Complex health care interventions in geriatrics

Development and evaluation of a multifactorial falls-prevention intervention

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Development and evaluation of a multifactorial falls-prevention intervention

An academic essay in
Medical Sciences

Doctoral Thesis

to obtain the degree of doctor
from Radboud University Nijmegen
on the authority of the Rector Magnificus **prof. dr. S.C.J.J. Kortmann**,
according to the decision of the Council of Deans
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by

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Contents

IA

Our society's population is aging rapidly. As of the year 2010, 2.5 million Dutch people, representing 15% of the population, were over 65, and the percentage of the population over 65 is expected to reach 25% in 2040.[1] Among older persons, geriatric syndromes are highly prevalent. A geriatric syndrome is a multifactorial health condition that occurs when the accumulated effects of impairments render an older person vulnerable to situational challenges. Thus, the use of the term "syndrome" in a geriatric context emphasizes multiple causation of a unified manifestation.[2]

Falling is among these frequently encountered multicausal problems. The ability to transfer and walk safely depends on coordination among sensory systems (vision, vestibular, and proprioception) as well as on coordination of the central and peripheral nervous systems and the cardiopulmonary and musculoskeletal body systems. Falls that occur during ordinary daily activities generally result from disease or impairment of one or more systems, making falling a geriatric syndrome.[2;3]

Falls

Prevalence, risk factors and consequences of falls

More than one-third of community-living persons older than 65 years of age fall each year. Previous falls, strength, gait, and balance impairments, and medications are the strongest risk factors for falling.[3] The risk of falling increases with the number of risk factors. The 1-year risk of falling increased from 8% to 78% as the number of factors present increased from 0 to 4 or more.[3]

Approximately 10% of falls result in a major injury such as a hip fracture (1-2%), other fractures (3-5%) serious soft tissue injury, or traumatic brain injury (5%).[3;4] In the Netherlands, falls are the leading cause of accidental death in persons older than 65.[4] Psychological consequences such as fear of falling are also frequently reported in this age group.[3;5] There are strong indications that older people who are afraid of falling and consequently avoid activities enter a debilitating spiral of loss of confidence, restriction of physical activities and social participation, physical frailty, falls, and loss of independence.[6] Falls are major contributors to functional decline and health care utilization and are associated with high health care costs.

Falls in frail community-dwelling older persons

Frail older persons are at an increased risk of falls.[3;7-9] Frailty is considered to be highly prevalent with increasing age and to confer high risk for adverse health outcomes, including mortality, institutionalization and hospitalization. Fried posed a widely accepted definition of frailty.[10]According to that definition, frailty is a biological syndrome of decreased reserve and

resistance to stressors resulting from cumulative declines across multiple physiologic systems and causing vulnerability to adverse outcomes.[10]

In 2007, 600,000 persons older than 65 years of age in the Netherlands, 95% of whom were community-dwelling, were considered to be frail based on the Tilburg frailty index.[11] Twenty-five percent of all community-dwelling older persons older than 65 years are frail. An increase in the number of frail older persons from 700,000 in 2010 to more than one million in 2030 is expected.[12]

In frail older persons, falls often coexist with cognitive impairment.[8] The annual incidence of falls in cognitively impaired older persons is 60%, twice the incidence in cognitively normal older persons.[13] About 25% of frail older persons are cognitively impaired.[14] Frail or cognitively impaired older fallers are less likely to achieve satisfactory recovery from a fall-related injury than non-frail, cognitively healthy older persons.[7;15;16]

Impact of care recipients' falls on informal caregivers

Because falls and fall injuries are among the most common causes of decline in the ability to care for oneself and to participate in social and physical activities, falling imposes a severe burden not only on patients but also on their informal caregivers. [17;18] In industrial countries, approximately 80% of help and care services to older persons is provided by informal caregivers.[19] Providing care for older adults has been described as a stressful experience that may erode the physical and psychological health and quality of life of the caregiver and may often result in a high caregiver burden.[19] It has been shown that caregivers of frail older fallers experience more caregiver burden than caregivers of frail, older non-fallers.[17;18]

Falls-prevention interventions in non-frail and frail community-dwelling older persons

A preponderance of evidence suggests that multifactorial interventions are effective in reducing falls in high-risk community-dwelling older persons.[3;20] However, the exact target group and intervention context are yet to be defined because a number of multifactorial interventions showed a lack of effect in the frail community-dwelling older fallers with the highest risk for falling.[3;20-22] Furthermore, older persons with cognitive impairment have been excluded from most trials evaluating multifactorial interventions.[3;20] To our knowledge, no prospectively evaluated multifactorial falls-prevention intervention has been proven to reduce the fall rate in frail community-dwelling patients with dementia or mild cognitive impairment (MCI).[20] Moreover, in frail cognitively impaired community-dwelling older persons, evidence-based strategies to reduce fear of falling are lacking.[5;23] A Tai Chi intervention reduced fear of falling in community-dwelling frail older persons[24], but the intervention was neither performed with nor likely appropriate for fallers with cognitive decline. In addition, it is unknown whether falls-prevention interventions alleviate informal caregivers' high burden related to recurrent falls of their care recipients.

Problem statement of the thesis

With the growing number of frail community-dwelling older persons with and without cognitive impairment and with an increased risk of falls, a falls-prevention intervention is greatly needed. Furthermore, little is known about the consequences care recipients' falls have for informal caregivers. The determinants of caregiver burden or quality of life of informal caregivers of older fallers are unknown. No research has been done on ways to support caregivers of older fallers or on whether falls-prevention interventions alleviate the caregiver burden.

