

Priority Medicines for Europe and the World  
"A Public Health Approach to Innovation"

Update on 2004 Background Paper

Written by MJC Willemen, PAF Jansen en HGM Leufkens

**Background Paper 7.3**  
**Priority Medicines for Elderly**

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### Executive summary and key research points

This cross-cutting background paper addresses special needs in the treatment of elderly patients that may not be covered in other parts of the Priority Medicines for Europe and the World Report and depicts developments since the previous edition of this report in 2004. These specific needs are a result of changing physiology over the course of their lifetime, the spectrum of diseases that the elderly face, the fact that they are often left out of the drug development process, and that, in daily practice, medicine use in the elderly is complicated as a result of many factors, such as polypharmacy.

People aged 60 and older are a growing part of both European and global communities. The proportion of the global population aged 60 and over will increase to more than 16% in 2030. In Europe, the growth of the elderly population is more pronounced. Demographics are further characterised by decreased fertility rates and increased life expectancy, with women living longer than men.

The diversity of older people is one factor contributing to their complex health issues and care needs. This paper describes three common conditions in the elderly that were not (fully) covered in other background papers: osteoporosis (including falls), cancer, and vascular dementia. Fall prevention is of the utmost importance in the elderly to prevent adverse outcomes. Various fall prevention programs exist, but implementation, uptake of, and adherence to evidence-based fall prevention programs need further attention. As the population grows older, the incidence of cancer increases. The elderly are a heterogeneous population responding differently to chemotherapy. Whether geriatric co-morbidities can predict specific clinical outcomes in cancer patients, such as quality of life, treatment tolerance or survival, has not yet been clarified. A robust screening tool is therefore needed in order to facilitate treatment decisions and offer tailored care. Although most cases of dementias are mixed cases in which a vascular component plays an important role, research has focused on Alzheimer disease over the past decade. More research on vascular dementia is needed to assess its epidemiology, improve diagnosis, and identify (new) targets for treatment.

For many reasons, the elderly may have difficulty taking medications. Tasks like opening packages, reading leaflet information and/or swallowing oral medication may be especially difficult. Some of these special needs have strong similarities with the needs of children. There is a call for the development of special geriatric formulations, and the example of paediatric adapted formulations could be a useful model here. When, in the near future, adapted formulations have been developed it will be necessary to study and evaluate how these products have influenced healthcare, and if they have indeed led to better health in the elderly.

The elderly are still underrepresented in clinical trials, resulting in a lack of information about the safety and efficacy of medicines in this population. A consensus definition of frailty, as well as better tools to evaluate it, are needed, as these may enable the selection and inclusion of elderly in clinical trials. Besides, new approaches such as the improved use of existing data (e.g. electronic health records) may be valuable in obtaining (better) data on the effectiveness of medicines in the elderly. Finally, ways to translate the obtained information

from clinical trials into practical recommendations—in the Summary of Product Characteristics and/or age specific recommendations in guidelines, should be further explored.

Various improvements can be made in the medicine usage environment of the elderly. Polypharmacy, defined as taking multiple medicines for chronic use at the same time (usually more than 4 or 5 medicines), is very common in the elderly, and medication reviewing has become common practice in some countries. However, the benefits of medication reviewing are not fully proven yet; medication reviewing leads to more appropriate prescribing, but benefits on harder clinical outcomes, such as hospital admissions or mortality and their cost-effectiveness, need to be confirmed. The potentially facilitating role of computerized systems in this instance should be explored. Electronic solutions could make the reviewing less time consuming and could help the reviewer to systematically select patients that might benefit most from reviewing, but the added value of these solutions remains to be established.

Adherence to medication regimes should be improved in the elderly. There is an important need for basic and applied research on interventions to assist patients in following the instructions on prescriptions for chronic medical disorders. Although this applies to the population as a whole, the elderly deserve special attention in this respect. Effective interventions may be quite complex and unsuitable for daily practice. More research into establishing the most (cost-)effective interventions is needed. Future emphasis should also be placed on the necessity to actively involve the patient in treatment decisions.

It is unknown if inequity in access to medicines exists in the elderly. Research to establish this is needed, especially in light of the ongoing economic recession and subsequent policy measures that have been taken. Underuse and under-prescribing are, however, also present in this population. The relative absence of guidance on prescribing in the elderly population in clinical guidelines may contribute to this situation. Improvement might be possible through quick and extensive data sharing with the aid of computerized systems, although this is yet to be confirmed.

Palliative care has become more important over the last few years and has been acknowledged as a serious part of healthcare. There is a need for further evaluation of the (cost-)effectiveness of interventions in the last phase of life. Still, many elderly near the end of life suffer from pain, hence improvements in pain management are needed. Identifying and resolving barriers to treatment with opioid medications is an important step forward, but for optimal treatment their effects need to be established. Further, polypharmacy is prevalent at the end of life, and medication review and simplification of drug regimes in this cohort have been called for.

Finally, integration of care in elderly patients is essential, to prevent medication errors due to loss of information for example. The elderly dwell in different environments depending on their care needs and experience more transfers between care settings than other populations. Each transfer introduces the potential risk of unintentionally discontinuing medications or of represcribing medicines that were initially stopped. Effort is put on ensuring accurate medication taking in second-line care (hospitals) through medication reviewing of complete geriatric assessments for example, but little effort is put into the communication between first and second-line care. It seems beneficial for the older patient to be treated in an

environment that provides multidimensional, interdisciplinary care; how such care is organised needs further investigation. There is a trend toward the elderly living longer independently, but medication management is complex and many elderly have difficulties that may hamper accurate medication management. Tools to assess their ability to manage their medication at home have been developed, but still need further evaluation. The role of caregivers in medication management, including adherence, should be further explored, especially because at-home populations rely heavily on their support. eHealth might help to facilitate quick and easy information exchange between healthcare professionals, making it easier to communicate and provide integrated care. Until now, the fact that eHealth solutions lead to better health in the general population has not been proven. Therefore, the role of eHealth in this population warrants further investigation.

In summary, the following key research priorities for elderly have been identified:

- Evaluation of the (cost-)effectiveness of ongoing programs and initiatives in the elderly with a focus on objective clinical outcomes:
  - Fall prevention programs
  - Medication reviewing
  - Interventions to improve adherence
  - Interventions in palliative care
- Development of a robust screening tool for oncology in order to establish which conditions are predictable for specific clinical outcomes of interest
- Development of adapted formulations for elderly adopting knowledge from paediatric formulations
- Assessment of tools that may improve participation of the elderly in clinical trials and new approaches to better use of real world data to establish effectiveness
- Translation of information about elderly into clinical guidelines and other sources of information for healthcare professionals that may guide better use of medicines and prevent under-prescribing
- Evaluation of the benefits of fast and extensive data sharing with the aid of computerized systems (role of eHealth)
- Integration of care and better self management for the elderly dwelling in different sites of care including their own homes; communication between health care professionals (especially at the interface of first and second line care), and medication management in the home situation need special attention.

### 1. Introduction

In 2004 the Priority Medicines for Europe and the World report was published. It included Section 7.2 on pharmaceuticals and the elderly. This background paper continues from and updates the 2004 background paper. With the population ageing, the number of older people is increasing rapidly worldwide, introducing a growing burden on global health systems (see Background Paper 5). The elderly consume more medicines than any other population and deserve special attention. Elderly patients have specific needs that may not be covered in other parts of the Priority Medicines for Europe and the World report. These needs are a result of changing physiology over a lifespan, the spectrum of diseases that the elderly encounter, the fact that they are often overlooked during the drug development phase, and that in daily practice the use of medicines in the elderly is complicated as a result of various issues— polypharmacy, for example— that result in additional risks of severe harm.

These issues require careful attention and analysis to guide future decision-making. This background paper addresses the special needs of the elderly. As such, this cross-cutting paper complements other background papers of this report, and cross references to other background papers are provided wherever relevant. In the present background paper, knowledge gaps, as well as implications for future research are discussed, giving an overview of the items and subjects related to the elderly that need more attention in the near future.

### 2. Demographics and diseases faced by the elderly

This section focuses on demographics and several diseases that are specific to the elderly. For more general or detailed trends in demography the reader is referred to Background Paper 5 of this report. Many of the conditions that the elderly suffer from are described in the various components of chapter 6 of this report. In this section, we focus briefly, but in more detail, on three very common diseases in the elderly that require additional attention: osteoporosis (including falls), cancer, and vascular dementia. These conditions were all urgent issues that appeared prominently on the agendas of several international geriatric conferences, such as those of the European Union Geriatric Medicine Society (EUGMS), the International Association of Gerontology and Geriatrics (IAGG), the British Geriatrics Society, and the American Geriatrics Society. Although the importance of healthy ageing and prevention (including vaccination, if appropriate) is acknowledged, this is regarded as outside the scope of this present cross-cutting background paper.

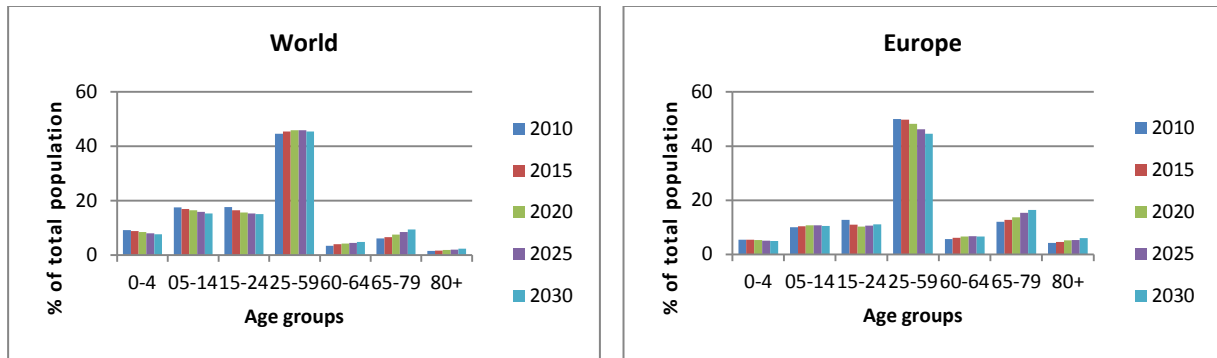
#### 2.1 Ageing

People aged 60 and older are a growing part of both European and global communities (see Figure 7.3.1). In 2010, about 11% of the population worldwide was aged 60 and over. By the year 2030, this proportion will increase to more than 16%. In Europe, the growth of the elderly population is more pronounced. By the year 2030, forecasts say that the percentage of the population who will be aged 60 and over will be about 29%.<sup>1, 2</sup> While the overall trend is virtually the same in all countries, there is considerable variation between individual

## Update on 2004 Background Paper, BP 7.3 Elderly

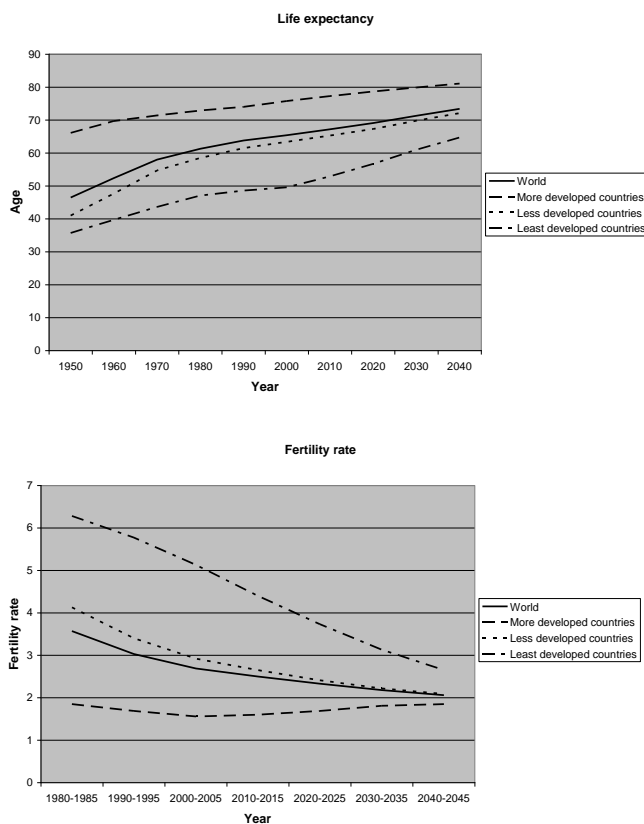
countries, and between Europe and the rest of the world, with respect to the speed of these developments.<sup>1</sup>

**Figure 7.3.1: Population distribution in the world and Europe: recent history and coming decades. From: World Population Prospects, the 2010 revision database, UN Population division.**



Source: United Nations , Department of Economic and Social Affairs. Population Database UNDoEaSA. <http://esa.un.org/unpd/wpp/index.htm>. 2012. Accessed May 13, 2013.<sup>1</sup>

**Figure 7.3.2: upper: life expectancy over time; lower: fertility rate over time**



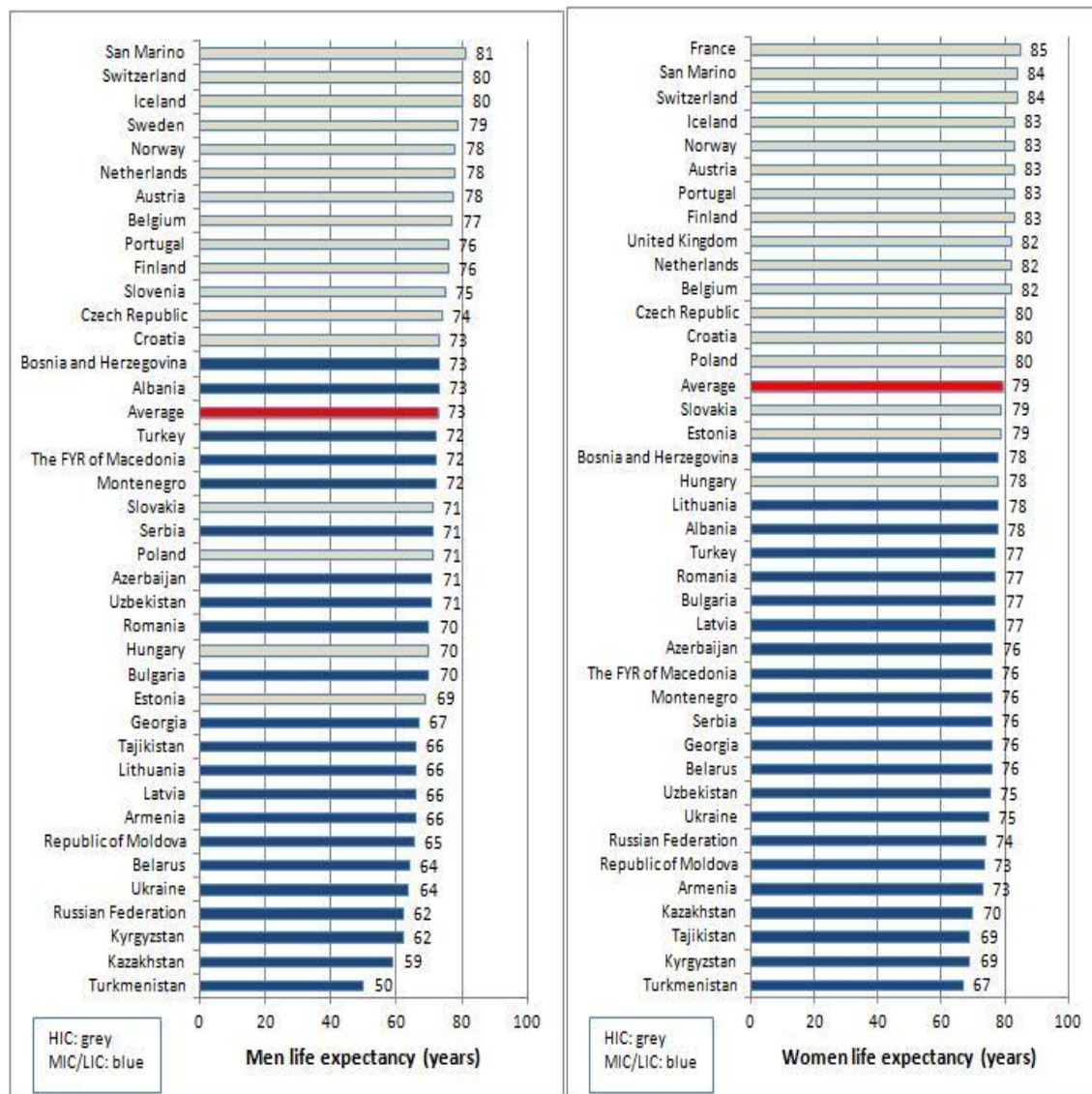
Source: UN population division. World Population Prospects, The 2002 revision database. 2002.<sup>3</sup>

## Update on 2004 Background Paper, BP 7.3 Elderly

Multiple factors contribute to the shift in population distribution. On one hand, life expectancy dramatically increased in the past century (see Figure 7.3.2, upper) due to a combination of improvements in both socio-economic and environmental conditions and in preventive (e.g. vaccines) and direct medical care.<sup>4</sup> On the other hand, fertility has decreased (as shown in Figure 7.3.2, lower). In more developed countries, fertility decreased below the replacement level. Furthermore, the baby-boom generation (born between 1946 and 1964) will reach the age of 70 in this and the next decade. These factors – discussed in more detail in Background Paper 5 – make the elderly population the fastest growing part of the total population.

