Risk management considerations for older adult populations

The population is ageing worldwide. In 1950, there were 205 million persons age 60 years or over in the world, and by 2012, the number of older persons had increased to almost 810 million. It is projected to be more than double by 2050, reaching two billion. Global trends point not only to an ageing population, but increased life expectancy, leading to growth in those at the extremes of age, known as “the oldest old.” As a result, the prevalence of chronic diseases associated with ageing is on the rise. For example, from 2010 to 2030 there is an anticipated 67% increase in cancer incidence among individuals age 65 years and older. As a result, new economic and healthcare challenges are emerging.

The ageing of the worldwide population has direct and indirect impacts on healthcare costs, as older adults take the majority of medications. Paradoxically, despite older adults taking the majority of medications, they have been under-represented in registration studies, which define the risks and benefits of these medications. Indeed, most dossiers – from nonclinical through Phases II/III – include limited data on older adults. Hence, clinicians and policy-makers frequently rely on clinical trials of middle age adults to provide supportive evidence for treating complex, older patients, but comorbidities, age-associated changes in drug pharmacology, a regulatory infrastructure not optimised for geriatric biopharmaceutical development, and other impediments to recruiting older persons for clinical trials render the evidence inaccurate at best. There is a critical need to improve the representation of older adults in clinical studies and for medication use in older persons to be optimised through a robust risk management strategy informed by an understanding of age-related physiological changes, age-associated diseases, and geriatric syndromes, as well as use of real-world evidence.

Age-related changes in the drug pharmacology

With increasing age, there are changes in drug pharmacokinetics (PK) and pharmacodynamics (PD). Though no significant changes in absorption have been found, older persons have decreased gastrointestinal and splanchnic blood flow, decreased Cmax and/or time to onset drug effect, and an increased bioavailability of some drugs due to a decrease in first pass metabolism. Older adults have a decrease in body weight starting in the seventh or eighth decade of life, a decrease in total body water, and a decrease in lean body mass concurrent with an increase in body fat. Furthermore, there is a decrease in liver mass and alterations in the cytochrome p450 enzyme system. Because of decreased hepatic blood flow, the rate of metabolism in older adults may be limited by drug delivery. Furthermore, older adults have decreased kidney mass and renal blood flow, and a decrease in glomerular filtration rate.

These age-related changes in PK can have practical implications in terms of the drug dose and interval, due to increases in drug half-life and/or decrease in clearance, as well as increased time to reach steady state drug concentration. For example, the half-life of diazepam in older persons is 90 hours, and steady state is not reached until up to two weeks after starting/dose increase. As a result, dosages need to be decreased and/or dosing intervals increased to counteract decreased clearance in older persons.

Pharmacodynamic differences that accompany ageing can alter receptors or post-receptor events, tissues, or end-organs, as well as lead to compensatory or homeostatic mechanisms. This leads to various differences in drug sensitivity. For example, decreased drug sensitivity is seen in older persons in the decreased heart rate response with isoproterenol due to a decreased proportion of high-affinity beta-adrenoceptors and decreased cyclic adenosine monophosphate (AMP). Conversely, increased drug sensitivity is observed in older persons in the following domains: increased sedation and memory impairment (eg, diazepam); increased pain relief (eg, morphine); and increased cardiac and central nervous system toxicity (eg, theophylline). These recognised changes in age-related PK and PD underscore the need for continued research that aims to mitigate the risk posed by medication in older adults. In particular there is a critical need to address the dearth of Phase II/III trials that focus on this population.
Focus – Older populations

Table 1: The advantages, disadvantages and limitations of data sources for older adults.

<table>
<thead>
<tr>
<th>Data source</th>
<th>Pros</th>
<th>Cons</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Nonclinical study</td>
<td>May provide early insights with regard to mechanism of action, potential age-related adverse effects</td>
<td>Findings may not translate to humans</td>
<td>Lack of animal models for many age-related changes/diseases</td>
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<td>Clinical trial</td>
<td>Scientifically robust data; can identify potential age-related adverse events; characterise events in older adults</td>
<td>Population studied does not generally include sufficient number of older adults</td>
<td>Barriers to enrolment of older adults with significant comorbidities, concomitant medications</td>
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<td>Postmarketing, spontaneous reports, adverse event reporting systems</td>
<td>Reflects general population; can detect severe/rare events in older adults</td>
<td>Subject to confounding by indication, recall bias, etc</td>
<td>Incomplete information</td>
</tr>
<tr>
<td>Postmarketing non-interventional research (eg, post-authorisation safety study)</td>
<td>Reflects general population; can detect rare events in older adults</td>
<td>Need sufficient post-marketing exposure.</td>
<td>Limited information; inability to follow up.</td>
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Under-representation: A complex multi-faceted problem

