Drug Burden Index is also a predictor of frailty, implicating anticholinergic and sedative drugs.[21] It is not clear whether deprescribing reverses frailty in the setting of polypharmacy in clinical trials.[22] There is evidence of reversibility of frailty caused by polypharmacy with high Drug Burden Index in preclinical models.[6] However, subgroup analysis of clinical trial data by baseline frailty status (e.g.[23]), suggests that cardiovascular drugs retain their beneficial effects in frail older people, indicating that these may not be a suitable target for deprescribing unless current actual or potential harms outweigh benefits in an individual.

How does frailty influence adverse drug reactions?

Frailty increases the risk of adverse outcomes with use of therapeutic drugs, as it does with other interventions. Adverse drug reactions frequently involve falls and impaired cognition, which can be misdiagnosed as part of the frailty syndrome or lack of effectiveness of a therapy. Frailty increases the risk of severe adverse drug reactions for many drug classes, e.g., antihypertensives.[24] This association can be explained through the changes in pharmacokinetics, pharmacodynamics, and medication use described above.

Frailty as a clinical trial outcome

Frailty is a clinically relevant outcome of studies in older adults. Clinical trials in geriatric patients have recently included different measures of frailty as outcomes, seeking to demonstrate change in the trajectory of frailty. There is emerging research defining a clinically meaningful difference in some measures.[25] The 'piggyback' trial methodology,[26] can be applied to understanding the impact of a broad range of interventions, from emerging interventions targeting aging itself to those targeting a disease or syndrome, on frailty as a primary or secondary outcome, with minimal additional cost through use of routine data to generate a frailty index during long-term follow-up.

Frailty in preclinical studies

Animal models of the different frailty measures have been developed and validated.[5] For drugs that are likely to be used by significant numbers of older adults, preclinical evaluation should be performed in aged animals, with subgroup analysis according to frailty. Preclinical evaluation should aim to replicate human exposure in terms of dose, duration, and co-medications, including polypharmacy. Frailty may also be a relevant outcome in preclinical studies. Animal care and ethics guidance

needs to enable drug testing in frail animal models, whereas providing appropriate monitoring and support to ensure animal welfare. Use of more clinically relevant models may improve the translation of preclinical study data to clinical drug effects.[27]

Personalized medicine in frailty

Providing personalized medicine and informed shared decision-making for older patients living with frailty is challenging due to the limitations of the evidence available and the multiple inter-related factors influencing clinical pharmacology and outcomes.[28] Artificial Intelligence methodology provides opportunities to generate and analyze complex data, facilitating more personalized, predictive, and patient-centered decisions (Figure 1) and thus enabling older adults to align their drug use with what matters most to them.

Feasibility of including people with frailty in clinical trials

Patients with frailty syndrome are usually less mobile, often require assistance for their activities of daily living and may also have cognitive dysfunction. Practical issues such as trial-associated visits, transportation, and any stressful tasks must be considered as potential barriers for participation of this vulnerable group in clinical trials. Thus, trial protocols may allow for pragmatic organization, home visits, video calls with caregivers, and other measures to ensure safe participation in clinical trials. Involvement of people with frailty, their caregivers and their health-care practitioners can help inform design of clinical trials that people with frailty can feasibly and safely participate in. Furthermore, members of scientific review and ethics committees should be trained to assess the issues of inclusion of frail patients in clinical trials.

Informed by the knowledge and knowledge gaps described above, the IUPHAR Geriatric Committee has made 12 recommendations for application of frailty in drug development and evaluation (Table 3).

INTERNATIONAL ISSUES

With the aging of the population internationally, it is important to consider international differences in aging and health care in drug evaluation.

