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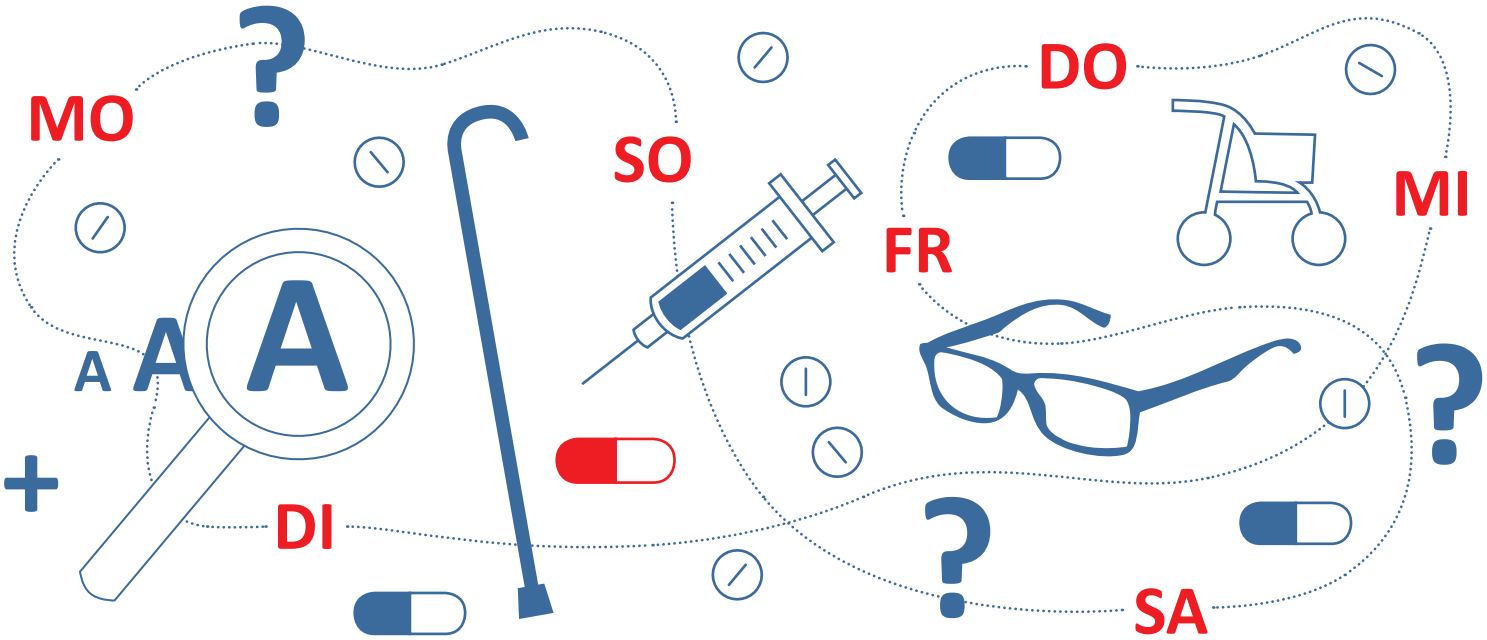
Statement

Medical care for older people – what evidence do we need?



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Medical care for older people – what evidence do we need?

Foreword

That people of any age should receive the best possible medical care is something that should be considered as an accepted fact, both socially and politically. It can also be stated that the existing high level of medical care in Germany has made a substantial contribution to the considerable increase in life expectancy over recent decades. But a closer look at the medical care situation for elderly people and considering their specific needs reveals a whole series of problematic deficits.

For instance, there is the question as to the basic treatment of patients suffering from multiple illnesses, when existing guidelines merely refer to the treatment of each individual illness respectively. Such multi-morbidity is a frequent phenomenon in elderly people. And what consequences arise as a result of taking a great number of different medications concomitantly? Are these pharmaceuticals at all suitable for an aged body with multiple ailments?

This report deals with these questions and their possible answers. The participating academies, i.e. the National Academy of Sciences Leopoldina, acatech – the German Academy of Technical Sciences, and the Union of German Academies of Science and Humanities, would like to take this opportunity to thank for their efforts all the scientists who have worked on the preparation of this paper over the last two years under Professor Cornel Sieber, and also all the experts involved in this project.

With this report, the academies hope to contribute to the necessary discussion about better medical care for older people. A discussion that should begin as soon as possible, particularly in the light of demographic change.

Halle (Saale) and Berlin, October 2015

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Summary

In Germany today, reaching a very old age is no longer an exception. About 4.5 million people (5.4 percent of the population) are 80 years of age and older, and their numbers continue to grow. In recent decades, the over 85-year-olds have been the group with the fastest and greatest gain in life span and many positive developments for this growing population group have been recorded. The increasing life expectancy and the improved health of older people over a longer period are also attributable to therapeutic and preventive measures, in addition to other factors. Sick old people, however, may possibly have entirely different medical needs than younger people; this is not sufficiently reflected in the German healthcare system.

The high standard in medicine, not only in relation to medical care, but also in research of diseases and the development of therapies, focuses typically on middle-aged patients with a single disease. Accordingly, knowledge gained from the treatment of middle-aged people is frequently also applied for older patients – although they differ both physically and mentally from younger people in terms of their medical care priorities and personal circumstances. This does not comply with good scientific practice, and often leads not only to inappropriate care, but may occasionally also actually endanger the concerned patients.

Older people, who frequently suffer from multiple chronic disorders, take many medications at the same time, each of which focuses on one individual ailment. This polypharmaceutical treatment does not at times correspond to the health targets of older patients and may even pose a considerable health risk. There is a lack of external evidence on how to improve treatment for multimorbid older and very old people. There is also a lack of guidelines that indicate the current knowledge gaps and risks. At the same time, important medications are often not offered. Therefore, research to provide specific scientific evidence specifically for older people is absolutely essential. New treatment objectives come to the fore and determine the indication for pharmacotherapeutic, surgical and other interventions: In younger patients cure, restoration of working ability or long-term prognoses determine the course of action. In older patients, these priorities are often replaced by independence, quality of life despite complaints, and the relief of symptoms.

The pressure for a quick and effective change to the healthcare situation of older people is growing continuously in line with the rapid demographic change. Physicians, therapists and carers alike must adjust to old and very old people in their daily work – particularly in hospital care. This also applies to basic, advanced and continuing staff training and the cooperation with other health care providers. At all points in the medical care chain, from the lack of scientific evidence to the implementation in practical care, the focus must be on older people and their specific needs.

Approaches to evidence-based medical care[1]

First of all, it must be pointed out that there is no such thing as "the old patient": no group of patients is as inter-individually different as that of the elderly. For that reason, in medical care particular attention must be paid to individual differences such as gender, socio-economic, ethnic-cultural and biographical backgrounds.

Relatives and the close environment are often extremely burdened with providing support for sick and/or functionally impaired older people and are therefore in need of particular attention and support (structural, psychosocial and financial) within the framework of regular care.

Changes in biological processes as well as in functional and social needs in older people have been intensively researched. Nevertheless, there are only few studies for the group of old and very old patients that meet the standards of evidence-based medicine (EBM). This has several reasons, one of the most significant of which is the fact that the established procedures of scientific knowledge acquisition and standardisation in the medical field do not correspond with the characteristics and health targets of older people. Science-based principles for evidence-based geriatric healthcare have to a large extent not yet been determined. This is why doctors and other health care professionals are not sufficiently prepared for their task of treating old and very old patients. An improvement in data availability and the health care situation is thus an absolute requirement.

Randomised, controlled studies should also be specifically conducted on elderly and very old people. Furthermore, other study methods are also available, which should be increasingly promoted and performed, as they are better able to demonstrate the needs and requirements of old people with regard to medical care: pragmatic studies that include the realities of the patients' lives, multiple-component interventions (complex interventions) as well as observational studies. The research subject should not (only) be the efficacy of a medicinal product, but an overall health care algorithm. The co-existence of risks should be examined and, if possible, individually presented in absolute figures. As these types of studies have not been sufficiently undertaken by the industry to date, more public funds need to be provided for this purpose.

Clinical studies on medicinal products to be prescribed for people above 65 and especially for those above 80 years of age must represent this age group sufficiently and carry out an age-related assessment. Here, age-specific characteristics, in particular frailty, should be taken into consideration in the inclusion and exclusion criteria and in the analysis and interpretation. The marketing authorisation for medicinal products should be subject to carrying out studies on old and very old patients, similar to the procedure usual for children (Paediatric Regulation of the EU).

In addition to conventional indicators of efficacy tests (such as cure, relief and survival), important functional and other objectives should be tested, in particular activities of daily living, participation and quality of life. Maintaining the functions of everyday life and hence also the quality of life is the predominant aim for old and very old people. Hearing, seeing and mobility play a crucial role in their participation.

1 By the term "evidence-based" medical care, we mean the decision for diagnostic and therapeutic measures based on current scientific knowledge, professional expertise and the values and preferences of those affected. This refers to individual and population-based decisions.

Methodological complexities are an important reason for the exclusion of old people from controlled studies. The emphasis has to be on patient-oriented study objectives, but also on challenges in terms of study design and evaluation (e.g. number of cases, missing data). The corresponding further development of methodological knowledge is therefore imperative. This requires the combination of geriatric-gerontological, biostatistical and information-related expertise. Ethical and legal aspects, such as the ability of the study participants to give their consent, also require particular consideration in research involving older people. Therefore, expertise on the medical treatment of such patients should be represented in research ethics commissions. In addition, information and consent documents within the framework of geriatric health care and studies must also be adjusted to the needs of old and very old people.

The investigation of interventions in the case of multi-morbidity must take top priority. As the parallel intake of medications is unavoidable, the interaction of active substances must be examined and validated. In addition, studies dealing with the reduction of polypharmacy are necessary, in particular with regard to the discontinuation of medicines.

Behavioural and technical interventions play an increasingly important role in maintaining independence and delaying the necessity of moving into a nursing home. Research in geriatric medicine should therefore also focus on the linking with such interventions. The benefits of auxiliary appliances, technology and adapted living space have hardly been examined. There is a lack of studies involving larger numbers of cases and representative participant groups including control groups, but also studies on the ethics of application. This also applies to telemedicine, the most frequently investigated field at the moment.

Evidence-based patient information as a prerequisite for the participation of patients in medical decision-making processes must also be available in geriatric care and must be adjusted to the prerequisites of older people. It is necessary to determine therapy expectations and preferences in groups of older people with different socio-economic and cultural backgrounds as well as in various care settings. Better knowledge assists the planning of clinical studies by taking adequate consideration of patient-relevant health targets.

There has as yet been hardly any diagnostic research in accordance with EBM standards in general and for all age groups. The demand remains for manufacturers not only to have to present proof of safety, but also of patient-specific benefit.

The treatment requirements of older patients are currently not identified at all, or not early enough. This often leads to expensive over-use, under-use, and misuse of health care services. Therefore, a geriatric assessment should take place in the emergency room, the patient's condition permitting. This is of particular significance when deciding whether the patient should be admitted to the geriatric ward or to a specialist one. The assessment should then be continued on the respective ward and be completed within the first 72 hours.

Transfer management and the flow of information between care settings, e.g. hospital and GP, need to be urgently optimised in such a way as to reduce losses of information to the detriment of the patients. The aim should be for a standardised and coordinated information management system of primary and secondary care service providers and facilities in order to improve intra- and inter-sectoral communication and consequently also improve care, and to gain scientific knowledge from the data collected.

Health care service providers must communicate with nursing home residents regarding their health targets and the organisation of their last stage of life, and negotiate these issues together. Returning to the home environment after being in a nursing home should be made easier, and should also be an important target factor in research projects.

Basic geriatric knowledge should be compulsory for all medical disciplines and health service professions; such teaching should begin at undergraduate level and be intensified in the post-graduate period. Multi-professional competence and EBM concepts play a significant role in basic, advanced and continuing professional training. Embedding them in such a way as to incorporate them in the standard repertoire of medical staff should be an important training objective.

It is essential to intensify and further develop methodological training in order to meet the challenges of medical research and health research for elderly people. In Germany there is a great deficit in this field. A first step would be to set up corresponding specialist professorships.

Finally, the aim must be to dispel negative impressions of old age in geriatric health care – for example through cross-disciplinary offers of advanced and continuing training in geriatric medicine.

In its expert reports from 2000 and 2009, the German Council of Experts on Developments in Health Care (SVR Gesundheit) has already explicitly pointed out that the “adequate care of elderly patients with chronic and multiple ailments” is one of the most pressing tasks in the health system. Despite, or perhaps even because of the precarious junior physician situation in medicine – and especially in geriatric medicine – it is urgently necessary to launch a geriatric health care campaign.

1 Introduction

1.1 Objective and background

In Germany today, reaching a very old age is no longer an exception. About 4.5 million people (5.4 percent of the population) are 80 years of age and older, and their numbers continue to grow.[2] In recent decades, the over 85-year-olds have been the group with the fastest and greatest gain in life span. The average life expectancy, which is currently about 80 years, will probably rise to 90 by 2050. More than half of the children already born in this century will even reach the age of 100 or older.[3]

Much positive can be reported about this growing population group. The increasing life expectancy and the improved health of older people over a longer period are attributable to therapeutic and preventive measures, in addition to other factors. Sick old people, however, may possibly have different medical needs than younger people, which is not generally taken into consideration in the German health care system. There are, for instance, no reliable medical standards for sick old people, and their medical care is not always the same as that for younger people.

Appointed by the National Academy of Sciences Leopoldina and its two partners in policy advice, the German Academy of Technical Sciences – acatech and the Union of German Academies of Science, a working group of fifteen scientists was set up from 2013 to 2015 not only to highlight the problems of medical care for older people in Germany, but also to point out the reasons and to draw conclusions for an improvement of the situation. The members of the working group represent several medical-clinical disciplines: nursing science, general practice, clinical pharmacology, psychology, biostatistics, gerontology, geriatric medicine, law and medical ethics.

The high standard in medicine not only in relation to medical care, but also in research of diseases and the development of therapies, focuses typically on middle-aged patients with a single disease. Accordingly, knowledge gained through the treatment of middle-aged people is frequently also applied to older patients – although they differ both physically and mentally from younger people in terms of their medical care priorities and personal circumstances. This does not comply with good scientific practice, and often leads not only to inappropriate care, but also occasionally even puts older people at risk. Therefore, research to provide explicit scientific evidence specifically for the elderly is absolutely essential. This must also be included in future treatment guidelines. Even advanced and continuing professional training is currently not enabling our system and its specialised personnel to provide evidence-based treatment for[4] older and very old people.

2 013 figures, Destatis (German Federal Statistical Office). Population. Available at: https://www.destatis.de/DE/ZahlenFakten/GesellschaftStaat/Bevoelkerung/Bevoelkerungsstand/Tabellen_/lrbev01.html[Release date: 09.07.2015]. Accessed July 20, 2015.

3 Schnabel S, von Kistowski KG, Vaupel JW (2005); Christensen K, Doblhammer G, Rau R, Vaupel J (2009).

4 By the term “evidence-based” medical care, we mean the decision for diagnostic and therapeutic measures based on current scientific knowledge, professional expertise and the values and preferences of those affected. This refers to individual and population-based decisions.

The pressure for a quick and effective change to the health care situation of older people is growing continuously in line with the rapid demographic change. With this report, our intention is to provide in particular decision-makers in municipal, provincial and federal authorities, health care institutions and scientific organisations with recommendations that can help to put the provision of medical care services together with the facilities of the health care system; this should result in a scientific basis tailored to the needs and wishes of the patients and to the benefit of older and very old people.

The report is structured as follows: In Chapter 2, we summarise what ageing at the beginning of the 21st century actually is and why older and very old people are not provided with sufficient health care by the conventional medical services.

In Chapter 3 we outline the principles of evidence-based medicine (EBM). In Chapter 4 we explain where and why it reaches its limits with regard to older patients. Finally, in Chapter 5, we formulate conclusions as to how medical research and health care in times of demographic change can be organised on the basis of current scientific knowledge and future research and in such a way as to ensure the evidence-based health care of older and very old people.

1.2 Evidence-based medicine (EBM) – Term definition

The following term description for EBM follows the definition proposals of the German Network of Evidence-based Medicine (DNEBM):[5]

The context of EBM is derived from the English word “evidence” and refers to information originating from scientific studies and systematically collected clinical experience, which can confirm or contradict a situation.

In accordance with this definition, EBM (evidence-based medicine) is a conscientious, explicit and sensible use of the best external scientific evidence available at a specific point in time in order to make decisions in the medical/ health care of individual patients.

EBM, also called evidence-based practice, refers to activities in medicine and health care, in which a medical or health care offer is communicated to an individual patient on the basis of the best available evidence. Uncertainties and contradictions in the external evidence must also be disclosed within the framework of EBM. Through high quality scientific studies, EBM helps to reduce uncertainty with regard to the benefit and risk arising from medical and health-related decisions.

The identification of suitable evidence presupposes a systematic search of medical literature for a specific clinical problem, the non-selective selection of meaningful external evidence though the critical assessment of validity in accordance with clinical-epidemiological aspects, and the assessment of the extent of the observed effect.

The best external evidence identified from empirical evidence obtains its significance in the application of this evidence to the specific patient, based on the clinical experience of those providing the treatment and taking into consideration the clarified health targets, ideas and values of the patients.

Another related term is evidence-based health care – EBHC, in which the principles of EBM are applied to all health care sectors, including decisions pertaining to the management of the health

5 Available at: http://www.ebm-netzwerk.de/was-ist-ebm/grundbegriffe/definitionen/; EBM-Glossar. Accessed July 20, 2015.

care system. EBM has thus moved from the historical understanding of EBM in the situation of an individual decision to the level of a general entitlement to services in hospitals and health care. This is based on Volume V of the Social Insurance Code (SGB V) which includes the standard that health care must comply with the generally approved status of medical knowledge.

The techniques and methods of EBM were also transferred to other professions, e.g. as evidence-based nursing care or evidence-based midwifery.

EBM necessitates the generation of meaningful external evidence that requires the performance of empirical studies under consideration of the current state of discussion regarding the methods of clinical epidemiology.[6]

1.3 Care of old and very old patients

The spectrum of patients and the range of their ailments alter with demographic changes. Older and very old patients often suffer from chronic and multiple illnesses. New treatment objectives come to the fore and determine the indication for pharmacotherapeutic, surgical and other interventions: While cure, restoration of working ability or long-term prognoses determine the course of action for younger patients, the priorities of older patients are often the maintenance of their independence or quality of life despite afflictions, and the short-term relief from symptoms instead of long-term life objectives.[7]

With increasing age, people become more individual and more different from one another (not only) in medical terms.[9] This increased heterogeneity is evident in all systems: physiologically, cognitively, but also in genome mutation rates and in epigenetic changes. In addition there are non-pathological degenerative changes, which are perceived as particularly drastic when they affect several systems at the same time, such as mobility and sensory perception. This is known as the frailty syndrome.[10] Age-re-

Box 1: Who is an "old" or "geriatric" patient?

In Germany in 2007 and in the EU in 2008, geriatric specialist associations formulated a definition: According to this, it is not the chronological age, but a **condition** that characterises "old" or "geriatric" patients.

These are defined as people of higher age, either suffering from several concurrent illnesses, or who are physiologically particularly prone to illness, which can result in complications and secondary diseases and the risk of chronicity and an increased risk of losing autonomy.[8]

Empirically, particularly people over 80 years of age are currently receiving geriatric health care (for information on changing age limits cf. Chapter 2). In clinical studies however, the age limit is usually drawn at 65 or even younger. Therefore, the question of evidence-based medical care cannot be restricted to "old" patients in accordance with the medical definition.

6 ibid.

7 Fried TR et al. (2011).

8 Sieber CC (2007).

9 See also the results of the Berlin Ageing Study (BASE). An overview of this can be found at: https://www.base-berlin.mpg.de/de. Accessed July 20, 2015.

10 Frailty: medical specialist term used in English. Bergman H et al. (2007).

lated physiological changes and multiple illnesses are not only highly relevant for research on the effects of medicinal products, but also for surgical procedures and technical rehabilitation. Particular significance is attached to the search for complex therapeutic concepts, requiring the cooperation of various professions (e.g. in patient discharge management) or technical innovation (keyword telemedicine).

Only very few controlled clinical studies are available on the treatment of these aspects of old age. Former evidence-based therapy concepts are usually focussed on the treatment or improvement of symptoms or on the positive influence of a single, clearly definable illness. Neither do they consider multiple illnesses nor age-related changes nor the significance of maintaining everyday functions and the particular importance of quality of life and autonomy. Usually, (medicinal product) studies are performed on patients of a clearly younger average age with few co-morbidities; the transferability of the results to older people is therefore questionable.[11]

In its expert reports from 2000 and 2009, the German Council of Experts on Developments in Health Care (SVR Gesundheit) already pointed out explicitly that the "adequate care of older patients with chronic and multiple ailments" was one of the most pressing tasks in the health care system.[12] Despite, or perhaps even because of the precarious junior physician situation in medicine – and especially in geriatric medicine – it is urgently necessary to launch a geriatric health care campaign.