There are several factors that contribute to the under-representation of older adults on clinical trials. Strict inclusion and exclusion criteria based on comorbidities, organ function, or concomitant medication use often lead to the exclusion of older adults. When they are included, the numbers are not only insufficient, but the individuals who enrol may not be reflective of the geriatric population as a whole. This is particularly true for clinical studies. For example, a seven-year study of FDA-approved cancer drugs (n=28,766 patients with cancer from 55 registration trials) showed that sample sizes of patients age ≥65, ≥70, and ≥75 years were 36%, 20%, and 9% of sample size, respectively, despite these individuals comprising 60%, 46%, and 31% of the cancer population, respectively. Further, a systematic review of Phase III/IV randomised controlled clinical trials in 2007 found that older persons were excluded from clinical trials based on protocol inclusion and exclusion criteria; that trials did not study relevant outcomes; and that they did not conduct appropriate age-group specific analyses.

The challenges of including frail, older persons in clinical trials are myriad. These include system-wide challenges, ranging from the shortage of personnel with geriatric expertise (including clinical trial staff) to the lack of a clinical trial’s infrastructure to support the time and space needed to care for this vulnerable population. Further exclusion criteria include practical considerations: older adults may require the involvement of family members, or may be unable to participate in clinical trials because of family and/or work commitments. Even if they do meet clinical trial criteria, other practical considerations as seemingly innocuous as transportation and accessible parking can cause difficulty with older adults’ enrolment.

Moreover, enrolling patients with multiple comorbidities, including older patients, may lead to significant challenges in the interpretation of clinical trial results. At one extreme, each of these patients may constitute a unique subpopulation. Since adverse events are generally more common in older individuals and those with multiple comorbidities, there is an increased possibility of imbalances that do not necessarily reflect the scientifically-based benefit-risk assessment for some patients with the greatest unmet medical need. This particular obstacle can be overcome by conducting “geriatric studies” (akin to paediatric studies) or using alternative study designs (eg, extended trial design with an expansion cohort to specifically assess adverse effects in older adults). Robust risk management plans can complete the limited data from clinical programmes by using larger comparative data sets to further evaluate and characterise these adverse events.

It is critical to develop a robust risk management strategy for older adults at an early stage, and refine it throughout product lifecycle with consideration of older persons at all phases – Phase I (clinical pharmacology), Phase II/III (clinical development), marketing authorisation (labelling), and Phase IV (postmarketing risk evaluation and mitigation strategies or risk minimisation).

Pre-authorisation and post-authorisation activities

Regulatory requirements for pre-authorisation are limited, as regulatory authorities recognise the need to increase enrolment of older adults in registered clinical trials. The US FDA and European Medicines Agency (EMA) have adopted International Council for Harmonisation (ICH) E7 recommendations to obtain data on older persons in different age groups, taking multiple concomitant medications, and with significant comorbidity, and to seek specific adverse events and age-related safety endpoints in the geriatric population, eg, effects on cognitive function, balance and falls, urinary incontinence or retention, weight loss, and sarcopenia.

The EMA’s Geriatric Medicines Strategy provides regulatory support – as well as external scientific expertise from a Geriatrics Expert Group (GEG) – for the development, evaluation, and labelling of medicinal products for older persons. According to Cerreta et al, the EMA encourages post-authorisation studies when data on older patients with comorbidities and polypharmacy concomitant medications are lacking at the time of marketing authorisation, and the agency is working with health technology assessment (HTA) bodies to ensure that data are available to support use of the medicinal product in routine clinical practice in the target population.