The aim of the research project

The overall aim of this research project was to develop and evaluate a falls-prevention program for frail community-dwelling older persons with and without cognitive impairment. Following development and piloting of the falls-intervention program, the major aim was to determine the effectiveness of the intervention on the falls rate. A second aim was to determine the effectiveness of the intervention on fear of falling in patients and on caregiver burden in primary informal caregivers.

The ***target population*** of our study was pairs of frail community-dwelling older fallers and their primary informal caregivers. In our studies, we operationalized frailty as the presence of two or more of the widely accepted frailty indicators: weakness, slow walking speed, low physical activity, self-reported exhaustion and weight loss [25], in addition to the fact that all patients experienced a recent fall.

A primary informal caregiver was defined as the non-professional who was most involved in caring for the patient who experienced falls, assisted with at least one personal or instrumental activity of daily living and monitored the patient at least two times a week.

We named the research project the 'Carthage-Phoenix Study' (CPS) in reference to the fall and resurrection of this ancient city.

The Carthage-Phoenix Study

Geriatric medicine focuses on diagnosing and treating geriatric syndromes and their underlying multiple causes or contributing factors rather than on diagnosing and treating single diseases. Based on the predominant geriatric paradigm of multicausality, complex multifactorial interventions are generally considered to be more powerful for treating falls (and geriatric syndromes in general) than single component interventions because they can address more potential risk factors.[26] Therefore, we decided to develop a complex multifactorial falls-prevention intervention. Complex interventions are defined as interventions that contain

several (multifaceted) components that act both independently and interdependently.[27] However, complex interventions are difficult to develop, document, and reproduce, and randomized controlled trials, which are required to demonstrate their effectiveness, are usually costly and challenging.[28]

Campbell et al. described the framework used by the UK Medical Research Council (MRC) for the development, evaluation and implementation of complex interventions (figure 1). In this framework, a phased approach in the development and evaluation of complex interventions is advocated. In this thesis, we carried out the process of development and evaluation of our intervention in a manner very similar to the phased approach recommended by the MRC. Although the MRC framework has not yet been widely referenced in the geriatric literature,[26;29-31] we believe that this framework may be of great value in geriatric research.

Medical Research Council framework

In 2000, the MRC developed a framework based on the linear sequenced phases that are used in drug development.[27] In 2008, a revised version of this framework was published in which the process of developing and evaluating complex interventions was described by cyclical phases (Figure 1).[28;32] In the *development phase*, the best available evidence and appropriate theories are identified and the process and outcomes are modeled. Modeling refers to defining and combining the components of the intervention; it further involves delineating an intervention's components, identifying how they may be interrelated, and understanding how key components may relate to either surrogate endpoints or final outcomes.

The *feasibility and piloting phase* includes the implementation of testing procedures to assess the feasibility of the intervention and subsequent evaluation, the estimation of the likely recruitment rate and retention rate of the research subjects, and the calculation of appropriate sample sizes.

The *evaluation phase* is the phase of the randomized controlled trial (RCT) in which the final intervention is evaluated. Both the design of the RCT and the intervention are developed based on information from the development phase and from the feasibility study. Ideally, the RCT is accompanied by a process-evaluation and cost-effectiveness study. In the *implementation phase*, the results are disseminated as widely and persuasively as possible, and further research is undertaken to assist and monitor the process of implementation.[32] The implementation phase is beyond the scope of this thesis.

Outline of the thesis

The ***development phase*** is described in chapters 1-4. *Chapter 1* provides an overview of the MRC framework and illustrates its use in geriatrics by showing how it was used to develop and evaluate our falls-prevention intervention. *Chapter 2* describes the impact of falling for frail community-dwelling older fallers with and without cognitive impairment and for their family caregivers. In this chapter, possible components of a future falls-prevention program are defined by the both patients and caregivers. *Chapter 3* summarizes the determinants of subjective caregiver burden and the quality of life of informal caregivers of community-dwelling, vulnerable older fallers. Those determinants could serve as targets for caregiver support.

The development phase also includes the planning of strategies for treatment allocation, recruitment, adherence, outcome measures, blinding and analysis. *Chapter 4* provides methods for the design, analysis and sample size determination of trials that evaluate interventions that, like our falls-prevention intervention, are delivered to individuals in groups. A new allocation method for such trials, optimal batchwise minimization, is also described.

In addition to showing how the MRC framework was used to develop and evaluate the Carthage-Phoenix falls-prevention intervention, *chapter 1* also reports on the main results of the studies described in *chapters 2, 3 and 4* and on the implementation of those results in the development and evaluation of the intervention.

In the ***feasibility and piloting phase***, both the intervention and evaluation were piloted to test their feasibility. The results of the pilot study are described in c*hapter 1*. *Chapter 5* evaluates the performance of a new method of treatment allocation, studywise minimization, for small trials in which all subjects are enrolled before the trial starts, for example, pilot studies.

The ***evaluation phase*** is described in *chapters 6 and 7*. *Chapter 6* reports the results of a randomized controlled trial to evaluate the effect of our complex falls-prevention intervention on falls and fear of falling in patients and on subjective caregiver burden in caregivers. *Chapter 7* presents a systematic and comprehensive guide to the development and application of a process evaluation for complex interventions in geriatrics. The use of the guide is demonstrated and clarified by applying it to the process evaluation of our intervention.

The last part of the thesis *summarizes* and *discusses* the results and presents the overall conclusions and implications arising from this thesis. We also discuss the ***implementation*** of our intervention.