In addition, there is a trend towards the feminisation of the elderly population due to the differences in life expectancies between men and women. This difference is more pronounced in Eastern European countries, as shown in Figure 7.3.3.

**Figure 7.3.3: European life expectancy rates for men and women [Source: WHO Pharmaceutical Country Project, 2011]**



Source: Development of Country Profiles and monitoring of the pharmaceutical situation in countries. [http://www.who.int/medicines/areas/coordination/coordination\\_assessment/en/index1.html](http://www.who.int/medicines/areas/coordination/coordination_assessment/en/index1.html). WHO, 2013.<sup>5</sup>



## 2.2 Osteoporosis

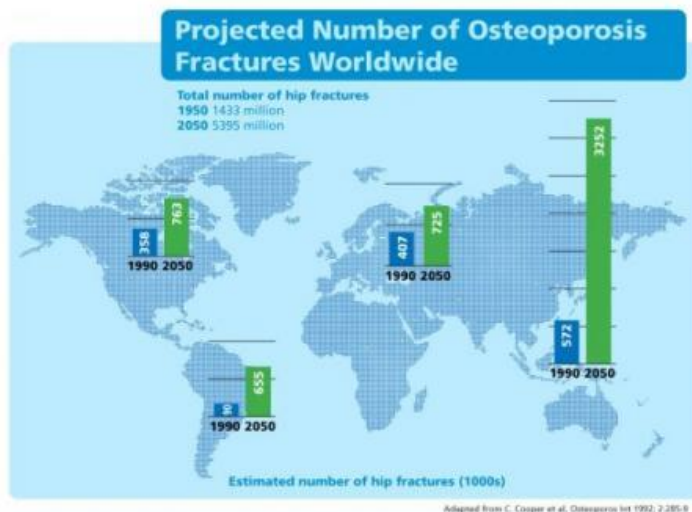
### Epidemiology and burden of disease

Osteoporosis is a disease characterised by a decrease in bone density resulting in an increased risk of fractures. Decreased bone formation by osteoblasts and the increased breakdown of bone by osteoclasts eventually lead to changes in the micro-architecture of the bone.<sup>6</sup>

The prevalence of osteoporosis increases with age, and women are much more affected than men. The prevalence rises from 5% in women aged 50, up to 50% in women aged 85 years. In men, the prevalence ranges from 2.4% (50 years) up to 20% (85 years).<sup>7</sup>

Osteoporosis is much more prevalent among Caucasian populations.<sup>8</sup> Due to the ageing and feminisation of the population, osteoporosis is becoming more prevalent.<sup>8</sup> Figure 7.3.4 shows the projected number of osteoporotic hip fractures worldwide. These are projected to rise from 1.6 million in 1990 to 6.3 million in 2050.<sup>9</sup>

**Figure 7.3.4: Projected number of osteoporosis fractures worldwide.**



Source: International Osteoporosis Foundation. Epidemiology, Home - Osteoporosis & Musculoskeletal Disorders - Osteoporosis - What is Osteoporosis? 2012.<sup>10</sup>

Most osteoporotic fractures occur in the hip, spine, or wrist, and cause considerable reductions in mobility and quality of life.<sup>11</sup> Most of these fractures require hospitalisation and are therefore associated with complications such as pneumonia or thrombo-embolism due to chronic immobilisation.<sup>11</sup> Hip and spine fractures are also associated with high mortality rates, increasing with age from 3% in people younger than 60 years and up to 51% for the very elderly (90+) within the first year after diagnosis of the fracture.<sup>12</sup>

Osteoporotic fractures are associated with high costs from hospitalisation, rehabilitation, and (premature) transition to institutional care. One United States study estimated that the total expenditures in the United States due to osteoporotic fractures were 16.9 billion dollars in the

year 2005. Three quarters of these costs were attributable to care for women.<sup>8</sup> More than half (62.4%) of the expenditures for osteoporotic fractures could be attributed to inpatient care and more than one quarter (28.2%) to nursing home care.<sup>13</sup> With the ageing of the population, it is predicted that osteoporotic fractures will cost about 25 billion dollar in the year 2025, an increase of 50%.<sup>8</sup>

### Diagnosis

Osteoporosis is often diagnosed once a patient presents with a fracture, although efforts are ongoing to increase diagnosis before fractures occur. The density of the bone mineral, expressed in a T-value, is a measure for the degree of osteoporosis.<sup>11</sup> A T-value less than -2.5 confirms the diagnosis of osteoporosis.<sup>6</sup>

### Therapy

Non-pharmacologic treatment for osteoporosis consists of life style changes, more physical activity (weight bearing exercises), cessation of smoking, and decreased alcohol consumption. The addition of vitamin D to achieve sufficient serum levels is usually advised. Pharmacologic treatments consist of compounds to increase bone density through the formation of bone (anabolic compounds, such as parathyroid hormone) or to decrease the breakdown of bone (antiresorptives such as bisphosphonates). These current therapies are known to be effective. A Cochrane Review on the effect of 10 mgs of alendronate daily (a bisphosphonate) showed statistically significant effects for the secondary prevention of vertebral, combined non-vertebral, hip, and wrist fractures. Relative risk reductions for secondary prevention were 45%, 23%, 53%, and 50%, respectively.<sup>14</sup> For primary prevention, only a significant relative risk reduction in vertebral fractures was observed (45% reduction). In another Cochrane Review, a dose of 5 mgs of risedronate daily (another bisphosphonate) showed similar effects; a statistically significant and clinically relevant benefit in the secondary prevention of vertebral, non-vertebral, and hip fractures, but with no effects in primary prevention.<sup>15</sup> Etidronate seems to have less effect in reducing fractures. Four hundred mgs daily showed only clinical significant benefit in the secondary prevention of vertebral fractures according to a Cochrane Review.<sup>16</sup> The use of bisphosphonates are hindered by side effects such as oesophageal irritation and drug-drug/drug-food interactions. Administration of oral bisphosphonates can be tedious: they require ingestion on an empty stomach, and after administration, along with drinking a full glass of water, the patient needs to sit upright or stand for 30-60 minutes.

### Novel insights

During the last decade, research revealed the pathogenesis of osteoporosis through linkages with tissue, cellular and signalling processes in more detail. Due to increased knowledge of molecular and cellular principles, novel therapies are being developed. An example is denozumab, a human IgG2 monoclonal antibody that interferes with Nuclear Factor-Kappa B (NFkB), which is an essential signalling compound in the activation of osteoclasts. Likewise, odanacatib inhibits the protease cathepsin K, which plays a role in bone degradation. This compound is currently under investigation in phase 3 trials.<sup>11</sup>

### Fall prevention programmes

Although osteoporosis leads to increased fracture risk, falls are the predominant predictor of fractures. About a third of the people aged 65 or over fall each year. Several risk factors for falls have been investigated. It is estimated that accidental/environmental causes account for 31% of falls, followed by gait/balance disorders (17%), and dizziness/vertigo (13%).<sup>17</sup> The use of psychotropic medicines is also another important risk factor.

About 10% of all falls result in fractures.<sup>18</sup> Therefore, various fall prevention programs have been developed. Different studies have shown that between 15 to 50% of the falls can be prevented with interventions. The interventions that have been developed and studied are mainly strength and balance training, reduction in the number of psychotropic medicines, or dietary supplementation with vitamin D and calcium.<sup>19</sup> A recent Cochrane Review (2012) assessed the effects of interventions designed to reduce falls in the elderly living in the community. They used two outcomes: rate ratios to compare rates of falls (falls per person per year) and risk of falling based on the number of people falling in each group. The study showed that group and home based exercise programs and home safety interventions significantly reduced the rate of falling (rate ratio, RaR) and risk of falling (RR), with a RaR of 0.71 and a RR of 0.81 for exercise programs, and RaR 0.81 and RR 0.88 for home safety interventions, respectively. Multifactorial approaches (in which participants receive more than one intervention based on an individual assessment) reduced the rate of falls, but not the risk of falls. Interventions that focus on psychotropic medications are of value; gradual withdrawal of psychotropic medication reduced the rate of falls and a prescribing modification program for primary care physicians reduced the risk of falling. The supplementation of vitamin D did not reduce falls.<sup>18</sup> In the future, the study recommended that effective programs should be better implemented into practice, e.g. translation of research into practice should be strengthened. Research should also focus on methods to deliver the evidence-based programs and methods for increasing the uptake of and adherence to these interventions by the elderly.<sup>18</sup>

These recommendations are in line with the recently announced action plan of the European Innovation Partnership on Active and Healthy Ageing – launched by the European Commission – which presents the basis for the future work of this action group on fall prevention.<sup>20</sup> Six different objectives have been described including the promotion of a systematic approach to identifying individuals at higher risk for fall and harm of falls who will benefit from tailored intervention, and promotion of a systematic and coordinated approach to implementing evidence based strategies for the prevention and optimal management of falls and fractures, in order to reduce the associated physical, psychological, and functional disability.

### 2.3 Oncology

The background paper belonging to chapter 6.5 (Cancer and Cancer Therapeutics: Opportunities to address pharmaceutical gaps) describes the developments over the period of 2004 to 2012 in cancer diagnoses and treatment and identifies gaps between current research and potential research issues that could make a difference. The elderly are not specifically addressed in that background paper. Therefore, the present paper focuses on important topics related to cancer treatment in elderly patients.

### **Prevalence of cancer in elderly patients**

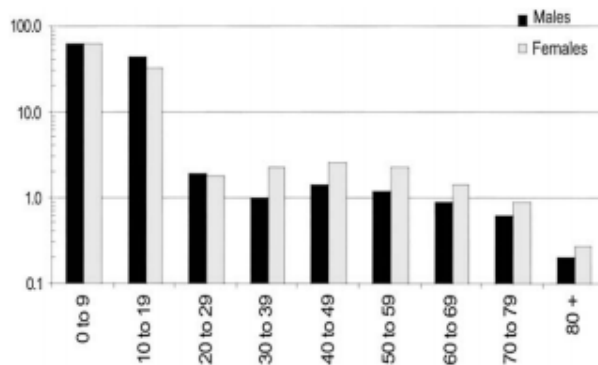
Cancer is highly prevalent in a relatively small proportion of the total population. In the United States, more than half of all new cancer diagnoses are in people older than 65,<sup>21</sup> and this population accounted for only 12.4% of the total United States population in 2005.<sup>22</sup> This trend will probably be more pronounced in the coming years due to the aging of the population. Likewise, the burden of cancer in this portion of the population will increase in the future.<sup>23</sup> Annex 7.3.1 shows the United States prevalence by cancer type and age at prevalence (2005-2009 data). In absolute terms, all types of cancer are more prevalent in the elderly except for Hodgkin Lymphoma and acute lymphocytic leukaemia. The most prevalent types of cancer in the elderly are prostate cancer in males; breast cancer in females; colon and rectum cancer, melanoma of the skin, and lung and bronchus cancer.<sup>21</sup> Although trends in prevalence are generally similar for the older population versus the younger population, disease profiles and the natural course of the disease may differ between age groups, with slower disease progression in the older population.

### **Participation of elderly cancer patients in clinical trials**

Despite the fact that the elderly account for the largest population group of cancer patients, their participation in clinical trials is low, see also Section 3.<sup>24, 25</sup> While 63% of United States cancer patients were 65 years and older, this age cohort comprised only 23% of oncology trial populations in 1999.<sup>25</sup> Figure 7.3.5 shows the percentage of United States cancer patients represented in National Cancer Institute sponsored clinical trials, divided by age group.

Some trials have been designed to investigate the effects of therapies in elderly cancer patients, but failed due to insufficient participation. For example, the ACTION trial, designed to evaluate the effect of chemotherapy versus observation in oestrogen receptor (ER) negative/ER weakly positive breast cancer in women over the age of 70. The investigators planned to include 1 000 patients from 43 research centres, but after 10 months only 4 of the 41 eligible patients were randomised and the study was discontinued.<sup>26</sup> The CASA study, set up to investigate the role of pegylated liposomal doxorubicin as an adjuvant chemotherapy in women with breast cancer aged 66 or older, also closed early due to poor recruitment.<sup>27</sup> Recruitment seems to be the complicating factor; this might be due to the treatment preferences of the clinician and the reluctance of this group of patients to agree to participate in trials in which the treatment arms differ radically.<sup>27</sup>

**Figure 7.3.5: Percentage of the estimated United States male and female cancer population represented in National Cancer Institute-sponsored cancer treatment clinical trials in 2002. (note the log scale on the y-axis)**



**Fig. 2 – Percentage of the estimated US male and female cancer population represented in National Cancer Institute-sponsored cancer treatment clinical trials: note the log scale for the y-axis**

Source: Sateren WB, Trimble EL, Abrams J, Brawley O, Breen N, Ford L, et al. How sociodemographics, presence of oncology specialists, and hospital cancer programs affect accrual to cancer treatment trials. *J Clin Oncol* 2002 Apr 15;20(8):2109-17.<sup>28</sup>

A factor that specifically complicates clinical research in the older oncology patient is their heterogeneity in terms of comorbidity, physical reserves, disability, and geriatric conditions.<sup>29</sup> This applies to older patients in general; but, for example, with cancer, it means that is not easy to predict how these patients will respond to chemotherapy. To enhance our understanding of patient response in relation to frailty, uniform tools to define and assess frailty are needed. There is an urgent need for a consensus on the definition of frailty, which is currently defined as the concept of a state of decreased physiological reserves due to an accumulation of deficits in physiological systems leading to a decreased resistance to stressors.<sup>29</sup> A uniform tool to assess frailty, with enough specificity and selectivity, would aid in deciding which patients are too healthy or too sick to participate in clinical trials,<sup>30</sup> and would guide therapy as well. The need for a clear and operable definition of frailty is also recognized by the International Society of Geriatric Oncology in their report on the ten priorities concerning geriatric oncology,<sup>31</sup> as part of the action plan on the 'Prevention and early diagnosis of frailty and functional decline, both physical and cognitive, in older people' of the European Innovation Partnership on Active and Healthy Ageing.<sup>32</sup>

### Comprehensive Geriatric Assessment

The recommendations of the oncology treatment guidelines, designed for younger patients, cannot be extrapolated to serve an elderly patient. For example, a study by Hoeben et al. investigated the patient factors associated with receiving adjuvant chemotherapy, treatment tolerance and outcome in patients older than 75 years of age with colon cancer. This study highlighted the necessity of screening a geriatric oncology patient before starting chemotherapy. In only 3% of the cases, the dose was adjusted before starting, but in 57% of the patients receiving chemotherapy, at least one adaptation was made after starting the therapy, as shown in Table 7.3.1.<sup>33</sup>

**Table 7.3.1: Type and prevalence of adaptation of chemotherapy for stage III colon cancer made after start with chemotherapy in elderly oncology patients.**

Type of adaptation	% of Patients
Type of chemotherapy	3
Dose	18
Time in between courses	23
Number of cycles	28
Total	57*

*\*In some patients more than one adaptation was made*

Source: Hoeben KW, van Steenberghe LN, van de Wouw AJ, Rutten HJ, van Spronsen DJ, Janssen-Heijnen ML. Treatment and complications in elderly stage III colon cancer patients in the Netherlands. *Ann Oncol* 2012 Nov 7.<sup>33</sup>

In an attempt to overcome this knowledge gap and to help guide treatment decisions, two features of geriatric medicine have been incorporated into geriatric oncology: frailty and the comprehensive geriatric assessment (CGA).<sup>29</sup> The CGA is a systematic procedure that assesses the health status of the elderly focusing on functional, somatic, and psychosocial domains.<sup>29, 34</sup> The CGA has proven to be beneficial for patients in general, as discussed in more detail in Section 5.6. A study evaluating the influence of a CGA on treatment decisions in 161 patients aged 75 or over and diagnosed with cancer showed that in 49% of patients the initially proposed chemotherapy dose was changed after the CGA. In 76% of all cases, the CGA led to a geriatric intervention, including management of nutrition (47%), polypharmacy (37%), depression (19%), and cognitive impairment (18%). These results show the capacity of a CGA to highlight treatment/diagnosis gaps and influence treatment decisions. In a similar study in 375 patients older than 70 with cancer, the CGA led to a change in the initial cancer treatment plan in nearly 21% of the patients; most patients switched from chemotherapy to supportive care.<sup>35</sup>

To perform the CGA, a variety of tools are used in order to assess specific geriatric conditions, such as the Mini-Mental State Examination (MMSE) for cognition. A systematic review investigated the association between the CGA and clinically relevant outcomes such as mortality, treatment toxicity, or chemotherapy completion. Different geriatric conditions were predictive for specific outcomes; frailty was predictive for toxicity of chemotherapy, and cognitive impairment and activities of daily living impairment were predictive for chemotherapy completion. However, evidence for the various conditions is too inconsistent to allow the CGA to guide decision making.<sup>36</sup>

Because the CGA is a time consuming process, patients are often preassessed with a quick screening tool to select them for the CGA or standard treatment. This is known as a 2-step method.<sup>29,37</sup> Different screening tools to perform the first step exist, but their predictive value in making a good pre-selection before the CGA, or even replacing the whole CGA is not sufficient.<sup>29,37</sup> A systematic review on the predictive value of seven frailty screening tools on the outcome of the CGA found no conclusive evidence for one of the tools; tools with the highest specificity lacked sensitivity and vice-versa. Several tools addressed only one or a few of the different geriatric domains,<sup>29</sup> which makes them less applicable for a general pre-selection. The evaluation of these rapid screening tools needs further research and evaluation.