1.4 Growing number of old people

The age group of over 85-year-olds is growing. Even though older and even very old people stay on average more frequently and longer healthy in a historical comparison and are physically and cognitively fitter than they used to be,[13] the need for medical and health care increases due to the strong rise in their numbers in absolute figures. At the same time, as the result of the increase in female employment, the extent to which women are available for the care of family members will become limited. About 3 times as many women as men of working age provide care. In general, full-time workers more rarely have time for care and spend less time on care than non-workers and part-time workers.[14]

Physicians, therapists and carers alike must adjust to old and very old people in their routine work – particularly in hospital care. This also applies to basic, advanced and continuing staff training and the cooperation with other health care providers. At all points in the medical care chain, from the lack of scientific evidence to the implementation in practical care, the focus must be on older people and their specific needs. We outline a few suggestions in this report.

11 E.g. Thürmann PA (2013).
12 SVR Health (2009).
13 E.g. Christensen K et al. (2013).
14 Klaus D, Tesch-Römer C (2014).

2 Ageing – health and illness

2.1 Individual ageing at the beginning of the 21st century

It is still one of the fundamental questions of ageing research, but also of politics and society, whether the years gained through the continuing rise in life expectancy are actually years with a high quality of life.[15]

Box 2: What is "old" from the point of view of ageing research?

Based on the different and characteristic experiences gained during the course of life, ageing researcher Paul Baltes has defined the terms "First age" for childhood and adolescence, "Second age" for the middle years of adult life and "third" and "fourth age" for the last third of life. Even though these terms are not unanimously accepted as standard (for example, people in the "fourth age" represent a very diverse group), they are helpful in differentiating the still frequently used terms "the aged" or "the elderly".

The emergence of a "third or young age" (about 60 to 80/85 years, partly even older) as a phase comparatively low in illness and disability can be considered a success.[16] This phase must be differentiated from a "fourth age" (from about 80/85 years, also referred to as "very old", as more than half of the contemporaries have died), which is even today not short and certainly will not be in the future, and in which the risks of illness accumulate, multi-morbidity (multiple illnesses) becomes standard and normal everyday functions are highly endangered by numerous simultaneous changes (e.g. loss of cognitive, motoric and sensory skills).[17] Findings based on research and pertaining to the course of cognitive ability, the need for nursing care and to well-being even suggest the definition of a future "fifth age". One of the particular assumptions of this new perspective is that changes at different levels (biological, psychological) in the extremely advanced time corridor of each individual life are no longer determined so much by the chronological age, but by the temporal distance to death.[18]

However, these chronologically focussed divisions of the phases of ageing can be criticised, for instance by arguing that the differences between individuals are extremely high and increase continually with age. In other words: there are considerable **o**verlaps between the various phases of ageing, and a significant number of the over 85-year-olds are well within the range of the 65 to 84-years-olds (and vice versa) in terms of health, functional and cognitive parameters.

15 Kocka J, Staudinger UM (2009).

16 ibid.

17 Wahl HW, Schilling O (2012).

18 Distance-to-Death Research; Terminal Decline or Terminal Drop. E.g. Gerstorf D et al. (2010); Gerstorf D, Ram N, Lindenberger U, Smith J (2013).

The portrayed scenarios of ageing with their pronounced focus on deficit and loss, however, are also coupled with gain-oriented developments, frequently pooled under the heading "new age". Older and even very old (over 80 years old) people today have new lifestyles, new competences and behaviour (for example with regard to travelling, forms of social relationships, sexuality, living, use of new information and communication media, indulging in various types of "wellness" and activity) and new expectations of ageing of themselves and of society. In this respect, the forms of productivity shown by older people and long underestimated in our society until now should be taken into consideration, for example voluntary commitment, care services (the third age cares for the fourth age) and intergenerational relationships.[19]

Box 3: "Anti-ageing medicine"

Apart from the desire to organise the ageing process and to find preventive measures that avoid, relieve or postpone losses, the fear of growing old still prevails. In the meantime, "anti-ageing medicine" has developed into a major market in Germany, yielding significant profits, similar to the USA.[20] The term "anti-ageing" suggests a reversibility of the ageing process that is not empirically sustainable. In individual medical fields (e.g. dermatology), expensive "partial" treatments are offered, which are hardly compatible with the geriatric view of a holistic approach to ageing with its gains and losses.

The rather vague term "anti-ageing medicine" comprises a wide range of concepts and resulting products. On a simplistic level, these could be differentiated into preparations – and surgical interventions – targeting the skin and the clearly visible physical changes accompanying normal ageing, and into approaches to slow down ageing processes in the body, which focus on hormone preparations. The availability of data confirming their efficacy in accordance with EBM standards is only very poor, and for which a warning regarding adverse effects must also be issued (for example a negative influence on tumour formation).[21] To warn against harm caused by these preparations, but also against misleading promises should be perceived and intensified as a joint task of medical professionals and consumer protection representatives. Quite possibly, it may be appropriate to propagate the term "pro-ageing" for geriatric medicine as the general maxim for the communication of its remit, in order to deprive the scientifically problematic idea of the reversibility of the natural ageing process of its substance.

Risk factors for ailments and functional impairments in later life can already be present in younger years. The long-term effects of life conditions including medical care from birth on and the significance of prevention in the broadest possible sense have led to "geriatric" medicine focussing not only on older people, but also on people in mid-adulthood and possibly throughout their entire lives.[22] Nutrition, exercise, social integration and psychological health are the known factors that throughout life constitute the resources or risks for the development of certain diseases in old age, for instance for cardiovascular disorders, diabetes and Alzheim-

19 Staudinger UM, Kessler EM (2012).

20 E.g. already Binstock RH (2003).

21 Dominguez LJ, Barbagallo M, Morley JE (2009) ("only" men); Maggio M et al. (2014).

22 Brandt M, Deindl C, Hank K (2012); Schafer MH, Ferraro KF (2012).

er's disease, or for mental and physical decline, e.g. in form of loss of hearing and sight.[23]

Participation in the organisation of the ageing working society in Germany is a challenging aspect of geriatric medicine. It is undeniably highly relevant to maintain and promote the health, productivity and creativity of the over 50-year-olds in their jobs until their retirement – also in view of the length of time after their working life. There is plenty of evidence that health and illness in this phase of life are highly relevant for the course of the subsequent ageing process. Mid-adulthood is the time when significant risk constellations predominantly develop, for example for the beginning, severity and duration of later diseases (e.g. musculoskeletal disorders, ailments of the cardiovascular and respiratory system as well as the sensory organs) and for the course of dependency and the need for care. This phase of life is therefore crucial for health in old age.

Furthermore, one central challenge for the medical care of older people – namely multi-morbidity – is not limited to (very) old people. For socio-economically weak people, it starts much earlier (about 10 to 15 years) than the average and affects in absolute figures more people below 65 than above.[24] The cohort-related increase of healthy life expectancy is also clearly associated with socio-structural characteristics, i.e. not only the current ratio of healthy life expectancy, but also the cohort-related increases are significantly higher in the case of older people in a strong socio-economical position (who as a rule have been in a better socio-economical position than others throughout their entire earlier lives). Educated and high-income people usually live considerably longer and enjoy better health. In Germany, the average life expectancy of the highest income group at birth was 11 years (men) above that of the lowest income groups (1995–2005).[25] Europe-wide, there are great differences in healthy life expectancy. For example, in Eastern European countries it is about a third less than that in Denmark and Sweden.

The increase in relative frequency of illnesses is greater at an older and particularly at a very old age than at any other age. Social losses are also common at a higher age: The loss of the life partner and the loss of a child are some of the most stressful life events, which are these days associated predominantly with the fourth age. These losses in the social environment also affect the options for coping with specific everyday tasks. Approaching death requires forms of coming to terms with the realities of life (such as the limit of life), which usually only rarely played a role in earlier life.

The plasticity of ageing[26] i.e. its formability and changeability at a behavioural and neuronal level finds expression in the positive changes to medical parameters from one generation to the next, and also in the tremendous increase in life expectancy itself. All answers to the challenges of ageing should therefore avoid projecting the status quo into the future in a simplified way, but must take the potentials and risks of the plasticity of ageing into account.

2.2 Health, impairments and diseases in old age

Spectrum of diseases

Elderly people are not only more frequently ill (28 percent of the age group above 75 compared to 14 percent of the

23 Exemplary review articles: Barnard ND et al. (2014); Abramson BL, Melvin RG (2014); Schiattarella GG et al. (2014); Behrman S, Ebmeier KP (2014); Fratiglioni L, Qiu C (2009).

24 Barnett K et al. (2012).

25 Lampert T (2009), S. 131.

26 Lövdén M, Bäckman L, Lindenberger U, Schaefer S, Schmiedek F (2010).

population average).[27] Their treatment also incurs much higher costs per head. The treatment costs for 65 to 84-year-olds amounted to double the average and more than five times that amount for the over 85-year-olds (figures for 2008).[28]

The reason for this is the high incidence of cardiovascular and metabolic disorders. Coronary conditions are the most frequent diagnoses for the hospital treatment of elderly people (figures for 2010).[29] Furthermore, elderly people have a lower infection resistance and are therefore more susceptible to infectious agents, combined with a higher hospitalisation rate and mortality (death rate) compared to younger people: In the event of influenza outbreaks, for example, the hospitalisation rate or mortality rate of 60 to 75-year-olds is 7 to 27 times higher than that of 20 to 39-year-olds.[30]

Furthermore, the somatic spectrum of diseases of old people is also defined by musculoskeletal disorders and diseases of the sensory organs. In addition, two thirds of cancer illnesses are suffered by people over 65, most of these intestinal or lung tumours.

At about 25 percent, the proportion of mental illnesses is roughly the same as in mid-adulthood. Dementia, depression and anxiety disorders are the most frequent of these ailments. Dementia disorders only increase significantly over the age of 80 and reach a prevalence of approx. 15–20 percent amongst over 80-years-olds, and 40–50 percent for those over 90 years of age. It is important to emphasize that the prevalence in younger cohorts (i.e. born later) is clearly lower than in the older ones,[31] which is crucial for the estimation of care requirements over the coming decades. For some clinical presentations in older age, there is often no meaningful separation of mental and somatic components.[32]

The subjective assessment of the health[33] of elderly people is important in this context, as it is directly correlated to objective health[34] and well-being on the one hand, and is essential for medical treatment on the other. There is often a great discrepancy between the subjective and objective assessment of health, with the subjective health assessment usually being the more favourable.[35] Despite the objective deterioration of their state of health, older people often do not subjectively consider themselves ill or restricted. This can affect decisions concerning treatment, as they may tend to seek medical assistance at a relatively late stage. For the sense of well-being and contentment, this subjective health assessment is far more important than objective health assessments.[36] Evaluations of one's own ageing process and attitudes towards growing older are closely connected to subjective health assessments.[37] Long-term studies have shown that such assessments of a person's own ageing process are clearly connected to health-related endpoints (including mortality).[38] They also appear to be important for preventive behaviour or the motivation to invest in such behaviour, and for rehabilitation.[39] This may for example mean that old men in particular often subjectively assess their own health

27 Results of the Microcensus 2013 Destatis (2014).

28 Destatis (2011).

29 Destatis (2012).

30 Steens A et al. (2011).

31 Matthews FE et al. (2013).

32 Kopf D, Hummel J (2013).

33 Individually experienced health.

34 Medically diagnosed condition.

35 Wurm S, Lampert T, Menning S (2009).

36 In general – regardless of age – subjective well-being is not derivable from the objective health condition without further information; with age-matched groups; however, it correlates with characteristics of well-being. Age-associated problems are absorbed mentally and have little or faint effect on well-being.

37 Diehl M, Wahl HW (2015).

38 Levy BR, Zondermann AB, Slade MD, Ferrucci L (2009); Levy BR, Slade MD, Kunkel SR, Kasl SV (2002); Westerhof G et al. (2014).

39 Levy BR, Slade MD, Murphy TE, Gill TM (2012); Levy BR, Myers LM (2004).

Box 4: Meaning of age stereotypes, ageism and age stigmatization

One special feature of geriatric medicine is that its patients – elderly people – are subjected to considerable stereotyping processes as a social group. This kind of stereotyping process is generally connected not only with negative aspects ("Old people are forgetful") but also with positive ones ("Old people are wise"). However, research on psychological ageing to date has consistently shown that negative stereotyping in turn has manifold negative effects. Negative images of ageing in society and the relevant professional groups, for example, lead to the fact that insufficient funds are invested in preventive health care for older people, with the long-term result of greater dependency, need for care and mortality.

Old people are also at a high risk of being considered less valuable, less worthy of support and less capable of change, simply because of their calendar age. Such processes of "ageism" and age stigmatization constitute an objective discrimination, a violation of the equality principle and ultimately also of human dignity.

The implications of these insights for geriatric medicine are highly diversified and complex. For example, the highest degree of sensitivity is called for in respect of the rights of old people in the medical care system. Concerning the activities of physicians and other professions involved in geriatric care, the aim must be to develop a comprehensive intuition and awareness of potential negative stereotyping. Ultimately, a comprehensive and highly differentiated view of old people that gives equal consideration to their strengths and vulnerabilities must be communicated at an early stage to medical students and students and trainees of all other professional groups dealing with older people.

too positively – and that necessary examinations also in terms of prevention are therefore not performed.[40] For that reason, it is highly relevant for geriatric medicine to know and take seriously older people's own prevailing individual health and ageing evaluations, and to resist the temptation of an increasing and one-sided objectification of findings.

For many serious illnesses (above all for cardiac disorders, but also for various types of cancer), survival time has significantly increased over recent decades. A substantial proportion of the continuous rise in life expectancy is even attributable to this increase.[41] Hence, an increasing number of old patients have already survived a life-threatening illness in early and middle age. Such an experience can have a strong impact on the subsequent life and development of these people and can also change their attitude towards diseases or disabilities that emerge anew at an older age, for example as a higher level of acceptance. Older people often handle chronic losses caused by diseases and functional deterioration quite efficiently (e.g. through great flexibility in adjusting their own life targets, various compensatory measures, proactive loss management); this needs to be taken into consideration in geriatric medical treatment. Even though physical resources diminish, mental strengths remain unchanged up to a high age and even gain in importance.[42] Contentment with life in old age can be considerably improved, even in the event

40 For example, 13 percent of men over 60, as opposed to 22 percent of women in this age group participated in preventive measures. Data from the Robert Koch Institute (2012).

41 Crimmins EM, Beltrán-Sánchez H (2011).

42 Schilling OK, Wahl HW, Oswald F (2013); Root C, Jopp DS (2012).

of chronic illness, if not only competences in coping with activities of everyday life are trained, but also psychological assistance is offered for adapting to health-related changes.[43]

In summary and from the point of view of medicine and care, emphasis should be placed in particular on multi-morbidity, on extended survival time even in the event of a severe illness that still permits an independent life perceived as having a high quality, and on the importance of subjective factors that characterise dealing with old patients.

Functional health, "healthy life expectancy" and the need for nursing care

In epidemiology, functional health refers to the extent of fulfilling daily requirements or performing the activities of daily living (ADL) and the ability to participate in social life. Functional health is largely determined by existing illnesses, but also depends on mental factors (e.g. motivation and coping strategies) of the ageing person[44] as well as on the social and physical-spatial environment in which the person is living (e.g. supporting relatives or barrier-free living conditions).

The sight of one in eight people over 75 and one in three over 85 is restricted, as is the hearing of 25 percent of people over 75 and of about 40 percent of the over 85-year-olds.[45] Approximately 25 percent of people between 75 and 84 are no longer capable of walking more than one kilometre without an aid or the assistance of another person. Dizziness is a frequent complaint at an old age.[46] More than a third (men/women) of people between 65 and 90 years of age experience at least one fall per year with corresponding injuries.[47]

Fundamental limitations in coping with everyday life only increase to clearly above 10 percent in people over the age of 80. The complex "instrumental" competences in everyday life (Instrumental Activities of Daily Living – IADL), which frequently take place outside the home, such as dealing with banking matters or using public transport, are more difficult than the fundamental limitations (Activities of Daily Living – ADL), including washing and dressing. In this respect, the prevalence of the limitations is slightly higher in 60 to 69-year-olds (approx. 2–3 percent) and increases even more at a very old age (approx. 15 percent). Old women exhibit a higher level of limitations in both competence areas than old men. However, international and German data support the assumption that the rate of limitations in everyday functions is lower in cohorts born later. Possible explanations may be a higher level of education (above all in old women) and higher cognitive capabilities compared to earlier born cohorts.[48] This new phenomenon of "performance capability" in old age has a multitude of implications for geriatric medicine. For instance, these improvements in the general functional condition might be accompanied by an overall increased resistance to age-related disorders and might improve re-convalescence. Another consequence might be that older people could be included in complex medical decision-making processes (for instance in geriatric oncology) due to their comparatively higher general functional and cognitive condition. It should be emphasized here that throughout the entire age spectrum the proportion of those old people without considerable losses in their everyday competences remains higher than that of those with considerable losses.

43 Schilling OK et al. (2013).

44 Somewhat in line with the Disablement process model. Verbrugge LM, Jette AM (1994).

45 Visual impairment: Visual acuity less than 6/12 with best correction. Hearing impairment: at least 30 dB hearing loss. Heyl V, Wahl HW (2014).

46 Walther L, Westhofen M (2007).

47 Rapp K et al. (2014).

48 Schneekloth U, Wahl HW (2008); Menning S, Hoffmann E (2009); Christensen K et al. (2013).

The need for nursing care finally gives rise to the question that is so important to old people, i.e. whether to stay within their "own four walls". Whereas about 5 percent of people aged over 65 years currently live in (nursing) homes, this increases to 20 percent of 80-year-olds and 40 percent of over 90-year-olds. The need for nursing care is a great challenge, particularly at a high age. Just over one in three women aged over 85 and just over one in four men aged over 85 in private households in Germany are in need of nursing care in accordance with care levels 1 to 3.[49] Despite the positive trend described above, it must be assumed for Germany that the absolute number of old people requiring nursing care will increase considerably over the next two to three decades, mainly as the result of the ageing of the baby boom generation. As the majority of these people is (will be) cared for within their own families, the stress on non-professional carers is an aspect of concern to geriatric medicine.

Basic and follow-up training as well as care must be able to react to the broad spectrum of ageing, extending from health and independence to palliative nursing care.[50] Overlappings between health, disease, functional limitations and disability pose challenges to the entire health system. A generally accessible provision of care must take target group specific, gender-related, ethnic-cultural and other socio-economically based differentiations into consideration.

2.3 Effects on the provision of medical care

The necessary adaptation of medical care to the complex needs of old people is no easy task. The provision of medical care, which is generally oriented toward a traditional understanding of the treatment of monopathologies, presides over an abundance of requirements, even if one only considers medical questions in a narrower sense.

In the case of limited senses (hearing, touch,[51] sight) and cognitive impairments (reduced concentration and memory, decreased responsiveness and information processing), instruments common and reliable for the treatment of younger patients cannot be used for diagnostics and may require the input of affiliated people (third-party medical history).[52]

In the course of therapy, medication dosages must be adjusted, as physiological changes due to age and illness cause changes in organ perfusion, distribution of body fat, etc., which alter the accumulation and chemical breakdown processes of medications.

In cases of multimorbidity, complexity increases further due to possible medication interactions (e.g. anticoagulants and anti-rheumatic agents) and sickness-related treatments, as well as other side effects of medications (e.g. anti-rheumatic agents which exacerbate cardiac insufficiency). Furthermore, interactions can occur between different illnesses (e.g. high blood pressure which intensifies the effects of diabetes on the cardiovascular system).[53]

49 Schneekloth U, Wahl HW (2008). The maintenance levels 1 to 3 are then determined by an assessor from the health insurance company, as to which temporal extent a person needs help with everyday tasks. Level 1 includes 1.5 hours total care, which includes 45 minutes personal hygiene, eating and mobility, incl. domestic maintenance and care. See Medical service of health insurance companies (MDK; http://www.mdk.de, accessed July 20, 2015).

50 The complex issues and challenges of adequate palliative medical care are not covered in this report; reference is made here to the academies' report "Palliative Care": National Academy of Sciences Leopoldina, Union of German Academies of Sciences (2015).

51 It can also lead to considerable functional impairments while writing, putting on glasses, or inserting a hearing aid.