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1

Developing and evaluating complex healthcare interventions in geriatrics: The use of the Medical Research Council framework exemplified on a complex fall prevention intervention

Abstract

Geriatrics focuses on a variety of multiorgan problems in a heterogeneous older population. Therefore, most geriatric healthcare interventions are complex interventions. The UK Medical Research Council (MRC) has developed a framework to systematically design, evaluate, and implement complex interventions. This article provides an overview of this framework and illustrates its use in geriatrics by showing how it was used to develop and evaluate a fall prevention intervention. The consecutive phases of the framework are described:

Phase I: Development. This phase began with a literature review, which provided the existing evidence and the theoretical understanding of the process of change. This understanding was further developed through focus groups with experts and interviews with patients and caregivers. The intervention was modeled using qualitative testing of the preliminary intervention through focus groups and through the completion of Delphi surveys by independent specialists.

Phase II: Feasibility and piloting. In this phase, a pilot study was conducted in a group of patients and caregivers. The feasibility of the intervention and evaluation was also discussed in focus groups of participants and instructors.

Phase III: Evaluation. The information from phases I and II shaped the design of a randomized controlled trial to test the effectiveness of the intervention.

Phase IV: Dissemination. The purpose of the final phase is to examine the implementation of the intervention into practice.

The MRC framework provides an innovative and useful methodology for the development and evaluation of complex geriatric interventions that deserves greater dissemination and implementation.

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Introduction

Geriatric medicine focuses on diagnosing and treating geriatric syndromes and their underlying multiple causes or contributing factors, rather than on diagnosing and treating single diseases. In addition, the geriatric population is a highly heterogeneous population, and most health care interventions in geriatric populations are therefore complex interventions. Complex interventions are defined as interventions that contain several (multifaceted) components that may act independently and interdependently.[1] Based on the predominant geriatric paradigm of multicausality, complex multifactorial interventions are generally considered to be more powerful in this population than single-component interventions because they can address more potential risk factors.[2]

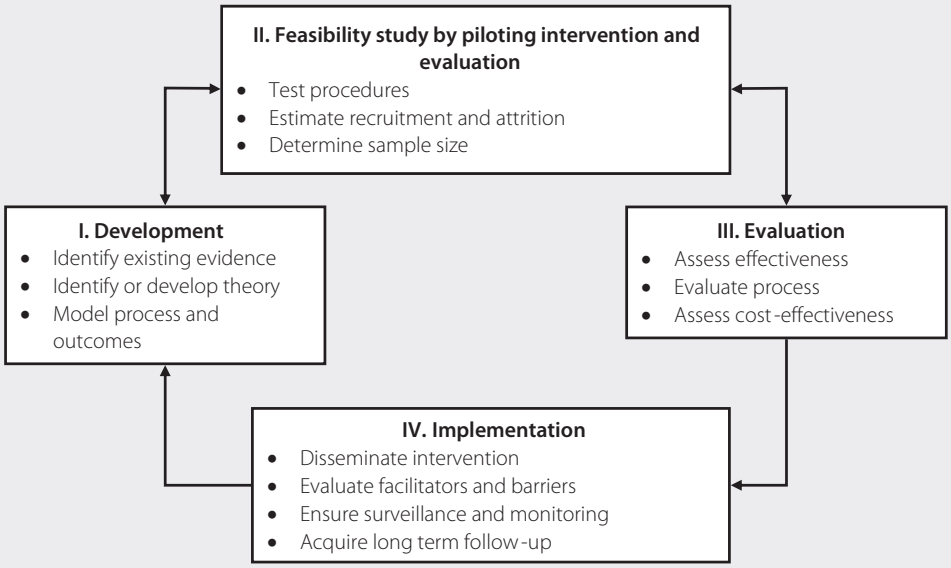
Complex interventions are difficult to develop, document, and reproduce. Randomized controlled trials (RCTs), which are required to demonstrate their effectiveness, are usually costly and challenging.[3] The extension of the CONSORT statement on trial reporting emphasizes that sufficient details regarding the intervention should be reported, although it does not specifically address the problems associated with describing complex interventions.[4] In 2000, the UK Medical Research Council (MRC) developed a framework based on the linear sequenced phases of drug development for use in the design, evaluation, and implementation of complex interventions.[1] In 2008, a revised version was published in which the process of developing and evaluating complex interventions was described according to cyclical phases (Figure 1).[3,5]

The major strength of the MRC framework is the systematic way in which it proposes developing the best intervention and the best evaluation methods. This involves using the best available evidence and appropriate theories. The intervention and evaluation should be tested and adapted to clinical practice using a carefully staged approach, starting with a series of small studies targeted at each of the important uncertainties in the design and the intervention. It should then move on first to an exploratory and subsequently to the definitive design of the evaluation, as well as from the pilot content to the final content of the intervention. Finally, the results should be disseminated as widely and persuasively as possible, and further research should be undertaken to assist and monitor the process of implementation.[5] Taken together, the various phases of the MRC framework may be of great value in geriatric research, although this framework has not yet been widely referenced in the geriatric literature.[2,6–8]

The MRC framework was used to guide the development and evaluation of a multifactorial fall prevention intervention for frail community-dwelling older persons, with and without cognitive impairment, and their informal caregivers. To the authors' knowledge, no fall prevention intervention has proven to be effective in frail community-dwelling patients with dementia or mild cognitive impairment.[9–11] This justifies new research investments but asks

for a thorough developmental stage to overcome the many restrictions found in this frail population. The first section of this article describes the four phases of the MRC framework for the development and evaluation of complex interventions. The second section describes the application of the MRC framework in geriatrics by illustrating its value in developing and evaluating our "Carthage-Phoenix Study," a complex fall prevention intervention.

Figure 1 Key elements of the phased development and evaluation of complex interventions in general terms (adapted from Craig et al.[5])



MRC framework

The MRC framework has four phases: development, feasibility and piloting, evaluation, and implementation.