It has not yet been clarified which geriatric conditions, such as quality of life, treatment tolerance or survival, are predictive of a specific clinical outcome in cancer patients. A robust screening tool is therefore needed in order to facilitate treatment decisions and offer tailored care. As long as this is not available, a complete multi-disciplinary geriatric assessment might be beneficial for all geriatric oncology patients,<sup>29</sup> in order to avoid under- or overtreatment and prevent complications or adverse treatment outcomes.<sup>38</sup>

### 2.4 Vascular dementia

Most cases of dementia that occur in the elderly are related to Alzheimer disease (AD). Background Paper Chapter 6.11 extensively focuses on the developments in AD since 2004. Here, we would like to focus on the knowledge gap around vascular dementia (VD). In most cases of dementia, there is a vascular component, which underlines the mixed character of dementia.<sup>39</sup> Attention is often paid more to AD, while VD is of great importance as well. Valid epidemiological data on the (age-specific) prevalence and incidence of VD are lacking. Depending on the different screening methods used, data differ considerably. It is assumed, however, that the incidence of VD is underestimated.<sup>40</sup>

VD is a term describing dementia resulting from vascular brain lesions. Pure VD seems to be rare, and differentiating between VD and mixed dementia is challenging. VD is heterogeneous in terms of pathogenesis, pathology, and clinical phenotype. Stroke seems to be a predisposing factor, but cognitive decline may develop slowly after stroke, and lesions may be visible, clouding the border between AD and VD.

VD patients benefit to a much lesser extent from cholinesterase treatment, and concurrent AD may have contributed to the positive results shown in some trials.<sup>40</sup> Current treatments focus on the prevention of VD, which is driven by the prevention of stroke. Targets for modifying vascular risk factors are similar to the well-described risk factors for cardiovascular disease and include hypertension, dyslipidemia, diabetes mellitus, blood hyperviscosity, carotid artery and intracranial artery stenoses, smoking, overweight, and physical inactivity.<sup>40</sup>

Much remains unclear about VD, including its epidemiology. As the aforementioned risk factors are the only etiological factors that can be prevented at present, and most of the cases of dementia are mixed, more research on VD is needed.

## 3. Product related issues in the elderly

There are several factors interfering with drug delivery in the elderly and two of those will be discussed in this background paper. First, the elderly have a different body composition, and their altered body functions are associated with changes in the pharmacokinetics and the pharmacodynamics of medicines. Second, the elderly are more vulnerable to factors influencing the administration of medication, such as difficulties with opening packages, swallowing or understanding health information. The development of special formulations aimed at older populations may help to overcome these difficulties.

### 3.1 Changes in body function in elderly

In older people body functions change, and almost all body systems alter in structure and/or function with increasing age. In a healthy elderly person, this change might not be an overt problem, but it may nevertheless be more difficult or take more time for an elderly person to recover from illness. It is also more likely for the elderly to be left with a permanent disability after illness. Changes in body function can influence the metabolism and/or excretion of medicines. Prescribers must be aware of the risk of altered body functions as it may cause unexpectedly higher or lower drug levels. This can result in preventable adverse drug reactions, or, conversely, in reduced therapeutic effectiveness.

**Table 7.3.2: Physiological changes in older people with direct relevance to drug handling.**

Altered function	Implications	Example of a drug
Change in body composition: decreased proportion of body water, relatively increased proportion of body fat	Differences in drug partition leading to different serum levels, depending on the polarity of the drug. Serum levels of hydrophilic drugs are likely to increase and serum levels of fat-soluble drugs are likely to accumulate in body fat which could prolong their effect.	Lipophilic medicines, e.g. benzodiazepines and morphine accumulate in fat and show longer t <sub>1/2</sub> . Hydrophilic medicines, e.g. aminoglycoside antibiotics, digoxin and lithium show higher serum levels and need a lower loading dose.
Small reduction in serum albumin	Easy intoxication with highly protein-bound drugs	Usually low clinical relevance, except for phenytoin
Decreased liver size and blood flow	Higher bioavailability of hepatic metabolized drugs and lower bioavailability of some pro-drugs	Metoclopramide shows higher serum levels due to decreased first-pass metabolism.
Decreased renal function	Decreased clearance in water-soluble drugs and glucuronized metabolites leading to higher serum levels	Aminoglycoside antibiotics, digoxin, lithium, with their small therapeutic window, cause serious adverse effect if they accumulate

Sources: Crome P. What's different about older people. *Toxicology* 2003 Oct 1;192(1):49-54.<sup>41</sup>

Jansen P, Brouwers J. Clinical Pharmacology in Old Persons, Review Article. *Scientifica* 2012. 2012.<sup>42</sup>

With advancing age, the body composition alters, there is a reduction in body water and lean body mass and a relative increase in body fat. This can induce a different partition of a drug in the body. Polar drugs will have decreased distribution volumes, resulting in higher serum levels. Non-polar drugs will have increased partition volumes, thereby resulting in prolonged half-lives. Thus, it is important to understand drug properties to ensure accurate dosage and dosage regime, especially in drugs with a narrow therapeutic range.

Many drugs are metabolised in the liver (first-pass metabolism), either to be excreted more easily or to be activated (pro-drugs). In elderly people, there is a reduced blood flow to the liver and the mass of the liver decreases. The implication thereof is that first-pass metabolism results in higher bioavailability for drugs that are metabolised for excretion. On the other hand, the bioavailability of pro-drugs will be decreased.<sup>41,43</sup> In the elderly, reduced renal



function is common. This kind of reduction decreases the clearance of mainly water-soluble drugs and glucuronized metabolites. Whether or not this becomes a problem is dependent on the toxicity and therapeutic range of the drug.<sup>43</sup> These and other changes in body compositions and their implications are shown in Table 7.3.2.

### 3.2 Product related problems

It is necessary to improve the delivery of medicines for the elderly. To illustrate the need for special formulations or packages, a patient with Parkinson disease (PD) might function as an example. First, these patients have difficulties with opening (blister) packages. This is also the case in many elderly, as shown in a study by van Geffen et al. using an internet-based medicine problem reporting system. A total of 10% of the reported problems were practical issues, of which almost 60% were related to difficulties with opening packages.<sup>44</sup> A study by Atkin et al. showed that almost three quarters of their study population (120 elderly with a mean age of 81 years) could not split a tablet and more than half of them could not open child-proof packages.<sup>45</sup>

Second, patients with PD have difficulties with swallowing medications, both because of their disease-associated dysphagia and because the capacity for swallowing decreases with age.<sup>46</sup> About 9% of people aged 65, and up to 28% of people aged 85 or over have swallowing issues. Not only PD but other diseases are also associated with dysphagia as a common co-morbidity (e.g., Alzheimer Disease, stroke, various oncological conditions and diabetes).<sup>47</sup> Levodopa, used to treat the symptoms of PD, has a short half-life ( $t_{1/2}$  = 1-2 hours) requiring frequent dosing of up to eight times a day.<sup>48</sup> To improve the dosing scheme and to provide stable serum concentrations, controlled release tablets have been developed. The controlled release tablets are often bigger, which then introduce difficulties with actually swallowing the tablet. The elderly often use many medicines which makes it more difficult to take them all. Capsules have been found to be easier to swallow than coated tablets, and coated tablets easier than uncoated tablets.<sup>46</sup> Patient centred care, stimulated by regulatory authorities and provided by manufacturers, is needed for the elderly with swallowing problems and other product-related problems.<sup>47</sup>

Third, the elderly are often subject to polypharmacy, and with the deterioration of cognitive function, organisation might be problematic. Leaflet information is not always suitable for the elderly patient due to small letter sizes, or their poor health literacy for example. A study revealed that two thirds of older Americans (over 60 years of age) have inadequate or marginal literacy skills, hampering their understanding of the information provided.<sup>49</sup> Due to the introduction of generics, the packaging of medications changes continuously, potentially leading to confusion for the patient. A study by Bakke et al. investigated if the standardisation of packaging improved accuracy of recognition and discrimination of the medicine packaged. In the older group, overall accuracy improved from 52% to 82% ( $p < 0.0001$ ).<sup>50</sup>

### 3.3 Potential solutions and implications for research

One solution for the above mentioned problem of polypharmacy could be the use of fixed dose combinations (FDC). These have been developed in order to improve adherence and to decrease the amount of individual pills a patient needs to take. This is also known as 'substitution indication'. Between 2008 and 2012, a total of 27 FDC procedures were

completed and accepted by the European Medicines Agency (EMA). Most combinations were anti-hypertensives, oral contraceptives, and bisphosphonates with vitamin D and/or calcium.<sup>51</sup>

Another relatively new development is the cardiovascular polypill for the treatment of ischaemic heart disease (IHD). Several variations exist, but in principle this is a tablet containing a fixed number and doses of more than two medicines, targeting a set of diseases or risk factors frequently co-occurring in patients. The IHD polypill has been developed for cardiovascular risks and contains a combination of blood pressure lowering drug(s), a cholesterol lowering drug, and/or a platelet aggregation inhibitor. For more information about the polypill as a FDC, the reader is kindly referred to Background Paper 6.3 on IHD.

Many of the difficulties that the elderly have with formulations are similar to the problems seen in the paediatric populations. Table 7.3.3 shows the basic criteria for paediatric and geriatric drug formulations. There are some key steps in the development of the medicines with regards to these patient groups concerning bioavailability, acceptability and palatability, dose adaptation and administration, socio-cultural acceptability, and product information. Adaptation of the dose is needed in both subpopulations. This is feasible for liquid formulations, but for tablets it is not as easy. Some formulations have special coatings, or are formulated in such a way that splitting disturbs the desired absorption profile. When the compounds are toxic, mutagenic, or have very narrow therapeutic indices, splitting is not appropriate. The main problem with using liquids is the taste. Newer formulation techniques using multiparticulate systems, such as mini pallets, might be an option for dose adaptation.<sup>52</sup> Many of these newer techniques have been designed for children and are extensively discussed in Chapter 7.1 (Priority Medicines for Children).

**Table 7.3.3: Basic criteria for both paediatric and geriatric drug formulations.**

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Sufficient bioavailability
Safe excipients
Palatable and/or acceptable properties
Acceptable dose uniformity
Easy and safe administration
Socio-cultural acceptability
Precise and clear product information

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Source: Breitkreutz J, Boos J. Paediatric and geriatric drug delivery. Expert Opin Drug Deliv 2007 Jan;4(1):37-45.<sup>52</sup>

The EMA has recognised the need for special formulations for the elderly, and established a Geriatric Expert Group that is currently investigating how to improve the situation. The agency wants to make sure that it takes the needs of the elderly into account during the development, approval, and use of medicines. In a document prepared for a two-day workshop session on 'Ensuring safe and effective medicines for an ageing population', attention was paid to topics related to drug formulations. The workshop brought together various stakeholders, including EU public bodies, regulators, academic researchers, patients, and healthcare professional representatives, as well as representatives from the pharmaceutical industry. The workshop highlighted the fact that poor formulations decrease

adherence, and there is no “one-size-fits all” solution; a number of factors need to be taken into consideration looking at the patient as a whole.<sup>53</sup>

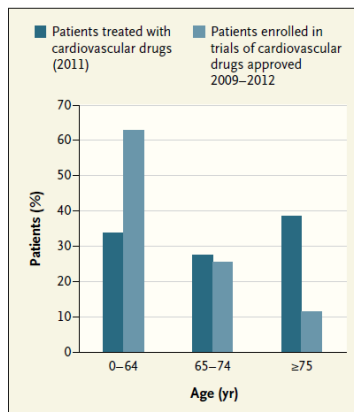
For the development of more appropriate formulations for the elderly, we should learn from what we already know, including how we have started developing specialised medicine formulations for paediatrics. In some aspects delivery and formulations problems may differ between these two populations, but in many other aspects they are similar. These differences and similarities need to be studied in more detail and it is time to take the first steps in this direction. When in the near future adapted formulations have been developed, it will be crucial to study and evaluate how these products have influenced healthcare, and if they have indeed led to better health for the elderly.

## **4. Regulatory aspects related to elderly**

### **4.1 Participation in clinical trials**

Despite their large consumption of medicines, and the fact that up to almost half of the total pharmaceutical expenditures is spent on the elderly,<sup>54,55,56</sup> they are still underrepresented in clinical trials.<sup>42,57,58</sup> Figure 7.3.6 shows the percentages of patients included in trials compared to the percentages treated with cardiovascular drugs, stratified by age. The very old and the elderly with multi-morbidities are particularly not often included in clinical trials. Several factors complicate their inclusion: fear of the researchers to include frail elder patients, hesitation of clinicians to randomise patients due to treatment preferences and use of existing medication, lack of patient consent to enrolment, and difficulties accessing the research centre might play a role.<sup>57,58</sup> Pharmaceutical (innovator) companies seek trial conditions leading to a high internal validity, in order to prove the beneficial effects of the new drug. Homogenous groups, without interfering factors such as multiple drug use and multi-morbidity, increase this internal validity; therefore, exclusion criteria are the predominant factor hampering the participation of this population. Because elderly are heavy drug consumers, often with multiple morbidities and high disease reoccurrence rates, the opportunities to include them are low.

**Figure 7.3.6: Percentage of patients enrolled in clinical trials of cardiovascular drugs compared to the percentage of patients treated with this medicines.**



The Example of Cardiovascular Drugs: Percentages of All Patients in a Given Age Group Treated with Cardiovascular Drugs (Italy) versus Percentages in Each Age Group Included in Cardiovascular Drug Trials (Globally).

Source: 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 Nov 22;367(21):1972-4.<sup>59</sup>

### Exclusion criteria

A 1997 study showed that 35% of the papers published between June 1996 and June 1997 in four high standard journals (n=409) excluded the elderly (older than 75 years of age) unjustifiably.<sup>60</sup> Another group reviewed studies admitted to a local research ethics committee during a period of seven months in 1999. They revealed that in over half of the studies relevant to the elderly (n=155), the age limit was unjustifiably set.<sup>61</sup> Another study in the USA compared the participation of different age groups in cancer clinical trials with the prevalence of cancer in these age groups. They found that patients with cancer aged 65 and over accounted for 25% in the trials, compared to a 63% prevalence in the United States population.<sup>25</sup> The situation seems to have not improved over recent years. A more recent study (2007) investigated the amount of numerous justifiable and unjustifiable exclusion criteria from randomised controlled trials (RCTs) published between 1994 and 2006. They selected 283 articles with a total of 2709 exclusion criteria. In 38.5% of the randomized clinical trials (RCTs) people aged 65 and over were excluded, and in 81.3% of the RCTs people with co-morbidities were excluded. A total of 54.1% of the trials had medication related exclusion criteria. The study categorised exclusion criteria as strongly justified, potentially justifiable, and poorly justifiable. As shown in Table 7.3.4, age (78.4%), medical co-morbidity (64.8%), and medication-related issues were common unjustifiable exclusion criteria.<sup>58</sup>

Choosing stringent eligibility criteria increases the internal validity and therefore efficacy, but the results are not always easy to extrapolate to patients that represent the actual treatment population in clinical settings. As a result, effectiveness is not adequately measured in these RCTs.