52 These people may not always be available for independent elderly people.

53 For more information on this, see chapter 4.

Especially crucial is the necessary but as of yet insufficient integration of general practitioner, outpatient, and inpatient specialist and nursing care with proposals for prevention, rehabilitation, and provision of medicine as well as social services and patient organizations.[54] Effective communication among parties belonging to these different occupational groups is essential for achieving comprehensive management of medical care. The decisive authority on medical and nursing arrangements is diagnoses coding in accordance with the International Classification of Diseases (ICD). This coding, which only extends to individual illnesses (and usually only those treated with medications) rarely suffices in a situation in which various symptoms and syndromes, as well as changing individual health goals are on the agenda. In the International Classification of Functional Disability and Health (ICF) the World Health Organization (WHO) thus depicts a broader understanding of health – mostly in the sense of high daily functioning despite illness, of the capacity to achieve meaningful life goals (in relation to interaction with family members) despite illness, and of "feeling healthy"[55] and "feeling well". In the meantime, though it is finding broad acceptance among experts, these concepts have yet to be implemented or evaluated in any concrete or regulated manner during creation of diagnostic and treatment measures.[56]

A large portion of geriatric patients receive their care from general practitioners. Unlike in inpatient care, general practitioners work primarily on the basis of reasons for encounter rather than diagnoses. These reasons for encounter are often non-specific and treatment may extend to multiple consultations which form a single treatment case. This situation also cannot be described adequately in the ICD system. As a result, the "International Classification of Primary Care" (ICPC)[57] was developed for general practice. This allows the coding of reasons for encounter, complaints or diagnoses, and process of care including medical interventions (e.g. diagnostics, preventive measures, medications, referrals). The ICPC is internationally implemented for the classification of primary care and is also recognized by the WHO as the official coding system for primary care.[58] In German primary care, the ICPC has so far only been used within research and pilot projects.[59]

A contrast to the highly complex medical situations of old people is the insufficient level of data and information. The evidence base of medical decisions is weak, and treatments are based on extrapolation, rules of thumb, and intuition, since comparable situations have not been examined in studies. This also applies to evidence pertaining to medical care provision processes. Correspondingly, we also lack guidelines for treating old and very old people.[60]

The effects of this situation are serious. The circumstances of old people as mentioned above are not depicted in the daily medical routine, and it is a fact that many sick old people are often both over- and under-treated.

This situation is true of all forms of treatment, though general practitioners in primary care, in acute inpatient care, and in nursing home care often have different central questions and problems which will be examined in more detail below.

54 Federal Health Council (2009).

55 See the reported findings on subjective health above.

56 Müller M, Grill E (2011); Federal Association of Geriatrics (2010).

57 WICC. The International Classification of Primary Care. Version 2. Available at: http://www.ph3c.org/PH3C/docs/27/000098/0000054.pdf. Accessed July 20, 2015.

58 WHO (2003).

59 Körner T et al. (2005).

60 Cf. chapter 4 for a more thorough explanation.

Primary Care

Box 5: Case study from general practitioner care

Mr. S. (85) has medical complaints – can you make a visit?

A general practitioner is called to the nursing home to see Mr. S. (85 years old) for anxiety and insomnia. How does she respond to these complaints?

Mr. S. has been seeing this general practitioner for several years. During the course of his life, he has had many medical complaints and illnesses treated by various specialists and general practitioners. It began at age 55, when he was diagnosed with high blood pressure. His general practitioner at the time prescribed him a medication that he has been taking ever since. At age 58, he developed rheumatoid back and joint pain which were treated with painkillers and temporarily with cortisone. At age 60, he was diagnosed with diabetes and his blood pressure had to be regulated more intensively (+2 medications). At age 66, he developed gout (+1), and at age 68, coronary heart disease (+3). At age 72, his general practitioner at the time diagnosed him with osteoporosis while treating a broken bone (+3 medications), and at age 73, he was diagnosed with cardiac insufficiency. At age 79, Mr. S. developed rheumatic disease (+2 medications) which drastically impaired his functioning, and at age 80, he was diagnosed with dementia. Mr. S. was placed in a nursing home.

If the general practitioner treats all of these chronic illnesses according to the specific evidence-based (individual) guidelines, then Mr. S. would need to take 16 different medications, some of them multiple times per day, and all of which have different recommended dosages. It is difficult for the general practitioner to interpret the current complaints: Are the complaints an expression of a new illness or disorder? Or are they merely the side effects of one of his medications? Are symptoms arising because medications are exacerbating the symptoms of other illnesses or ailments? Or is the perception of these complaints altered by the patient's dementia?

More than half of the consultations that a general practitioner makes concern multimorbid, mostly chronically ill older people such as Mr. S. This is also true of half the patients in primary care.[61] Certain illness constellations occur particularly frequently. Studies show a accumulation of anxiety, depression, somatoform disorders and pain in women, while men are more likely to suffer from cardiovascular (e.g. cardiac insufficiency) and metabolic disorders (e.g. diabetes mellitus).[62] There are also significant connections between education and social status and multimorbidity incidence. The lower the degree of education (and, correspondingly, income), the higher the incidence of multimorbidity. As expected, as the number of chronic ailments increases, the number of physician visits increases correspondingly. Certain occurrences are still "drivers" for frequent contact with physicians, in particular anaemia, kidney failure, and incontinence, as well as care provision through the care insurance. Old age and gender alone have little influence on the number of physician visits.[63] Issues such as incontinence, dizziness,

61 Salisbury CC, Johnson L, Purdy S, Valderas JM, Montgomery AA (2011); Barnett K et al. (2012).

62 Schäfer I et al. (2012).

63 Van den Bussche H et al. (2011).

and other ailments join the common diagnosis clusters of cardiovascular diseases, pains, and psychological symptoms. Patients are mostly interested in treating psychological problems and in the ability to manage their daily lives, while general practitioners value the treatment of the aforementioned somatic illnesses more highly.[64]

General practitioners receive little support for dealing with this complex situation.[65] They lack treatment guidelines and pathways suited to the multimorbidity and heterogeneity of patients. The "Chronic Care" model according to Wagner, the internationally most frequently discussed treatment model, is based on newly-structured treatment that responds not just to acute illnesses, but also has the goal of proactively recognizing indications of declining health by means of regular consultations symptoms. Treatment from teams in various occupational groups should be adapted to the needs of chronically ill patients with support from the health system and the community. The results of a systematic review are available, which show the positive effect on multiple chronic illnesses in cases where at least one element of the "Chronic Care" model is implemented.[66] Multimodal, secondary preventive approaches which include a number of measures such as education, support of self-management, structured care, and case management are more effective than individual measures, though.[67] Parts of the model are now being implemented in the German health system. This is taking place in the form of disease management programs or integrated treatment agreements. However, these are generally not adapted to the particular situations of the mostly older people with multiple chronic illnesses.

A particular deficit exists in the cooperation between primary care and clinics or other providers in the health care system. Information pertaining to inpatient stays is often lost, so that general practitioners cannot respond adequately, and rapid re-admission or need for nursing care rank among avoidable consequences.[68]

64 Theile G, Müller CA (2012).

65 Schuling J, Gebben H, Veehof LJ, Haaijer-Ruskamp FM (2012); Anthierens S, Tansens A, Petrovic M, Christiaens T. (2010).

66 Tsai A, Morton SC, Mangione CM, Keeler EB (2005).

67 Ouwens M, Wollersheim H, Hermens R, Hulscher M, Grol R (2005).

68 SVR Gesundheit (2012).

Acute Inpatient Care

Box 6: Case study from inpatient care

After dinner on a Friday evening at the nursing home – Mr. S. has regained his appetite – he has diarrhoea twice during the night. This is reported the next morning, and Mr. S. seems oddly apathetic. Around noon, Mr. S. vomits profusely, and the emergency physician is called. The general practitioner cannot be reached because it is Saturday. Mr. S. is referred to emergency admission in the nearby hospital. He seems lethargic upon admission, and his answers are imprecise and potentially unreliable.

The nurses ask the following urgent questions:

- When did Mr. S. last take his pills (luckily the patient has his medication list)?
- In the case of diabetes, is the patient hypoglycemic?
- Are there signs of infection?
- Are the electrolyte values abnormal?
- Can the lack of reliable medical history be explained by dementia or is it the result of the acute illness?
- If his condition should deteriorate significantly: Is there an advance health care directive (with power of attorney)?
- Are there relatives who should be contacted in addition to the nursing home?

If the patient came from his own home, the following (non-urgent) questions would be asked:

- Can Mr. S. return immediately to his home environment?
- Does he require geriatric rehabilitation after his stay in the acute care hospital?
- Do outpatient services need to be organized?

Mr. S's deteriorating condition, which led to hospital admission, must be treated with an overarching medical plan, involving numerous specialists and a clinical geriatric team. His medication situation makes it necessary to check whether the number of drugs and the dosages are all necessary. Rehabilitative treatment must be planned differently to the treatment of a single organic disease. Mr. S's social environment must also be clarified, since follow-up care corresponding to his reduced capacity must begin in this environment.

This example demonstrates how tremendously important interdisciplinary care is, especially for multimorbid old patients, along with the concurrent involvement of all people involved in the treatment ("caregivers"). An integrated interdisciplinary team is necessary, since the patient's functionality and hence his independence is continually (further) threatened, in addition to the onset of the acute illness. The example also shows that planning of post-inpatient care should begin as early as possible and for this the geriatric assessment ("comprehensive geriatric assessment" – CGA)[69] is essential.

In the case of emergency admissions, the initial assessment is of great importance, as it helps direct the patient to the appropriate department. Emergency admission procedures are not generally tailored to the specific needs of older

69 Describes a process of determining a patient's functional capacity, ability to manage daily life, as well as cognitive and emotional state with the help of questionnaires and tests. Carpenter CR et al. (2015); Ellis G, Whitehead MA, O'Neill D, Langhorne P, Robinson D (2011).

patients, however. Their complaints are often underestimated or not recognized due to atypical, unclear symptoms. Thus, there is a danger that adequate treatment will be provided too late, if at all.[70]

Acute inpatient care can also be improved considerably if organ-specific specialists begin working with the geriatricians as soon as possible. The complex treatment needs of old people can be determined if a geriatric assessment is completed immediately upon emergency admission, which would help to avoid rapid re-admission (revolving-door effect).[71] This allows decisions pertaining to the need and capacity for rehabilitation to be made early on, thus reducing the time spent in acute care.[72]

One promising approach is the geriatric early rehabilitative complex treatment, which can be reimbursed fairly adequately within the DRG system[73] if the indications are good. In too many cases, compensation for charges is still not possible due to regulations, despite the necessity of geriatric early rehabilitative complex treatment. Other approaches could be centres focused on aging patients, such as geriatric trauma centres. With regard to geriatric trauma centres, there is research on the effectiveness and cost efficiency of such structures and processes.[74]

Treatment paths adapted to age are generally lacking in hospitals. These are derived from the corresponding scientific therapy guidelines, which still – as described earlier – only represent old people in a few specific cases.[75] Courses of treatment adapted to the specific needs of old people must be assessed by teams. This includes the discussion of possible intensive medical measures including mechanical respiration and resuscitation. One must consider that relaying information can take longer and may be less reliable. Friends or relatives should be involved if possible and if desired. In emergency situations, this can often lead to difficulties in decision-making between medical possibilities and an old person's right of autonomy. This exposes a further need for interdisciplinary gerontological geriatric research taking ethicists and legal practitioners into account.

So-called transition management is a particular challenge both within and outside the inpatient sector. This creates an interface in today's health care system which can be associated with serious consequences for old people. Not infrequently, loss of information and communication breakdowns can lead to rapid re-admission (revolving-door effect) or to a need for nursing care, which results in institutionalization without a chance of the patient returning to his or her own home.[76]

Nursing Home Care

An increasing number of old people with multiple illnesses and severe infirmities live in nursing homes.[77] Care needs have thus grown more complex, but unfortunately, the reality of the situation is often characterized by inappropriate health care that is structural in nature. On the one hand, certain specialist services are difficult to obtain, especially high-quality dental and psychiatric services, as well as treatment for vision and hearing impairments. On the other hand, nursing home residents are also over-treated in some instances, to their disadvantage. For ex-

70 Singler K, Christ M, Sieber C, Gosch M, Heppner HJ (2011); Singler K et al. (2014).

71 Rummer A, Schulz R (2012).

72 Thiem U et al. (2012); Singler K et al. (2013); Gray LC et al. (2013).

73 Diagnosis related groups – case groups in the billing system.

74 Lüttje D, Gogol M (2014); Taraldsen K et al. (2014); Biber R et al. (2013).

75 Lüttje D, Varwig D, Teigel B, Gilhaus B (2011).

76 SVR Gesundheit (2012).

77 Destatis (2013).

ample, study results pertaining to the discontinuation of psychotherapeutic drugs are not implemented, and patients often receive these medications for too long a period of time.[78]

It is particularly important that health care providers speak with residents about their personal health goals and how best to shape their final stage in life. Conventional goals such as prolonging life are often not desired, and also make little sense under the circumstances.

For nursing home residents and their loved ones, it is essential that referral to a nursing home is not a one-way street, and that it remains possible for patients to return home – indeed, this should be a goal. This would be medically possible for a not inconsiderable percentage of patients. The current practice of preventing patients from leaving nursing homes and returning to their home environments also leads to a negative assessment of nursing homes. Model projects for care administered by nursing home physicians are rarely evaluated, so that no assertions can be made as to their quality.[79]

German data about treatment structures and their effects is lacking and is urgently needed. A number of regional models are currently practised;[80] in the interest of the patient, it is essential to test the quality of options as well as the limitations of heath care providers.

Summary

Ageing is no longer defined primarily by illness. This is substantiated by abundant data proving the increase in healthy life expectancy and also an increase in the number of people who are able to manage their daily lives independently, despite their advanced age. For most people, retirement is the start of a phase of new activities. The goal of health care treatments must be to retain or even improve functionality and quality of life despite (chronic) illness or limitations. Psychological support has a special role in managing daily life with chronic illnesses.

The serious socio-economic differences in illness, health, and life expectancy of old people must be addressed in the course of treatment, but must also be discussed within a socio-political framework.

Medicine and medical treatment are called upon to support old people primarily in living independently for as long as possible. This task differs from traditional goals focused largely on healing. Diagnostics, treatment, structures, and organizational processes of medical care must be adapted accordingly. A variety of well-evaluated approaches are available which should be disseminated above all by targeted and broad education, training, and continuing education: e.g. the “chronic care” model for general practitioners, early geriatric rehabilitation, and geriatric trauma centres in inpatient care.

Health goals should be negotiated early by means of Advance Care Planning (ACP). Communication between health care providers could be improved by use of the “International Classification of Functional Disability and Health” (ICF) and “International Classification of Primary Care” (ICPC) rankings.

ICF and ICPC serve to depict the individual in his private life as broadly as possible. They also have a clear interaction with preventive measures (behavioural, relational, and medical prevention). Thus, the long-term effects of certain lifestyles in middle age upon the

78 O’Mahony D et al. (2015); Balzer K, Butz S, Bentzel J, Boulkhemair D, Lühmann D (2013).

79 Ebd.

80 For example, http://www.innovative-gesundheitsmodelle.de/ of the Institute for General Medicine of the Johann Wolfgang Goethe University of Frankfurt and the Robert Bosch Foundation. Accessed July 20, 2015.

severity and course of later illness, but also the growing importance of employees over 50 years of age for the job market, are compelling reasons to address those 50 to 65-year-olds.

3 Evidence-based medicine (EBM) and medical practice

Modern clinical expertise in medicine and health care treatment means the integration of current meaningful external evidence, health care provider experience, and the health goals and values of individual patients in order to reach the optimal decision for the patient.[81]

In order to be able to act according to the best current external evidence without requiring time-intensive individual research and review of literature, the individual physician or health care provider may also use evidence-based guidelines or systematic reviews. Evidence-based guidelines include treatment recommendations determined by a group of experts on the basis of the best scientific evidence in a transparent process. They are mostly set up on behalf of associations of medical experts. In the "National Health Care Guidelines" program (an initiative of the German Medical Association, the National Association of Statutory Health Insurance Physicians, and the Association of Scientific Medical Societies), guidelines are created by consensus on the basis of the best scientific proof available.

In guidelines, as in other literature-based secondary publications of the EBM (systematic reviews, Health Technology Assessment [HTA] Reports), relevant studies are reviewed for their validity and are consequently included, with varying weightings, in decisions and deductions. Thus, multiple randomized controlled studies or their summaries within a systematic review or a meta-analysis are seen as the best data pool or highest level of evidence for therapeutic and often diagnostic questions. This is not true in all cases, though. Questions based on the progression of a disease (prognoses), cause of disease (aetiology), or based on frequency of occurrence of an illness require different study designs. Expert opinions are seen as the lowest level of evidence since practical knowledge is selective and cannot be generalized.

Guidelines do not replace decision-making with individual patients, even if patients and authorized representatives were involved in setting up the guideline.[82] Up to now, guidelines have hardly taken multimorbidity into account (cf. Chapter 4.1) which often limits their significance in geriatric medical and health care provision.

81 Guyatt G, Cook D, Haynes B (2004).

82 Stiggelbout AM et al. (2012).

Box 7: Evidence basis and heterogeneity of patients

The effect of treatments and medications varies greatly from patient to patient for a multitude of reasons. Age, sex, and ethnic or cultural heritage are important distinguishing characteristics. Moreover, older people show the largest inter-individual variability of all age groups. This means that standard values based on age are highly questionable.

Advanced age is still "female" – even though the discrepancy in life expectancy between men and women will most likely be eliminated in the future. Active pharmaceutical ingredients and therapies may have gender-specific effects.[83]

The same is true of differences between children, middle-aged adults, and the older people. Cellular and hormonal factors and living conditions mean here too that results of clinical studies are not readily applicable if the studies are not carried out within these specific groups. Accommodating patient preferences means paying special attention to varying sociocultural needs within the field of medical care.[84]

3.1 Legal framework

Medical decisions are made by the physician and the patient together. The physician, however, remains responsible for justifying the course of treatment and must therefore keep to certain standards. In legal assessments of medical activities, this standard – not the EBM – is the central key term. The standard determines what due diligence is required during medical treatment acc. to § 276 section 2 of the German Civil Code (BGB). Physicians should not fall short of this, if they do not want to take the risk of being liable according to civil law or even becoming liable to prosecution.[85] The term "standard" is not legally defined, which is explained by the rapid advancement of medical knowledge.

The standard can be defined as the treatment or method which a specialist of average qualifications could render, based on the current state of medical science and practice in terms of a minimum standard of experience, knowledge, capability and awareness.[86]

Precise determination of the standard takes place in many ways: by means of medical scientific publications, statements from associations of experts and medical associations, consensus conferences with expert panels or from conclusions drawn from medical practice. Ideally, the EBM method should be used as a basis.

The current guidelines of medical expert associations are an important tool for evaluating the standards. As the most methodologically demanding type of guidelines, the so-called S3 guidelines are based on the best scientific evidence. Guidelines are not legally binding, however, as they often merely introduce a framework for action. Hence, it may be advisable that an attending physician/staff justifiably deviate from the guidelines. This can be the case if multimorbid patients are treated[87] or if guidelines contradict one another. Consequently, the

83 Thürmann P (2008).

84 Position paper of the German National Committee for Migration and Public health. Available at: http://www.bundesregierung.de/Content/DE/_Anlagen/IB/2012-04-05-positionspapier-arbeitskreis-migration-gesundheit.pdf?__blob=publicationFile. Accessed July 20, 2015.

85 Kifmann M, Rosenau H (2008), S. 64.

86 Katzenmeier Ch (2002).

87 Katzenmeier Ch (2014), S. 61.

notion that guidelines define the standard has not been able to establish itself either in medical law or in jurisprudence.[88]

The EBM becomes more significant in the framework of those regulations which serve as the standard for statutory health insurance. Though these refer to the generally recognized state of medical knowledge (§ 2 Sect. 1 S. 3 SGB V), services are still limited to the extent necessary according to the efficiency principle of § 12 Abs. 1 SGB V. The guidelines of the Joint National Committee (G-BA) play a large role here. Among other things, this committee can limit the payment obligations of the statutory health insurance acc. to § 92 SGB V. New examination and treatment methods (NUB) can therefore only become a part of the medical care agreement if the G-BA has recommended their usage acc. to § 135 SGB V. With its decisions, the G-BA is expected to orient itself based on EBM findings.[89] Furthermore, the Federal Constitutional Court (BVerfG) has decided that non-evidence-based measures may only be implemented if conventional medicine treatments are not available in a life-threatening situation (ruling from 06 December 2005, the Nikolaus Ruling).[90]

EBM is also important for approval of medications, since it must be proven that these treatments are effective, based on the current state of medical knowledge (arg. ex § 25 Art. 2 No. 4 of the German Medication Act – AMG). For this purpose, clinical tests must be carried out according to standardized processes. The requirement for clinical effectiveness demands a clinically relevant effect, so that non-specific improvement in the illness's progression such as spontaneous healing can be ruled out. This requires regular (randomized) control studies which are required by legislation in the German Medication Act.[91] This means that EBM (though not explicitly mentioned) is the basis for the approval of medications. The Regulation for the Examination of Medications from 16 April 2014,[92] which came into effect in June of 2014 and will be directly applicable in Germany as of 28 May 2016, explicitly recognizes in Recital No. 15 the need to test medications in a detailed and appropriate manner for vulnerable groups such as older people, especially in cases of multimorbidity, in order to improve their treatment options. Implementation of these goals will take place in moderate steps. On the one hand, this should achieve that the study protocol must state explicitly which reasons and justified criteria are used to determine how older people, for instance, can be excluded from clinical trials.[93] On the other hand, the regulation extends the admissibility of absolute group research beyond the sphere of minors and allows this type of clinical trial under strict regulations – such as minimum risk and minimum burden – to be carried out also among people, including older people, who are incapable of giving consent.[94] In any case, it should be noted that this regulation does allow stricter national regulation.[95]

It is currently being discussed whether this rule of the EU regulation should also be maintained in Germany, so that respective research does not migrate to countries with considerably lower standards of ethical and legal protection, and so that questions important to medical treatment can be examined in Germany, too.