The World Health Organization estimates that between 2015 and 2050, the proportion of the world's population >60 years will nearly double from 12% to 22%. In 2050, 80% of older people will be in low- and middle-income countries (LIMC). The prevalence of

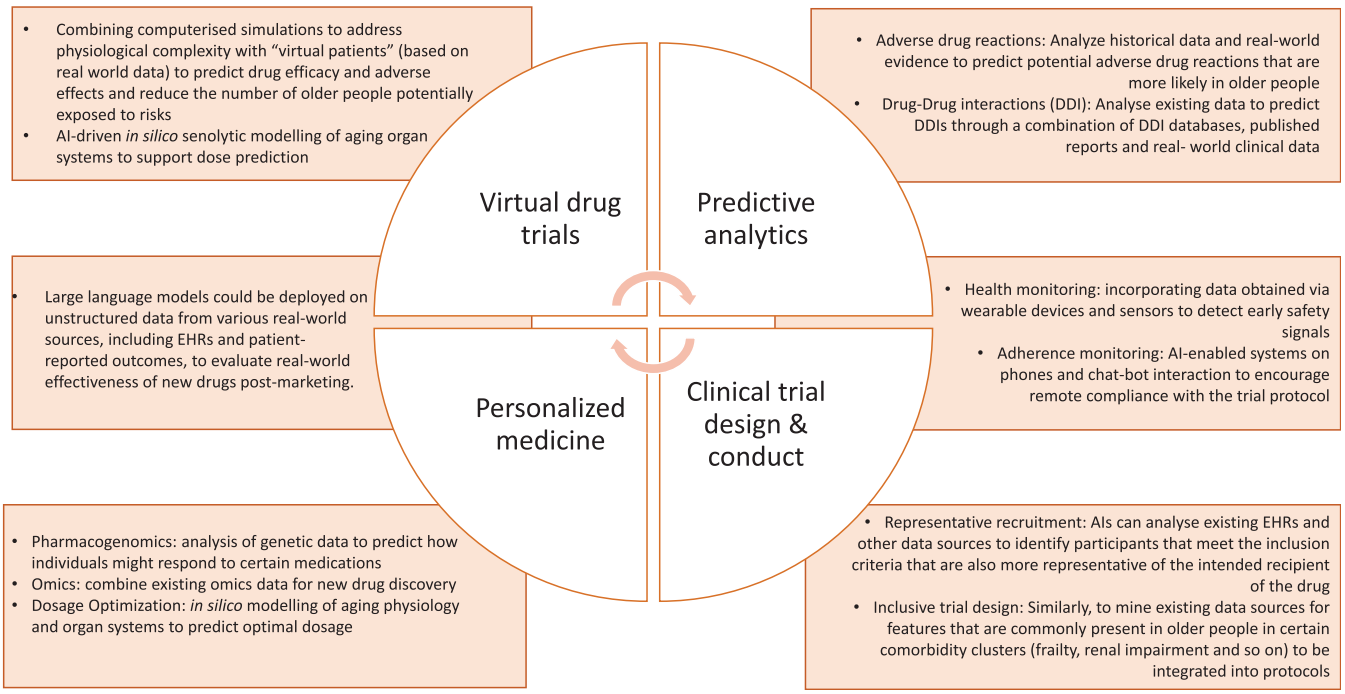

FIGURE 1 Detailing the ways in which artificial intelligence (AI) has the potential to make drug evaluation in older people more personalized, predictive, and patient-centred. EHR; electronic health record.

TABLE 3 Recommendations of the IUPHAR Geriatric Committee on frailty in drug development and evaluation.