**Table 7.3.4: Justification of exclusion criteria from JAMA 2007.**

	No. (%) of Trials *
Grading of individual exclusion criteria	
Total number of exclusions	2709 (100.0)
Strongly justified	1275 (47.2)
Potentially justified	430 (15.9)
Poorly justified	1004 (37.1)
At least 1 poorly justified exclusion criterion	238 (84.1)
Category with poor justification	
Age	160 (78.4)
Medical comorbidity	149 (64.8)
Sex	70 (52.6)
Females	69 (62.2)
Males	1 (4.5)
Medication-related	56 (36.6)
Socioeconomic status	31 (79.5)
Percentage of poorly justified exclusion criteria	
≥10	228 (80.6)
≥25	174 (61.5)
≥50	83 (29.3)
≥75	24 (8.5)
Exclusions per trial, mean (SD)	9.5 (6.1)

\* Unless otherwise indicated

Source: Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. JAMA 2007 Mar 21;297(11):1233-40.<sup>58</sup>

### Role of authorities

Regulatory authorities play an important role in the encouragement of the participation of the elderly in clinical trials. In 1989, The FDA issued the 'Guideline for the Study of Drugs Likely to be Used in Elderly', in order to regulate and promote the inclusion of the elderly in clinical trials, so that sufficient information could be gained about medicine use in the elderly. In 1993, the International Conference on Harmonisation (ICH) developed the ICH E7 guideline: 'Studies in Support of Special Populations: Geriatrics', which was adopted by the FDA, EMA and the Japanese regulatory authority (PMDA). In 2010, a Questions & Answers report was developed by the ICH in order to implement the ICH E7 guideline. The aim was to make some recommendations in order to improve the implementation of the existing guidelines.<sup>62</sup>

Recently, different attempts have been made to increase the participation of the elderly in RCTs. The PREDICT group, a multi-disciplinary and multinational consortium of health care professionals, supported by the Seventh Framework program, developed a Charter in order to promote the participation of the elderly in clinical trials.<sup>63,64</sup> First, the consortium prepared a systematic review to establish whether the elderly had been inappropriately under-represented in trials of treatments for specific conditions. They recognised barriers to and promoters of participation, from a professional and patient point-of-view. The outcomes of this review were the preparation basis for the second step where, with the use of 521 questionnaires, they gathered the views of experts in nine European countries and asked if the elderly were under-represented in clinical reviews, and if so, what could be done to

overcome this. A total of 71% of the professionals did not consider the regulations and present arrangements for the conduct of clinical trials to be satisfactory, while 60% felt that national or European regulations needs alteration. Based on this information, they finally developed the Charter for the Rights of Older People in Clinical Trials,<sup>65,66</sup> which was launched in February 2010. This Charter contains guidelines and statements about this topic (see Annex 7.3.1). The PREDICT group gained attention from regulatory agencies, which resulted in EMA establishing a Geriatric Expert Group.

### Geriatric Medicines Strategy

At a regulatory level, attempts have been made to improve knowledge about drug use in the elderly. In 2011 the EMA launched their Geriatric Medicines Strategy and established a Geriatric Expert Group (GEG), which provides scientific advice to the CHMP (Committee for Medicinal Products for Human Use) and the agency secretariat on issues related to the elderly.

The Geriatric Medicines Strategy has two main aims to ensure that medicines used by the elderly are appropriately researched and evaluated throughout the lifecycle of the product. Firstly, the strategy recognises the elderly as the main users of medicines and seeks to ensure that the development and evaluation of new medicines take into account specific safety and efficacy aspects related to ageing. Secondly, they wish to improve the availability of information for patients and prescribers on the use of medicines in this population, in order to improve safety.<sup>59,67</sup> The strategy has identified that the very elderly (older than 75 years of age), with their frailty, should especially receive more attention. This group uses a disproportionate amount of medicines and should be represented in clinical trials following existing guidelines. In 2011, GEG members proposed several instruments that, in their opinion, are the most appropriate (although not free from methodological limitations) for the characterisation of the frailty level of older people enrolled in a clinical trial, both at baseline and at study completion: the Short Physical Performance Battery<sup>68</sup> and the Study of Osteoporosis Fracture Index.<sup>69,70</sup> Parameters considered by the GEG members when making their choice included an instruments validation status, predictive value, ease, and breadth of use. Additionally, the GEG has identified a scale that it considers more appropriate for monitoring change in the frailty levels.

The Geriatric Medicines Strategy promotes the investigation of population pharmacokinetics, or a specific pharmacokinetic study including the very elderly, in order to recommend dose regimens and identify patients at risk. For these studies modelling and simulation might be helpful.

The establishment of the Geriatric Medicines Strategy has been warmly welcomed by the AGE Platform Europe, a network of 165 European organisations focusing on a wide range of policy areas that impact older and retired people. The platform has promised to closely monitor the implementation of this strategy.<sup>71</sup>

A recent position statement from the American Geriatric Society addressed this subject again and proposed several possible approaches to address the lack of representation of elderly patients in clinical trials. They suggested policies that call for the inclusion of elderly in government supported research, or laws to ensure that all drugs are tested for their use in this population prior to prescription. The creation of incentives, like patent extensions, when

older adults are included in industry supported research, as has been implemented for paediatrics, or allowing Medicare coverage of healthcare costs during clinical trials was also suggested. The society also proposed close examination of exclusion criteria in each protocol in a clinical trial design to ensure that these are scientifically justified. Finally, the society wants to persuade healthcare workers to highlight the importance of clinical trial participation to their older patients, and encourage them to enrol in studies.<sup>72</sup>

### **4.2 Information about the elderly in product information and other information sources**

Because of the under-representation of the elderly in clinical trials, medicines are often prescribed 'off-label' in this patient group. Sometimes there is already enough scientific evidence to prescribe in the elderly, but, due to delays in regulatory procedures, the Summary of Product Characteristics (SPC) has not yet been updated. Preliminary results from a study that investigated the availability of information revealed that in the information transfer process, much information is lost. For 53 new medicines, a maximum of 19 items derived from the ICH E7 guideline for studies involving geriatric populations were scored per new medicine. A large proportion (79%) of the information specified in the ICH E7 guideline is provided by the pharmaceutical companies and is available in the EPAR (European Public Assessment Report), the scientific report made by the EMA with regard to the registration of the product. However, only 56% of this information is available in the SPC text.<sup>73</sup> There is apparently no uniform European or international source of information for the treatment of elderly patients in daily practice. Treatment guidelines appear to be more disease-driven than patient-centered, and specific guidance on the treatment of elderly patients is frequently lacking, which may cause not only overuse but also underuse of medicines in this population. Ongoing and much needed research focuses on how physicians obtain their information to adequately treat the elderly in daily practice and how this information is being updated on a regular basis, but data are not available yet.

It is estimated that 55% of people aged 75 and over suffer from four or more chronic conditions.<sup>74</sup> Guidelines developed in order to offer evidence based care usually focus on a single condition. These guidelines do not consider the cumulative impact of treatment recommendations, nor do they help to prioritise treatments. Therefore, they are not generally applicable to the multi-morbid patient.<sup>75</sup>

Several groups have investigated the extent to which national guidelines addressed patient co-morbidity.<sup>75,76</sup> A paper examining the application of NICE (National Institute of Health and Clinical Excellence) guidelines to people with multi-morbidity showed that the guidelines consider older patients to varying degrees. They investigated if the guidelines made notes on age, co-morbidity and patient-centred care. Most guidelines contained only some general statements on the elderly, e.g. the clinician should consider individual drug characteristics and prescribe age-adjusted doses of relevant medications. Multi-morbidity was inconsistently accounted for in guidelines, usually without detailed discussion. In their introduction, most guidelines emphasised the importance of patient-tailored care, without offering disease-specific recommendations to do so. The guideline giving the most extensive and specific recommendations was the depression guideline, in which age adjusted medication use, tailored care, cases of co-morbidity and issues addressing adherence were discussed. The paper gave some recommendations on improving guidelines in the future, as

shown in Table 7.3.5.<sup>75</sup> One recommendation that was given was the cross-referencing of guidelines when the recommendations are synergistic or contradictory, using an internet-based format. Here again, the need for specific and easy accessible information on medication use in the elderly population is highlighted. Pharmacists could play an important role as they are in a unique position to assess all prescribed medications and the strengthening of their role in this respect should therefore be further explored.

**Table 7.3.5: Recommendations for improving clinical guidelines**

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Providing summarised and comparable information about the relative benefits and risks of different recommend treatments would help inform prioritisation in multimorbid patients
Existing guidelines should explicitly cross-reference each other when recommendations are synergistic or contradictory, and identify high-risk interactions between recommend treatments and other commonly prescribed drugs. <i>This may be done in a internet-based format</i>
Clinical guidelines should include a small number of specific patient case examples for common combinations of comorbidity seen in clinical practice
Guidelines should note some specific advice for practitioners when treating older patients (e.g, drug doses of class)
Concerted action is needed to increase the participation of older people in clinical trials.

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Source: Hughes LD, McMurdo ME, Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. *Age Ageing* 2012 Aug 21.<sup>75</sup>

Because there is a lack of knowledge about the safety and effectiveness of the use of medicines in the elderly, more clinically generated information should be collected in order to enhance the informed prescribing of medicines. For example, prescribers worldwide should be encouraged to report all adverse drug reactions related to their prescription in elderly.<sup>77</sup> This information should be collected and presented in such a way that it is available in an integrated format for all healthcare professionals, thus leading to more informed prescribing.<sup>42,59,77</sup> Besides the inclusion of an adequate number of elderly patients in clinical trials and the collection of relevant data during the post-marketing phase, new and innovative approaches are needed to ensure the assessment of the effectiveness of medicines in the elderly (see Chapter 8.4).

## 5. The usage environment

Medicine use in daily practice is or may be complicated in elderly patients, especially because elderly patients are often treated for multiple morbidities; treating co-morbidities often leads to polypharmacy. In addition, a full understanding of complex patients is often lacking. This section discusses the problem of polypharmacy, including the increased risk of adverse drug reactions and (non-)adherence, and provides insights into screening tools and interventions to monitor and improve polypharmacy. Furthermore, this section addresses other cross-cutting themes related to medicine use in the elderly such as access to medicines, palliative or end-of-life care, and integration or continuity of care, which poses particular challenges, as the elderly frequently move between different healthcare settings when diseased.



## 5.1 Polypharmacy

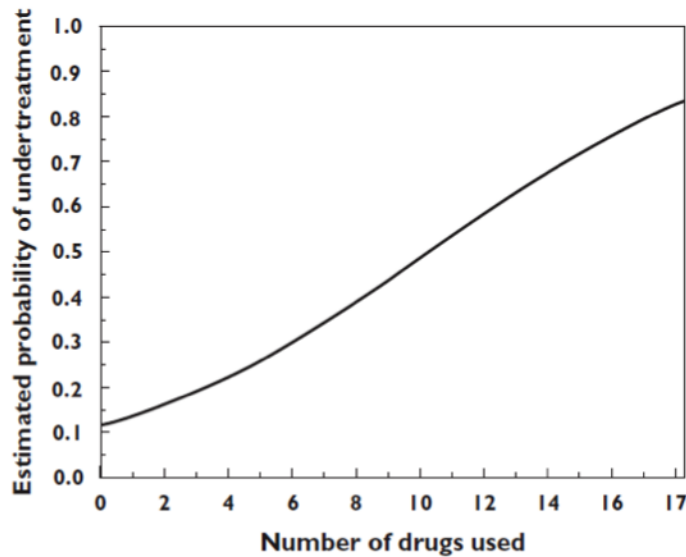
The first edition of the Priority Medicines for Europe and the World report (2004) already acknowledged that if one speaks about polypharmacy as 'using multiple medicines' it does not appoint polypharmacy as a bad event. The use of fewer medications does not necessarily mean better treatment for the patient, and neither does more medication use imply over-treatment; the focus should not be on the number of medications, but on appropriate prescribing.<sup>78,79</sup> The treatment and prevention of cardiovascular disease e.g. ischaemic heart disease, is a good example of appropriate polypharmacy. To obtain optimal pharmacotherapy, the use of several different drugs is often required (e.g. antiplatelet therapy, cholesterol-lowering drugs, and blood pressure lowering drugs).<sup>80</sup> For many physicians, appropriate prescribing is not that easy. To obtain optimal prescription, it is necessary for physicians to have a good understanding of the pathophysiology of the disease, the changes of pharmacology with increasing age,<sup>42</sup> and in drug pharmacology. Several studies have shown that inappropriate prescribing occurs frequently among the elderly and that it is often related to polypharmacy.<sup>81,82,83</sup>

Recent literature shows that this is still the case. A cross-sectional study from 2012 with 302 frail elderly persons (above 75 years of age) admitted acutely to a hospital were screened for potentially inappropriate prescribing (PIM). PIM was significantly associated with polypharmacy (more than five daily medications; OR 1.9, 95% CI 1.1-3.5 and  $p = 0.026$ ).<sup>84</sup> Another study showed a relationship between under-prescribing and polypharmacy. Patients with five or more medications were more likely to be under-treated than patients with four medications or less (OR 4.8, 95% CI 2.0-11.2).<sup>85</sup> Figure 7.3.7 shows the estimated probability of under-treatment related to the number of drugs.

Despite the advantages of polypharmacy in some specific cases, it is not favourable in all cases. If polypharmacy is seen as the 'administration of more medications than are clinically indicated', a negative event, which has to be avoided, occurs. In the elderly, it has been found that the percentage of medication prescribed without indication or a less than optimal indication ranges from between 55 and 59% of all prescriptions.<sup>86,87</sup> This kind of polypharmacy is problematic, especially in the elderly, because it unnecessarily increases the risks of adverse drug reactions, geriatric syndromes (like cognitive impairment and delirium) and healthcare costs.<sup>88</sup>

A more recent study by Dedhiya investigated the incidence of PIM in the elderly living in nursing homes. They found a one-year incidence of 42.1%. The elderly using a PIM were more likely to be hospitalised OR = 1.27; (95% CI 1.10 to 1.46), and more likely to die OR 1.46 (95% CI 1.31 to 1.62).<sup>89</sup>

Figure 7.3.7: Estimated probability of under-treatment related to the number of drugs.



Source: Kuijpers MA, van Marum RJ, Egberts AC, Jansen PA. Relationship between polypharmacy and underprescribing. *Br J Clin Pharmacol* 2008 Jan;65(1):130-3.<sup>85</sup>

Another problem stems from the discontinuity of geriatric care. Many patients are treated by different physicians concurrently, who are often unaware of the other medications a patient is using, which have been prescribed by other doctors. In most countries, people do not have a regular pharmacist or a family doctor who can review all of a patient's medications. Moreover, many people use not only prescription medications, but they also use a large amount of 'over-the-counter' (OTC) products. These OTC medicines include not only things like NSAIDs and antihistamines, but also vitamins, minerals and herbals. Most patients do not realize that the OTC-medications they are using can also influence their therapy, by interacting with their prescribed medications, for example, or augmenting the effects or side-effects of prescribed medications (e.g. NSAIDs and antihistamines). Because of this ignorance, most patients do not report the use of OTC medications.<sup>90</sup>

A study from 2005 showed that less than 5% of the OTC drugs were reported on drug charts, while almost two thirds of inpatients used them.<sup>91</sup> A recent Danish study showed that 74% of the elderly (above 65 years of age) used OTC drugs not listed in the Danish 'online prescription report'. Fifty per cent of patients taking OTC drugs were exposed to potential interactions.<sup>92</sup>

Polypharmacy has received a lot of attention since the first edition of this report in 2004. Recent data confirm that the elderly still consume many medicines and will always do so by virtue of their complex health needs. From 1996 to 2006, the average amount of medicines prescribed to elderly in the United Kingdom almost doubled.<sup>93</sup> This patient group consumes an average of four to five prescription medicines and two over-the-counter medicines at any given time.<sup>94</sup> Moreover, among people aged 65 or over, 40% consume between five and nine medicines weekly, and 18% consume more than 10 medicines on a weekly basis.<sup>95,96,97</sup> Polypharmacy is still associated with drug interactions, adverse drug reactions, increased risk of hospital admissions, falls, lower adherence and higher costs.<sup>98,99</sup>

### Screening tools

To assess suboptimal (misuse, underuse and overuse) or inappropriate prescribing, different tools have been developed and validated. The explicit and implicit methods both assess suboptimal prescription.<sup>100</sup> The explicit method makes use of standard (check-)lists or tools and focuses on the disease state or specific medicines. Examples of these lists are the Beers Criteria<sup>101,102</sup>, the STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) criteria, and the START (Screening Tool to Alert doctors to Right, i.e. appropriate indicated Treatment) criteria.<sup>103</sup> These tools are quite rigid and do not take specific patient information into account. They specify inappropriate drug combinations or contraindications. In contrast, implicit methods take the individual state of the patient into account to assess the appropriateness of prescription, thereby providing an opportunity to conduct a complete and flexible assessment of the pharmacotherapy of the patient.<sup>42</sup> A validated tool that could help with the implicit method is the Medication Appropriateness Index (MAI).<sup>104</sup> The applicability of the MAI score is limited in clinical practice because it is time consuming. Another example of an implicit method, which may be easier to use in clinical practice, is the Prescribing Optimisation Method (POM) that has been developed by the Expertise Centre Pharmacotherapy in Old Persons (Ephor).<sup>105</sup>

### Interventions to improve polypharmacy

Several different interventions have been developed in order to improve polypharmacy. These interventions include the education of healthcare professionals, medication review clinics, the promotion of generic prescribing, or computerized decision support systems. A systematic Cochrane Review investigated the effects of different interventions on polypharmacy in the elderly. The primary outcomes were the appropriateness of medications prescribed (with the Beers List or the MAI), the prevalence of appropriate medication (using START criteria), and hospital admissions. Ten studies were included, of which nine were multifaceted interventions of pharmaceutical care performed by a pharmacist collaborating with the physician, patient, and carer. One was a computerized decision support system (CDSS) provided to the general practitioners. Most of the studies examined the appropriateness of prescribing using the MAI score. Table 7.3.6 shows the pooled data of the primary outcome, e.g. the mean reduction in the summated MAI score post intervention was -3.88 (95% CI -5.40 to -2.35). The review found evidence that pharmaceutical interventions increase appropriate prescribing; however, it could not find evidence for clinically significant improvements, such as hospital admissions or adverse drug reactions.<sup>106</sup> It should be noted, however, that the quality of the underlying evidence was classified as 'very low', which hampers the interpretation of the results. This could be due to the great heterogeneity of the studies.