88 Ebd., S. 6of.; BGH ruling from 15.04.2014 – VI ZR 382/12, NJW-RR 2014, 1053 (1055).

89 Barth D (2011); § 92 SGG V, Rn. 5.

90 BVerfGE 115, 25ff.

91 Deutsch E, Spickhoff A (2014), Rn. 1297; Rosenau H (2000), S. 72.

92 VO (EU) No. 536/2014, Abl. L 158 from 27 May 2014.

93 VO (EU) No. 536/2014, Abl. L 158 v=from 27 May 2014; Attachment I, Art. 17, lit. y).

94 Art. 31 Sect 1 lit. g) ii) VO (EU) No. 536/2014, Abl. L 158 from 27 May 2014.

95 Art. 31 Sect 2 VO (EU) No. 536/2014, Abl. L 158 from 27 May 2014.

3.2 The three pillars of EBM and methodological challenges

Introduction

Patients are presented with questions relating to prevention, diagnosis, treatment, rehabilitation, prognosis and the organization of care plans. Behavioural intervention and pharmacotherapy are crucial to medical care for the elderly, and have particularly severe consequences. These two areas of treatment will be examined in more detail below.

The best empirical evidence for the usage and safety of a treatment or treatment process (first pillar of EBM) comes from meta-analyses of methodologically first-class randomized controlled studies or from individual meaningful randomized studies. Since the participants in a clinical study often differ from patients in everyday clinical practice with regards to their prognosis (e.g. severity of illness, comorbidity, co-medication), one must always ask about the arguments against transferring the results of a clinical study to a particular patient care situation. In randomized controlled studies on geriatric issues, "typical" patients are often not selected. The participants are often younger, have better prognoses (especially in oncological studies) and the gender ratio is often unbalanced.[96] Thus, the generalizability of these results, i.e. the external validity of studies pertaining to geriatric questions, is often limited.

Usually, these results are obtained from clinical studies proving the effectiveness of a treatment and deal with the likelihood of successful treatment. In other words, a treatment is examined to find out if it is on average better than an alternative method, i.e. in a population which has received this treatment in comparison to a population which has not received this treatment. It is therefore difficult to derive meaningful assertions about effectiveness in individual cases. This means that in individual cases the attending specialist can never be certain whether a treatment will be effective, and so must choose the treatment option most likely to elicit the desired result and yet simultaneously only pose acceptable risks in the sense of adverse drug reactions (ADR) and complications. Specialist expertise, the next pillar of EBM, is imperative for considering the applicability of clinical study results to individual treatment situations. Diagnostic procedures in individualized medicine may possibly support this expertise in the future.[97]

The third pillar of EBM is patient involvement in medical decisions in the sense of joint decision-making (Shared Decision Making – SMD) and informed patient-consumer choice. Informed patient decision-making about health care matters and services in front of the background of their personal preferences and desires requires comprehensive, objective and understandable information about the illness and its progression, the available treatment options, their advantages and disadvantages, and the plausibility of scientific proof. Shared Decision Making and Evidence-based Patient/Consumer Choice are especially important for medical interventions whose use is limited, potentially unsafe, or associated with relevant side effects. Here, non-utilization of diagnostic, preventative or treatment measures is explicitly intended. This type of patient involvement far surpasses the traditional conception of obtaining patient consent. Examples of medical areas in which these procedures are relevant include preventive medicine, treatment of risk factors, check-ups, early detection examinations, but also treatment of malig-

96 Van Spall HGC, Toren A, Kiss A, Fowler RA (2007); Travers J et al. (2007); Dowd R, Recker RR, Heaney RP (2000).

97 National Academy of Sciences Leopoldina, acatech – German Academy of Technical Sciences, Union of the German Academies of Science (2014).

nant (cancerous) or other chronic illnesses. Despite the strengthening of patient rights both in this country and throughout Europe, systematic implementation of this concept has only occurred in part, and only in controlled studies which exclude geriatric populations.

For EBM to be consistently adopted, it is important to disclose uncertainties and questions about the applicability of study results to the geriatric care situation of the patient. The actual advantages and disadvantages of treatment options should be explained. In the case of older or very old patients, certain challenges arise as a result of the complexity of their health status.

Some studies suggest that old people prefer a more passive role in medical decision-making or prefer the paternalistic decision-making style, and would rather defer to medical professionals.[98] A wide variation in the preferred decision-making style is probable, especially as this is not static and can vary according to the situation during the progression of the illness.[99] For physicians and other health care providers, the professional challenge arises of determining the patient's preferred decision-making style and adapting the medical decision-making process accordingly.[100]

Medication treatment and authorization

Clinical studies are expensive. They are carried out much more often on behalf of the drug industry than on behalf of public research, for instance at university clinics. Generating positive results for their own substances is paramount in industrial drug research and development. This can lead to methodical bias in favour of their own medicinal compounds and to negative study results which are not published.[101] Questions which cannot lead to authorization of a medication or which pertain to non-patented medications are generally not considered by the industry. This situation is problematic for pharmacotherapy for older people.

It is well-known that in the USA the drug industry is the main sponsor of biomedical research, with a contribution 59 billion US dollars. That corresponds to 58% of research funding. The member companies of the German Association of Research-Based Pharmaceutical Companies (VFA) contribute roughly 5.6 billion Euro annually for research and development. Federal funding in the USA (predominantly from the National Institutes of Health (NIH)) accounts for 33 % of funding.[102] In Germany, the funding rate, especially for non-industrial clinical studies, is much lower. Both public research funders, the German Research Association (DFG) and the Federal Ministry for Education and Research (BMBF), sponsor clinical studies with an annual contribution of 15–20 million Euro. That corresponds quantitatively to a much lower percentage of industry-funded research.[103]

Evidence compiled by the industry is often of high quality, though economic interests – especially the development of new, marketable medications – do not necessarily correspond to the interests of older patients. It is therefore crucial that relevant questions concerning the latter are researched with support from public funding.

98 Brom L et al. (2014).

99 Belcher VN, Fried TR, Agostini JV, Tinetti ME (2006); Brom L et al. (2014).

100 Brom L et al. (2014).

101 Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R (2008). Publication of negative results is often refused by trade journals.

102 Dorsey ER et al. (2010).

103 In addition to clinical and pre-clinical studies, statements from the VFA include basic research which is applied to the vast majority of clinical studies; VFA: http://www.vfa.de/download/kompakt-2013.pdf. Accessed July 20, 2015. Public research does not differ systematically according to the type of study, so institutional funding (e.g. health centers) is also applied to studies without centrally available statements.

Regulatory authorities[104] often predefine the type of studies necessary to bring a medication onto the market. Measurements of effectiveness (called endpoints), length of study, and definition of patients are a part of this. Usually, an outcome can be demonstrated as being as clean as possible on patients with "clearly-defined" illnesses. At the same time, manufacturers can reduce safety hazards by selecting patients with a very low risk for side effects. This selection of ideal patient groups systematically excludes old, multimorbid patients.[105]

More stringent regulation requirements in the debate

In 2006, a group of experts in the European Commission had already come to the conclusion that regulatory authorities should require that clinical studies consider the needs of old patients.[106] In 2008, a research consortium within the framework of European research funding launched a study about the participation of the elderly in clinical studies. A "Charter for the Rights of the Elderly in Clinical Studies" (2011) was developed, with detailed recommendations, in support of the right of the elderly to evidence-based medical care.[107]

That same year, the European Medicines Agency (EMA) determined that data for the evidence-based prescription of medications was missing for old and very old patients, both before authorization and afterwards in treatment application. Medical treatment should take place based on evidence – that is, it should be properly researched and evaluated – and it must also be prescribed in an informed manner.[108]

Previous authorization requirements for medication in Germany, Europe, and the USA can be described as insufficient with respect to the population of older people. Thus, the required number of senior citizens aged 65 or older in a group of 100 patients is independent of the age group in which the medication will most likely be prescribed later. This leads to a striking underrepresentation of the target treatment group, especially for cardiovascular medications, psychiatric medications, and medications for treating Parkinson's disease. Modifications to the ICH-7E guidelines of the EMA provide for an increase in the number of seniors in clinical studies, as well as the inclusion of very old patients, and, above all, for a close analysis of the effect of undesired side effects on the central nervous system. However, these modifications do not explicitly provide for a separate, age-specific evaluation of advantages and disadvantages. To date, there have been few concrete recommendations for adding frailty to the inclusion criteria and to consider this in the stratification, or to develop age-appropriate formulations or even different endpoints which could be relevant to elderly patients (e.g. falls, activities of daily living – ADLs).

After positive experiences with the "Paediatric Investigation Plan" (PIP), a "Geriatric Safety and Investigation Plan"[109] should be compulsory for all active substances which are used to a rele-

104 The European Medicines Agency (EMA) is responsible for medication authorization throughout the EU. If a medication is only meant to be released on the German market, then the responsible agency is the Federal Institute for Drugs and Medical Devices (BfArM).

105 Cho S et al. (2011).

106 EMA (2006). Adequacy of Guidance on the Elderly Regarding Medicinal Products for Human Use. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500049541.pdf. Accessed July 20, 2015.

107 PREDICT study – Participation of the Elderly in Clinical Trials http://ec.europa.eu/health-eu/doc/predict2010.pdf. Accessed July 20, 2015; Crome P, Cherubini A, Oristrell J (2014).

108 EMA (2011). Geriatric Medicines Strategy. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/02/WC500102291.pdf. Accessed July 20, 2015.

109 EMA (2006); Adequacy of Guidance on the Elderly Regarding Medicinal Products for Human Use. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500049541.pdf. Accessed July 20, 2015. EMA (2011).Geriatric Medicines Strategy. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/02/WC500102291.pdf. Accessed July 20, 2015.

vant extent for older patients. These plans should include not just randomized clinical studies, but also observation studies and routine data.

When authorizing medications care should be taken that old and very old patients are represented in clinical studies. A much larger number of the required complex interventions must be evaluated in non-commercial, publicly-funded studies than previously.[110]

Behavioural and technical interventions

Parallel to the development of Geriatrics since the 1970s, it has become customary to develop highly behaviour-oriented interventions relating to age (often described as "interventional gerontology" or "non-medication intervention"). As a result, cognitive training and dual task training are nowadays often a part of geriatric rehabilitation. On the other hand, psychiatric therapy with the older people or the use of self-management programs, as when dealing with chronic loss of functions such as vision or hearing impairment, are linked less often with geriatric care. In any case, behaviour-orientated interventions have long been a part of the care landscape and should for this reason be taken into consideration by geriatric medicine. These interventions also supply valuable insight with respect to the aforementioned plasticity of the aging process and reveal knowledge fundamental to geriatric medicine. In addition, increasing evidence is available pertaining to the effectiveness of these interventions/programs.[111]

Psychiatric therapy is often carried out in cases of mental and psychosomatic disorders (e.g. depression, anxiety, somatic disorders), and the effectiveness of this treatment for older and very old patients is clearly documented.[112] The positive effects of increased physical activity on mobility, cardiovascular fitness, prevention of falls, cognitive function, general wellness and nutrition are also documented.[113] The picture is less clear with respect to purely cognitive training. Improvements are often observed only with respect to capacities which were explicitly trained; general competency is only improved by cognitive training to a relatively limited degree.[114] General physical training for elderly patients with dementia give rise to a certain degree of optimism in the area of dual task training.[115] Overall, too little research has been done on self-management programs and interventions focused on mastering critical events in life. They are also meaningful for special groups often ignored in geriatric medicine, such as the rehabilitation of elderly patients with vision or hearing impairments.[116] To date, intervention programs for family members/relatives have only displayed low to moderate effectiveness, meaning that their practical significance is minimal, especially with regard both to dementia patients and their caregivers. Overall, there are suggestions that the future could belong to multi-component programs implemented simultaneously on multiple levels (e.g. cognitive training + physical training + living environment adaptation).

In contrast to randomized studies in the area of pharmacology, the focus in this research field is on older patients and extremely vulnerable people, though these studies often suffer from limited sample size and a lack of control groups. Furthermore, systematic implementation

110 One very good approach was 6 research collaborations funded by the BMBF, each over a period of 6 years, which have now ended and whose perpetuation is not currently planned (cf. http://www.gesundheitsforschung-bmbf.de/de/4329.php. Accessed July 20,2015).

111 Wahl HW, Tesch-Römer C, Ziegelmann JP (2012).

112 Pinquart M, Duberstein PR, Lyness JM (2006); summarizing: Pinquart M (2012).

113 Erickson KI, Miller DL, Weinstein AM (2012).

114 Martin M, Clare L, Altgassen AM, Cameron MH, Zehnder F (2011).

115 Schwenk M, Zieschang T, Oster P, Hauer K (2010); Hauer K er al. (2012); Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S (2015).

116 Heyl V, Wahl HW (2014).

of available evidence in different practice contexts has been researched very little to date, particularly in Germany.[117]

Overall, geriatric medicine should decidedly address these types of behaviour-oriented interventions. It should be expected that these will play an even more important role with respect to older people in the future, for instance to maintain independence for as long as possible and to reduce an overpopulation in nursing homes despite serious chronic illnesses. They also contain promising implications with respect to new interdisciplinary alliances between different health care professions in which geriatric medicine has to participate.

Auxiliary appliances and technology

Medical products are not widespread merely in diagnostics and clinical or outpatient medical care. They are often also used in the day to day lives of old and very old people, both as treatment and as a general support for everyday life. According to the Medicinal Products Act (MPG), manufacturers must prove that their products satisfy the stipulated requirements and also show how this stands in relationship to possible risks. However, the MPG does not explicitly require that the effectiveness and benefits for patients be proven within the framework of a clinical trial. In contrast to medications, manufacturers of medical supplies can, in some cases, use data from similar products (e.g. clinical trials of predecessor products) in order to avoid invasive clinical trials (such as operations) with human test subjects. This is especially true for the further development of existing medical products. This does not prevent even high-risk products from being placed on the market without referring to clinical data. The evaluations do not have to be made publicly available.

On the other hand, since 2012 and within the framework of new examination and treatment methods (NUB) according to the GKV Supply Structure Act (GKV-VersorgStruktG), the Joint National Committee (G-BA) can request clinical studies by an "independent scientific institution" for new medical products before these can be reimbursed by the Statutory Health Insurance (GKV). Designation of a sufficient number of independent scientific institutions according to the GKV-VersorgStruktG is still pending, however.

The authorities responsible for the authorization procedure according to the MPG do not always operate in a standardized fashion. If a clinical study is required by the designated authority according to the MPG or by the G-BA according to the GKV-VersorgStruktG, then the MPG essentially includes clear information about formal and procedural requirements for conducting clinical trials. Requirements for testing medical productions are based on § 20 MPG, but the consent of the ethics commission and approval from the Federal Institute for Medications and Medical Products (BfArM) is also essential. It can be assumed that for clinical trials the same scientific and ethical regulations must be complied with as for medications.

For medical products associated with high risks (such as implants), scientific testing of the clinical effectiveness and safety should be ensured for the benefit-risk assessment.[118] It remains to be seen whether future regulations of the European Parliament and the Council on Medical Products lead to changes in the guideline 2001/83/EG, and in the regulations (EG) No. 178/2002 and (EG) No. 1223/2009, improving the regulatory requirements in this sense.

117 Wahl HW, Diehl MK (in print).

118 SVR Gesundheit (2014). Cf. also the German Network of Evidence-Based Medicine and Association in Support of Technological Assessment in Health Care (http://www.health-technology-assessment.de/). Accessed July 20, 2015.

There has been little research on widespread conventional tools with special significance for older people (e.g. screen readers, magnifying glasses, external hearing aids, all types of walking aids, bathtub lifts, patient's own blood pressure monitoring devices, etc.) with regard to their effects on the old people. "Sustainable" introduction to the correct usage of tools remains a particularly sensitive topic, whereby certain special features, such as a cognitively limited processing capacity, must be considered. Systematic adaptation of structural conditions in the home to the needs of older people (e.g. following a stroke, fall, significant vision loss) is apparently meaningful for the patient's independence, according to previous studies, though the data pool is, again, rather limited.[119] In Germany, there is hardly any data on the effectiveness of residential adaptations on illness or injury.

Furthermore, too little focus has been given both publically and scientifically to the superimposition of the demographic trend of an aging population with that of a rapidly progressing permeation of daily life with technology. For all of us, technology, mostly in the form of advancing information, communication and automation technology, will lead increasingly to new environmental demands, but it will also lead to enriched environments for older people. Technology for the elderly (as for any age group) includes the potential for optimization or developmental enhancement of the individual.[120] Development of studies should also be adapted to the speed of technological change.

One of the best-researched areas of technology are online-supported telemedical applications, including those for heart and lung disease, psychiatric illnesses, diabetes and cognitive behavioural therapy programs related to anxiety and depression. The corresponding studies have methodically limited quality and are often built upon small numbers of cases and non-representative samples.[121] More recent studies of higher quality come to the conclusion that the effects of technology-based interventions (transferring vital data from home to the physician; daily telephone-based queries about symptoms and weight) are relatively low in comparison to normal care when seen in relation to repeated hospital admissions and mortality.[122] Nevertheless, the benefits of Telemedicine could lie in other areas, such as the facilitation of (instrumental) activities of daily living ((I) ADL).

It should also be noted that elderly people are increasingly able to inform themselves about health and illness with the support of the Internet. Geriatric medicine must face up to these developments and incorporate them increasingly as part of the patient environment during treatment.

In many areas of the field sometimes described as "gerotechnology," evidence is only minimal with respect to effectiveness (in view of the course of illness and independence). Geriatric medicine should therefore initiate enhanced research (in cooperation with other professionals, such as engineers, psychologists and designers). The interconnection of health and technology (e-health) is growing stronger, and this will be apparent for old and very old people, too, in the not-too-distant future. Some questions arise regarding the potential of these technologies (e.g. for preventive medicine or in the area of robotics for patients with dementia), but also regarding the ethics of using technology for old and very old patients, and geriatric medicine should take a decisive stand in this connection in the future.

119 Wahl HW, Fänge A, Oswald F, Gitlin LN, Iwarsson S (2009).

120 Schulz R et al. (2014).

121 Ekeland AG, Bowes A, Flottorp S (2010); Wootton R (2012).

122 Cartwright M et al. (2013); Chaudhry SI et al. (2010).

Needs and preferences of elderly patients

Respect for and support of patient autonomy are central medical-ethical principles and are demonstrated in numerous decisions regarding professional treatment and fair health care systems.[123]

Patients have the right to make informed decisions about the course of their treatment. National and international surveys document that patients desire a high degree of participation in medical decision-making. This desire is partially dependent upon health status, education, and age.[124] The concept of Shared Decision Making (SDM), meaning joint or participatory decision-making, is a method of involving patients in their own treatment.[125] SDM and EBM are crucial requirements of a modern health care system striving for the highest quality of care. In the last few years, SDM coupled with EBM has been researched, but it has barely been used in medical practice.[126]

SDM is related not only to treatment situations between physicians and patients. Studies are being carried out where the role of a decision coach (a specially trained caregiver who accompanies the patient in the decision process, contributing to the implementation of SDM) is investigated. Decision coaches initiate the recording of the decisions needed, prepare evidence-based decision aids, accompany and support the decision-making process, and monitor factors and needs which may influence the implementation of decisions.[127] In the context of geriatric care, the concepts of SDM and informed decision-making supported by evidence-based patient information (EBPI) have barely been researched.[128]

EBPI is indispensable for informed, participatory decision-making.[129] EBPI increases relevant knowledge, reduces false conclusions, and allows patients to make individual decisions.[130] Foregoing the provision of information relevant to decision-making can lead to patients having false expectations about treatment, especially overestimating the effect of a treatment and making erroneous assumptions about the prognosis.[131] Missing patient information can be a reason for initiating non evidence-based and harmful therapies. The consequences are injudicious therapies, for instance in the care for very old patients, such as using PEG (percutaneous endoscopic gastrostomy) in advanced dementia.[132] Very little research has been done into how EBPI is accepted by geriatric patients, what the proper formats and access paths might be, which specific EBPI requirements must be set in a geriatric setting, and to what extent EBPI is relevant to decision-making in geriatric medicine.[133]

Decision-making during the course of treatment is dependent upon timely planning and external help, especially in cases of cognitive impairment. Patients with dementia are dependent upon authorized representatives or caregivers in this regard.

For old and very old patients, participation in medical decision-making is not enough – they must also plan the course of care and treatment in advanced stages of care (Advance Care Planning – ACP). ACP

123 European Charter of Patients' Rights 2002; Medical Professionalism Project 2002.

124 Brom L et al. (2014); Hamann J et al. (2007); Müller H (2007).

125 Härter M et al. (2011).

126 Hoffmann TC, Montori VM, Del Mar C (2014).

127 Stacey D et al. (2008).

128 Légaré F et al. (2014); Gionfriddo MR (2014); Joosten EA et al. (2008).

129 Bunge M, Mühlhauser I, Steckelberg A (2010).

130 i.e. Schwartz LM, Woloshin S, Welch HG (2009); Fagerlin A et al. (2010).