1	Research design should comprehensively involve consumers and clinicians, to enable relevance of research, recruitment, and participation of frail older people.
2	Frailty has a significant impact on a wide range of outcomes. Therefore, frailty should be assessed in clinical trials of drugs in older people.
3	Until there is consensus about which tool to use to measure frailty in pharmacological studies, informed by research on the association of frailty with pharmacokinetics and pharmacodynamics, it is prudent to utilize one or more comprehensive, validated scales. This is not burdensome, because many frailty tools are based on routinely collected data.
4	Frailty should be measured at baseline and as an efficacy and safety outcome in clinical trials.
5	Outcomes in frail older people should be reported along with the statistical power of such analyses, acknowledging that this is a subgroup analysis.
6	Regulatory organizations should collect data on subgroups of participants with frailty if it is likely that they will be a significant patient population in the real world. This subgroup should be reported in the prescribing information/label.
7	Clinical trials should include outcomes relevant to older people, such as functional independence and patient reported outcomes.
8	Addition of frailty, as a long-term outcome through 'piggyback' trials, provides an opportunity to discover drugs that affect the aging process.
9	Physiologically based pharmacokinetic and pharmacodynamic modeling should include the emerging understanding of biology of frailty.
10	Objective measures of frailty should also be included in pharmacovigilance studies to understand real-world use and outcomes relevant to frail older adults.
11	Preclinical evaluation should be performed in aged animals, including frailty measurement. Models should replicate duration of treatment, comorbidities, and co-medications likely to be seen in clinical practice.
12	There are opportunities to harness the emerging Artificial Intelligence technology, including cluster analyses, to understand the complexity of individualized therapies for frail older adults (Figure 1).

frailty is higher in LMICs than in High Income Countries (HICs)[29] and is probably influenced by health and its social determinants. The definition of successful aging differs with ethnicity and societal factors, and this needs to be considered in designing objective and patient reported outcome measures.

Priority health care issues in LMICs are shifting from communicable diseases to include noncommunicable diseases. With aging of the population, there is a rise in multimorbidity. In HICs with publicly funded health-care for older adults, inappropriate polypharmacy is a major therapeutic challenge with multimorbidity. In contrast, access to essential medicines is the major issue in LMICs.

There is growing clinical trial activity in LMICs, which includes treatment of not only communicable but also noncommunicable diseases. More than half of the pivotal trials of new cancer, cardiovascular, and neurologic drugs approved by the FDA from 2012 to 2019 recruited participants from LMICs.[30] The ages of participants recruited from different countries was not reported. However, issues for recruitment in LMICs,[31] such as lack of financial and human capacity, ethical and regulatory system obstacles, lack of research environment, operational barriers, and competing demands are clearly applicable to recruitment of older adults. Involvement of older adults and clinicians from LMICs in clinical trial design, conduct, and interpretation, and use of validated frailty measures, should help ensure that research results are relevant to the aging populations internationally.

CONCLUSION

The IUPHAR Geriatric Committee position statement brings together key principles for drug evaluation for frail older adults, for advocacy, education, and research. We consider the full spectrum of drug development and evaluation, from basic to clinical research. Through the international networks of IUPHAR, we aim to provide guidance with broad application, which will improve development and evaluation of drugs to improve outcomes for the aging population internationally. This will facilitate informed shared decision-making and personalized medicine, so that drugs are used to help older adults achieve what matters most to them.

AUTHOR CONTRIBUTIONS

All authors contributed to the conceptualization of the paper. SNH and DLC drafted the manuscript. LEW drafted Figure 1. All authors edited drafts and approved the final manuscript.

ACKNOWLEDGMENTS

Open access publishing facilitated by The University of Sydney, as part of the Wiley - The University of Sydney agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST STATEMENT

All authors are unpaid members of the IUPHAR Geriatric Committee. This paper is based on an oral

presentation at the American Geriatrics Society Annual Scientific Meeting, May 2023 by Sarah Hilmer in the Symposium, 'Evaluation of New Drugs: A changing landscape for older adults and diverse populations', which was entitled, 'An international perspective through the International Union of Basic and Clinical Pharmacology (IUPHAR).'

SPONSOR'S ROLE

None.