Phase I: Development

Identify existing evidence

The first step is to define and quantify the target population and to identify previously published data regarding similar interventions and the methods that have been used to evaluate them.[5,12] This may help exclude implausible interventions, reveal possible facilitators or barriers to the research project, and predict major confounders. This process helps ensure that the best choices are made regarding the intervention and proposed hypothesis and elucidates strategic design issues.[1,13]

Identify or develop theory

The second step is to develop a theoretical understanding of the process by which change is likely to occur in one's intervention by drawing on existing evidence and theory from literature. If necessary, new primary research can supplement this.[5] Insight into the theoretical basis of change may lead to adjustment of the hypothesis and identification of potential useful components or organizational structure of the intervention.[13]

Model process and outcomes

Modeling refers to defining and combining the components of the intervention. An understanding of the intervention and its possible effects should also be developed. This involves delineating an intervention's components, identifying how they may be interrelated, and understanding how important components may relate to surrogate endpoints or final outcomes. Modeling may identify the potential vulnerabilities of an intervention. The researcher should overcome these vulnerabilities to improve the intervention. Modeling the intervention will inevitably prompt the planning of strategies for randomization and the selection of outcome measures and analytical methods.[1] A series of small studies may be required to define most relevant interventional components and reveal ways to tailor the intervention contents to the participants.[1] Complex interventions often work best if they are designed for local contexts as opposed to being completely standardized.[5]

Another useful approach to modeling is to undertake a pretrial economic evaluation. This may identify weaknesses and lead to refinements or even show that a full-scale evaluation is unwarranted.[5,14]

Phase II: Feasibility study by piloting intervention and evaluation

The feasibility and piloting phase includes the implementation of testing procedures to assess the feasibility of the intervention and subsequent evaluation, the estimation of the likely recruitment and retention rates of the research subjects, and the calculation of appropriate sample sizes. Special attention should be paid to the burden the intervention and evaluation poses on the participants. The benefit:burden ratio should be maximized.[15]

A combination of qualitative and quantitative methods is likely to be needed during this phase. Several guidelines are available for the conduct and report of qualitative research.[16-17]

A variety of assessments must be performed, including those that will help the investigators understand barriers to participation, estimate response rates, and identify the critical components of the intervention that should be standardized or controlled, versus those that could be varied systematically. Depending on the results of this phase, a series of studies may be required to progressively refine the design before embarking on a full-scale evaluation.[1] Piloting results in moving forward (evaluation) or backwards (remodeling), depending on the pilot study's outcome.

Phase III: Evaluation

To design and conduct a trial, researchers must make final decisions about the nature of the intervention and address standard design concerns.[5]

Assess effectiveness

Randomization is always preferred, to prevent selection bias. If an experimental approach is not feasible, a quasiexperimental or observational design may be considered.[5]

Measuring outcomes

Researchers need to decide on primary and secondary outcome measurements and how to address multiple outcomes in the analysis. It is also important to consider potential sources of variation in outcomes and to plan appropriate subgroup analyses so as to further examine them.[5]

Understand change process

Process evaluations, which explore the way in which the intervention under study is implemented, can provide valuable insight into why an intervention fails or has unexpected consequences. Conversely, they can also provide insight into why a successful intervention works and how it can be optimized. Researchers should consider including a process evaluation nested within a trial to clarify causal mechanisms, identify contextual factors associated with variations in outcomes, and assess the fidelity and quality of the implementation.[5]

Assess cost-effectiveness

To ensure that the potential benefit of the evidence the intervention will generate justifies its costs, an economic evaluation should be included in the study design. This will make the results far more clinically useful for decision-makers.[3]

Phase IV: Implementation

Dissemination

A full description of the intervention, allowing any planned variation and facilitating further publications, is essential for successful dissemination. Furthermore, to ensure that the findings are translated into routine practice or policy, they should be made available such that the material is accessible and convincing to decision-makers and can be easily and actively disseminated.[3,13]

Surveillance, monitoring, and long-term follow-up

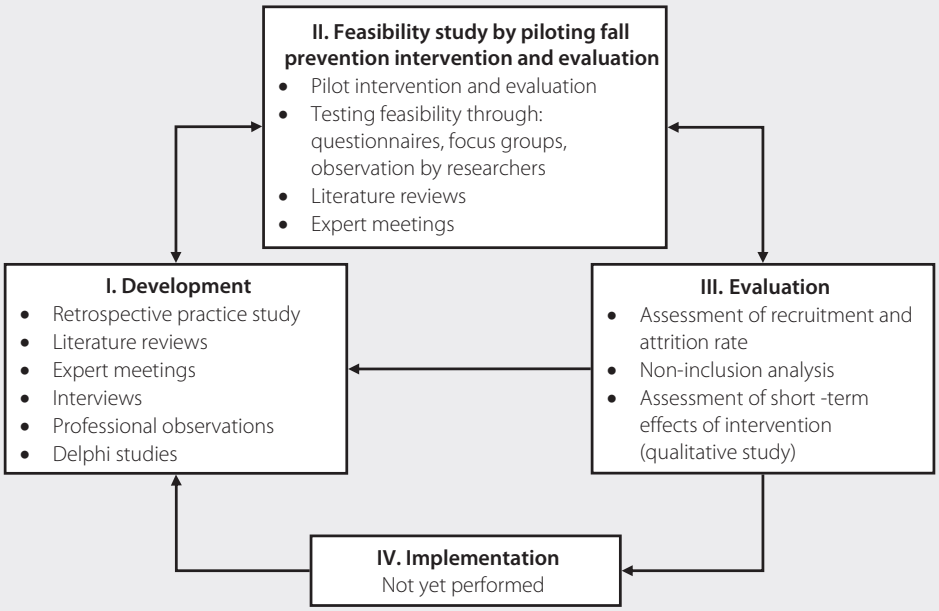
It should be assessed whether others can reliably replicate the intervention and results in uncontrolled settings over the long term. Particular attention should be paid to the rate of uptake, the stability of the intervention, any broadening of subject groups, and the possible existence of adverse effects. As in the case of drug trials, this might be done using long-term surveillance.[3,13] The implementation phase can be conducted after or partly alongside the evaluation. The challenge is to phase the implementation such that the choice is not between doing nothing until the evidence is ready and going for broke and hoping that observational data will show that the program works. The stepped wedge design may be used as an acceptable solution for this dilemma. In this experimental design, the whole population receives the intervention but with randomization built into the phasing of implementation.[3]