**Table 7.3.6: Pharmaceutical care interventions versus usual care in older patients.**

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	Number of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk (95% CI)			
	Usual care	Pharmaceutical care			
<b>Summated MAI score</b> Follow-up 0 to 12 months	The mean summated MAI score in the control groups was 1.44	The mean summated MAI score in the intervention groups was <b>3.88 lower</b> (5.4 to 2.35 lower)		965 (five studies)	Very low
<b>Change in MAI score</b> The change in the MAI Follow-up 0 to 3 months	The mean change in MAI in the control groups was 1.43	The mean change in MAI score in the interventions groups was <b>3.81 higher</b> (1.17 lower to 8.78 higher)		424 (four studies)	Very low
<b>Number of Beer drugs per patient.</b> The Beers criteria Follow-up 0 to 12 months	The mean number of Beer drugs per patient in de control groups was 0.23	The mean number of Beers drugs per patient in the intervention groups was <b>0.06 lower</b> (0.16 lower to 0.04 higher)		1 440 (three studies)	Very low

Source: Patterson SM, Hughes C, Kerse N, Cardwell CR, Bradley MC. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst Rev 2012;5:CD008165.<sup>106</sup>

### Medication reviews

A specific type of intervention to improve polypharmacy is the medication review. Medication reviewing is a structured evaluation and reconciliation of a patient's medications, which often leads to some interventions in order to improve pharmacotherapy. When done, these reviews are usually performed by pharmacists in both primary and secondary health care.<sup>107</sup> Knowing that only 50% of medications are taken as directed<sup>108</sup>, this review may improve pharmacotherapy, especially when performed with the participation of the patient. Different groups investigated the effects of medication reviews on outcomes such as appropriate prescribing, medication adherence, ADRs (adverse drug reactions), hospital admissions, or death.<sup>109,110,111,112,113</sup>

Medication reviewing has been established to increase appropriate prescribing with regards to the reduction of polypharmacy, more appropriate formulation, and the more appropriate choice of medicine.<sup>1076,109,1109,1110,1132</sup> Pharmacist led reviewing often leads to the implementation of recommendations made towards the physician. A 2001 study by Krska showed that in elderly patients reviewed at home, 82.7% of the pharmaceutical care issues (PCI) were wholly or partially solved after the three-months follow up, in contrast to the 41.2% of the patients receiving usual care. GPs agreed with 95.8% of the documented PCIs and accepted 87.3% of the actions to resolve them.<sup>113</sup>

A 2006 study by Zemansky et al. measured the impact of pharmacist performed clinical medication reviewing on the number of changes in medication for the elderly living in care

homes. They showed that medication reviewing was associated with a significant increase in the number of drug changes per patients, with a mean of 3.1 for the intervention group versus 2.4 for regular GP care,  $p < 0.0001$ . Their secondary outcomes, such as drug costs (£42.24 and £42.94 per 28 days,  $p$ -value unknown), hospitalisations (means 0.2 and 0.3,  $p = 0.11$ ), and deaths (51/331 and 48/330,  $p = 0.81$ ) did not show any statistical significance for the intervention versus regular care, respectively. A total of 75.6% (565/747) of the recommendations made by pharmacists were accepted by the GPs; 76.6% of these (433/565) were actually implemented.<sup>110</sup>

A 2008 systematic review and meta-analysis by Holland et al. investigated the effects of medication reviewing on hospitalisations and mortality in the elderly. They pooled data and found no significant effect on all-cause admissions, RR 0.99 (95% CI 0.87 to 1.14,  $p = 0.92$ ) or mortality, RR 0.96 (0.82 to 1.13,  $p = 0.62$ ). On the other hand, reviewing was associated with improved knowledge and adherence in elderly patients.<sup>1121,114</sup> Table 7.3.7 shows the secondary outcomes of the systematic review.

Until now, the positive effects of reviewing in the elderly such as more appropriate prescribing, a tendency toward improved adherence and improved knowledge that the patients have, have not been translated in positive effects on 'harder' clinical outcomes such as decreased hospital admissions, improved quality of life, or reduced mortality.<sup>98,106,1121</sup> Some of the studies did not have enough power to detect the above mentioned clinical outcomes, while in some larger studies there seemed to be a diluting effect of involving more pharmacists and more patients. In the larger settings, it was not the highly trained pharmacist performing the medication reviews. Because the design of the studies investigating the effects of reviewing varied widely, with some of them lacking a description of the interventions performed as a consequence of the review, systematic evaluation is difficult.<sup>115</sup>

Due to a lack of robust research in this area, it has not been established if medication reviewing in the elderly is cost-effective.<sup>107,115</sup> Trials evaluating the effects of reviewing measured different outcomes and did not always measure costs.<sup>114</sup> A review conducted on this topic concluded that, generally, the costs of the interventions were not greater than the benefits, although in some cases there was a cost reduction in terms of the savings on medication costs.<sup>1154</sup> These savings could be due to more generic prescribing or to the deletion of unnecessary medication.

**Table 7.3.7: Secondary outcomes of a meta-analysis on the different effects of reviewing in the elderly.**

	No. of trials reporting outcomes compared with control	No. reporting a significant positive effect (%)	No. reporting a non-significant positive effect (%)	No reporting no effect (%)	No reporting either a non-significant or a significant negative effect (%)
Quality of life	12	0	4 (33)	8 (66)	0
Patient satisfaction	4	2 (50)	1 (25)	0	1 (25)
Drug-related problems	4	4 (100)	0	0	0
Knowledge	11	6 (55)	2 (18)	3 (27)	0
Adherence	14	7 (50)	4 (29)	3 (21)	0
Adverse drug reactions	9	1 (11)	3 (33)	3 (33)	2 (22)
Storage problems	3	2 (66)	0	1 (33)	0
Unnecessary drugs	7	5 (71)	2 (29)	0	0
Cost analysis*	14	4 (29)	6 (43)	2 (14)	2 (14)

\* Three studies reported some form of cost-effectiveness analysis

Source: Holland R, Desborough J, Goodyer L, Hall S, Wright D, Loke YK. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. *Br J Clin Pharmacol* 2008 Mar;65(3):303-16.<sup>112</sup>

### Implementation of reviewing in daily care

Despite a lack of evidence on harder clinical outcomes, medication reviewing has been recommended and implemented by different authorities and pharmacist associations. The General Medicines Contract, which is the contract of the GPs with the primary health organisations United Kingdom wide, advises that patients who receive prescribed medicines undergo medication reviewing at least every 15 months. The reviews may be performed by the GP, the practice based pharmacist, or the practice-based nurse.<sup>107</sup> Community pharmacists in England and Wales perform medication use reviews (MURs) as part of their NHS contract. They must be accredited to perform this task, and their pharmacy must have a consultation area that fulfils the NHS standards of privacy. Nowadays, they are focusing on specific patients groups such as those on warfarin, asthma/COPD patients, or patients recently discharged from the hospital.<sup>107</sup> In Australia, as an initiative of the Australian government, the GP, along with the preferred community pharmacist, reviews polypharmacy patients using a team approach; the GP's medication information is shared with the pharmacist, and the pharmacist performs the 'Home Medicines Reviews' and reports back to the GP.<sup>107,116</sup> In the United States, pharmacists working for two collaborating non-governmental associations provide reviews as part of a 'Medication Therapy Management' service, in order to optimise drug therapy.<sup>117</sup> In the Netherlands, an

interdisciplinary guideline for polypharmacy was implemented this year (2012). It states that for the elderly patients (65 years or over) using five or more medicines and having one or more risk factor such as non-adherence, impaired cognition, or a decreased renal function, a medication review should be performed every year. For the elderly living at home, this can be performed by the GP in collaboration with the community pharmacist.<sup>118</sup> In this interdisciplinary guideline, the STRIP-method (Systematic Tool to Reduce Inappropriate Prescribing) is recommended to perform the review. This method consists of five steps, as shown in Table 7.3.8.

**Table 7.3.8: The five step STRIP-method in order to structure the medication review.**

1	Structured history taking of the patient
2	Pharmacotherapeutic analysis (effectiveness, under treatment, drugs without indication, ADRs, interactions, dosages)
3	Development of treatment plan by physician and pharmacist
4	Discussion of the plan with the patient
5	Follow up and monitoring

Sources: Jansen P, Brouwers J. Clinical Pharmacology in Old Persons, Review Article. Scientifica 2012. 2012.<sup>42</sup>

Nederlands Huisartsen Genootschap. Multidisciplinaire richtlijn Polyfarmacie bij ouderen, 2012. 2012.<sup>118</sup>

Thus, different countries are performing medication reviews as a routine practice. The initiative of this reviewing differs from purely governmental (United Kingdom) to non-governmental (United States and The Netherlands), depending on how the healthcare service is designed.

Other publications emphasize the importance of the participation of the patient in the review process. A review by Blenkinsopp et al. on medication reviewing notes that the full participation of the patient supports ‘partnership in medicine taking’, achieving a more appropriate outcome for that particular patient.<sup>107</sup> The STRIP method explicitly includes the patient; there is direct contact with the patient in steps 1 and 4.<sup>118</sup> Further research evaluating the different methods to perform medication reviewing, including the assessment of the added value of involving patients is warranted.

### **The necessity of an increased role for Information and Communications Technology (ICT)**

Reviewing is extremely time consuming. A thorough screening, with the collection of all the data, the interviewing of the patient, and the interaction of the pharmacist with the prescriber, is estimated to take at least two hours.<sup>118</sup> This estimate will be different depending on which tasks are performed by which healthcare professional. In order to facilitate appropriate prescribing and conduct medication reviewing more efficiently, there is a need to improve the supporting role of electronic health records and use of ICT. Only when computerised systems are more connected and clinical information about the patient is shared, can reviewing be efficient and cost-effective. In some countries, such as the Netherlands, parts of the review process are incorporated into daily pharmaceutical care in the hospital setting. A CDSS (computerised decision support system) can be incorporated into a computerised physician order entry (CPOE). These systems give basic alerts about

drug-drug interactions or contraindications. Nowadays, with the so-called 'clinical rules', more advanced and appropriate advice can be generated to provide clinical guidance. Using additional patient information, the system can guide the dosing of drugs that are eliminated by the kidneys using information about laboratory values such as renal function.<sup>119</sup> The software can be developed in such a way that it is in alignment with the treatment guidelines.<sup>120</sup> The system could also be used to select high-risk patients, who would benefit from a full medication review.

The implementation of an adverse drug event alerting system (ADEAS), consisting of about 121 clinical rules, in a hospital pharmacy in the Netherlands resulted in both the selection of different patients by the ADEAS and in more interventions performed by the pharmacist when compared to the conventional medication surveillance method. The added value of the ADEAS were warnings for declined renal function and for the omission of essential concurrent medications.<sup>119</sup>

The hospital setting, with more data being shared between health care professionals, could serve as an example for primary care. The need for more information in order to offer high quality and tailored care, is described in more detail later in this background paper.

### **Opportunities for improving medication reviewing**

More research is needed to clarify if medication reviewing in the elderly is cost-effective and indeed improves clinical outcomes such as hospitalization, mortality, and quality of life. There is still ongoing research in the field of medication reviewing that might give us an answer in the future.<sup>121</sup> It seems that a multi-disciplinary approach in which at least the GP and community pharmacist participate, is beneficial for the outcome; focusing on patients more likely to benefit from the intervention increases the effectiveness of reviewing as well.<sup>1076,1143</sup> In addition, research should be directed towards the intersection of hospital and primary care, and more developed computerised systems, using shared data on clinical values, such as renal function, might offer benefits.<sup>42</sup> Finally, educational programmes in geriatric pharmacology are limited and have not been thoroughly evaluated.<sup>122</sup> Education in geriatric pharmacology should receive more attention in the curricula of health professionals and include topics such as polypharmacy and dose adjustment in organ dysfunction.

## **5.2 Adverse drug reactions**

The risk of adverse drug reactions (ADRs) increases with the number of individual medicines a patient is using. Because the elderly are using more medicines in comparison to the younger population, it is expected that more adverse drug reactions occur in people aged 65 and over.<sup>123</sup> The incidence of ADRs in the elderly was found to be about 5%, approximately half that of the non-elderly populations.<sup>124</sup> A meta-analysis suggested that adverse drug reactions rank between the fourth and sixth cause of death in hospitalized patients.<sup>125</sup>

A study by Wester (2008) suggested that fatal ADRs were the seventh most common cause of death in the Swedish population, accounting for 3% of all deaths; anti-thrombotic medicines and NSAIDs were most commonly involved.<sup>126</sup> An eight-year survey (1999 to 2006) studied ADR related deaths in populations in the United States. This survey observed an overall increase in ADR related deaths. The age groups of 55-75 and over 75 years were associated



with a significant increase in ADR related deaths, with the greatest risk being seen in patients 75 years and over; OR 6.96 (95% CI 6.30 to 7.69).<sup>127</sup>

## Hospital admissions due to ADRs

ADRs are responsible for unnecessary hospital admissions, which result in a loss of health and a waste of money. In several studies prior to 2004, the percentage of hospital admissions due to adverse drugs reactions already ranged from 4.1% in young people, up to 16.6% in the elderly.<sup>128</sup> It is important to realise that many adverse drug reactions are preventable, with the percentage of preventable ADRs in the elderly ranging between 27.6% and 51%.<sup>124,129,130</sup>

In line with the results of these studies, new data from the HARM (preventable Hospital Admissions Related to Medication) study showed that 5.6% of unplanned hospital admissions were medication related, of which 46.5% were potentially preventable.<sup>131</sup> More than a third of the elderly (above 65 years of age) who presented at an emergency department with an ADR needed to be hospitalised.<sup>132</sup> Table 7.3.9 shows the reasons for potentially preventable medication related hospital admissions and the associated medicines found by the HARM study. Of the preventable ADR related hospital admissions, almost 15% were due to gastrointestinal bleeding, and 6% were due to problems of the endocrine system.<sup>131</sup> This study found that anti-platelet agents and insulin were most often associated with possible preventable hospital admissions. Recent research confirms these results; a study from 2011 found that, among patients 65 years or older, warfarin, insulin, and oral anti-platelet agents together account for more than 60% of hospitalisations.<sup>132</sup> Both warfarin and insulin require ongoing monitoring, due to their narrow therapeutic index, demonstrating that they are of higher risk with regards to causing adverse drug reactions.

**Table 7.3.9: Reasons for potentially preventable medication related hospital admissions and the associated drugs.**

Reason for Admission	Preventable Admissions, No. (%) (n=332)	Associated Drug (No. of Admission*)
Digestive system		
GI tract bleeding	48 (14.5)	Antiplatelets (34), NSAIDs (14), anticoagulants (12), oral corticosteroids (4)
GI tract symptoms (e.g., diarrhoea, constipation)	22 (6.6)	Oral antidiabetics (4), laxatives (4), diuretics (4), opiates (3), loperamide (3), statins (3), antibacterial drugs (3)
Circulatory system: cardiovascular symptoms (e.g., dysrhythmias, heart failure)	35 (10.5)	β-Blockers (15), drugs affecting the RAAS (9), calcium antagonist (9), anticoagulants (7)
Respiratory symptoms (e.g., dyspnoea)	26 (7.8)	Diuretics (12), respiratory drugs (6), β-blockers (6), NSAIDs (5)
Endocrine system: hypoglycaemia of hyperglycaemia	20 (6.0)	Insulin (18), oral antidiabetics (12), corticosteroids (3), diuretics (3)

Abbreviations: GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; RAAS, renin angiotensin aldosterone system.

\* Ad admissions can be associated with more than 1 drug and is then mentioned more than once in the list.

Source: Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med 2008 Sep 22;168(17):1890-6.<sup>131</sup>

In addition to specific medication use, the HARM study revealed patient-related risk factors – all common attributes of older populations – that are significantly associated with preventable hospital admission due to ADRs, as shown in Table 7.3.10.

**Table 7.3.10: Patient-related risk factors significantly associated with preventable hospital admission due to ADRs.**

Risk factors	Odds ratio (95% confidence interval)
Impaired cognition	OR = 11.9 (3.9-36.3)
Four or more diseases in the patient's medical history	OR = 8.1 (3.1-21.7)
Dependent living situation	OR = 3.0 (1.4-6.5)
Impaired renal function before hospital admission	OR = 2.6 (1.6-4.2)
Non-adherence to the medication regimen	OR = 2.3 (1.4-3.8)

Source: Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med 2008 Sep 22;168(17):1890-6.<sup>131</sup>

A recent study by Merten et al. showed the incidence of adverse events (AE) in older (65 years or over) as compared to younger (below 65 years of age) hospitalised patients. They showed that the occurrence of AEs was significantly higher among the elderly than among younger people, with an incidence of 6.9% for the older and 4.8% for the younger patients. A fifth of all AEs were medication related in the elderly, and one third of these were preventable. In the younger population, the prevalence of this type of AEs was half of this, which further confirms that we need to focus on the appropriateness of medication in the elderly population.<sup>133</sup>

### Burden of ADRs

ADRs are not only associated with undue harm to the patient, but can also be costly. These costs can be direct medical costs or indirect costs due to the loss of productivity by the patients (when younger than 65 years). Different groups calculated costs due to hospital admissions associated with ADRs, as was described in the first version of this report:

In several studies the costs of hospital admissions due to adverse drug reactions have been calculated. The amounts ranged between €182 927 per year (29-bed ward of general medicine)<sup>134</sup> to €261 220 per year (23-bed ward of general medicine).<sup>135</sup> These costs are considerable, certainly at a (inter)national level, and may have increased in more recent years because this segment of the population has grown.