131 Weeks JC et al. (2012); Keidan J (2007).

132 Sampson EL, Candy B, Jones L (2009).

133 Schrijvers J, Vanderhaegen J, Van Poppel H, Haustermans K, Van Audenhove C (2013); Lins S, Icks A, Meyer G (2011).

may become ineffective or impossible to carry out due to the presence of cognitive impairment or dementia.[134] It is ethically necessary and numerous studies have demonstrated and evaluated that elderly people are able to make sustainable and well-informed ACP decisions at an early stage.[135] ACP goes above and beyond the widespread patient living wills.[136] A plan for end-of-life care and treatment created at a time of decision-making competency is the best support for relieving relatives and proxies of the burden. However, it must be actively initiated and documented. Appropriate structures are lacking in this country, apart from model projects.[137]

Information and consent documents regarding medical treatment and participation in studies must be adapted to the needs of old and very old patients. It is important to clarify, both ethically and legally, to what extent the texts of consent documents may be simplified and at which point the decisions of authorized representatives (proxies) should be adopted. A fundamental ethical-legal analysis is required here, as well as empirical studies evaluating the clarity of information and consent documents for older people. Factors such as hearing or vision impairments must always be taken into consideration.

Summary

Evidence-based medicine (EBM) should be the basis for negotiation in health care provision and in the authorization of medications, medical products and operations. In current practice, EBM is often geared towards treating monopathologies. Clinical studies are performed with the aim of proving the advantages and disadvantages of interventions as unambiguously as possible in a study population in order to transfer those results to a target population. Study and target population can differ considerably, depending for instance on average age and the setting, both of which influence the effectiveness of treatment.

Pharmacological studies are generally performed with the aim of proving the effectiveness of new substances. Studies on the discontinuation of medications, on interaction between treatments and medications, and on complex interventions not solely comprised of medications are rarely performed and receive little public funding.

The requirements of the regulatory authorities for the representative nature of study groups are very low with respect to old people. As a result, study participants are chosen in such a way that only a few old people (and a healthier subset of them) are included.

These points result in health care professionals having only a few scientifically-based recommendations at their disposal.

In the case of non-pharmacological interventions, the data pool is similarly inadequate with regards to old people. Several examples of meaningful studies on behavioural and technology-based interventions and auxiliary appliances are available. In the light of increasing technological permeation of daily life, it is crucial to examine the medical and health-related effects of technological and operative interventions on old people, especially in Germany. This is also true of conventional tools and adapted living spaces, as well as information and communication technology.

Patient participation in medical decision-making is a part of EBM and is also desired by old people. In reality, this occurs only rarely. Participatory decision-making requires an adequate infor-

134 Robinson L et al. (2013).
135 Volandes AE et al. (2009).
136 in der Schmitten J et al. (2014).
137 ibid. and in der Schmitten J, Marckmann G (2013).

mation base. Evidence-based patient information (EBPI) still has to be prepared for the care of old people, and its format, access paths and effectiveness still need to be researched. To date, this has only been done for individual questions. It should be pointed out that proactive planning and preparation of decisions regarding nursing home care and sickness at an advanced age help to ease the burden on relatives, though the structures required for this endeavour remain to be built.

4 Scientific evidence for medical care of old and very old patients – fields of application

4.1 Insufficient evidence for medical care: Over-treatment, under-treatment, and mistreatment

Too much or too little? Multimorbidity and polypharmacy of elderly patients

If older patients suffer from several illnesses simultaneously, they are often treated with numerous parallel-administered medications in accordance with monopathology-oriented guidelines. If a person takes more than 5 medications daily, this is referred to as polypharmacy.[138] It is not uncommon for an older person with 5 illnesses to take 10 different medications.[139] About one-half of patients over age 65 are affected by polypharmacy.[140]

Polypharmaceutical treatment is problematic in a number of ways. Parallel administration of medications lead to unintended and harmful side effects and medication interactions which, in some cases, must also be treated with even more medication. The results are so severe that approx. 10 percent of hospital admissions are related to medication complications.[141] Numbers from the Netherlands demonstrate that nearly 20 percent of hospital admissions for older patients (though only 5 percent of admissions for younger patients) are related to medication side effects or interaction, whereby the majority of these cases were characterized as avoidable.[142] Falls and delirium are also common side effects and interactions, which can severely impede very old or frail patients in managing their daily lives and can limit their quality of life.[143] Based on the data from the Network of Regional Pharmacovigilance Centres (NRPZ), it can be demonstrated that the current prescription practice creates risks that increase with age, firstly of being hospitalized due to adverse drug reaction (ADR), and secondly of having these ADR which are caused not by a certain active substance, but rather by a medication interaction.[144]

Since pharmacokinetics (mode of action of medication components in the body) change in old and very old patients, partially due to altered absorption, metabolizing (biotransformation), distribution due to reduced muscular body mass (sarcopenia) and higher body fat percentage, or by changes to excrement, dosages which are too low or too high, or an incorrect dosage frequency can lead to negative consequences.[145]

Polypharmacy is not considered adequately in the guidelines which are meant to help physicians familiarize themselves with a treatment. As a result, it is vital that age-appropriate guidelines be developed for specialist disciplines. The same applies if the scientific evidence

138 There is no scientific reason to attribute any particular meaning to the number five, though. van den Akker M, Buntinx F, Knottnerus A (1996); Viktil KK, Blix HS, Moger TA, Reikvam A (2007).

139 Boyd C et al. (2005).

140 Thürmann PA, Selke GW (2014).

141 Estimate of the WHO, cf. BMG (2013).

142 Petrovic M, van der Cammen T, Onder G (2012).

143 Wehling M, Burkhardt H (2011); Petrovic M et al. (2012).

144 Schmiedl S et al. (2007); Schmiedl S et al. (2013).

145 Petrovic M et al. (2012).

is unclear or insufficient.[146] The general practice guideline for handling polypharmacy in primary care depicts an attempt to draw attention to problems in cases of an inadequate data pool, and, in doing so, try to avert harming patients. This indicates clearly that the likeliness of patients with severe ADR being admitted to hospital increases with the number of medications administered.[147]

In addition, lists such as the PRISCUS and FORTA have been compiled, indicating inappropriate medications in advance. The FORTA list also offers information on the best-suited medications for old patients. The overarching aims of these lists are to optimize treatment using medications and to reduce adverse drug reaction (ADR). This, however, may also lead to old patients being deprived of important medications. Dementia, osteoporosis, and administration of supplements for malnutrition are examples of under-treatment and mistreatment. As a decision-making tool for medication prescribers, the lists also disregard the fact that old and very old patients are interested in functionality and independence as an outcome and that these goals are more important to them than merely extending lifespan, which is the primary goal of clinical medication trials.

Old patients are often prescribed non-indicated medications corresponding to their overall situation, though other important medications, which might also improve their prognoses, are at the same time withheld.[148] One example of this is the acute coronary syndrome.[149] The aim of the "choosing-wisely initiative" is to avoid unnecessary or harmful medical services and to take logical diagnostics and therapy recommendations into consideration.[150]

Education, continuing education and further education for the medical care of old people

The special medical care requirements of old patients must be adequately implemented in pre- and postgradutate education and training. The focus of this should be directed toward the treatment of multimorbidity and maintenance of mental and physical functionality. In this case, it does not suffice to concentrate solely on the course of study. Even in postgraduate areas, the corresponding continuing education and further education must be offered for the care of older people.

Geriatric medicine must be integrated in the job training of numerous other subject areas, especially the training of general practitioners, internists, emergency surgeons (geriatric trauma), ENT specialists, optometrists and dentists (gerodontology).

Furthermore, associations of medical experts have been trying for years to introduce specialists for internal medicine and geriatrics as extensively as possible; this could be a contribution to improved academic foundations and attractiveness, but could and should not replace continuing and further education in geriatric medicine as a cross-sectional task for expert disciplines.

Generally speaking, evidence-based medicine (EBM) should be anchored more securely in all forms of education and training. Both the knowledge of scientific standards and evaluation methods used for treatment and expert consulta-

146 For an example in oncology: Hurria A et al. (2008); Ritchie CS, Kvale E, Fisch MJ (2011).

147 Bergert FW et al. (2014).

148 Kuijpers MA, van Marum RJ, Egberts AC, Jansen PA; OLDY (Old people Drugs & deregulations) Study Group (2008); Cherubini A, Corsonello A, Lattanzio F (2012).

149 Schoenenberger AW et al. (2008).

150 The "choosing-wisely" initiative was developed by US physicians. Since 2012, they have published lists indicating unnecessary medical services. Analogous to this initiative, the German Society for Internal Medicine founded the "klug entscheiden (choose wisely)" initiative. Gogol M (2014); Grunert D, Siegmund-Schultze N (2015).

tion of patients, as well as that of effects and processes of appropriate patient communication are not adequately addressed.

In a further step, methodological knowledge must be established and taught with greater emphasis at university level so that studies can be carried out that depict more closely the needs of older people. An immense backlog demand is accumulating in this area for the very reason that the data conditions are poor.

Data pool for treating elderly patients with multi-morbidities

Current research primarily examines the prevalence of multimorbidity, though it rarely examines the effectiveness of interventions.[151] Existing studies deal first and foremost with possibilities for improving patient care, such as appropriate prescription, better administration of medications by the patient, and altered care organization and multidisciplinary teams. Interventions are often rather imprecise and therefore of varying levels of effectiveness. Positive results have been achieved, in that interventions have concentrated on specific risk factors or functional problems.[152]

All the instruments for responding better to polypharmacy and multiple (chronic) illnesses of older people (Beers list,[153] PRISCUS list especially for the German medication market,[154] FORTA list,[155] START- and STOP criteria[156]) lack scientific proof of effectiveness, safety and sustainability.[157] They are based on expert consensus, but not on controlled studies. Validation of these instruments is urgently required.

The difficulty here is that the spectrum of reasons for severe result parameters (death, hospital admission) is large for old, multimorbid patients, and that a single specific intervention often has difficulty generating biometrically conclusive results. It is thus also necessary to test complex, multi-professional interventions on old and multimorbid patients. Complex interventions must be theoretically substantiated and carefully prepared. The individual components must be established and their effects and interactions must be explored. This requires a number of preparatory studies before proof of effectiveness can be established in a controlled study.[158] The UK Medical Research Council published a framework model for this purpose in 2000 and 2008 which has been propagated in the meantime and which is continually and methodically updated.[159]

It is also true that diagnostic procedures are often not adapted to the characteristics and thus to the specific needs of patients. The importance of diagnostic procedures for the treatment and quality of care is also not well-researched, even for younger patients. There are hardly any controlled studies for the meaningful use of clinical diagnostics. This plays a very special role for older patients with functional impairments, decreased mobility, or other similar ailments. Diagnostics generally only take functions into consideration which are not decisive for the patient's independence and quality of life. Aspects relevant to this remain unconsidered: Neither are daily competencies established as the main criteria of diagnostics, nor do mental, sensory, or behavioural symptoms play a significant role, and the patient's social network is not recorded in a standardized manner either.

151 Smith SM, Soubhi H, Fortin M, Hudon C, O'Dowd T (2012).

152 France EF, Wyke S, Mercer SW (2012).

153 AGS (2012).

154 Holt S, Schmiedl S, Thürmann PA (2010).

155 Kuhn-Thiel A, Weiß C, Wehling M; FORTA authors/ expert panel members (2014).

156 Gallagher P et al. (2011); O'Mahony D et al. (2015).

157 Frohnhofen H, Michalek C, Wehling M (2011).

158 Mühlhauser I, Lenz M, Meyer G (2011).

159 Campbell M et al. (2000); Craig P et al. (2008); Craig P, Petticrew M (2013); Moore GF et al. (2015).

The health targets of old patients should also be considered in diagnostic studies, as well as the benefits of diagnostic tests – that is, insofar as testing actually leads to reduced morbidity (reduction in illnesses) and mortality.

Manufacturers must prove only the safety and reliability of a process in the framework of medical device regulations to obtain approval for diagnostic devices or processes. As a result, they conduct virtually no clinical studies on diagnostic matters. Disease-specific questions are processed typically through clinical academic research. However, they rarely extend beyond examinations of diagnostic accuracy in observed studies. In particular, there are no examinations of diagnostic algorithms which pursue patient-relevant treatment targets (endpoints). Thus, we lack data on whether the usual diagnostics for ischemia (blood circulation insufficiency), or coronary catheterization (cardiac catheter examination) lead to treatment relevant to the life expectancy or quality of life of old patients.

For old and very old patients, implementation of diagnostic medical devices should moreover be evaluated differently than for younger or middle-aged patients. The reference values for older patients must often be determined beforehand. Based on the high heterogeneity of old people, reference values associated with specific chronological ages are often useless. Pathological findings often have a different physiological relevance than those of younger patients. Diagnostic measures often have milder effects on treatment in older patients as compared to younger people, while at the same time an increased risk of complications arises (e.g. in the case of slow-progressing illnesses). In front of this background, it is necessary to generate evidence on the advantages and disadvantages of diagnostic medical devices for old and very old patients.

Summing up, there is a lack of outcome-related research on diagnostics, including those based on missing legal, regulatory, and reimbursement guidelines. This applies especially to old and very old people, since they are more severely affected by potential complications.

Box 8: Cardiovascular medicine

Cardiovascular medicine involves mainly advanced age medicine. It is especially suited for discussing the chances and problems in a medical field of apparently near-limitless possibilities in the context of (very) old and multimorbid patients at the end of life.

Cardiovascular medicine can show enormous success in diagnostics and treatment. Rapidly-increasing life expectancy in more privileged countries can be attributed largely to reduced mortality in relation to cardiovascular diseases.[160] For elderly patients, symptomatic, functionality-retaining treatments are offset by an extension of life; the data pool on this topic is very limited and there is an urgent need for research.

One example is the prevention of sudden cardiac death by implantable cardioverter defibrillators (ICDs). Clinical studies were conducted with the endpoint of "sudden cardiac death" or "overall mortality," and the patients studied were comparably young. ICD treatment is now being extended to patients of advanced age (see above), without considering any specific

160 Weiland St, Rapp K, Klenk J, Keil U (2006).

requirements for this. Another example is the comparison of coronary intervention with the medication treatment for stable Angina Pectoris. In contrast to acute myocardial infarction, the treatment target in this case is generally purely symptomatic – a treatment target that can also be attained with a medication treatment. Investigations on treatment expectations as compared to medical treatment targets are a rarity, and the importance of patient competence and participation on the overall treatment result has not been clarified.

Box 9: Dementia

Dementia arises first in old age – two-thirds of those afflicted are older than 80. The most common cause of dementia is Alzheimer's; in second place is so-called vascular dementia, caused by damage to blood vessels. The risk of illness has not increased in comparison to earlier, but dementia should still not be treated as causal, as it generally continues until death.

Scientific studies for the treatment of dementia have been conducted predominantly for pharmacological interventions. As with many other illnesses related to old age, participants in this study are considerably younger and healthier (and take fewer medications) than the vast majority of dementia patients.

Non-pharmacological interventions must also be examined in high-quality studies in order to generate reliable evidence.

Diagnostic processes generally only take cognitive functions into consideration even though they are not solely decisive for the patient's independence and quality of life.

Treatment of dementia patients is only selectively supported by evidence and is generally oriented towards local availability, which can hardly be examined in a cost-benefit analysis.

Overall, a systematic research agenda oriented towards the reality of old dementia patients is lacking.

Exclusion of older participants from clinical studies should minimize the influence of comorbidity and the resulting variability in causes of death and co-medication to the statistical result and thereby reduce the size of necessary samples. Even a mental or cognitive impairment can be an appropriate reason for exclusion if participation in the study requires a certain minimum standard of mental or cognitive competence.

Very often, a certain age is listed as a criterion for exclusion without a specific reason. In a retrospective analysis of 155 study protocols submitted to a local ethics commission and examining questions relevant to older patients, 85 studies (55 percent) could be identified as having an age limit.[161] For clinical studies examining methods that should be applied to old people, proof of effectiveness is necessary for this collective, not just for scientific validity, but also for principles of research ethics and social reasons. It must be assumed that discrimination against old and very old patients in clinical studies leads to a less valid generation

161 Bayer A, Tadd W (2000); Strech D, Mertz M (2012).

of evidence and thus to less suitable medical care.[162]

4.2 Research approaches

Research can improve the generation of evidence for medical care for old people in a variety of ways and thereby adapt it to the standards valid for younger patients:

Including old patients in clinical studies

Similar to research with children, proof of the effectiveness of medical interventions for old and very old patients is imperative. The possible positive effects and risks must be determined and weighed up in a patient-oriented manner, especially regarding whether they support overall health and daily function, and not whether the treatment combats individual illnesses. Public institutions (e.g. EU, BMBF, DFG) or foundations (e.g. German Cancer Aid) which fund studies should create and finance specific research programs with the participation of old people, or additional studies focused upon this group (ideally, in conjunction with the industry). This should stimulate corresponding industrial research. Studies which test not just the effectiveness of individual medications, but also the application of a treatment algorithm based on guidelines with which "usual care" is compared, could be of special significance for old, multimorbid patients. No such studies currently exist. It may be necessary to develop new statistical processes and as yet unused study endpoints (see below). To date, research on multimorbidity has only been approached, and we are a long way away from fully understanding multimorbidity and determining the interaction of illnesses, causes and risk factors. Studies could be oriented primarily towards particularly common combinations of multiple illnesses.[163] Though it is not simple to conduct randomized controlled studies with multimorbid old patients, there are examples of successful attempts in the field of cardiovascular medicine.[164] It is interesting to note that these studies have led to further, large-scale analyses.

The majority of older patients is treated in primary care. Clinical studies to date have not been sufficiently established in this context. It is urgently required that a reliable infrastructure be established for non-commercially motivated studies.

Ethics commissions should be sensitized to the ethical problems of the scientific and ethically unjustified exclusion of older patients from clinical studies. Based on the large demand of studies relevant to old patients, and based on the partially special requirements for recruiting and following up with old people, an effective step might be the integration of geriatric / gerontological specialists into ethics commissions, as in the case of paediatrics. If this is not possible, then at least relevant expert opinions in this field should be presented to the commission.

Pragmatic studies

New knowledge about the complex medical care of old people depends on the quality of the study design. While traditional clinical studies test the effectiveness of measures under highly standardized conditions, so-called pragmatic studies test effectiveness under the conditions most closely resembling routine medical care. The target criteria of pragmatic studies often differ from those of traditional clinical studies: Quality of life or functionality in daily life are in the foreground of the study, instead of factors such as intensity of pain. Traditional highly standardized studies can lead to different results

162 Watts G (2012); European Forum of Good Clinical Practice (2013).

163 Diederichs C (2011).

164 Flather MD et al. (2005); Beckett NS et al. (2008).

than pragmatic studies. Interventions can show reduced effectiveness, more side effects, or insufficient effects based on low feasibility under more realistic assessment parameters.

The inclusion criteria for study participants are undifferentiated and the patients correspond to those receiving standard care. Pragmatic studies are especially suitable for examining interventions with many components addressing individual risks. Patients may participate as long as they display at least one risk factor.

This does, however, create new challenges in comparison to conventional randomized studies. Often, provision of patient care is made according to the physician's decision. In that case, the physician's decision-making process is examined for its effectiveness. Some of the patients examined receive the intervention, and some do not. In a pragmatic study it is not always possible to comply with the otherwise valid quality requirements of clinical studies. For example, the patients examined in a pragmatic study are often not "blind," meaning that they know which study group is receiving which treatment.

Generally, the number of cases must be set higher for pragmatic studies in order to accommodate not only a larger variability but also the higher rate of older participants who will drop out of the study.

The interaction of risk factors of intervention components must be examined methodically. Pragmatic studies encounter practical barriers when examining all questions relevant to treatments and patients in cases of multimorbidity.

Pragmatic studies are usually not funded by the industry, and thus public funding should be made available for this purpose. In order to ensure high scientific quality, it is necessary to involve the relevant experts immediately upon setting up the study protocol and aspects for conducting the study.

Complex interventions – disease management

A prospective detailed specification of the intervention and carefully-standardized documentation are prerequisites for proof of the effectiveness of complex interventions. One pertinent example here is the INH study (interdisciplinary network of cardiac insufficiency), which examined the effects of the "HeartNetCare-HF Würzburg®" disease management program for patients with cardiac insufficiency and an average age of 69 years.[165] HeartNetCare-HF Würzburg® is based on telephone aftercare administered by specially trained carers, in which both general medical and physical parameters were collected, in addition to parameters adapted to the severity of illness and social boundary conditions, especially age, and parameters standardized specifically for cardiac insufficiency. The patients had an average age of 69; with approx. one-third of the patients the intervention took place through the cardiac insufficiency caregivers contacting the general practitioner, specialist or other medical provider. Quality of life, capabilities, and survival time were considerably improved; follow-up care shortly afterwards showed a reduced hospital re-admission rate and demonstrated that the program can be adapted to a non-university clinic. Consequently, it is entirely possible to verify the effectiveness of complex interventions scientifically using health care research methods. Similar investigations are urgently required, especially for older patients.