The MRC framework applied to a complex geriatric intervention: The Carthage-Phoenix study

The motivation for the development of this intervention arose from the lack of an evidence-based fall prevention intervention for frail community-dwelling older persons, including patients with cognitive impairment. Existing interventions were not effective or excluded patients with cognitive decline.[10] The study was named the Carthage-Phoenix Study (CPS), in reference to the fall and resurrection of this ancient city, and targeted the intervention, among others, at helping cognitively frail older persons to rise after falling.

The guidelines for the development and evaluation of behavior change interventions of the National Institute for Health and Clinical Excellence (NICE)[13], the causal modeling approach of Hardeman and colleagues[18], and the recommendations of Campbell and colleagues regarding complex interventions[19] were used to supplement the official recommendations of the MRC framework. Table 1 shows methods that were used to design the intervention and the evaluation. Figure 2 gives an overview of the content of the specific phases as they were specifically applied to the CPS. Below, a summary of the findings on each of these tasks is provided.

Figure 2 Content of the specific phases as exemplified for the Carthage-Phoenix Study



Phase I: Development of the CPS

Identify existing evidence

Define and quantify the target population

The descriptive analysis of the target population revealed that all of these patients were frail according to the criteria of Fried and colleagues, that 50% of the patients experienced a fall at least every month, and that 7% of the patients fell daily.[20] The mean Mini-Mental State Examination (MMSE) score of these patients (range 0–30) was 24.5±4.6.[21] These patients had a high level of fear of falling, as measured using the Falls Efficacy Scale.[22]

Define the health outcome

The main health outcome of the study was fall reduction. Research on the characteristics of the population and the existing literature revealed that fear of falling is a frequently reported and serious consequence of falling. Therefore, the project team targeted the intervention to two outcomes: fall reduction and decreasing fear of falling.

Table 1 Methods used for the development phase and the piloting and assessing feasibility phase of the Carthage-Phoenix Study (CPS)

General phases according to the MRC framework	Specific methods applied in the CPS fall prevention intervention
Phase I: Development	
Identify existing evidence	
Define and quantify the target population	- Descriptive analysis of the characteristics of the cohort of 43 patients who were seen in outpatient geriatric fall clinic between January and July 2007 (results not published). - Literature review of epidemiological studies on falls in frail, community-dwelling older persons, focusing specifically on cognitively impaired older persons - Project team meeting (geriatrician, neurologist, clinical human movement scientist, resident in geriatrics)
Define the health outcome	- Literature review of the available evidence regarding the importance of falls, e.g., the physical, psychological, and social consequences of falls - Project team meeting
Understand the pathways that cause and sustain the problem	- Literature review of the available epidemiological evidence regarding risk factors of falls
Identify similar interventions	- Literature review of interventions to prevent falls and reduce fear of falling in frail community-dwelling older persons with and without cognitive impairment
Identify outcome measures	- Literature review of the outcome measures used in fall prevention trials and objective ways of measuring falls and fear of falling
Predict major confounders, barriers and strategic design issues	- Literature review of the methodology used in fall prevention trials - Project team meeting
Identify or develop theory	
Specify changes that are expected and theory-based determinants	- Semi-structured interviews with 10 frail community-dwelling older patients (3 cognitively unimpaired patients, 4 patients with mild cognitive impairment, and 3 patients with dementia) who experienced a recent fall and 10 primary family caregivers - Literature review of behavioral change theories and strategies to reduce fear - First expert meeting: focus group with the project team and additional experts in various fields (geriatrics, human movement sciences, medical psychology, geriatric physical therapy, geriatric nursing, and geriatric psychiatry) - First professional, non-participatory observation: cognitive-behavioral group and individual therapy to reduce fear, as delivered by psychologists
Specify intervention points and behavior change techniques	- Literature review on behavioral change techniques and cognitive restructuring techniques - First expert meeting - Meetings with a medical psychologist and a geriatric physical therapist

Model process and outcomes	
Select the best available combination of intervention components and intensities	- Second expert meeting - Semi-structured interviews with experts - Semi-structured interviews with patients and caregivers - Project team meeting - Delphi study including independent specialists recognized in the different domains of the intervention (geriatric nursing, clinical neuropsychology, geriatric physical therapy, occupational therapy, geriatric psychiatry, geriatrics, human movement science, rehabilitation medicine, gerontology, and medical psychology) - Second professional, non-participatory observation: session for physical therapists, who were trained to deliver a fall prevention intervention for non-frail older persons
Identify barriers to application of the intervention	- Literature review - Third professional, non-participatory observation: physical training sessions for demented older persons, as conducted by physiotherapists
Plan strategies for randomization, blinding, recruitment, adherence, outcome measures and analysis	- Literature review on the available evidence regarding the recruitment and adherence of older persons in aging research - Second expert meeting - Project team meetings - Consultations with a biostatistician - Consultations with an expert in health technology assessment
Phase II: Feasibility study by piloting intervention and evaluation	
Test the feasibility of the recruitment process, intervention and measurement	- Observation of the intervention by independent researchers - Project team meetings - Evaluation of each session with the researchers and the instructors - Focus group with patients, caregivers, instructors, and researchers - Focus group with researchers and instructors - Questionnaires administered to patients, caregivers, and instructors evaluating the (1) performance of the intervention according to protocol; (2) attendance of participants; (3) adherence of participants; and (4) opinion of patients, caregivers, and instructors on the intervention - Evaluation of the baseline assessment with patients and caregivers - Third expert meeting
Estimate recruitment and retention	- Project team meeting - Literature review
Determine sample size	- Project team meeting - Literature review of the effectiveness of similar interventions - Experiences and data on attrition in former studies - Consultation with a biostatistician