A recent cost analysis study using data from the HARM study calculated the burden of potentially preventable ADRs and analysed which factors or subgroups contribute most to this burden. The average medical costs of one preventable hospital admission due to an ADR was €5 461, or US\$ 7 934. For individuals younger than 65 years old, the total costs were higher than those for the elderly due to production losses. Looking only at medical costs, the elderly accounted for a higher burden (€5 637) than the younger patient (€5 088).<sup>136</sup> More research is needed in order to assess whether interventions to prevent ADRs, such as medication reviewing, lead to a reduction in these ADR related costs.

### 5.3 Adherence

Medication adherence is defined as the extent to which patients follow the instructions they are given for prescribed treatments. The adherence rate is said to typically be 50% for prescribed medications, but rates vary widely ranging from 0% to 100% depending on for example population and type of medication.<sup>137</sup> Good health outcomes and the benefit of therapies are hindered when a patient is poorly adherent or non-adherent. Poor adherence leads to higher healthcare costs, preventable hospitalisations, and higher mortality.<sup>42,138</sup> A recent report by the IMS Institute for Healthcare Informatics estimated that they improvement of adherence could lead to a global cost saving of US\$ 269 billion of the total of US\$ 475 billion avoidable costs in the year 2011.<sup>139</sup>

There are many different causes for non-adherence, which can be both intentional and unintentional.<sup>140</sup> Non-intentional causes are due to barriers that are beyond the control of the patients, such as lack of understanding, or an inability to pay for the treatment. Intentional non-adherence occurs when the patient decides not to follow the treatment recommendations.<sup>141</sup>

A Cochrane Review (2008) investigated the results of RCTs of interventions to increase medication adherence, also measuring treatment outcomes. They divided the interventions into short-term and long-term interventions; an example of a simple short-term intervention was the instruction that all of the medications needed to be consumed. For short-term interventions, only four of the 10 studies showed improvement in adherence and at least one clinical treatment outcome. An example of an intervention on long-term treatment was the simplification of the dosage regimen. This was found to increase adherence significantly, as shown by Claxton et al. They demonstrated that adherence was 79% with one daily dose, 69% with two daily doses, and 51% with three times a day.<sup>142</sup> Complex interventions, such as the combination of thorough patient instructions, close follow-up, rewards for success, reminders or family therapy, were more often seen in chronic therapy. A total of 36 of the 83 interventions reported in the RCTs led to increased adherence, but only 25 improved treatment outcomes. These complex interventions are not very effective, despite the amount of effort and resources they consume. There is an important need for basic and applied research on interventions to assist patients in following the instructions on prescriptions for chronic medical disorders.<sup>137</sup> Although this also applies to the population as a whole, the elderly deserve special attention in this respect.

A meta-analysis by Conn et al. investigated the existing evidence on the effects of interventions designed to improve adherence, especially in the elderly.<sup>138</sup> The authors estimated the overall mean effect sizes (ES) of interventions by means of random effect models. Outcomes of interest, besides medication adherence, were increased knowledge of a patient having high blood pressure. Table 7.3.11 shows the mean ES of the interventions on these outcomes. Larger ESs correspond with a larger intervention effect, meaning that interventions certainly had a positive effect on adherence, and they improved knowledge to a larger extent. In addition, this study showed larger adherence from interventions employing special medication packaging, dose modification, participant monitoring of medication effects and side effects, and brief written instructions. The meta-analysis also emphasised the need for more primary research in this area, especially on the effects of behavioural rather than cognitive strategies for improving medication adherence. Individuals taking three to five medicines seemed to benefit most from the interventions.

Fewer medications were easier to handle for the patients, leading to the intervention having less additional value, while more medication taking might require more intense and complex interventions to improve medication adherence.<sup>138</sup>

Shared decision making plays an important role in medication adherence. A literature review states that when a patient participates in the decision making process, their perspectives can be evaluated concerning the therapy, and in this way short- and long-term goals can be negotiated.<sup>143</sup> Medication reviewing might be a strategy to improve adherence, but only if the patient fully participates in the process.<sup>107</sup> It should be acknowledged that this may not always be possible in patients with cognitive impairments, which are prevalent among older patients. The NICE guideline on Medicines Adherence adopts this strategy and states that decisions should be made together and that it is a patient's own right to reject a treatment, provided that he or she is completely informed about its risks and benefits.<sup>141</sup> Patient and caregiver empowerment related to adherence is one of the key objectives of the action plan on 'prescription and adherence to treatment' of the European Innovation Partnership on Active and Healthy Ageing.<sup>144</sup> Further general objectives of this plan are to improve patient adherence to medication care plans, deliver improvements in the health care system in order to promote adherence, contribute to the research and methodology on ageing and adherence, and foster communication between different partners/actors in the healing and caring process to improve adherence.

**Table 7.3.11: Effect sizes of interventions to improve adherence on different outcome variables.**

Outcome	Effect size
Adherence	0.33***
Knowledge	0.48***
Health care service utilisation	0.16
Systolic blood pressure	0.21
Diastolic blood pressure	0.19*

Levels of significance compared to control group:\*\*\*P=0.001, \*p=0.05

Source: Conn VS, Hafdahl AR, Cooper PS, Ruppar TM, Mehr DR, Russell CL. Interventions to improve medication adherence among older adults: meta-analysis of adherence outcomes among randomized controlled trials. *Gerontologist* 2009 Aug;49(4):447-62.<sup>138</sup>

In their 2012 report, IMS Health suggested four strategies to improve adherence: (i) adoption of cross-disease leanings, i.e. the way adherence in HIV therapy was improved in Africa could provide lessons for improving adherence in therapies such as type II diabetes in Western countries, (ii) applying a patient centred approach, comparable to the NICE guideline on 'shared decision making', (iii) supporting data collection efforts to enable targeted interventions, similar to the marketing and product strategies that target consumer behaviours, (iv) strengthening the role of the pharmacists, who are in a unique position to assess all prescribed medications and who can substantially improve adherence.<sup>1398</sup>

In conclusion, the best strategy to improve adherence in general, but particularly in the elderly, has not been found; effective interventions may be too complex and unsuitable in

daily practice. More research into establishing the most cost-effective interventions is needed. Future emphasis should also be placed on the necessity to actively involve the patient and/or caregivers in treatment decisions when possible.

### 5.4 Access to medicines

Not all patients have equal access to healthcare, including medicines.<sup>145</sup> Access to healthcare might be compromised by multiple factors like discrimination (on the basis of age, gender, race, socio-economic status), lack of reimbursement, or perceived biases in outcomes leading to unintentional underuse. There is variation in access to healthcare within and between countries; for example, lower-income countries show more shortfalls in the use of drugs for the secondary prevention of a cardiovascular disease than middle-income or high-income countries.<sup>146</sup> In this section we focus on the equity of care and the unconscious underuse of medicines in the elderly.

#### Access to medicines

Access to healthcare highly depends on the socio-economic situation in a country or a population. For example, in low- and middle-income countries, healthcare is mostly financed by out-of-pocket payments,<sup>147</sup> while the governments of OECD (Organization for Economic Cooperation and Development) countries are more committed to ensuring equitable access to high-quality medical care.<sup>148</sup> Very limited data on inequity in access to medicines in Europe due to age discrimination could be found in the literature. A Spanish study on access to a GP showed the presence of a pro-poor inequity; seniors with a lower income had more access to GP services and used their service more frequently.<sup>145</sup> A Belgian study on the influence of social-economic status on healthcare utilisation showed that it exerted no influence in the elderly population when corrected for healthcare status; this is in contrast to the situation observed in the younger population. However, the elderly with less education did have more frequent contact with a GP.<sup>149</sup> Although the current data do not suggest poor access as a result of age discrimination, the paucity of data hampers drawing firm conclusions. In addition, it is unknown to what extent the ongoing economic recession, and the subsequently undertaken policy measures, might impact healthcare consumption and medicine utilisation in the elderly.

#### Underuse of medicines in the elderly

Underuse of medicines is an underestimated problem in the older population; misuse and overuse gain much more attention. A study using a full CGA to estimate the prevalence of prescribing omissions in older people who presented at a geriatric acute care ward, showed that 73.5% of the population under study (n=200) had at least one omission in his or her medication. Those most commonly omitted were treatments for osteoporosis, depression, and dementia, as shown in Table 7.3.12.<sup>150</sup> These results should be interpreted with caution however, particularly because treatment for dementia is only effective for short-term benefit. Another study evaluating the treatment of older persons presenting in an internal medicine ward (n=123), whose treatment was compared with the recommended pharmacological treatment guidelines, showed that under-prescribing occurred in 39% of the participants.<sup>151</sup> In this study, the conditions associated with under-prescribing were myocardial infarction, osteoporosis, diabetes mellitus, and heart failure. After evaluating the medication, the GP was asked to explain his or her prescribing choices. In 65% of the cases, the GP had a clear

reason for not prescribing; the most reported explanations were limited life expectancy, adverse events, and the indication for a treatment no longer present. These results therefore show that it is important to distinguish between appropriate and inappropriate under-prescribing. Another reason for under-prescribing is the relative absence of guidance for prescribing in the elderly in clinical guidelines (see Section 3.2).<sup>151</sup> In Section 5.1, several tools to assess underuse are described, such as the START tool (explicit method) or the CGA. The START tool helps the physician to detect underuse, but is not intended to guide careful clinical decision making. In that case, the Complete Geriatric Assessment, which is time consuming but allows for the assessment of more parameters, such as clinical, cognitive, functional, nutritional and social determinants, could be of use.<sup>150</sup>

**Table 7.3.12: Therapeutic classes most frequently underused.**

Therapeutic Class	Individuals with Indication, n	Individuals in Underuse, n (%)
Antiosteoporotic medication	60	39 (65.0)
Vitamin D	190	123 (64.7)
Dementia treatment	65	32 (49.2)
Antidepressant	63	14 (22.2)
Angiotensin-converting enzyme inhibitor or angiotensin-2 receptor antagonist	101	19 (18.8)
Statin	90	13 (14.4)
Antivitamin K	49	7 (14.3)
Antiplatelet agent	87	9 (10.3)
Beta-blocker	46	2 (4.3)

Source: Andro M, Coutard A, Gentric A. Underuse in elderly adults: an underestimated suboptimal prescribing. J Am Geriatr Soc 2012 Aug;60(8):1582-3.<sup>150</sup>

The recent IMS Health report 'Advancing the Responsible Use of Medicines' calls for awareness about the timely use of medicine, which can only occur when there is access to healthcare. This report used type II diabetes mellitus and hepatitis B/C as examples. They defined three strategies for more timely use of medicines in these conditions and estimated cost savings in health care, despite costs for medication use increasing once all patients were treated appropriately. First, support for a national focus on early diagnosis, so that complications can be prevented. Second, leverage economic evaluations, evaluate factors such as the number of cases needed to treat for prevention of communicable conditions. Third, ensure the use of targeted disease management programmes, such as those for diabetes. This way, significant costs can be avoided by preventing macrovascular events.<sup>139</sup>

Further research is warranted to assess the extent of inappropriate under-prescribing in the elderly, to evaluate the effectiveness of tools to identify and correct this under-prescribing, and to assess other proposed strategies for more timely use of medicines.

## 5.5 Palliative care

There has been increased amount of attention paid to palliative, or end of life, care over the past few years. End of life care is not easy to handle, given that the prevailing medical philosophy is focused on curing illnesses and prolonging life. Now that people tend to

survive acute diseases, they often suffer from chronic diseases, which end in a period in which the patient needs additional support. According to a USA study, about 25% of Medicare expenditures arise in a patient's last year of life, indicating an intense and health consuming phase.<sup>152</sup> Palliative care is therefore becoming more important,<sup>153</sup> as it aims to relieve suffering and to improve the quality of life of patients with advanced illnesses, as well as providing support to their families.<sup>154,155</sup> In 2002, the WHO defined palliative care as *'an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness'*.<sup>156</sup> In the development of palliative care, the focus was initially on terminal cancer care, usually in hospices, but this has been expanded to include patients with other diseases and is starting earlier in the disease course.<sup>155,157</sup>

In a 2004 WHO report 'Better Palliative Care for Older People', the second in a series of three reports, made recommendations for future research; such as the investment in research into the geographical variations between and within countries in palliative care that the elderly receive. They promoted collaboration in research between palliative and geriatric medicine, and supported the inclusion of older people in all kinds of innovative research on physical interventions, including drug treatments. They also promoted the development of standardised assessment tools for palliative care in older people;<sup>157</sup> but the needs are far from being met. Because this report lacked specific details about how practices could be changed, a third report was written; 'Better Palliative Care for Older People: better practices'. In this report, more practical suggestions are presented to improve palliative care in various settings such as hospitals, nursing homes, and at home.<sup>158</sup>

Polypharmacy is prevalent at the end of life, but optimal prescribing at this stage of life remains largely unexplored. There is, however, increasing acknowledgement that treatment goals may need to be redefined, and guiding principles for appropriate prescribing in end-of-life patients have been suggested.<sup>159</sup> These include, for example, revision of therapeutic targets, discontinuation of medications for primary and secondary prevention, avoidance of taking more than five daily medicines, and the graduated withdrawal of medicines, unless the patient or caregivers are unable to cope with the reduced lifespan. Medication review and the simplification of drug regimes in this cohort have been called for. The most important research question related to this topic is whether the presented principles indeed lead to better end-of-life quality.

Palliative care generally consists of various aspects, with the most important ones being symptom management; particularly pain, dyspnoea, and depression. Care planning and continuity of care and relieving the burden on caregivers are also key components of palliative care. A systematic review assessed the evidence for several interventions to improve palliative care. Table 7.3.13 gives an overview of the findings.<sup>160</sup> The strongest evidence was found in the symptom domains of palliative care such as pain, dyspnoea and depression. Less evidence was found on the more complex domains, such as advance care planning, continuity of care, or caregiver burdens.

**Table 7.3.13: Summary of systematic reviews and additional intervention studies of palliative and end-of-life care.**

Domain	Literature identity*	Summary of Evidence and GRADE Ratings **
Symptoms		
Pain	Nine systematic reviews (25-33) and 24 reports of interventions (34-57)	Strong evidence supports approaches to treating cancer pain with nonsteroidals, opioids, radionuclides and radiotherapy. Less consistent evidence supports use of bisphosphonates for pain of painful complications (for example, fracture). Weak evidence supports multidisciplinary teams. No evidence addressed pain management in advanced heart failure or dementia.
Dyspnoea	Seven systematic reviews (27, 28, 61-65) and 12 reports of interventions (37, 41, 42, 45, 46, 48, 57, 66-70)	Strong evidence supports treating dyspnoea with $\beta$ -agonists and opioid use in COPD, although these trials are small and short in duration. Weak evidence supports opioid use for relieving dyspnoea in cancer. Strong evidence supports pulmonary rehabilitation and oxygen for improving symptoms during short-term exercise in COPD. Evidence for oxygen use in cancer is weak, and few studies address it. Weak evidence supports care delivery interventions for dyspnoea. No evidence addressed symptomatic dyspnoea management in advanced heart failure.
Depression	Four systematic reviews (26, 27, 30, 71) and 9 reports of interventions (35, 37, 39-42, 72-74)	Strong evidence supports psychotherapy, as well as tricyclic antidepressants and SSRIs, for depression treatment in cancer.
Advance care planning	9 systematic reviews (25, 29, 75-81) and 32 reports of interventions (35, 82-112)	Moderate evidence supports multicomponent interventions to increase advance directives; however, such studies seldom measure clinically important outcomes. Recent research supports care planning through engaging values, involving skilled facilitators, and focusing on key decision makers (for example, patients, caregivers, and providers)
Continuity	Nine systematic reviews (25, 27, 29, 113-118) and 12 reports of intervention (103, 104, 112, 119-127)	Moderate evidence supports multidisciplinary interventions that target continuity to affect utilization outcomes. Evidence is strong for reducing readmissions in heart failure, but insufficient evidence was available for other conditions. Successful interventions involved multidisciplinary teaming, addressed patient needs across settings and over time, and facilitated communication by personal and technological means.
Caregiver burdens	Eight systematic reviews (25, 27, 29, 129-133) and 19 reports of interventions (103, 104, 134-150)	Weak to moderate evidence suggests that caregiver interventions especially when comprehensive and individually targeted, can improve various measures of caregiver burden, although effect sizes are small. Moderate evidence suggests that palliative care interventions improve caregiver satisfaction. Existing research has focused on dementia and, to a lesser extent, cancer.