Observation data and causal effects

Studies on real-time effectiveness that use registry data and record numerous patient-oriented results allow the calculation

165 Angermann CA et al. (2012).

of individualized absolute risks. In order to check the patient characteristics, statistical processes such as "propensity score matching" (PSM) are utilized.[166] These can be combined with long-term population studies. Absolute risks are seldom conveyed, though this is an important prerequisite for participative decision-making in all age groups.

Nevertheless, methodical developments for improving the validity of study results must be made. One well-described problem is the heterogeneity of treatment effects, since treatments are often associated with a course of illness or a prognostic factor in a non-randomized fashion.

Discontinuing medications in the case of polypharmacy

Parallel administration of several medications can be very burdensome or even dangerous for patients and requires prioritization of health targets and problems. The result may be that, with the patient's permission, medications and treatments may be halted or discontinued entirely. There is no legal precedent, even if reducing medications deviates from the guidelines. If there is a medically valid reason, deviating from guidelines may even be requested, as the standards (not the guidelines) have legal significance (cf. Chapter 3.1). There is, however, to date hardly any evidence for the benefits of discontinuing medications or interrupting treatment based on re-prioritization of health targets. Some studies prove the feasibility of pragmatic discontinuation of medication and, in some cases, reducing medication treatment corresponded with an improved quality of life.[167] In international literature, the term "de-prescribing" is used, and concrete suggestions are being proposed for study designs.[168]

Due to multimorbidity and polypharmacy, but also because of hearing and vision impairment, patients find it difficult to adhere to a prescribed treatment, so that there is again currently a tendency toward therapies with combined medications.

Quality of life as a target for patients and medical studies

In the complex situation of old and very old patients, other targets become apparent apart from the most important traditional study target of mere extension of life (the primary endpoint). Some examples of studies which successfully test old and very old patients with other health targets apart from the extension of life are the HYVET study (hypertension in the very elderly trial)[169] for reducing blood pressure, which was conducted with patients aged 80 and older – with the aim of reducing strokes – and the SENIORS study[170] on people aged 70+ suffering from cardiac insufficiency, the primary target of which was to test the reduction in cardiovascular hospital re-admissions and which also tested functionality (while mortality remained unchanged).

In 2006, health-related quality of life was confirmed by law as a patient-relevant result parameter.[171] It is becoming increasingly acceptable (not only in palliative care) to forego a minor extension of life span if the medical treatment necessary for this would severely reduce the patient's quality of life. In these cases, the endpoint of the quality of life is not just complementary to the reduction of mortality, but is also generally understood as a priority.

Since introducing the evaluation of additional benefits of a medication in 2011 (Medication Market Reorganization Act –

166 Solomon DH et al. (2010).

167 Iyer S, Naganathan V, McLachlan AJ, Le Couteur DG (2008).

168 Scott IA, Gray LC, Martin JH, Pillans PI, Mitchell CA (2013); Scott IA et al. (2015); Reeve E, Shakib S, Hendrix I, Roberts MS, Wiese MD (2014).

169 Beckett NS et al. (2008).

170 Flather MD et al. (2005).

171 § 35 Sect. 1b SGB V.

AMNOG, § 35a SGB V), the quality of life has still not led to a positive benefit assessment. Though great significance was attributed to this target figure, it was not recognized due to methodical shortcomings such as missing validation data.[172]

Theoretical concepts and quality criteria exist for quality of life, though measuring devices may be used differently. Thus, the Joint National Committee (G-BA) insists on the further development of quality of life research and that quality of life should be considered as a primary or secondary endpoint in clinical studies.[173]

The question of measuring quality of life is also posed in view of health economic perspectives. An attempt at cost-benefit comparison has been made in view of increased lifespan in relation to overall health due to "quality-adjusted life years" (QUALYS) after the introduction of certain health care services. A main problem of the different concepts for measuring quality of life is the subjectivity of the matter: Assessing one's own life and health cannot be objectified or generalized either for the individual or for a larger group of people, and estimating life expectancy can vary considerably according to social context and individual life goals. As a result, these approaches are problematic for general decisions on prioritization.

Geriatric expertise and medicine for old patients

The Geriatric Assessment (CGA)[174] is the prerequisite for a comprehensive treatment plan based on competency in daily life, implemented by multidisciplinary treatment teams, a valuable tool in geriatric medicine. Its effectiveness has been shown in many studies both for the functional endpoints and for morbidity and mortality.[175] If possible, this assessment should be compulsory for future studies that include old and very old patients.

There are still shortcomings in identifying patients at early stages who might benefit from interdisciplinary diagnostic and geriatric treatment, and in conducting scientific evaluations of outpatient and inpatient geriatric care. Physical frailty is of great importance during diagnosis. The main pathophysiological reason for frailty in old age is excessive muscle loss, known as sarcopenia.[176] Both entities can be summarized and classified with relative ease.[177] They are currently of great importance to research.

Summary

If treated strictly according to guidelines, old patients who often suffer from several chronic illnesses take many medications simultaneously which are oriented towards the treatment of individual illnesses. This polypharmaceutical treatment does not correspond to the health targets of old patients and can even pose significant health risks. There is a lack of external evidence on better treatment options for old and very old patients with multi-morbidities. There is also a lack of guidelines indicating current knowledge gaps and dangers. One approach which may be worth validating scientifically with regard to safety, effectiveness and sustainability is the PRISCUS list, which indicates potentially dangerous medications and offers alternatives. At the same time, important medications are often not offered to patients.

172 Blome C, Geithner L, Augustin M (2013).

173 Klakow-Franck R (2013).

174 The Geriatric Assessment includes structured determination of physical, mental, and social functionality and independence of elderly patients by means of validated tests.

175 Stuck AE, Iliffe S (2011); Ellis G et al. (2011).

176 Muscaritoli M et al. (2010); Cooper C et al. (2012).

177 Fried LP et al. (2001); Berrut G et al. (2013).

Scientific evidence for appropriate treatment of old patients is often inadequate or lacking entirely. In particular, diagnostics, interventions in cases of multimorbidity, and complex interventions have not been researched adequately. It would also be prudent to develop this methodology further in Germany. Cardiovascular diseases and dementia are prominent examples of diseases of old age where the evidence basis for medical care is missing.

Research should concentrate on the following approaches and fields in order to quickly and effectively lay the groundwork for improved health care provision for old people:

- The effectiveness of medications must be proved for old and very old patients, as is done for children. After positive experiences with the "Pediatric Investigation Plan" (PIP), a "Geriatric Safety and Investigation Plan" should be compulsory for all active substances which are implemented to a relevant extent for old patients. These plans should include not just randomized clinical studies, but also observation studies and routine data.
- For old patients, it is especially important to prove not just the effectiveness of individual medications or medical products, but also to examine the course of treatment in comparison to conventional treatment practice.
- Primary care lacks clinical studies; no reliable research structure is available.
- Pragmatic studies are suitable for fulfilling the priority of retaining functionality in old people.
- Discontinuing medications ("de-prescribing") has not been researched adequately, though it is a promising approach for reducing and preventing unnecessary multiple prescriptions.
- Quality of life should be purposefully and methodologically developed as an endpoint of medical studies.
- Ethics commissions should possess expertise in geriatric medicine.
- The study types and targets listed above are currently implemented only sporadically in industrial research. Publicly funded research cannot singlehandedly spring into action in order to adapt the health care provision of old people to EBM standards.

5 Research and development for the improved care of old and very old people: Conclusions

The number of healthy and independent older people is continuing to increase, and the biological and social age limits are being extended. However, these gains in ageing need to be supported by appropriate medical care for old people that takes into account the distinctive features of this group of patients.

First of all, it must be pointed out that there is no such thing as "the old patient": no group of patients is as inter-individually different as that of the elderly. Therefore, when it comes to medical care, particular consideration has to be given to individual distinctions such as gender, socio-economic, ethnic-cultural and biographical differences. Maintaining the functions of daily living and hence the quality of life is the predominant aim of old and very old persons when they take advantage of preventive and therapeutic health care services. Hearing, sight and mobility play a major role in the participation of older people. Illness, functional impairment and disability frequently overlap in old age and should therefore be jointly addressed. Relatives and the immediate environment are often extremely stressed by supporting the ill and/or functionally impaired older people and are thus in need of particular attention and support (structural, psychosocial and financial) within the framework of regular care.

Hence, health care for old people must be multi-disciplinary and multi-professional. Medicine, care, psychology, sport, dietetics and other professions need to be involved in the development and implementation of geriatric care services. The existing instruments to facilitate inter-professional communication, e.g. between medicine and care, such as the ICF and ICPC classification in geriatric health care, may appear to be promising, but still need better evaluation.

Changes in biological processes and in functional and social needs of older people have been intensively researched. Nevertheless, there are only a few studies for the group of old and very old patients which meet the standards of evidence-based medicine (EBM). This has several reasons, one of the most significant of which is the fact that the established procedures of scientific knowledge acquisition and standardisation in the medical field do not correspond with the characteristics and health targets of older people. Science-based principles for evidence-based geriatric health care have therefore yet to be specified. This is why the physicians and other health care professionals are not sufficiently prepared when treating old and very old patients. An improvement in data availability and the health care situation is thus absolutely essential. Specific approaches towards this objective are listed below.

5.1 More precise research, tailored to the distinctive interests and aims of older patients

Randomised, double-blinded studies should also be carried out for old and very old people. Furthermore, other study methods are also available that should be increasingly promoted and performed, as they are better able to portray the medical

care needs and requirements of old people: pragmatic studies, which include the realities of patients' lives, multiple-component interventions (complex interventions) as well as observational studies based on registry data. The subject of research should not (only) be the efficacy of a medicinal product, but also an overall health care algorithm. The co-existence of risks should be examined and, if possible, individually presented in absolute figures. As to date these types of studies have not been sufficiently undertaken by the industry, more public funds need to be provided for this purpose.

a) In pharmacology:

Clinical studies on medicinal products to be prescribed for people over 65 and especially for those above 80 years of age must sufficiently represent this age group and carry out an age-related benefit-risk assessment. Age-specific characteristics, in particular frailty, should be taken into consideration for the inclusion and exclusion criteria as well as for analysis and interpretation. The marketing authorisation of medicinal products should be subject to the performance of studies with old and very old patients, similar to the procedure that is standard practice for children (Paediatric Regulation of the EU).

Apart from conventional indicators for the efficacy testing of medicinal products (such as cure, relief and survival), important functional targets and other objectives should be tested, in particular activities of daily living, participation and quality of life. The geriatric assessment is an established instrument for this purpose (domains are: activities of daily living, cognition, mood, nutrition). The quality of life as the endpoint of clinical studies should be systematically developed in research.

Methodological complexities are an important reason for the exclusion of old people from controlled studies. Patient-oriented study objectives, but also challenges in terms of study design and evaluation (e.g. number of cases, missing data) need to be highlighted. For that reason, it is imperative that such methodological knowledge be developed further. This requires the combination of geriatric-gerontological, biostatistical and information-related expertise. In research involving elderly people, particular consideration has to be given to ethical and legal aspects such as e.g. the capacity to consent of study participants. Expertise in the medical treatment of old people should therefore be represented in research ethics commissions. In addition, information and consent documents within the framework of geriatric health care and studies must also be adjusted to the needs of old and very old people.

The investigation of interventions in cases of multi-morbidity must take top priority. As the concomitant taking of medications will remain unavoidable in the future, the interactions of active substances must be examined and validated. In addition, studies dealing with the reduction of polypharmacy are essential, in particular with regard to the discontinuation of medicines.

b) Regarding behavioural and technical interventions:

Behavioural and technical interventions play an increasingly important role in maintaining independence and delaying the necessity to move into a nursing home. Research in geriatric medicine should therefore also specifically target the combination with such interventions. The benefits of aids, technology and adapted living space have hardly been examined. There is a shortage of studies with larger numbers of cases and representative participant groups including control groups, but also studies on the ethics of the application. This also applies to telemedicine, the most frequently investigated field at the moment.

c) Regarding participative decision-making:
The participation of patients in medical decision-making processes by means of Shared Decision Making (SDM) is theoretically and ethically well justified and has been examined for its effectiveness in clinical studies. However, the concepts must be transferred to old and very old patients and evaluated in studies in order to be included ultimately in standard care.

Evidence-based patient information as a prerequisite for the participation of patients in medical decision-making processes must also be available in geriatric care. They must be adjusted to the prerequisites of elderly people. At present, there is a lack of empirical studies on the effects of various formats and contents. The therapy expectations and preferences in groups of older people with different socio-economic and cultural background as well as in various care settings should be determined. Better knowledge is advantageous for the planning of clinical studies since then patient-relevant health targets can be adequately taken into consideration.

d) In diagnostics:
Diagnostic agents in general and for all age groups have as yet been insufficiently researched in accordance with the standards of evidence-based medicine. Manufacturers should be required to provide not only proof of safety but also of patient-specific benefits.

Clinical studies on diagnostics must use endpoints geared to the health care targets of old people. It is far more difficult to define reference values for old people from diagnostic tests that differentiate findings considered to be normal from pathological ones. For this, too, empirical principles need to be established.

5.2 Conditions and possible implementations for quality health care for old people

a) With regard to primary health care:
Primary providers should be supported in offering health care that is tailored to the needs of chronically ill and multimorbid patients. Corresponding health care models such as the “Chronic Care” model need to be evaluated and, if necessary, adapted to the German care system and their benefits also evaluated for the group of old and very old patients.

Multi-modal, secondary preventive concepts may be promising approaches, but have not been sufficiently examined in terms of necessary components and their design.

Transfer management and the flow of information between the care settings, e.g. hospital and GP urgently need to be optimised in such a way that losses of information to the disadvantage of patients can be reduced. A uniform and coordinated information management system of primary and secondary care service providers and facilities should be targeted in order to improve intra- and inter-sectoral communication, resulting in improved care, and to gain scientific knowledge from the data collected.

b) With regard to inpatient care:
The treatment requirements of old patients are currently not identified at all, or not at an early enough stage. This often leads to expensive over-use, under-use, and misuse of health care services.

A comprehensive geriatric assessment (CGA) should therefore begin in the emergency room – the patient’s condition permitting. This is of particular significance for the decision as to whether the patient should be admitted to the geriatric ward or to a specialist one. The assessment should then be continued on the

respective ward and be completed within the first 72 hours.

Therapies must be adapted to the health care requirements of old people, i.e., multi-professional cooperation is necessary to permit early rehabilitation planning. Research on the efficacy and cost-effectiveness of therapies is required.

c) With regard to health care in nursing homes:

Health care service providers must communicate with nursing home residents regarding their health targets and the organisation of the final phase of life, and must negotiate them jointly, preferably applying the "Advance-Care-Planning" approach. Structural, pharmacological and non-pharmacological health care services must be better evaluated.

The return to the home environment after moving to a nursing home should be made easier, and should be an important target factor within research projects.

5.3 Implications for basic, advanced and continuing training

Basic geriatric knowledge should be compulsory for all medical disciplines and health service professions; teaching should begin at university level and be intensified in post-graduate studies. Multi-professional competence and evidence-based concepts play a significant role in basic, advanced and continuing training. It should be an important training objective to embed them in such a way that they become part of the standard repertoire of medical staff.

The nationwide introduction of a professional qualification for doctors as geriatric specialists could improve the care situation if it is done in addition to general basic and advanced training.

It is essential to intensify and further develop methodological training in order to meet the challenges of medical research and health research for old people. In Germany, there is a great deficit in this field. A first step would be to establish specialist professorships in this field.

A final target must be to eliminate negative associations with geriatric health care – including interdisciplinary offers of advanced and continuing training in geriatric medicine.

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The group of research scientists named below was involved in the preparation of the present report. This was then submitted to the external experts listed below whose comments were taken into consideration for the final version of the report.

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List of abbreviations

ACP	Advance Care Planning
ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AMG	German Medication Act
AMNOG	Pharmaceuticals Market Reorganisation Act
BGB	German Civil Code
BGH	Federal Supreme Court
BMBF	Federal Ministry of Education and Research
BMG	Federal Ministry of Health
BVerfGE	German Federal Constitutional Court
CGA	Comprehensive Geriatric Assessment
Destatis	Federal Statistical Office
DFG	German Research Foundation
DNEBM	German Network for Evidence-based Medicine
DRG	Diagnosis-Related Group
EBHC	Evidence-based Health Care
EBM	Evidence-based Medicine
EBPI	Evidence-based Medicine Patient Information
EMA	European Medicines Agency
EU	European Union
G-BA	Federal Joint Committee
GKV	Statutory Health Insurance
GKV-VersorgStruktG	Statutory Health Insurance Restructuring Act
IADL	Instrumental Activities of Daily Living
ICD	International Statistical Classification of Diseases and Related Health Problems
ICF	International Classification of Functioning, Disability and Health
ICPC	International Classification of Primary Care
MPG	Medicinal Products Act
NUB	New Diagnostic and Treatment Methods
SDM	Shared Decision Making
SGB	Social Insurance Code
SVR Gesundheit	Advisory Council on the Assessment of Developments in the Health Care System

vfa	Association of Research-Based Pharmaceutical Companies
VO (EU)	Directive of the European Union
WHO	World Health Organization
WICC	Wonca International Classification Committee
Wonca	World Organization of Family Doctors

Appendix

Expertise: Design and Analysis of Studies with Older Adults with Multiple Chronic Conditions

Working paper for Evidence-Based Medicine For Older People Working Group of the National Academy of Sciences Leopoldina

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PCORI Methodology Report – Executive Summary -V

PCORI's 47 standards fall into 11 categories, the first five of which are relevant to most PCOR studies. Researchers should refer to all of these cross-cutting standards when planning and conducting their projects. These categories are:

- Formulating research questions
- Patient-centeredness
- Data integrity and rigorous analyses
- Preventing and handling missing data
- Heterogeneity of treatment effect

The other six categories of standards are applicable to particular study designs and methods. Two of the categories provide guidance on developing specific types of data and using them in studies:

- Data registries
- Data networks as research-facilitating infrastructures.

The final four categories apply to studies that have varying designs and purposes. The standards in each of these categories should be used for guidance when it is relevant to a particular study:

- Causal inference methods
- Adaptive and Bayesian trial designs
- Studies of diagnostic tests
- Systematic reviews

A growing proportion of the population has multiple chronic conditions (MCC).[1] Approximately 75 % of adults over the age of 65 years in the United States are affected by two or more chronic medical conditions.[2] Considering their impact on the US population, the Department of Health and Human Services published "Multiple Chronic Conditions: A Strategic Framework"[3] and outlined strategies for addressing health needs of affected patients. Methods for readily identifying chronic disease clusters and developing coordinated care management strategies are among the goals outlined in the Framework. The Patient-Centered Outcomes Research Institute (PCORI) published a Methodology Report in 2013, which presents guidelines and priorities for patient-centered outcomes research (side panel).[4] The field of Gerontologic Biostatistics[5] was developed to provide statistical design and analytic methodologies appropriate for research with older adults with complex health and patient-centered outcomes.

Knowledge Gap Related to Treatment of Patients with Multiple Chronic Conditions

The prevalence of MCC is increasing, especially among older adults.[6] As Boyd astutely noted, few clinical guidelines even acknowledge the role that co-occurring conditions might play in forming treatment recommendations.[7] In her investigation of the guidelines of national specialty organizations, Boyd found few instances in which authors discussed how treating the disease of interest might be related to the presence of co-existing diseases.[8] Given the ever expanding availability of treatments designed to treat persons with MCC, it is imperative that we develop studies designs and methodologies to understand how treating the disease of interest might be related to the presence of co-existing diseases.[9]

While evidence of the benefits of guideline-recommended medications for treating indicated conditions have been demonstrated, often these studies exclude older adults with more than one condition and focus on condition-specific outcomes. For example, antihypertensive medications are commonly prescribed for reducing the risk of stroke, myocardial infarctions and mortality in older adults, yet some studies suggest that these medications by lowering blood pressure could increase the rate of falls in older adults.[10] It is difficult to generalize results showing the benefit of individual treatments on condition-specific outcomes to other areas of functioning, especially in older persons with multiple conditions who commonly take more than one medication.

This focus on condition specific outcomes, fails to acknowledge that older

1 Multiple Chronic Conditions-A Strategic Framework: Washington DC. U.S. Department of Health and Human Services; 2010 [cited 2013 January 29]; Available from: http://www.hhs.gov/ash/initiatives/mcc/mcc_framework.pdf; Anderson G. Making the Case for Ongoing Care. Robert Wood Johnson Foundation; 2010 [cited 2013]; Available from: http://www.rwjf.org/en/library/research/2010/02/chronic-care.html

2 ibid.