Understand the pathways that cause and sustain the problem

The risk factors for falling and fear of falling are well known,[11,23] and it has been suggested that different pathways exist for different groups of fallers. Patients with dementia walk relatively too fast in the context of their frailty, which leads them to have a high risk of falling.[24] Cognitively unimpaired patients with an inappropriately low fear of falling based on their fall risk also seem to overrate their physical capacities,[25] and this lack of insight leads to a higher fall risk in these patients. Another group of patients has an inappropriately high fear of falling, which is a contributing factor to falling because this fear results in activity restriction, which leads to loss of strength and joint mobility, which in turn increases the risk of falling.[26,27] Therefore, this intervention should address two types of patients: fearful individuals and impulsive individuals with a lack of insight.

Identify similar interventions

Although contradictory evidence exists on this topic, most evidence suggests that community-dwelling older persons at high absolute risk for falling, with MMSE scores of 20 or above, or both should be offered a multifactorial intervention to prevent falls. Such an intervention begins with a multifactorial fall-related patient assessment and is followed by an individualized multicomponent exercise intervention that focuses on gait, balance, strength, flexibility, and endurance.[9–11,28–32] In the outpatient geriatric fall clinic at Radboud University Nijmegen Medical Centre this type of assessment was already part of the usual care algorithm, so there was no need to develop an assessment.

Research in community-dwelling older persons with dementia has demonstrated that these individuals can adhere to interventions known to reduce risk of falls in cognitively healthy populations and has also shown that these interventions can modify targeted risk factors for falls in this population,[10] but no convincing evidence exists that falls can be prevented in older persons with dementia.

In cognitively unimpaired older persons, fear of falling can be reduced,[33] but evidence regarding reducing fear of falling or fear in general in cognitively impaired older persons is lacking, indicating that this intervention is the first intervention aiming at reducing fear of falling in frail older persons with and without cognitive impairment.

A recent investigation of cognitive-behavioral therapy (CBT) treatment for older persons with generalized anxiety disorder (GAD) found that some individuals with executive dysfunction showed positive treatment response, whereas others showed virtually no response.[34]

Identify outcome measures

The Prevention of Falls Network Europe (ProFaNe) has recommended important domains (falls, fall injury, physical activity, psychological consequences, and generic health-related quality of life) for outcome assessment in fall prevention trials. It has also suggested specific

outcome measures within each domain.[35] Based on these recommendations, fall incidence rate and the Falls Efficacy Scale-International score, a valid and reliable measure of fear of falling,[36] were selected as the major outcome measures. Physical activity and quantitative gait and balance analysis were selected as secondary outcome measures.

Predict major confounders, barriers, and strategic design challenges

The benefits of interventions in cognitively impaired older persons are better maintained when caregivers act as co-therapists for the patients.[37] Patients indicated that the negative attitudes of others (e.g., family and friends) regarding an intervention were a barrier to participation and adherence.[38] To overcome this problem, it is important to explore the attitudes of the caregivers toward fall prevention and to transform a negative attitude into a positive one when performing this type of study. The project team suggested including informal caregivers in the intervention and addressing their attitude toward the fall prevention program.

The project team sent a review of the acquired evidence to the participants in the expert meetings (Table 1) to further shape the intervention and evaluation.

Identify or develop theory

Specify changes that are expected and theory-based determinants

At their first meeting, the experts agreed with the project team that informal caregivers should be included in the intervention, which is unique among fall prevention programs. To gain insight into the role of the caregiver and the needs of patients and informal caregivers, in-depth interviews were conducted with patients and caregivers. The interviews revealed, among other things, a high caregiver burden among caregivers of frail fallers and resulted in the addition of several active ingredients to the intervention.

Because primary informal caregivers were included in the intervention, the hypothesis was extended to state that the intervention should also be able to reduce caregiver burden.

At the expert meeting, it was decided that the intervention should have two interacting components: a physical component and a psychological component. The physical component consisted of exercises focusing on the functional performance of activities of daily living, familiar to patients even with (mild) cognitive impairment, and known to reduce falls. The intensity of the exercises was based on recommendations in the literature.[9,39] The psychological component focused on reducing patients' fear of falling and decreasing the avoidance of activities but also on high-risk behavior in impulsive fallers and changing the home environment to reduce fall risk.

To accomplish the goals of the intervention, patients and caregivers had to change their health-related behaviors. Psychological theories providing a way to link beliefs about health and motivation (e.g., intention and self-efficacy) with behavior (e.g., adopting falls preventive advices) were also applied. Specifically, the Theory of Planned Behavior (TPB), which specifies

causal links between determinants of intentions to change and actual behavior,[18,19] was chosen as one of the theories to underpin the intervention. The bolstering of individuals' intentions is important, because the interviews revealed that risk awareness and the associated motivation to adopt measure to prevent falling were not always present in patients and family caregivers. The interviews also revealed that these groups expressed a low level of self-efficacy.

CBT has been shown to be effective in older patients with fear of falling and to have some effectiveness in older cognitively impaired persons with GAD.[34,40] Therefore, the experts decided to use elements of this therapy to reduce patients' fear of falling.