Source: Lorenz KA, Lynn J, Dy SM, Shugarman LR, Wilkinson A, Mularski RA, et al. Evidence for improving palliative care at the end of life: a systematic review. *Ann Intern Med* 2008 Jan 15;148(2):147-59.<sup>160</sup>

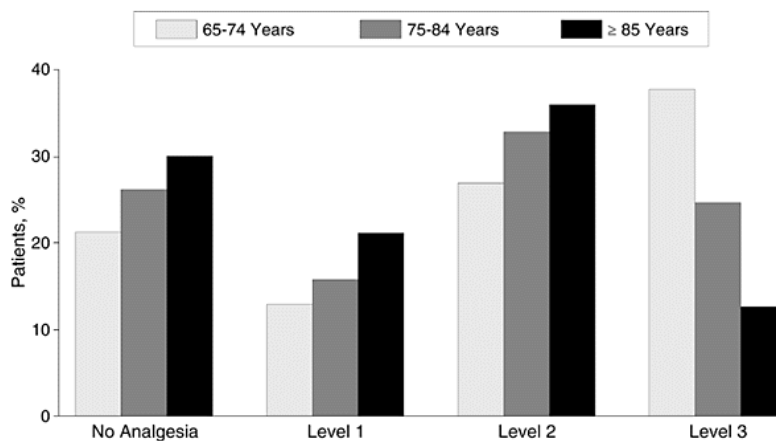
Another systematic review evaluated the effectiveness of specialised palliative care in terms of improving quality of life, satisfaction with care, and economic cost. This study found scant evidence for specialised palliative care in these domains. The only statistically significant effect was seen for caregiver satisfaction. The studies included were hindered by methodological challenges and often lacked power or sample size calculations, decreasing the quality of this evidence. Moreover, the tools used to assess quality of life were not validated for the terminally ill patient. Cost calculations indicated a shift from hospital costs



towards the costs from hospices and home care that are associated with specialised palliative care. There was a trend in cost-reduction but no cost-effectiveness studies have been performed. These researchers concluded that carefully planned trials using standardised palliative care interventions and measures constructed specifically for this population are needed.<sup>155</sup>

Although strong evidence was found for interventions focusing on pain treatment, one of the most difficult aspects of end of life care is pain management. It starts with under-assessment, as stated in the 2004 WHO report on palliative care.<sup>157</sup> A large 1998 survey among 4 000 patients with cancer reporting daily pain showed that 25% did not receive any kind of pain therapy, and an inverse relation with age was observed; the older the patient, the less pain relief was given.<sup>161</sup> Figure 7.3.8 shows the outcome of pharmacological treatment divided by the patient groups of this survey.

**Figure 7.3.8: Pharmacological treatment of cancer patients with pain according to the World Health Organization's (WHO's) 3-level ladder. The WHO's level 1 is non-opioid analgesics; level 2 is weak opiates; and level 3 includes morphine or similar substances.**



Source: Bernabei R, Gambassi G, Lapane K, Landi F, Gatsonis C, Dunlop R, et al. Management of pain in elderly patients with cancer. SAGE Study Group. Systematic Assessment of Geriatric Drug Use via Epidemiology. JAMA 1998 Jun 17;279(23):1877-82.<sup>161</sup>

Unfortunately, more recent research does not indicate an improvement in pain treatment in the last phase of life. A study by Yao et al. on the pain management of 1425 end-of-life patients showed that only 42.7% of the patients with pain showed the predicted pain outcome (goal) at discharge or death. This study showed an under-diagnosis and under-documentation of pain, with only 70% of the pain episodes of the patients on surgical wards were documented.<sup>162</sup>

Different barriers exist that hinder adequate pain management: patient barriers such as misconceptions about pain and treatments, and fears and concerns about pain medications and side effects; reluctance to report pain and symptoms; and the complexity of the symptom experience. Barriers related to providers are, for example, lack of knowledge of, skills in, and time for adequate pain and symptom assessment; lack of knowledge about

analgesics; symptom interventions; and side effects of therapies. There is also insufficient knowledge on mechanisms underlying pain at the end of life.<sup>163</sup>

In December 2009, the EU--funded Access to Opioid Medication in Europe (ATOME) project was started. The project strives to improve access to opioids in 12 Eastern European countries. The commonality between these countries is statistical evidence of very low morphine consumption per capita.<sup>164</sup> To improve access to controlled medicines used for the relief of pain, in harm reduction, and in palliative care, the ATOME project collaborates with national country teams – including government officials and healthcare professionals – to review national policies and legislation and make recommendations for improvement. One of the first achievements of the ATOME project was the publication of new WHO Policy Guidelines Ensuring Balance in National Policies on Controlled Substances; Guidance for availability and accessibility of controlled medicines, which provides a basis for all subsequent activities.<sup>165</sup> Country workshops confirmed the diversity of aspects that play an important role in limited access, including the lack of education and training, overly restrictive regulations, lack of financial resources and fear of opioids.<sup>166,167</sup> The effectiveness of the approach taken, in terms of access to and use of controlled substances, is unknown and needs to be evaluated.

All of the above mentioned results strongly indicate the need for additional focus on pain diagnosis, interventions, and outcomes for end of life patients. In addition, access to controlled substances needs further attention with a focus on understanding and diminishing existing barriers. There is also a need to translate pain science into practice. Practice based datasets may provide insights in practices associated with better outcomes. In conclusion, the focus should lie on pain management and on the evaluation of effective interventions in palliative care.

### 5.6 Integrated care

The integration and continuity of care is extremely important, especially when a patient is multi-morbid, which is the case for many of the elderly. The transitions an older patient makes between sites of care may introduce risks as well as risk opportunities in their medication management; risks in the sense of the loss of information and/or medication discontinuation, and opportunities in the way that these transitions provide a chance to review the patient's medication profile. It has been shown that the highest risks are among patients admitted to an intensive care unit. Now, efforts to reduce medication discontinuation are based on hospital-based medication reconciliation (as described in Section 5.1), medication reviewing, or a complete geriatric assessment (CGA). In contrast, little effort seems to have been done to ensure good communication between physicians (and other health professionals) across different sites of care, including the transfer to a private home or a care residence.<sup>168</sup> It is also important to know what happens with medications when the patients return to their homes. Can the patient manage his/her complex medication regimen, and if not, what can go wrong?

To illustrate the challenges of achieving integration of care, we use, as an example, the case of an 82-year-old woman, living alone, who falls and breaks her hip and then moves from her home to the hospital, then to a nursing home, and eventually back to her own home. This example demonstrates the importance of integrated care, and the many points at which things can go wrong.

**Table 7.3.14: The Structure History Taking on Medication use questionnaire (SHIM).**

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**Questions asked per drug on the medication list, provided by the community pharmacist**

1. Are you using this drug as prescribed (dosage, dose frequency, dosage form)?
2. Are you experiencing any side effects?
3. What is the reason for deviating (from the dosage, dose frequency, or dosage form) or not taking the drug at all?
4. Are you using any other prescription drugs that are not mentioned on this list? (view medication containers)
5. Are you using non-prescription drugs?
6. Are you using homeopathic drugs or herbal medicines (especially St. Johns wort)?
7. Are you using drugs that belong to family members or friends?
8. Are you using any "as needed" drugs?
9. Are you using drugs that are no longer prescribed?

**Questions concerning the use of medicines?**

10. Are you taking your medication independently?
11. Are you using a dosage system?
12. Are you experiencing problems taking your medication?
13. In case of inhalation therapy: What kind of inhalation system are you using? Are you experiencing any problems using this system?
14. In case of eye drops: Are you experiencing any difficulties using the eye drops?
15. Do you ever forget to take your medication? If so, which medication, why and what do you do?

Other

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**Would you like to comment on or ask a question about your medication?**

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Source: Drenth-van Maanen AC, Spee J, van HL, Jansen PA, Egberts TC, van Marum RJ. Structured history taking of medication use reveals iatrogenic harm due to discrepancies in medication histories in hospital and pharmacy records. *J Am Geriatr Soc* 2011 Oct;59(10):1976-7.<sup>169</sup>

When a patient is admitted to the hospital, the first step is medical history taking. This is a crucial step in the management of the older patient, especially when they are taking multiple medications. Still, much can go wrong in the taking of a medication history, which leads to discrepancies between medication lists in primary and secondary care. A study on the newly designed method for Structural History taking of Medication use (SHIM, shown in Table 7.3.14) showed that there was a discrepancy between the usual care provided and SHIM in 92% of older participants. A mean of three discrepancies per patient was found, with omissions being most prevalent. A total of 5% of the discrepancies had a clinical consequence, occurring in 21% of the patients.<sup>169</sup> When a patient is admitted, the medication is adjusted to the formulary of the hospital. Hospitals frequently have their own formulary and the 'Pharmaceutical and Therapeutic Committee', usually consisting of physicians, hospital pharmacists, the hospital management and others, decides which drugs are included. Hospital formularies may differ substantially from formularies in the community. They are restricted, in comparison to the reimbursement lists of the outpatient-sector. The PHIS (Pharmaceutical Health Information System) Project, commissioned by the Executive Agency for Health and Consumers (EAHC) and co-funded by the Austrian Federal Ministry of Health (BMG), investigated the policies on procurement, distribution, pricing, financing, and use of medicines in the inpatient sector. They used five case study countries to collect prices of medicines in hospitals. It was shown that considerable discounts and rebates are common and in some cases, medicines are provided cost-free to the hospital.<sup>170</sup> Such inpatient policies may affect the hospital formulary and account for the need of patients to change medication when hospitalised and when discharged.

Because of the formulary, a transition step from the home medication list to the hospital medication list needs to be included, introducing risks of omission of drugs, or errors in dosing. It is conceivable that some new drugs have been started during admission, such as bisphosphonates and vitamin D for osteoporosis in a hypothetical patient, for example. It is also possible that the hospital has discontinued a drug, due to an adverse event or when an indication is no longer present. When the latter occurs, it is of importance to document the discontinuation. A study has shown that in almost 40% of the cases, reasons for the discontinuation of drugs in the hospital were not documented.<sup>171</sup> Another study showed that ADRs requiring discontinuation were poorly mentioned in discharge letters to the GP and were not communicated at all to the pharmacies. Only 22% of the letters that mentioned ADRs were incorporated into the patient's GP file.<sup>172</sup> In this case, poor documentation and communication can lead to renewed prescription in primary care, which occurred in 27% of the reported cases within six months after discharge.<sup>171</sup>

With electronic prescribing systems, CDSS can be used to support the documentation of discontinuation and generate warnings when drugs are prescribed again after discontinuation. In a pilot study, the implementation of such a system was user friendly and fulfilled the aims of documenting discontinuation and alerting physicians when they prescribed the discontinued medicine again.<sup>173</sup> This type of system works within the same hospital, but when the information does not reach the primary care, there is a chance that drugs are prescribed again in this setting. This illustrates the need for more communication between primary and secondary care. As such, ICT must play a bigger role, making it easier to exchange information.<sup>168</sup>

A few decades ago, placing the frail elderly in an innovative geriatric unit with the intention of providing improved diagnostic assessments, therapy, rehabilitation, and placement, resulted in reduced mortality (23.8 versus 48.3%,  $p < 0.005$ ) and time spent in nursing homes (26.9 versus 46.7%,  $p < 0.05$ ).<sup>174</sup> Similar results were found in a study from 2002, where, after a triage, the frail elderly were placed on a special ward. Here, all relevant disorders were assessed, resulting in significantly increased diagnoses of psychiatric disorders.<sup>175</sup> A 2011 Cochrane meta-analysis evaluated the effects of CGA in elderly people presenting at an emergency ward on outcomes such as being 'alive and at home' (primary outcome) and various secondary outcomes such as death, residential care, or dependence. They included 22 RCTs with more than 10 000 elderly and showed that CGA increased the chance of a patient living at home after follow up (mean 12 months; odds ratio 1.16 (95% CI 1.05 to 1.28);  $p = 0.003$ ). Patients receiving CGA were less likely to live in residential care, experience deterioration, or die. However, CGA was only effective when performed in special wards, not when performed by mobile geriatric teams. A possible explanation for this is that the mobile teams find it difficult to modify the behaviour of other healthcare professionals.<sup>34</sup> Evidence suggests that it is important to treat elderly in a geriatric environment.

The next step for our hypothetical elderly patient with a hip fracture is discharge from the hospital and a move to a nursing home for further rehabilitation. Some hospitals make use of discharge planning, bridging the gap between the hospital and nursing home environments or the hospital and home. A Cochrane Review from 2010 investigated the effectiveness of discharge planning in terms of appropriate use of care, patient outcome, and costs. They found a small reduction in the hospital length of stay; mean difference of -0.91 days (95% confidence interval -1.55 to -0.27 days), and more patient satisfaction, but no effects on patient outcomes such as mortality. The decreased length of the hospital stay was not

necessarily associated with fewer costs, as it could have led to a shift in costs from secondary to primary care. Future research should continue to collect data about hospital lengths of stay and readmission, and attention should be paid to the communication between primary and secondary care, which was often the reason for implementing discharge planning.<sup>176</sup>

After discharge, our imaginary patient is transferred to a nursing home. Again, a translation of the medication needs to be effected, introducing new risks of errors. A study published in the JAMA evaluated the risk of potentially unintentional discontinuation of chronic medication following ICU or hospital admission. It was shown that discontinuation of anticoagulant therapy, for example, was more prevalent in patients after hospital admission than in controls, adjusted odd ratio (AOR) 1.86 (95% CI 1.77 to 1.97). This was more pronounced after ICU admission; AOR of 2.31 (95% CI 2.07 to 2.57). More detailed results for other medications are shown in Table 7.3.15. These findings illustrate the need for a systematic approach to the transition of healthcare to ensure continuity of care.<sup>177</sup>

**Table 7.3.15: Outcome of Unintentional Discontinuation by Medication Group.**

	No (%) of Patients			ICU Stay <sup>a</sup>	
	Control Group	Hospitalized	AOR (95% CI) <sup>b</sup>	No *(%) of Patients	AOR (95% CI) <sup>b</sup>
<b>Medication discontinued</b>					
Statins	11 627 (10.7)	13 277 (13.6)	1.33 (1.29-1.37)	1484 (14.6)	1.48 (1.39-1.57)
Antiplatelet or anticoagulants	2535 (11.8)	5564 (19.4)	1.86 (1.77-1.97)	522 (22.8)	2.31 (2.07-2.57)
Levothyroxine	7114 (11.0)	6831 (12.3)	1.18 (1.14-1.23)	614 (15)	1.51 (1.38-1.66)
Respiratory inhalers	79 (3.0)	231 (4.5)	1.50 (1.15-1.97)	20 (5.4)	1.84 (1.10-3.08)
Gastric acid suppressors	4330 (9.4)	7394 (12.9)	1.50 (1.43-1.56)	670 (15.4)	1.87 (1.71-2.05)

Abbreviations AOR: adjusted odds ratio; CI, confidence interval; ICU, intensive care unit.

<sup>a</sup> Patients with an ICU stay compared with the control group.

<sup>b</sup> Adjusted for age, sex, low-income (defines as individual income <\$16,018 or combined household income <\$24,175), number of different prescriptions, and number of primary care physician or specialist visits.

<sup>c</sup> There is detailed information for each medication group in eTable 3 at <http://www.jama.com>.

Source: Bell CM, Brener SS, Gunraj N, Huo C, Bierman AS, Scales DC, et al. Association of ICU or hospital admission with unintentional discontinuation of medications for chronic diseases. JAMA 2011 Aug 24;306(8):840-7.<sup>177</sup>

The elderly dwell in different environments, depending on their health state, their financial situation and the culture in their country amongst other factors. They may move between the community, nursing homes, residential care, and hospital environments. Nowadays, a greater proportion of the elderly remain living in their own homes, especially in high-income countries such as Europe, the United States, and Japan.<sup>178,179</sup> A strong preference to remain at home is behind this trend.<sup>180</sup> At the same time, hospital stays are kept as short as possible to reduce costs. Thus, home based care has become more important over the years, and new

initiatives have arisen to promote and guide home care. Despite many good initiatives, such as those mentioned in the previous section on 'polypharmacy', much can go wrong when the elderly patient actually takes medication at home. This can, for example, be due to vision and hearing loss, memory impairment, or osteoarthritis which may hamper their ability to open the packages.<sup>181</sup>

It is important to establish how the elderly take their medication at home, what can go wrong, and what is needed in order to improve medication management in the home setting. The concept of patient empowerment, where the patient has the right to decide whether or not to take a drug or to follow the instructions of the healthcare professionals, plays an important role in his or her own home environment. A qualitative study by Tordoff et al. investigated what goes wrong with medication taking in the community-dwelling elderly. A total of 23 elderly were interviewed and the researchers concluded that these elderly could access, afford, and manage their medication well. Three quarters had experienced side effects at least once in the past. It is likely that some bias was present, e.g. elderly giving the socially desirable response.<sup>182</sup>

A study by Beckman among 492 community-dwelling elderly (a random selection of elderly aged above 77 years) assessed their cognitive, physical, and visual abilities related to medication taking. Results showed that almost 10% of them could not read the leaflet instruction, and almost 15% of them could not open the plastic flip-top medicine bottle. More than three quarters of the study population did not pass all the tests included in this study. This demonstrates that medication taking is a difficult task and the elderly have difficulties (cognitive, physical, and visual) that may hinder accurate medication taking.<sup>181</sup> Little is known on the potential role of caregivers in medication management in the home environment, and this topic warrants further research, including an assessment of (cost)effectiveness of caregiver support.