ORCID

Sarah N. Hilmer https://orcid.org/0000-0002-5970-1501
Janice Schwartz https://orcid.org/0000-0002-5171-7824
Mirko Petrovic https://orcid.org/0000-0002-7506-8646
Lauren E. Walker https://orcid.org/0000-0002-3827-4387
Petra Thürmann https://orcid.org/0000-0001-9724-1422
David G. Le Couteur https://orcid.org/0000-0002-4227-5817

REFERENCES

1. Liu Q, Schwartz JB, Slattum PW, et al. Roadmap to 2030 for drug evaluation in older adults. *Clin Pharmacol Ther*. 2022;112(2):210-223. doi:10.1002/cpt.2452
2. Kashyap M, Thuermann P, Le Couteur DG, Abernethy DR, Hilmer SN. IUPHAR international geriatric clinical pharmacology curriculum for medical students. *Pharmacol Res*. 2019;141:611-615. doi:10.1016/j.phrs.2019.01.032
3. Hilmer SN, Petrovic M, Le Couteur DG, Schwartz JB, Thuermann P. Development, evaluation and use of COVID-19 vaccines in older adults: preliminary principles for the pandemic and beyond. *Br J Clin Pharmacol*. 2021;87(9):3459-3461. doi:10.1111/bcp.14967
4. Bellantuono I, de Cabo R, Ehninger D, et al. A toolbox for the longitudinal assessment of healthspan in aging mice. *Nat Protoc*. 2020;15(2):540-574. doi:10.1038/s41596-019-0256-1
5. Kane AE, Hilmer SN, Mach J, Mitchell SJ, de Cabo R, Howlett SE. Animal models of frailty: current applications in clinical research. *Clin Interv Aging*. 2016;11:1519-1529. doi:10.2147/CIA.S105714
6. Mach J, Gemikonakli G, Logan C, et al. Chronic polypharmacy with increasing drug burden index exacerbates frailty and impairs physical function, with effects attenuated by deprescribing, in aged mice. *J Gerontol A Biol Sci Med Sci*. 2021;76(6):1010-1018. doi:10.1093/gerona/glaa060
7. Abellan Van Kan G, Sinclair A, Andrieu S, et al. The geriatric minimum data set for clinical trials (GMDS). *J Nutr Health Aging*. 2008;12(3):197-200. doi:10.1007/BF02982620
8. Thürmann PA. Clinical studies in geriatric population. In: Hock F, Gralinski M, eds. *Drug Discovery and Evaluation: Methods in Clinical Pharmacology*. Springer; 2020.
9. Denkinger M, Knol W, Cherubini A, et al. Inclusion of functional measures and frailty in the development and evaluation of medicines for older adults. *Lancet Healthy Longev*. 2023;4(12):e724-e729. doi:10.1016/S2666-7568(23)00208-8
10. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381(9868):752-762. doi:10.1016/S0140-6736(12)62167-9
11. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. *Lancet*. 2019;394(10206):1365-1375. doi:10.1016/S0140-6736(19)31786-6
12. de Souto BP, Rolland Y, Ferrucci L, et al. Looking at frailty and intrinsic capacity through a geroscience lens: the ICFSR & Geroscience Task Force. *Nat Aging*. 2023;3:1474-1479. doi:10.1038/s43587-023-00531-w
13. Arakelyan S, Mikula-Noble N, Ho L, et al. Effectiveness of holistic assessment-based interventions for adults with multiple long-term conditions and frailty: an umbrella review of systematic reviews. *Lancet Healthy Longev*. 2023;4(11):e629-e644. doi:10.1016/S2666-7568(23)00190-3
14. Goede V, Neuendorff NR, Schulz RJ, Hormigo AI, Martinez-Peromingo FJ, Cordoba R. Frailty assessment in the care of older people with haematological malignancies. *Lancet Healthy Longev*. 2021;2(11):e736-e745. doi:10.1016/S2666-7568(21)00184-7
15. Salvioli S, Basile MS, Bencivenga L, et al. Biomarkers of aging in frailty and age-associated disorders: state of the art and future perspective. *Ageing Res Rev*. 2023;91:102044. doi:10.1016/j.arr.2023.102044
16. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-M156. doi:10.1093/gerona/56.3.m146
17. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci*. 2007;62(7):722-727. doi:10.1093/gerona/62.7.722
18. Hilmer SN, Kirkpatrick CMJ. New horizons in the impact of frailty on pharmacokinetics: latest developments. *Age Ageing*. 2021;50(4):1054-1063. doi:10.1093/ageing/afab003
19. Hilmer SN, Wu H, Zhang M. Biology of frailty: implications for clinical pharmacology and drug therapy in frail older people. *Mech Ageing Dev*. 2019;181:22-28. doi:10.1016/j.mad.2019.111119
20. Pazan F, Petrovic M, Cherubini A, et al. Current evidence on the impact of medication optimization or pharmacological interventions on frailty or aspects of frailty: a systematic review of randomized controlled trials. *Eur J Clin Pharmacol*. 2021;77(1):1-12. doi:10.1007/s00228-020-02951-8
21. Liu BM, Kouladjian O'Donnell L, Redston MR, et al. Association of the Drug Burden Index (DBI) exposure with outcomes: a systematic review. *J Am Geriatr Soc*. 2023;72(2):589-603. doi:10.1111/jgs.18691
22. Ibrahim K, Cox NJ, Stevenson JM, Lim S, Fraser SDS, Roberts HC. A systematic review of the evidence for deprescribing interventions among older people living with frailty. *BMC Geriatr*. 2021;21(1):258. doi:10.1186/s12877-021-02208-8
23. Butt JH, Jhund PS, Belohlavek J, et al. Efficacy and safety of dapagliflozin according to frailty in patients with heart failure: a prespecified analysis of the DELIVER trial. *Circulation*. 2022;146(16):1210-1224. doi:10.1161/CIRCULATIONAHA.122.061754