3 Multiple Chronic Conditions-A Strategic Framework: Washington DC. U.S. Department of Health and Human Services; 2010 [cited 2013 January 29, 2013]

4 PCORI (Patient-Centered Outcomes Research Institute) Methodology Committee. 2013. The PCORI Methodology Report. Available from: http://www.pcori.org/research-results/research-methodology

5 Van Ness PH, Charpentier PA, Ip EH, Leng X, Murphy TE, Tooze JA, Allore HG. Gerontologic Biostatistics: The Statistical Challenges of Clinical Research with Older Study Participants 2010. J Am Geriatr Soc 2010;58(7):1386–92. PMID: 20533963 PMC2918405

6 Marengoni A, Winblad B, Karp A, Fratiglioni L. Prevalence of chronic diseases and multimorbidity among the elderly population in Sweden. Am J Public Health 2008;98:1198–200. PMC2424077.

7 Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA 2005;294:716–24.

8 ibid.

9 ibid.

10 Tinetti ME, Han L, Lee DS, McAvay GJ, Peduzzi P, Gross CP et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. JAMA Intern Med 2014;174(4):588–95; Tinetti ME, McAvay G, Fried T, Allore HG, Salmon JC, Foody JM et al. Health outcome priorities among competing cardiovascular, fall injury and medication-related symptom, outcomes. J Am Geriar Soc 2008;56(8):1409–16; Akishita M, Ishii S, Kojima T, Kozaki K, Kuzuya M, Arai H et al. Priorities of health care outcomes for the elderly. J Am Med Dir Assoc 2013;14(7):479–84.

adults have varying priorities in the face of the trade-offs regarding the potential benefits and harms of pharmacological treatments.[11] In a large sample of community-dwelling older adults asked to rank 12 health outcomes, high priority was given to improvement of physical function and maintenance of a high level of activity, while reduction in mortality was given the lowest priority.[12] One approach to studying these issues is to examine the effects of conditions and the medications prescribed for these conditions on universal health outcomes, typically patient-centered outcomes,[13] that are applicable across multiple diseases.

Clinical Relevance

The goal of health care, namely "the maximization of benefit and minimization of harm," has to date largely focused on single diseases. However, it is not uncommon for older persons to have between 5 and 10 medications for a comparable number of specific conditions. No one has yet undertaken an in depth examination of how the treatment of these multiple conditions affects patient-centered outcomes and universal health outcomes, such as function and self-reported health. Shared clinical decision-making must eventually be predicated on the explicit goal of maximizing benefit and minimizing harm to overall health, rather than with respect to individual diseases. The potential harms inherent to disease-specific treatments in patients with multiple diseases have been previously documented.[14] Clinicians, policy makers, and investigators have called for innovative and feasible methods for enhancing shared clinical decision-making with patients having multiple diseases.[15] Understanding how patient characteristics and MCC contribute to heterogeneity of treatment effects is particularly important because unexamined treatment tradeoffs hold unknown potential for harm. It is likely that unintentional adverse effects are widespread and undetected. Determining quantitatively how the effects of specific treatments for a primary disease on outcomes are influenced by patient characteristics and co-existing diseases will heighten awareness of this issue and potentially lead to constructive changes in clinical practice, including development of treatment plans that account for the heterogeneity of treatment effects induced by MCC.

When embarking upon new research to address the care of complex older adults the quality depends on the design of the studies conducted. The choice of study designs has practical implications for the timeliness, validity, and relevance

11 Tinetti ME, McAvay G, Fried T, Allore HG, Salmon JC, Foody JM et al. Health outcome priorities among competing cardiovascular, fall injury and medication-related symptom outcomes. J Am Geriar Soc 2008;56(8):1409–16.

12 Akishita M, Ishii S, Kojima T, Kozaki K, Kuzuya M, Arai H et al. Priorities of health care outcomes for the elderly. J Am Med Dir Assoc 2013;14(7):479–84.

13 Tinetti ME, McAvay GJ, Chang SS, Newman AB, Fitzpatrick AL, Fried TR et al. Contribution of multiple chronic conditions to universal health outcomes. J Am Geriatr Soc 2011;59(9):1686–91 PMC3622699; Tinetti ME, McAvay G, Chang SS, Ning Y, Newman AB, Fitzpatrick A et al. Effect of chronic disease-related symptoms and impairments on universal health outcomes in older adults. J Am Geriatr Soc 2011;59(9):1618–27. PMC3287052.

14 Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA 2005;294:716–24; Tinetti ME, Fried T. The end of the disease era. Am J Med 2004;116:179–85; Tinetti ME, Bogardus ST Jr, Agostini JV. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. N Engl J Med 2004;351:2870–4; Tinetti ME, McAvay GJ, Fried TR, Foody JM, Bianco L, Ginter S et al. Development of a tool for eliciting patient priority from among competing cardiovascular disease, medication-symptoms, and fall injury outcomes. J Am Geriatr Soc 2008;56:730–6; Tinetti ME, McAvay GJ, Fried TR, Allore HG, Salmon JC, Foody JM et al. Health outcome priorities among competing cardiovascular, fall injury, and medication-related symptom outcomes. J Am Geriatr Soc 2008;56:1409–16. PMC3494099; Fried TR, McGraw S, Agostini JV, Tinetti ME. Views of older persons with multiple morbidities on competing outcomes and clinical decision-making. J Am Geriatr Soc 2008;56:1839–44. PMC2596278.

15 Fried TR, Bradley EH, Towle VR, Allore H. Understanding the treatment preferences of seriously ill patients. N Engl J Med 2002;346:1061–6; McNeil BJ, Pauker SG, Sox HC Jr, Tversky A. On the elicitation of preferences for alternative therapies. N Engl J Med 1982;306:1259–62; Cauley JA, Ensrud KE. Considering competing risks. Not all black and white. Arch Intern Med 2008;168:793–5; Committee on Quality of Health Care in America. Crossing the quality chasm: A new health system for the 21st century. Washington, D.C.: National Academies Press; 2001.

of the research agenda. Two broad approaches, randomized clinical trials and observational studies, may be taken, each with methodological considerations and areas of further development to unbiasedly address research questions.

Trial Designs

In traditional (non-clustered) multi-site randomized clinical trials, balance of risk factors is easier to achieve because the sample sizes are usually large enough to ensure that the groups being randomized are balanced on all factors[16] and there is typically a single treatment compared with control. Maintaining balance on risk factors is often much more difficult in cluster-randomized trials because of the small to moderate number of clusters being randomized. It can become even more difficult if after the initial randomization, additional clusters need to be added after trial initiation to meet recruitment goals. Several methods of restricted randomization have been proposed to achieve overall balance in trials, especially when a small number of units (i.e. participants or clusters) are being randomized, but each has its own advantages and disadvantages. A summary of some of the most common methods available is presented in Table 1. Randomization methods that allocate units in a sequential manner (e.g. baseline covariate adaptive randomization)[17] allow for the addition of participants later in the trial. However, these methods are not usually practical in a cluster-randomized trial because of the need to randomize all clusters at one time at beginning of the trial, unless investigators are willing to artificially impose an order on the clusters. For methods that randomize practices simultaneously (e.g. covariate constrained randomization)[18], there is no clear way to add clusters once the initial randomization is completed, especially when trying to maintain balance on the criteria set forth for the initial randomization.

16 Suresh KP. An overview of randomization techniques: An unbiased assessment of outcome in clinical research. Journal of Human Reproductive Sciences 2011;4(1):8–11. PMID: 21772732; PMCID: PMC3136079. ; Hayes RJ, Moulton LH. Cluster Randomized Trials. Boca Raton: Chapman & Hall/CRC Taylor & Francis Group; 2009.

17 Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31(1):103–15. PMID: 1100130; Signorini DF, Leung O, Simes RJ, Beller E, Gebski VJ. Dynamic balanced randomization for clinical trials. Statistics in Medicine 1993;12(24):2343–50. PMID: 8134737.

18 Moulton LH. Covariate-based constrained randomization of group-randomized trials. Clinical Trials 2004;1(3):297–305. PMID: 16279255; Chaudhary MA, Moulton LH. A SAS macro for constrained randomization of group-randomized designs. Computer Methods and Programs in Biomedicine 2006;83(3):205–10. PMID: 16870302.

Table 1: Description of Available Randomization Procedures

Randomization Procedure	Description	Advantages	Disadvantages
Simple Randomization	Unrestricted technique, based on single sequence random assignment. All allocations of units randomized are possible.	Simple and easy to implement. Balances covariates with large sample sizes.	Subjects enrolled may not have balance on covariates when the sample size is moderate or small.
Stratified Randomization	Restricted technique: Create a strata for each combination of covariates being considered. Units are then randomly assigned to treatment arms within each strata.	Reduces imbalance between treatment groups on important covariates. Able to control and balance covariates of importance.	Limited number of factors can stratified on, and need to be willing to categorize continuous variables. Number of strata needed increases rapidly as the number of covariates of increases.
Matching	Restricted technique: Select from a smaller set of all possible allocations, those fulfilling certain restrictions (i.e. meet the matching criteria), and then randomly allocate to the treatment arms within each match.	Reduces imbalance between treatment groups on important covariates. Able to control and balance covariates of importance.	Need to identify pairs of clusters that are well-matched on all of the risk factors, which is often not feasible, especially when subsets of people are enrolled in each cluster post-randomization. Need to set suitable balance criteria.
Covariate Constrained Randomization[19]	Restricted technique: Find the number of allocations meeting a set of balancing criteria for the covariates of interest. Ensure that overly constrained designs do not exist (e.g. clusters always appear in the same group) – otherwise need to adjust balance criteria. Randomly select one allocation for the study.	Can attain balance (or near balance) on covariates related to outcome resulting in a gain in efficiency. Do not need to categorize covariates.	Need to set suitable balance criteria. If balance criteria are too restricted, it could result in biased or invalid design. Performed at the start of trial, so infeasible when need to add more clusters.
Minimal Sufficient Balance[20]	Restricted technique: Distribution of covariates between treatment arms assessed using imbalance tests, and depending on results units are assigned treatment based on biased coin or simple random assignment	Prevents serious imbalance on important covariates, while maintaining randomness of treatment allocation. Do not need to categorize covariates.	Expected that units are being randomized sequentially could be deterministic. Need to set suitable balance criteria.

19 Moulton LH. Covariate-based constrained randomization of group-randomized trials. Clinical Trials 2004;1(3):297–305 PMID: 16279255; Chaudhary MA, Moulton LH. A SAS macro for constrained randomization of group-randomized designs. Computer Methods and Programs in Biomedicine 2006;83(3):205–10. PMID: 16870302.

20 Zhao W, Hill MD, Palesch Y. Minimal sufficient balance – a new strategy to balance baseline covariates and preserve randomness of treatment allocation. Stat Methods Med Res 2012;1–14. PMID: 22287602; PMCID: PMC3474894.

Randomization Procedure	Description	Advantages	Disadvantages
Minimization[21]	Restricted technique: Sequentially assign units to treatment groups taking into account the balance on covariates and previous randomization assignments.	Maintains balance among several covariates, while minimizing imbalance in the distribution of the treatment across whole trial and each stratification variable.	Expectation is that units being randomized are available sequentially, which is usually not the case in a cluster-randomized trial. Could have imbalance in specific strata. Criticized for being too deterministic.
Dynamic Randomization[22]	Restricted technique: For each level of a stratification hierarchy, a balance criteria is set, to keep imbalances from exceeding these limits. If imbalance is within limits for all levels, unit is randomly assigned, otherwise allocation is forced at stratification level where limits exceeded to reduce imbalance.	Maintains balance on treatment assignments across the whole trial and within each strata. Most useful in unblinded trials.	Need a centrally administered trial. Expected that units are being randomized sequentially.
Outcome Adaptive Randomization[23]	Restricted technique: Class of methods including those proposed by Bather,[24] Thompson,[25] Zelen,[26] Sobel and Weiss,[27] and Berry and Fristedt,[28] in which treatment assignment is dependent on response of previous individuals.	Objective is to maximize the number of overall successes, maximize effective treatment.	Expected that units are being randomized sequentially. Need real time reporting of outcomes that can be measured shortly after treatment initiation, (e.g. pain relief for a treatment).

21 Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31(1):103–15. PMID: 1100130.

22 Signorini DF, Leung O, Simes RJ, Beller E, Gebski VJ. Dynamic balanced randomization for clinical trials. Statistics in Medicine 1993;12(24):2343–50. PMID: 8134737.

23 Berry DA, Eick SG. Adaptive assignment versus balanced randomization in clinical trials: a decision analysis. Statistics in Medicine 1995;14(3):231–46. PMID: 7724909.

24 Bather JA. Randomized allocation of treatments in sequential medical trials (with discussion). Journal of the Royal Statistical Society, Series B 1981;43(3):165–292. WOS: A1981MN31000001.

25 Thompson WR. On the likelihood that one unknown probability exceeds another in view of the evidence of two samples. Biometrika 1933;25(3–4):275–94. WOS: 000200863100003.

26 Zelen M. Play the winner rule and the controlled trial. Journal of the American Statistical Association 1969;64(325):131–46. WOS: A1969D204500008. DOI: 10.1080/01621459.1969.10500959

27 Sobel M, Weiss GH. Play-the-winner rule and inverse sampling in selecting the better of two binomial populations. Journal of the American Statistical Association 1971;66(335):546–51. WOS: A1971K518200016.

28 Berry DA, Fristedt B. Bandit Problems: Sequential Allocation of Experiments. London: Chapman and Hall; 1985.

For many years randomized clinical trials have had a highly refined inclusion criteria that excludes the majority of older adults and a single biologic endpoint, typically not patient-centered. On the other hand, pragmatic clinical trials are advantageous for testing interventions with multiple components that are tailored to an individual's risk factors, i.e. standardly-tailored.[29] When a cluster design is used it permits easier implementation of treatment that can be applied to an entire group of participants (e.g. healthcare system, practice, community center, or residential community). The standardly-tailored intervention allows participants to be enrolled in the trial as long as they have at least one of the risk factors. Thus, a cluster-randomized trial of a standardly-tailored multi-component intervention more closely represents clinical practice or the community setting and may lead to more generalizable patient-centered findings. It also presents methodological challenges as these designs rely heavily on certain assumptions, violations of which may bias results. The design of such a trial needs to account for 1) clustering, both the number of clusters (usually not very large) and the correlation of individuals within clusters[30] (e.g. patients nested within practice nested within healthcare system) and 2) a population in which individuals may not be eligible or need every component of the intervention given their risk factor profile. The latter, which better represents how patients are actually treated in clinical practice, will most likely introduce overall treatment heterogeneity because the distribution of risk factors may create heterogeneous subgroups given that the individual components of the intervention may be applied differentially across the entire population with different outcomes based on risk factor profiles.

In addition to the challenges with randomization and sample size,[31] obtaining an unbiased estimate of the individual components of a multi-component intervention is a challenge. While it is important to demonstrate treatment efficacy, most work on standardly-tailored, multi-component interventions have focused on the net effect of the overall treatment effect. However, in order to translate the results into practice, it is often important to know which components of the intervention are most potent.[32] Estimation of the individual components of a multi-component intervention is straight forward in a traditional factorial design because it assumes balance, and no preference to intervention components. However, the traditional factorial design is not patient-centered. It does generalize to a larger population but only to those meeting a common set of inclusion/exclusion criteria. Furthermore, factorial designs are limited by the number of components that can be realistically evaluated, unless the sample size is impractically large or a fractional factorial design is used, which has its own limitations. In addition, it is often difficult to generalize the results of a factorial design to the overall population, since it usually requires a fairly restrictive set of inclusion/exclusion criteria to ensure that every participant is eligible for all intervention components. Thus, factorial designs generally fall under the spectrum of explanatory and not pragmatic trials.

29 Allore HG, Tinetti ME, Gill TM, Peduzzi PN. Experimental designs for multicomponent interventions among persons with multifactorial geriatric syndromes. Clin Trials 2005;2:13–21. PMID: 16279575.

30 Preisser JS, Reboussin BA, Song EY, Wolfson M. The importance and role of intracluster correlations in planning cluster trials. Epidemiology 2007;18(5):552–60. PMID: 17879427; PMCID: PMC2567827.

31 Manatunga AK, Chen S. Sample size estimation for survival outcomes in cluster-randomized studies with small cluster sizes. Biometrics 2000;56(2):616–21 PMID: 10877325; Jahn-Eimermacher A, Ingel K, Schneider A. Sample size in cluster-randomized trials with time to event as the primary endpoint. Statistics in Medicine 2013;32(5):739–51PMID: 22865817; Xie T, Waksman J. Design and sample size estimation in clincial trials with clustered survival times as the primary endpoint. Statistics in Medicine 2003;22(18):2835–46. PMID: 12953283.

32 Allore HG, Murphy TE. An examination of effect estimation in factorial and standardly-tailored designs. Clinical Trials 2008;5(2):121–30. PMID: 18375650; PMCID: PMC3477845

In a recent staff memo, Dr. Robert Temple, Deputy Director for Clinical Science at the FDA's Center for Drug Evaluation and Research "stressed the FDA's interest in encouraging a broad population sample in the development of new drugs."[33] The standardly-tailored intervention is more pragmatic, as it more closely mirrors clinical practice, is open to a greater proportion of the population, with at-risk patients being treated for the risk factors that they have, and not necessarily all risk factors. However, this design poses methodological challenges. Inherently, there will be correlations between risk factors, as well as the components of the intervention that act upon those risk factors. Thus, it is important that any method used to assess the impact of the individual components take into account their correlation and inter-dependence.

Optimizing Trial Efficacy

Optimizing trial efficiency is important; it reduces participant burden, cost, and utilization of resources. There are three key aspects of the design of a cluster-randomized trial for a multi-component, standardly-tailored intervention: 1) the randomization procedure; 2) the sample size determination; and 3) the precision of the individual component effects of the intervention. Each of these components can have a substantial impact on the interpretation, validity, reproducibility and dissemination of the trial findings. First, a study that has improper randomization could introduce selection bias, whether consciously or unconsciously, and impact the credibility of the results.[34] It could also lead to imbalances on key covariates and risk factors at the unit of analysis (i.e. cluster or individual level), which affect the comparability of the treatment groups and the validity of the treatment comparisons.[35]

Second, underpowered studies due to inadequate sample size are problematic and can lead to inconclusive results when a treatment difference exists but cannot be detected. They also misuse valuable time provide by study participants and may cause harm to patients if an effective treatment is not made available to the general population due to a lack detection of a statistically significant treatment effect. To this end, they also drain resources. Thus, proper sample size calculations are essential in the planning and design of a trial.[36] A sample size calculation must account for all of the variability that may be introduced in the trial. For a cluster-randomized trial, such as the recently NIA/PCORI funded Strategies to Reduce Injuries and Develop confidence in Elders (STRIDE) Trial, testing a standardly-tailored intervention to prevent serious fall injuries in high risk elderly patients, there are multiple considerations in the sample size calculation: 1) censoring, due to loss-to-follow-up, 2) the effect of clustering (i.e. the number of clusters and the correlation of participants within clusters), 3) competing events, such as death, and 4) the potential attenuation of the treatment effect because of the standardly-tailored intervention (Figure 1). For example, accounting for clustering is important because correlations between units, whether that be individuals or clusters, reduces the amount of information that is available in the data, and thus the effective sample size, leading to an underpowered study.[37]

33 FDA: Policies and Procedures for Proposed Trial Design Aimed at Multiple Chronic Conditions 2014. Retrieved October 28, 2014 from http://www.policymed.com/2014/02/fda-policies-and-procedures-for-proposed-trial-design-aimed-at-multiple-chronic-conditions.html

34 CONSORT Transparent Reporting of Trials 2010. Retrieved October 28, 2014 from http://www.consort-statement.org/

35 Byar DP, Simon RM, Friedewald WT, Schlesselman JJ, DeMets DL, Ellenberg JH et al. Randomized clinical trials. N Engl J M 1976;295(2):74–80. PMID: 775331.

36 Friedman LM, Furberg CD, DeMets DL. Fundamentals of Clinical Trials. 3rd ed. St. Louis: Mosby – Year Book; 1996.

37 Xie T, Waksman J. Design and sample size estimation in clincial trials with clustered survival times as the primary endpoint. Stat Med 2003;22(18):2835–46. PMID: 12953283.

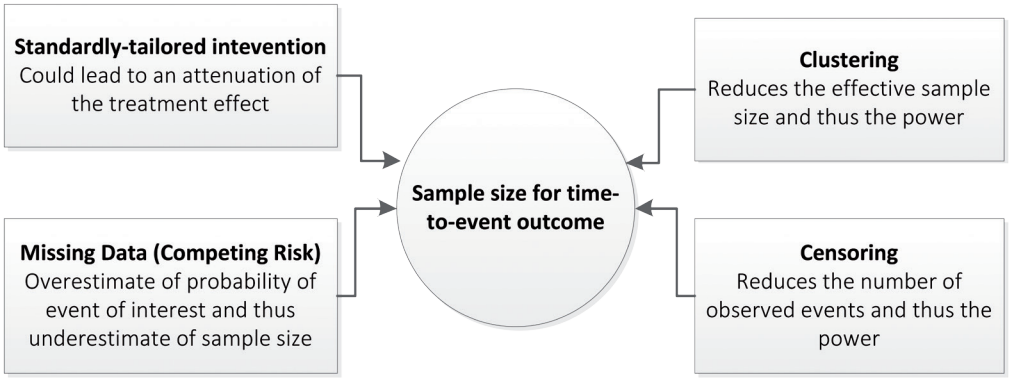

Figure 1: Impacting of ignoring the components of the study design on sample size estimation

Finally, the precise estimation of the individual component effects is essential for the translation of the results of the trial to clinical practice. Given the emphasis the National Institutes of Health have placed on translational research with their Clinical and Translational Science Award program,[38] determining the most potent components of the intervention and disseminating these findings to the clinical community is important in order to conduct second stage translational research. This would not only align with these goals, but it would directly influence patient care and burden as it could reduce the number of interventional components needed, while maintaining an efficacious treatment.