Different tools have been developed to assess the ability of patients in managing their medication, and the majority were developed for or validated in the elderly. About 50 specific tools exist in the international literature to assess the functional ability of the elderly in managing their medication that can be applied at home or in a standard setting (e.g. healthcare centre). The Medication Management Ability Assessment (MMAA) and the Drug Regimen Unassisted Grading Scale (DRUGS) were the most frequently applied tools. It has been shown that cognitive impairment and increasing age are determinant factors in the ability to manage one's own medication.<sup>183</sup> These factors need to be evaluated in order to judge if the tools can predict who is at the greatest risk for drug related problems due to non-adherence.<sup>184</sup> It is of utmost importance to be able to detect inability early, in order to preserve a patient's independence and health.

The more medication patients use or the worse their cognitive function is, the more often problems arise. In the Netherlands, a Red Flag Project was designed in which home care nurses document risk situations associated with medication use, e.g. falls, difficulties with opening packages, dizziness when standing up, or the absence of a medication overview. With the use of a checklist, they signal problems and actively react in order to improve the situation. The checklist seems to be valid, but more research is needed to show the effects of using it.<sup>185</sup>

To provide integrated care to the elderly patient, a multi-disciplinary approach is needed and CGA may be an appropriate tool. When the elderly move between different healthcare settings, information may get lost, leading to the unintentional discontinuation of medication, as well as the represcribing of ADR-causing compounds and other medicines that were intentionally discontinued. This translational care can be improved with organisational changes. First, healthcare information must be collected systematically and exchanged to a greater extent between healthcare professionals, both between and within care settings.<sup>99,168</sup> Now that patients take more medications than ever, a hospitalisation requires more management than before. ICT can present opportunities to achieve this, e.g. with development of software such as the clinical rules mentioned in Section 5.1. Nationally available electronic patient dossiers with relevant information filtered for the healthcare professional could be of high value. This way, laboratory values such as renal functions can be used when pharmacists perform medication reviews, or an up-to-date medication list is available when elderly present at an emergency department in a hospital. Now, a lot of time is lost collecting the correct information before an intervention can be made. This can be of considerable benefit, especially in the frail elderly who are taking many medicines. It should be acknowledged however that eHealth cannot be the solution to everything. Until now, the evidence that eHealth solutions lead to higher quality and safety in healthcare remains absent. Recently, both Great Britain and the United States invested in national eHealth programs and the extent to which this will lead to better care should be studied. In addition, the best way to implement eHealth remains unclear.<sup>186</sup> Second, a multi-disciplinary approach and the development of special geriatric wards in hospitals seem to be beneficial for the elderly. Whether this specific care is cost-effective and/or leads to better health remains uncertain.

In conclusion, integrated care is of the utmost importance in order to guarantee the continuation of care when patients move between different (health care) settings. Although various initiatives in this area are ongoing, many of them need further evaluation in order to establish their contribution to better health for elderly. The mapping of existing tools, instruments, methodologies, and best practices, as well as the development of new and better toolkits in this area are the key components of the action plan on 'replicating and tutoring integrated care for chronic diseases, including remote monitoring at regional levels' of the European Innovation Partnership on Active and Healthy Ageing.<sup>187</sup>

Communication between primary and secondary care should be facilitated and improved because, current, information is often lost, leading to the inappropriate discontinuation of medications. Medication reviews have become routine practice, but it should be evaluated as to its cost-effectiveness and its capacity to improve clinical outcomes such as hospitalisation, mortality, and quality of life. ICT may provide opportunities to facilitate many of these aspects of integrated care. The role of eHealth in medication reviewing, however, warrants further assessment; issues that need attention are design, implementation, and the (cost-)effectiveness of eHealth. Furthermore, the effectiveness of specialised geriatric care, such as geriatric wards, should be investigated to determine if and how this leads to better care. As the importance of home based care has increased and more elderly remain living in their homes, medication management in this environment needs careful consideration. Initiatives to improve this management should be supported and appraised, and best practices need to be identified and shared.

## 6. Conclusion

This cross-cutting background paper addresses special needs in the treatment of elderly patients and describes developments since the previous edition of this report in 2004. It highlights existing knowledge gaps and describes implications for future research.

First, the treatment of osteoporosis with current medicines is relatively effective, but falls should always be prevented. Various fall prevention programs exist with differing effectiveness, so research should focus on methods to deliver evidence-based fall prevention programs in different care environments, as well as methods for increasing the uptake of and adherence to these interventions by the elderly. As the population grows older, the incidence of cancer increases. The elderly are a heterogeneous group, therefore it is not easy to predict how they will respond to chemotherapy. Which geriatric conditions are predictive of specific clinical outcome in cancer patients, such as quality of life, treatment tolerance, or survival has not yet been clarified. A robust screening tool is therefore needed in order to facilitate treatment decisions and offer tailored care. During the past decade, research has focused on Alzheimer disease, but most cases of dementia are mixed cases in which a vascular component plays an important role. More research on vascular dementia is needed including epidemiology, diagnosis, and treatment.

Second, it is clear that the elderly have difficulties with taking their medication, especially with tasks like opening packages, reading leaflet information, and/or swallowing oral medication. Many of these special needs have strong similarities with the needs of children. There is a call for the development of special geriatric formulations, and the steps taken in the development of formulations for paediatrics might serve as an example, taking into account the differences between these groups, of course.

Third, it is clear that the elderly are still under-represented in clinical trials. This results in a lack of information about the safety and effectiveness of medicines in the elderly. Therefore, new approaches are needed to assess effectiveness in the elderly. Because the elderly are part of a heterogeneous group, a consensus definition of frailty is needed, as well as better tools to evaluate frailty. This might be of help for the selection and inclusion of elderly in clinical trials. In addition, ways to translate information about treatment of elderly obtained in clinical trials into practical recommendations, in the SPC and/or age specific recommendations in guidelines, need to be further explored.

Fourth, various improvements can be made in the medicine usage environment of elderly. Polypharmacy is very common in the elderly and medication reviewing has become daily practice in some countries. However, the benefits of medication reviewing have not been fully proven yet; benefits on harder clinical outcomes such as hospital admissions or death need to be confirmed. The role of computerised systems could be further explored to help achieve this. It could make the reviewing less time consuming and it could help the reviewer to more systematically select those patients that might benefit most from reviewing.

Adherence to medication regimes should be improved in the elderly. It is not clear which intervention programs improve adherence in this patient population, so more research in this field is needed. The active participation of the patient in treatment decisions should be further strengthened to achieve better outcomes.



It is unknown if inequity in the access to medicines exists for elderly. Research to establish this is necessary, especially in light of the ongoing economic recession and the subsequent policy measures that have been undertaken. Under-use and under-prescribing are present in this population. One of the reasons might be the relative absence of guidance on prescribing in the elderly in clinical guidelines. This situation could be improved, similarly to the knowledge gaps on safety and effectiveness of medicines in elderly— through fast and extensive data sharing with the aid of computerised systems.

Palliative care has become more important over the last few years and is acknowledged as a serious part of healthcare. There is a need for further evaluation of the cost-effectiveness of interventions in the last phase of life. Still, many elderly suffer from pain at the end of life, which calls for improvements in pain treatments. Identifying and resolving the barriers to treatment with opioid medications is also an important step forward, but their effects on optimal treatment need to be further established.

Finally, the integration of care in elderly patients is essential to prevent, for example, medication errors due to a loss of information. The elderly dwell in multiple care sites, and each transfer between settings can introduce the potential risk of the unintentional discontinuation of medicines or the re-prescribing of medication that was initially stopped. Effort is put into accurate medication taking in second-line care (hospitals); making use of the medication reviewing of complete geriatric assessments, for example, but little effort is put into communication between first-and second line care. It seems to be beneficial for the older patient to be treated in a geriatric environment; in order to provide them with specialised care in a multi-disciplinary environment, however, how such care should be organised needs to be further investigated. There is also a trend toward the elderly living longer independently, but medication management is complex and many elderly have difficulties that may hinder accurate medication self-management. Tools to assess their ability to manage their medication at home have been developed, but are in need of further evaluation. eHealth might enable faster and easier information exchange between healthcare professionals, making it easier to communicate and thus provide integrated care. Until now, eHealth solutions have not been proven to lead to better health in the general population, consequently, the role of eHealth in this population warrants further investigation.

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## Annexes

## Annex 7.3.1: Cancer prevalence by age at prevalence (US data 2005-2009)

Table 1.22  
U.S. Complete Prevalence Counts, Invasive Cancers Only, January 1, 2009<sup>a</sup>  
By Age at Prevalence

Site/Sex	Age at Prevalence								
	All Ages <sup>c</sup>	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70+
All Sites									
Males	5,809,017	18,156	41,323	80,500	150,710	346,280	815,636	1,465,844	2,890,567
Females	6,740,016	15,649	35,203	83,134	219,550	622,449	1,226,028	1,600,054	2,937,950
Oral Cavity & Pharynx									
Males	172,502	67	418	1,505	3,416	14,153	41,881	49,752	61,309
Females	91,610	101	493	1,453	3,530	8,334	17,445	21,205	39,049
Esophagus									
Males	24,657	0	0	38	186	1,059	4,426	8,360	10,588
Females	7,170	0	0	0	39	314	1,070	1,656	4,091
Stomach									
Males	39,694	0	17	78	688	2,436	6,519	9,680	20,275
Females	30,232	4	11	165	643	2,169	4,233	5,764	17,243
Colon & Rectum									
Males	558,408	11	69	1,116	5,277	24,270	77,071	129,789	320,804
Females	581,302	0	86	1,202	5,090	22,495	64,292	107,339	380,797
Liver & Intrahep									
Males	24,615	438	554	494	438	1,581	8,481	7,111	5,516
Females	10,913	466	435	332	473	786	2,384	2,609	3,430
Pancreas									
Males	18,537	0	23	68	321	1,356	4,100	5,731	6,939
Females	19,649	0	47	135	418	1,377	3,454	5,181	9,036
Larynx									
Males	71,550	0	0	66	221	2,095	10,475	20,267	38,425
Females	17,521	0	0	48	143	1,051	3,163	4,474	8,642
Lung & Bronchus									
Males	178,447	45	80	454	1,086	5,587	24,209	52,348	94,640
Females	209,203	34	47	363	1,291	7,893	27,437	57,808	114,331
Melanoma of the Skin									
Males	427,519	72	764	5,002	17,503	47,272	91,489	111,843	153,573
Females	448,192	95	950	10,770	33,163	72,253	104,576	99,252	127,133

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Table 1.22 - continued  
U.S. Complete Prevalence Counts, Invasive Cancers Only, January 1, 2009<sup>a</sup>  
By Age at Prevalence

Site/Sex	Age at Prevalence								
	All Ages <sup>c</sup>	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70+
Breast									
Males	14,303	0	0	22	103	498	2,093	3,896	7,691
Females	2,747,209	0	86	2,487	35,584	212,685	522,225	733,979	1,240,161
Cervix									
Females	247,556	0	68	2,050	16,434	42,782	59,350	52,979	73,893
Corpus & Uterus, NOS									
Females	589,789	0	56	412	5,572	24,294	82,675	148,774	328,006
Ovary <sup>d</sup>									
Females	182,710	66	932	3,503	6,560	19,171	39,536	45,524	67,418
Prostate									
Males	2,496,420	34	69	89	247	19,652	216,595	687,644	1,572,090
Urinary Bladder									
Males	411,161	56	110	595	2,405	11,643	42,320	94,909	259,122
Females	143,089	34	56	162	1,087	4,412	13,373	29,661	94,303
Kidney & Renal Pelvis									
Males	188,341	1,507	2,373	2,601	4,936	16,313	37,165	53,360	70,087
Females	131,799	1,408	2,607	2,769	4,642	11,613	22,637	30,925	55,198
Hodgkin Lymphoma									
Males	90,420	168	2,316	9,264	16,301	23,466	20,120	12,217	6,567
Females	84,475	146	1,642	9,767	16,451	22,548	18,024	9,302	6,597
Non-Hodgkin Lymphoma									
Males	252,012	810	3,472	7,162	12,801	28,228	49,236	62,729	87,574
Females	232,051	387	1,793	4,203	8,302	19,927	39,219	53,951	104,268
Myeloma									
Males	38,403	0	6	50	485	2,628	7,535	12,343	15,356
Females	32,754	0	0	22	276	2,112	5,612	9,822	14,911
Leukemia									
Males	152,597	6,389	12,636	11,647	10,425	12,678	20,796	29,694	48,332
Females	119,096	5,232	10,502	10,167	9,042	9,418	13,463	19,494	41,777
Acute Lymphocytic Leuk									
Males	36,576	5,244	10,969	9,000	5,888	3,114	1,140	773	448
Females	29,614	4,381	8,829	7,398	4,995	2,241	767	687	315



## **Annex 7.3.2: Charter for the rights of older people in clinical trials**

### **Charter for the Rights of Older People in Clinical Trials**

1. OLDER PEOPLE HAVE THE RIGHT TO ACCESS EVIDENCE-BASED TREATMENTS
  - 1.1 Older people have the right to be offered evidence-based treatments.
  - 1.2 Older people should expect to be offered drugs and other treatments that have been properly evaluated in clinical trials and demonstrated to be effective in people their age.
2. PROMOTING THE INCLUSION OF OLDER PEOPLE IN CLINICAL TRIALS AND PREVENTING DISCRIMINATION
  - 2.1 Older people should not be discriminated against in the recruitment for clinical trials.
    - 2.1.1 Older people should be informed about and invited to participate in clinical trials of treatments that are intended for use in older people.
    - 2.1.2 National and international regulators should ensure that older people are included in clinical trials without discrimination on grounds of age, gender, ethnicity or social class.
    - 2.1.3 Research ethics committees, sponsors, medical journal editors and regulators should review all studies critically for unjustified exclusions based on age, other illnesses, disability and existing drug treatment. All such exclusions must be justified.
  - 2.2 The participation in clinical trials of people with multiple morbidities should be encouraged
    - 2.2.1 National and international regulators should require that trials with drugs or other treatments intended for use in older people include those with multiple morbidities that are common in later life.
    - 2.2.2 National and international regulators should require that trials with drugs or other treatments intended for use in later life include older people who are taking commonly prescribed medications.
3. CLINICAL TRIALS SHOULD BE MADE AS PRACTICABLE AS POSSIBLE FOR OLDER PEOPLE
  - 3.1 Clinical trials should be designed so that older people can participate easily.
    - 3.1.1 Older people should receive information about clinical trials that helps them make an informed decision about participation. Informed consent procedure should be adapted to the specific needs of older people, taking into account their level of literacy, any sensory deficits, and involving their family or caregiver if needed.
    - 3.1.2 Specific training is needed in order to perform clinical trials in older people. Researchers should be trained to conduct clinical trials in people with communication, sensory, mobility or cognitive problems.
    - 3.1.3 Researchers should be prepared to spend additional time with older people participating in a clinical trial in order to support their participation and adherence.

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3.1.4 Trial sponsors should recognise that older people may need extra support to take part in trials. Trial sponsors should provide support to enhance the inclusion and adherence of older people, especially those with mobility and communication problems and those who also have responsibilities caring for others.

3.1.5 National and international regulators should encourage clinical trials that are designed to make the participation of older people easier.

### **4. THE SAFETY OF CLINICAL TRIALS IN OLDER PEOPLE**

4.1 Clinical trials in older people should be as safe as possible.

4.1.1 Researchers should assess the benefits and risks of older people's participation in clinical trials.

### **5. OUTCOME MEASURES SHOULD BE RELEVANT FOR OLDER PEOPLE**

5.1 Clinical trials for common conditions in older people should employ outcome measures that are relevant for older people.

5.1.1 Researchers, trial sponsors and regulators should ensure that clinical trials for common conditions in older people use outcome measures that are relevant for older people, including quality of life measurements.

5.1.2 Clinical trial sponsors should involve older people and carers in the design of clinical trials and in the choice of outcome measures for clinical trials of diseases of later life.

### **6. THE VALUES OF OLDER PEOPLE PARTICIPATING IN CLINICAL TRIALS SHOULD BE RESPECTED**

6.1 The individual values of each older person participating in clinical trials should be respected.

6.1.1 Researchers should respect the values of each older person as an individual.

6.1.2 Older people should be able to withdraw from clinical trials without detriment to other treatments and their overall care.