24. Sheppard JP, Koshiaris C, Stevens R, et al. The association between antihypertensive treatment and serious adverse events by age and frailty: a cohort study. *PLoS Med*. 2023;20(4):e1004223. doi:10.1371/journal.pmed.1004223
25. Jang IY, Jung HW, Lee HY, Park H, Lee E, Kim DH. Evaluation of clinically meaningful changes in measures of frailty. *J Gerontol A Biol Sci Med Sci*. 2020;75(6):1143-1147. doi:10.1093/gerona/glaa003
26. Le Couteur DG, Anderson RM, de Cabo R. Can we make drug discovery targeting fundamental mechanisms of aging a reality? *Expert Opin Drug Discovery*. 2022;17(2):97-100. doi:10.1080/17460441.2022.1993818
27. Mitchell SJ, MacArthur MR, Kane AE. Optimizing preclinical models of ageing for translation to clinical trials. *Br J Clin Pharmacol*. 2023. doi:10.1111/bcp.15902
28. Fujita K, Masnoon N, Mach J, O'Donnell L, Hilmer S. Polypharmacy and Precision Medicine. *Cambridge Prisms: Precision Medicine*; Cambridge Press. 2023;1(E22). doi:10.1017/pcm.2023.10
29. Siriwardhana DD, Hardoon S, Rait G, Weerasinghe MC, Walters KR. Prevalence of frailty and prefrailty among community-dwelling older adults in low-income and middle-income countries: a systematic review and meta-analysis. *BMJ Open*. 2018;8(3):e018195. doi:10.1136/bmjopen-2017-018195
30. Awan FA, Becker AB, Wang Y, Kimmelman J. Participant recruitment from low- and middle-income countries for pivotal trials of drugs approved by the U.S. Food and Drug Administration: a cross-sectional analysis. *Ann Intern Med*. 2022;175(12):1675-1684. doi:10.7326/M22-1857
31. Alemayehu C, Mitchell G, Nikles J. Barriers for conducting clinical trials in developing countries- a systematic review. *Int J Equity Health*. 2018;17(1):37. doi:10.1186/s12939-018-0748-6

How to cite this article: Hilmer SN, Schwartz J, Petrovic M, Walker LE, Thürmann P, Le Couteur DG. Addressing the gaps in evaluation of new drugs for older adults: Strategies from the International Union of Basic and Clinical Pharmacology (IUPHAR) Geriatric Committee. *J Am Geriatr Soc*. 2024;1-9. doi:10.1111/jgs.18826