Post-authorisation, routine pharmacovigilance (drug safety monitoring) is key to ensuring patient safety and protecting public health. The purpose of the Pharmacovigilance (PV) Plan is to obtain missing information on population(s) not studied, eg, to address gaps in knowledge about a medicinal product related to the anticipated utilisation patterns in particular patient populations, which could be clinically significant, and further characterise potential risks (safety specification). The PV Plan includes routine PV (safety surveillance) and additional PV activities (APVA). APVA are PV activities that are not considered routine. Studies in the PV Plan may be nonclinical...
studies, clinical trials, or non-interventional studies. Examples of APVA include post-authorisation safety studies or PASS (long-term follow-up of patients from clinical trial populations), cohort studies to provide additional characterisation of the long-term safety of the medicinal product), drug utilisation studies (DUS), and effectiveness evaluations of additional risk minimisation activities related to the safety concerns identified in the safety specification.

It is essential, therefore, that the safety specification be developed with a full understanding of age-related physiological changes, age-associated diseases, and geriatric syndromes, those “multifactorial health conditions that occur when the accumulated effects of impairments in multiple systems render an older person vulnerable to situational challenges.” For example, a drug that causes mild to moderate diarrhoea in middle-aged clinical trial subjects may be associated with severe dehydration, severe electrolyte imbalances including hyponatremia, and syncope/falls with bone fractures in older adults. These adverse effects may be mitigated by an understanding of age-related physiological changes (eg, blunted thirst response, changes in the renin-angiotensin-aldosterone system, blunted cardiovascular response to hypovolemia), age-associated diseases (eg, osteoporosis), and geriatric syndromes (eg, syncope/falls, confusion), and implementation of the appropriate risk minimisation measures (eg, labelling, educational materials).

It is worth taking advantage of postmarketing experience – including populations not studied in clinical trials, eg, older persons – as an opportunity to understand product safety (and efficacy) with real-world evidence (see Table 1 for data sources for older adults).

The FDA considers risk management to be an iterative process of: (1) assessing a product’s benefit–risk balance; (2) developing and implementing tools to minimise its risks while preserving its benefits; (3) evaluating tool effectiveness and reassessing the benefit–risk balance; and (4) making adjustments, as appropriate, to the risk minimisation tools to further improve the benefit–risk balance. Risk management may also be considered in terms of those activities or interventions associated with risk identification, characterisation, prevention, and mitigation (or minimisation) and measurement of the effectiveness of risk minimisation measures. In either case, risk management (risk assessment plus risk minimisation) is part of a continuous, iterative process that starts early in development and continues throughout the product’s lifecycle, with the results of risk assessment informing subsequent decisions on risk minimisation activities.

An understanding of age-related physiological changes and common geriatric syndromes can aid in identifying and characterising drug-associated risks. Significant drug-associated sedation or confusion may be detected earlier in older than younger adults who have more sensitive opioid and benzodiazepine receptors. This drug-associated adverse effect may be manifest by spontaneous reports of falls, urinary incontinence, and/or delirium, all common, inter-related geriatric syndromes. This type of real-world evidence can then inform the strategy for risk mitigation.

The risk minimisation plan consists of routine and additional risk minimisation measures (ARMMs; also known as additional risk minimisation activities – ARMAs), which are public health interventions intended to prevent or reduce the occurrence of adverse reactions associated with exposure to a medicine or reduce their severity or impact on the patient should they occur. Routine risk minimisation activities include the legal status of the product (eg, prescription only) and the label (eg, “geriatric use”). However, age-related changes in nearvision and accommodation (presbyosis) as well as age-associated diseases (eg, cataracts, glaucoma, macular degeneration) may hinder the effectiveness of labelling that specifies dose adjustments and/or warnings and precautions for older adults. In the US, the minimum for a medication guide is 10pt font size and for other labelling – such as that accompanying promotional materials – it is 8pt font, too small for many older adults to read without magnification. Few ARMAs are currently targeted to older adults or their caregivers.

Conclusion

As the global population ages, more medicinal products will be prescribed for older adults. It is important to understand the potential differences in the benefit–risk profile of these products in populations >65, >75, and >85 years of age. Ideally, clinical trials will include adequate numbers of older adults, but if we continue to exclude individuals taking multiple concomitant drugs and with significant comorbidities from study and analysis, and maintain barriers to enrolment of frail, older adults, that situation is unlikely to improve. To protect patient safety and improve public health, we need to think about the specificities of this population, conduct safety surveillance activities against a backdrop of understanding, and develop post-authorisation safety studies that acknowledge the challenges and complexity of drug safety analysis in this heterogeneous population.

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References


Further reading