Specify intervention points and behavior change techniques

In the interviews, patients had expressed that contacting other patients with similar experiences would be helpful. Therefore, a small-group learning environment was used for this intervention, with groups including patients and caregivers. An additional argument for using a small-group learning environment was the proven effectiveness of group interventions to reduce falls in patients without cognitive impairment.[9]

The NICE behavior change techniques used in this intervention are based on the TPB and other behavioral change theories.[18] Cognitive restructuring (an element of CBT) was chosen as a technique to reduce patients' fear of falling. It employed the technique of promoting realistic and adaptive views regarding individuals' fall risk and fear of falling.[40] Moreover, experts stated that fear should be elicited during the intervention to teach participants how to manage it.

Modeling process and outcomes

Based on two Delphi studies, an earlier literature review, and expert opinion, the project team decided on the total number, frequency, and duration of the sessions of the intervention; selection of intervention instructors; and ways to involve caregivers in the intervention. The team ultimately decided to have 10 sessions (twice a week) that lasted 2 hours each and were administered by a psychologist and geriatric physical therapist.

To tailor the intervention to a specific dyad, caregivers and patients should be asked to set realistic goals that they hope to accomplish from the intervention. Furthermore, the intervention should include a supportive session for the caregivers.

The experts suggested several measures to facilitate habit formation of healthy behavior in patient and caregivers (homework exercises, mainly physical exercises), repetition of the main topics of a session several times in the current session and repetition in the next session, and a booster session 3 months after the last regular session had been completed. The Delphi studies determined the content and amount of homework. From a second professional, nonparticipatory observation (Table 1), it became clear that teaching patients about how to fall safely was not suitable for the population of frail patients and should not be part of the intervention.

Identify barriers to application of the intervention

In the interviews, patients and caregivers expressed their opinions regarding the requirements that the venue should meet to stimulate their adherence to the intervention.

Although it is beneficial to include caregivers in these types of interventions, the experts also identified their inclusion as a potential barrier. For example, it might be challenging for caregivers to attend the sessions because of work or childcare obligations. Therefore, the experts suggested that the researchers should clearly explain the benefits of the intervention and the need for caregiver participation to those who were considering taking part in the study.

Plan strategies for randomization, blinding, recruitment, adherence, outcome measures, and analysis

Because randomization at the level of the individual patient was judged possible with this type of intervention, a RCT was considered to be the most appropriate design. Dyads in which the patient and the caregiver provided informed consent were chosen as the unit of randomization.

Recommendations were adopted from the literature regarding the engagement and the adherence of older people in activities to prevent falls and aging research in general,[15,38] as well as recommendations regarding type and number of outcome measures and lowering attrition rate in RCTs in frail older persons. Frail older persons are more likely to miss appointments because of disease, tiredness, or lack of transportation to the hospital. To lower attrition rate, it was decided that the actual assessment date should be within 1 month before or after the anniversary assessment date.[41] One of the recommendations regarding enhancing patient adherence stressed the need for investigators to design interventions for the specific situation and values of each participant.[38] The independent specialists proposed this recommendation (among several other measures) as well.

Based on practical experience with the target group, a multistage recruitment process was designed for the RCT. Geriatricians would first identify eligible patients in the outpatient geriatric fall clinic by completing a screening form for every patient. Next, the eligible patients and caregivers would be given a flyer with information about the study, and their personal details would be passed on to the researchers. The researchers would subsequently call the patients and caregivers to provide a short overview of the study. Next, extensive written information would be sent to the patient and caregiver or a follow-up visit would be scheduled to provide them with more information. Finally, the researchers would call the patients and caregivers again to address remaining questions and ask for their participation. The expert panel endorsed this multistage personalized recruitment and inclusion process, which is in line with recommendations that were made in an earlier article in this series on clinical aging research methods.[15]

Fall incidence rate was measured by asking patients to mail a follow-up fall calendar to the researchers every 2 weeks. Each fall was further characterized by directly telephoning the patients.[41] If a patient could not complete a fall calendar independently, the caregiver was asked to do so. Nonresponders were contacted over the telephone so that the fall history for the missing calendar weeks and underlying reasons for their lack of response could be assessed.

Outcome measures that were applicable to cognitively impaired and cognitively unimpaired patients were chosen based on the outcome measures recommended by ProFaNe.

The project team and a health technology assessment specialist designed the economic evaluation. Main outcomes of the economic evaluation are the total care costs per successfully treated patient (no fall in the 6-month follow-up, a 20% reduction in fear of falling, or both) and per fall prevented.

Phase II: Feasibility study by piloting intervention and evaluation of the CPS

Test the feasibility of the recruitment process, intervention, and measurement

Once the draft intervention had been designed and described in a series of guidelines, the researchers explicitly trained the instructors to deliver the intervention in the pilot study. Next, a guide was written for the patients and caregivers that included practical information regarding the intervention, the goals of the intervention, and a brief outline of the intervention.

Recruitment process

The participating geriatricians completed screening forms for all patients they saw during the pilot period. Based on the screening form, eight dyads received written information. Researchers provided additional information and answered questions, which patients and caregivers greatly appreciated. Four dyads provided informed consent for their participation in the pilot study. After the first session, one dyad dropped out because of hospitalization of the patient.

Intervention: content

During the first pilot session, it became clear that the functional and cognitive levels of the patients were lower than had been expected. Therefore, it was necessary to reduce the number of exercises and psychological components in the intervention.

Instructors', patients´, and caregivers´ opinions about the intervention were evaluated through the use of focus groups and questionnaires. Based on these questionnaires, the recommendations produced during the expert meeting, and the suggestions of the

researchers and instructors, a basic set of intervention components and several additional components were established to tailor the intervention to each individual participant.