Using Observations Data for Causal Effect Estimates: Minimize Bias and Variance of Estimated Treatment Effects with Propensity Score Matching

As previously described randomized controlled trials are powered to measure a primary endpoint, but often exclude those with MCC. Even with more relevant randomized controlled trial designs, the number of possible treatments and condition combinations may make it prohibitive to address all treatment questions. Real time treatment studies using registries are beginning to be used and further method development would enhance their application. For these reasons detailed calculations of individualized absolute risks for persons with MCC are often best performed from analyses of observational data that may have multiple patient-centered outcomes. Because observational studies are at risk of unbalanced patient characteristics including each of the chronic conditions, the use of causal inference methods, such as propensity score matching, allows construction of a reference group (those not taking a specific treatment) that is well-balanced with the treatment group regarding important covariates. There are recent simulation-based findings regarding optimal selection of the variables included in the propensity score models.[39] These practices are intended not simply to balance the covariates, but to also minimize the bias and variance of the estimated treatment effects that are the primary motivation for employing propensity scoring. Propensity score matching, first introduced by Rosenbaum and Rubin in 1985,[40] is used and validated in hundreds of clinical and epidemiological studies over the last 30 years.

Rigorous Methods for Observational Studies

Larson stated that observational studies need more rigorous methods, ideally in

38 CTSA: Clinical & Translational Science Awards 2014. Retrieved on October 28, 2014 from https://www.ctsacentral.org/

39 Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T. Variable selection for propensity score models. Am J Epidemiol 2006;163:1149–56. PMC1513192

40 Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41–55.

ongoing population-based studies.[41] Researchers at Yale University are developing new approach to combining propensity score and longitudinal individualized absolute risks estimates for competing patient-centered outcomes methods because results in the medical literature are typically presented in relative terms, such as odds ratios, risk ratios or hazard ratios, which are not easily interpreted by patients or their physicians. The longitudinal individualized absolute risks for competing outcomes is the gross probability of an outcome within a specific period of time in the context of a competing outcome. It is increasingly common in the medical literature for measures of relative risk to be partnered with a presentation of absolute risks to bring clearer meaning and interpretation of research results.

Methodologies recommended by experts in medication-related research include precisely defining medications; establishing temporal precedence; addressing clinical indication and contraindication bias; and adjusting for confounding or for the propensity to receive the medication of interest.[42] Similarly, there are several prerequisite elements to justify causality in chronic disease, such as strength (graded association between cumulative dose or duration of use and outcome), biological gradient, consistency, biological plausibility (coherence), and the establishment of temporal precedence. Quantifying the absolute risks of competing clinical outcomes and patient-centered outcomes, for persons receiving medication for a primary condition in the presence of multiple diseases and including patient characteristics, is one of the most pressing areas in patient-centered decision-making. With careful attention to design and analytical issues, such a methodology that has potentially wide-spread use.

The challenges of assessing treatment effects in observational studies have been well chronicled.[43] Treatments are non-random factors often intricately linked to the diseases and their severity and to other predisposing or prognostic factors. Furthermore, within a drug class, different agents may have different effects. Thus, methodology should address these forms of heterogeneity of treatment effects.

Methodological Concerns Regardless of Study Design: Missing Data and Competing Risk

Older adults with complex health problems have a high risk of missing data.[44] Prevention of missing data is more effective than analytic methodologies to impute or model missingness. Effective strategies to prevent missing data include 1) quality control plans to monitor and minimize missing data; 2) maximizing benefits and minimizing burdens of participants; 3) seeking input from stakeholders to address infeasible measures or

41 Larson EB. Evidence, guidelines, performance incentives, complexity, and old people: a clinician's dilemma. J Am Geriatr Soc 2009;57:353–4.

42 Rubin DB. Estimating causal effects from large data sets using propensity scores. Ann Intern Med 1997;127:757–63; Shah BR, Laupacis A, Hux JE, Austin PC. Propensity score methods gave similar results to traditional regression modeling in observational studies: a systematic review. J Clin Epidemiol 2005;58:550–9; Foody JM, Cole CR, Blackstone EH, Lauer MS. A propensity analysis of cigarette smoking and mortality with consideration of the effects of alcohol. Am J Cardiol 2001;87:706–11; Braitman LE, Rosenbaum PR. Rare outcomes, common treatments: analytic strategies using propensity scores. Ann Intern Med 2002;137:693–5; Glynn RJ, Schneeweiss S, Sturmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. Basic Clin Pharmacol Toxicol 2006;98:253–9. PMC1790968.

43 Standards for the Diagnosis and Management of Patients with COPD. American Thorascic Society/ European Respiratory Society [cited 2013 January 15, 2013]; Available from: http://www.thoracic.org/clinical/copd-guidelines/resources/copddoc.pdf; Laupacis A, Mamdani M. Observational studies of treatment effectiveness: some cautions. Ann Intern Med 2004;140:923–4; Glesby MJ, Hoover DR. Survivor treatment selection bias in observational studies: examples from the AIDS literature. Ann Intern Med 1996;124:999–1005; Giordano SH, Kuo YF, Duan Z, Hortobagyi GN, Freeman J, Goodwin JS. Limits of observational data in determining outcomes from cancer therapy. Cancer 2008;112:2456–66; Vandenbroucke JP. When are observational studies as credible as randomised trials? Lancet 2004;363:1728–31.

44 Hardy SE, Allore H, Studenski SA. Missing Data: A Special Challenge in Aging Research. J Am Geriatr Soc 2009;57(4):722–9. PMID: 19220562 PMC2695652

survey questions leading to non-response; and 4) anticipating the increased resources needed to maintain participants with health and functional problems in the study. When, despite these efforts, missing data are present, several techniques exist that can address missing data at the analytic stage.[45] Use of effective strategies to minimize missing data can promote inclusion of a broad range of older adults in research and ultimately produce valid yet generalizable evidence to guide practice.

Missing data are a special challenge in clinical aging research because older adults are more likely than younger adults to produce missing data during study. Both death, a competing risk, and loss to follow-up in longitudinal studies increase with age.[46] In addition, missing data for individual measures increase with age, as cognitive or physical deficits can lead to inability to perform some assessments.[47] Missing data from any of these causes can bias results, reduce power, and reduce generalizability, reducing both the internal and external validity of study results.

Analytic Methods for Missing Data and Competing Risks

Some analytic methods for longitudinal studies can use available data for participants with incomplete follow-up. One common method is time-to-event analysis, which uses all participants with complete predictors up to the time they either experience the outcome or are censored (lost to follow-up due to death, drop-out, or other factors). Unfortunately, if the censoring is informative (i.e. the censored participants are either more or less likely than those not censored to experience the outcome) then the results may be severely biased. There are few ways to test for informative censoring.[48] For longitudinal studies with multiple outcome assessments on each participant, linear and non-linear mixed effects models or generalized estimating equations can include participants as long as they have predictors and at least one outcome assessment. However, mixed effects models also regard death as ignorable either by simply treating death as a cessation of measurement or by assuming the trajectory for the longitudinal response after death similar to that on the same time frame without death conditional on measured variables. Although methods of generalized estimating equations[49] can be used for binary or ordinal longitudinal response, as well as for a continuous longitudinal response, inferences can only be made on the population trajectory for the longitudinal response. When there is missing data due to death, a population approach makes it difficult if not impossible to account for the association between the longitudinal response, risk of death and the within-subject correlation.

Another approach is a shared latent variable model. Two separate models for the longitudinal response and for measurement cessation are linked by a shared latent variable (e.g. by including a random effect) that is included in both the mixed effects model for the longitudinal response and the model for measurement

45 Van Ness PH, Murphy TE, Araujo KLB, Pisani MA, Allore HG. The use of missingness screens in clinical epidemiologic research has implications for regression modeling. J Clin Epid 2007;60(12):1239–45. PMID: 17998078 PMC2443713

46 Missing data are a special challenge in clinical aging research because older adults are more likely than younger adults to produce missing data during study. Both death and loss to follow-up in longitudinal studies increase with age. In addition, missing data for individual measures increase with age, as cognitive or physical deficits can lead to inability to perform some assessments. Missing data from any of these causes can bias results, reduce power, and reduce generalizability, reducing both the internal and external validity of study results.

47 Di Bari M, Williamson J, Pahor M. Missing-data in epidemiological studies of age-associated cognitive decline. J Am Geriatr Soc 1999;47:1380–1.

48 Huang X, Wolfe RA, Hu C. A test for informative censoring in clustered survival data. Stat Med 2004;23(13):2089–107.

49 Liang KY, Zeger SL. Longitudinal data-analysis using generalized linear-models. Biometrika 1986;73(1):13–22.

cessation.[50] Conditional independence is usually assumed in these "joint models" given that the shared latent variables, the longitudinal response and measurement cessation are independent. Although the conditional independence assumption may not always be met, these joint models are may be more inferentially sound than pattern mixture[51] and selection models[52] when measurement cessation is caused by death that may be informative of the longitudinal response. For example, methods that uses the shared random effect parameter models for the analysis of longitudinal dementia data with missing data due by death[53] are particularly relevant to studies in clinical aging[54] research.

Yet another approach for a time-to-event outcome is a "competing risk model" where outcomes may not be observed due to the presence of an external event (e.g. death). The assumptions regarding competing risk take the form of what logicians called "counterfactual conditionals," that is, statements in which one states the consequent of an antecedent condition that one knows has not occurred. For instance, one makes an assumption about the probability of dead study participants being hospitalized under the supposition that they had not died.

In studies whose outcome is the time to an event of clinical interest, two types of assumptions are commonly made regarding competing risks. They imply two different types of study designs, in the sense that distinctive hypotheses are made, and two different types of analyses, with characteristic interpretations of analytical results.

One type of assumption yields competing risks described by cause-specific hazards. In this case it is assumed that a study participant who suffers a competing risk like death will have the same hazard for the primary outcome, like hospitalization, as other study participants who are at risk for this primary outcome at the time that death occurs and who share the same profile of covariate characteristics at that time. Another way to state this assumption is to say that the competing risk, meaning here the probability of death, is independent of the risk or probability of the primary outcome. For instance, if the death of a study participant occurs because of a car accident then it can be considered independent of hospitalization; however, if it occurs because of a chronic medical condition that it probably would not be independent in this sense.

A second type of assumption yields competing risks described by hazards of subdistributions. (Subdistributions in this context are the distributions of the individual outcomes for which study participants are at risk, e.g., deaths and hospitalizations.) In this case it is assumed that a study participant is at risk for the competing risk outcome but that it does not occur. (Statistically, this means that a study participant who suffers a competing risk is retained in the analytical risk set, i.e., the set of study participants who are considered to be at risk of the primary outcome at a given time point at times subsequent to the occurrence of the competing risk. In the cause-specific hazards approach such a study participant is deleted from such risk sets at subsequent time points.)

50 Wulfsohn MS, Tsiatis AA. A joint model for survival and longitudinal data measured with error. Biometrics 1997;53:330–9; Lin HQ, McCulloch CE, Mayne ST. Maximum likelihood estimation in the joint analysis of time-to-event and multiple longitudinal variables. Statistics in Medicine 2002;21(16):2369–82; Gao SJ. A shared random effect parameter approach for longitudinal dementia data with non-ignorable missing data. Statistics in Medicine 2004;24:211–9.

51 Pauler DK, McCoy S and Moinpour C. Pattern mixture models for longitudinal quality of life studies in advanced stage disease. Statistics in Medicine 2003;22:795–809.

52 Touloumi G, Pocock SJ, Babiker AG, Darbyshire JH. Estimation and comparison of rates of change in longitudinal studies with informative drop-outs. Stat Med 1999;18(10):1215–33.

53 Gao SJ. A shared random effect parameter approach for longitudinal dementia data with non-ignorable missing data. Statistics in Medicine 2004;24:211–9.

54 Arbeev KG, Akushevich I, Kulminski AM, Ukraintseva SV, Yashin AI. Joint Analyses of Longitudinal and Time-to-Event Data in Research on Aging: Implications for Predicting Health and Survival. Front Public Health 2014;2:228.

It may seem counterintuitive to the idea of competing risks to include dead persons in an analytical risk set after they have died. The rationale for maintaining study participant in the risk set becomes apparent when the characteristic hypotheses and interpretations for the cause-specific hazards and the hazards of the subdistributions are differentiated.

The epidemiologic interest of the researcher in a study for which cause-specific hazards are appropriate is directed more toward causal efficacy and risk factors than real-world effectiveness and event incidence. The interest of the researcher in a study for which hazards of subdistributions are appropriate is directed more toward effectiveness than efficacy.

Another way to differentiate the two perspectives is to say that the public health interest of the researcher in a study for which cause-specific hazards are appropriate is directed toward primary prevention while the hazards of subdistributions approach is more appropriate for tertiary prevention.

Consider again the example of a time-to-hospitalization study in which death is a competing risk. If researchers are interested in identifying risk factors for hospitalization, i.e., factors which cause the hospitalization such that when the causal nexus between the factor and hospitalization is interrupted by some intervention the hospitalization will be prevented, then they should adopt the cause-specific hazards approach. The most (but not only) relevant measure of association for this type of analysis is a measure of relative risk such as a hazard ratio.

If researchers are interested in identifying the probabilities that persons with certain characteristics will be hospitalized for some specific health condition like Alzheimer's disease (AD) so that public health officials can make realistic plans for caring for them, then they should adopt the hazards of subdistributions approach. The most (but not only) relevant measure of association for this type of analysis is a plot of stratified cumulative incidence curves showing the cumulative probability over time of study participants in groups of interest having a given outcome and a test for differences between the curves.

It should now be evident why it is reasonable in the hazards of subdistributions approach to assume that dead persons remain in the analytical risk set. Given a real-world public health research interest such as described immediately above, dead persons and persons without AD can be treated similarly because neither of them will be in need of hospital services for AD.

However, competing risk models are not solely used for cessation of observations due to death. Competing risk models can be used when the occurrence of one outcome does not necessarily remove the person from eligibility to experience another outcome. The hazard functions of the competing outcomes, i.e., the cause-specific hazard functions, and their temporal behavior can estimate the probability of one occurring before the other. For example, going to the hospital does not prevent the occurrence of disability or mobility limitations and these events occur in different temporal orderings. This was demonstrated for transitions between states of functional disability.[55] The absolute risk per month of functional transitions between states of no, mild and severe disability and death were calculated for three predictors: hospitalization, restricted activity, and no intervening event, respectively, in the presence and absence of physical frailty. Values for the absolute risk represent the probability of develop-

55 Gill TM, Allore HG, Gahbauer EA, Murphy TE. Change in disability after hospitalization or restricted activity in older persons. JAMA 2010;304:1919–28. PMC3124926.

ing a specific outcome per unit of time given the competing outcomes. Thus, this approach addresses death, as well as multiple possible outcomes from any disability state. A recent approach that combines the strengths of shared latent variable model, nonlinear trajectory modeling and competing risks was recently published.[56]

Missingness screens[57] help address the impact of missing data and provide guidance in covariate selection for regression modeling. First, a complete case analysis is performed to eliminate variables that have weak associations with the outcome or strong correlations among themselves, and thus to yield a manageable group of candidate variables. Next, testing for ignorability of the missingness[58] is undertaken. If the missingness meets the criteria for missing completely at random or missing at random then imputation or weighting can be performed. Next, the model selection process should be repeated with the imputed or weighted data set. Since there are now no missing values traditional model selection process can be used. Methods of assessing goodness-of-fit should be examined, e.g., residual analysis, influence diagnostics, and goodness-of-fit statistics. A final crucial step is model validation. If an external validation data set is not available, then bootstrapping methods[59] should be used to assess the extent to which bias might have been introduced into parameter estimates by drawing upon information from this particular data set during the process of model selection.

Imputation methods assign plausible values to missing data. Over the past two decades, imputation methods for missing values have been developed and reviewed and corresponding statistical software has become available.[60] In brief, single imputation methods substitute a single value for a missing value and include replacement with mean, regression imputation, hot-deck, maximum likelihood estimation, propensity scoring and approximate Bayesian bootstrap. Most of these methods incorporate multiple assumptions and can lead to biased estimates if they are not met. The most commonly used method, maximum likelihood estimation, assumes missing values are missing at random, but often results in artificially reduced variances and can lead to over-correction or modeling of noise. Multiple imputation addresses the underestimation of variance that occurs with single imputation by representing missing data uncertainty. Most methods assume that variables are normally distributed and can be represented by a linear function of all the other variables, and only produce unbiased results when the data are missing at random or missing completely at random. The basic method involves replacing each missing value with a set of plausible values (based on correlated variables), resulting in multiple different complete data sets. Each set is then analyzed using standard procedures and the results are combined, yielding correct variance and parameter estimates. For longitudinal data of older adults which experience death during follow-up two methods for imputation are sequential and simultaneous multiple imputation. The sequential

56 Lin H, Han L, Peduzzi PN, Murphy TE, Gill TM, Allore HG. A dynamic trajectory class model for intensive longitudinal categorical outcome. Stat Med 2014;33(15):2645–64. doi: 10.1002/sim.6109. PMID:24519416.

57 Van Ness PH, Murphy TE, Araujo KLB, Pisani MA, Allore HG. The use of missingness screens in clinical epidemiologic research has implications for regression modeling. J Clin Epid 2007;60(12):1239–45. PMID: 17998078 PMC2443713.

58 Troxel AB, Ma G, Heitjan DF. An index of sensitivity to nonignorability. Statistica Sinica 2004;14:1221–37; Little RJA. A Test of Missing Completely at Random for Multivariate Data with Missing Values. J Am Stat Assoc 1988;83:1198–202.

59 Efron B, Tibshirani RJ. An Introduction to the Bootstrap. London: Chapman & Hall/CRC; 1993.

60 Twisk, J, de Vente, W. Attrition in longitudinal studies: how to deal with missing data. J Clin Epidemiol 2002;55:968–76; Schafer JL, Graham JW. Missing data: our view of the state of the art. Psycho Methods 2002;7:147–77; Rubin DB. Multiple imputation after 18+ years (with discussion). J Am Stat Assoc 1996;91:473–89; Arnold AM, Kronmal RA. Multiple imputation of baseline data in the cardiovascular health study. Am J Epidemiol 2003;157:74–84; Engels JM, Diehr P. Imputation of missing longitudinal data: a comparison of methods. J Clin Epidemiol 2003;56:968–76.

approach imputes missing data at each time point after removing participants who died since the previous observation. In contrast to the time ordering and exclusion of subjects after death in the sequential approach, the simultaneous approach imputes all of missing data together, including those post-death; then, before the analysis stage, all of values imputed after a participant's death are removed. A studying comparing these approaches found removing the decedents from future imputation waves yielded more accurate imputed values.[61] However, it was suggested that improved sequential imputation method be developed that uses information both before and after missing values for non-decedents.

Summary

This report can only touch on the highlights of the methodological considerations and needs for further research when conducting trials and studies with older adults. Issues are intertwined as the design is not separate from the control of missing data, analytic plans nor sample size calculations. Collaborative research teams with expertise for clinical, biostatistics and informatics are required to address research questions address the efficacy of treatments for older adults with MCC. Such research teams are also needed to address pressing issues of public health, such as patient-centered outcomes of self-rated health, function and outcomes most important to older adults' lives.

On such collaborative team biostatisticians ensure that statistical inferences are sound and informative. Good designs foster good inference. Standardly-tailored study designs which better reflect actual clinical care draw informative inferences about multi-component interventions. Chance, bias, ambiguity, and unaccounted for data dependencies are potential threats to good inference. Adjustment methods for multiple outcomes minimize the threat of chance; missing data methods combat bias from losses to follow-up; and qualitative methods can clarify the meanings of key ideas in clinical research. Data dependencies can lead to artificially small estimates of variability and uncontrolled associations between study variables can cause confounding. To identify and correctly account for such dependencies requires subject matter knowledge gerontological and clinical geriatric expertise, as well as statistical skill. This interdisciplinary combination is actively promoted by the field of Gerontologic Biostatistics to develop new methods and to apply these to aging research.

61 Ning Y, McAvay G, Chaudhry S, Arnold A, Allore HG. Results Differ by Applying Distinctive Multiple Imputation Approaches on the Longitudinal Cardiovascular Health Study Data. Exp Aging Res 2013;39:(1):27–43. PMC354738.

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