Intervention: organization

The presence of the caregivers proved to be of added value for the intervention, although they needed encouragement from the instructors to help the patients with their homework exercises.

As the instructors, caregivers, and patients indicated in the questionnaires and focus groups, they were all satisfied with the duration, number, and frequency of the sessions. The intervention was not burdensome to patients and instructors. The caregivers felt burdened by the need to attend all sessions. The project team decided that caregivers should attend as many sessions as possible but could be replaced by another caregiver in case of prior obligations. Caregivers and patients reported that a group with three dyads was too small and that one with eight dyads would be better, but to ensure patient safety, a maximum of six dyads will be included.

Based on the results of the pilot study and the discussion in the third expert meeting, the intervention was revised. Eventually, a final intervention emerged that all of the experts and stakeholders thought would function in a real-world setting and would be suitable for the evaluation.

Measurement

The patients in the pilot study used the fall calendar to record their falls during the 5-week pilot period. The caregivers had to remind the patients to fill out their calendars. Patients reported that, if they were asked to continue to fill out the calendar over a longer period of time, they would probably forget to do so. Furthermore, obtaining high-quality reports of falls is resource intensive for researchers, as well as for patients and caregivers, so a pilot study was initiated that was performed alongside the RCT to evaluate the feasibility, validity, and reliability of a telephone inquiry system to detect falls.[42]

The feasibility of the baseline assessment (questionnaires in patients and caregivers and quantitative gait and balance assessment only in patients) was also tested in this pilot study. The questionnaires were sent to participants´ homes a week before they came to the hospital for their baseline assessment, which allowed patients and caregivers to complete the questionnaires at their convenience. The researchers asked patients and caregivers to give their opinion of the assessment in focus group. The baseline assessment was completed in a timely fashion for patients and caregivers. The assessment was not overly burdensome for patients or caregivers.

Estimate recruitment and retention and determine sample size

The main goals of the pilot study were to evaluate the feasibility of the intervention and to inform the final selection of intervention and outcome measures, although the sample size estimations had to be based largely on reports available in the literature.[43] An attrition rate of 15% was estimated based on a pilot study and prior research that had been performed in frail older persons.[44]

To identify as many eligible patients as possible, patients were recruited from all geriatric outpatient clinics, and two neighboring hospitals were recruited to participate in the study.

Phase III: Evaluation of the CPS

This section provides examples of certain parts of the evaluation process that required specific attention based on the MRC framework.

The multicenter RCT began recruitment in January 2008 and closed in September 2009.

Assess effectiveness

For logistic and capacity-related reasons, the dyads entered the allocation procedure in batches of 10 dyads that included five controls that received usual care and five dyads that received the intervention. To overcome allocation predictability and imbalance, treatment allocation was based on a recently developed minimization algorithm. This algorithm balances prognostic factors between treatment groups within batches and overall. Prognostic factors were identified based on the literature and the pilot study.

In May 2008, it became clear that only 20% of the eligible patients had consented to participate in the study. According to the framework, a second feasibility study was started and a noninclusion analysis conducted to reveal the reasons for nonconsent and to identify differences in the characteristics of patients and caregivers who consented to participate in the study and those who did not.

Following the recommendations of the instructors, the project team moved up the booster session from 3 months to 6 weeks after the last regular session.

Based on results of the noninclusion analysis and the preliminary results of the full-scale evaluation, the researchers developed an additional intervention alongside the RCT in which the original intervention was adapted to a home program. This meant moving backward in the framework from phase III to phase I again.

Measure outcomes

To determine whether short-term changes persisted in the patients, long-term follow-up measurements (quantitative gait and balance assessment only in patients and questionnaires in patients and caregivers) were scheduled in the hospital. The three follow-up assessments

are similar to the baseline assessment. After the start of inclusion, to lower the burden on patients and caregivers, the project team omitted one of the quantitative gait and balance assessments in patients for which a hospital visit was required. As a result, patients and caregivers needed to complete only a mailed questionnaire that could be returned in the pre-addressed stamped envelope with which the caregivers were provided.

If patients were too ill or tired to come to the hospital for the quantitative gait and balance assessment or to complete the questionnaires, they were offered a brief telephone assessment to measure fear of falling and falls (the primary outcome measures).

As recommended in the literature, missing data was re-collected to the extent that it was possible, and the demographic characteristics of participants who had missing data and the reasons that the data was missing were added.[41]

Evaluate process

Questionnaires were administered to patients, caregivers, and instructors to gain insight into the factors that were potentially influencing the effectiveness of the intervention and to identify factors that would facilitate the future implementation of the intervention. Four main process factors that the researchers felt had the potential to modify primary outcome measures were assessed: performance of the intervention according to protocol, attendance of participants, adherence of participants, and opinion of instructors and participants regarding the intervention. These process measures also represent potential confounders.

Phase IV: Implementation of the fall prevention intervention

Because it was decided to adapt the original intervention, which meant that it was necessary to move backward again in the framework, the original fall prevention intervention was not implemented, so the implementation phase is not described in this article.

Funding of complex interventions

The resources needed to develop, evaluate, and disseminate a complex intervention are highly dependent on the type of intervention and evaluation. It is the challenge for geriatric researchers to explicitly explain the preconditions to be met to enable scientifically sound research on complex interventions with frail older subjects. This article and the MRC framework may contribute to the body of evidence that can be referred to when specifying special needs for design and funding of such studies.[3]

Apart from researchers, funders may use this article and the MRC framework to assess whether developmental research sufficiently addresses the challenges of the four subsequent MRC framework phases and the criteria directly related to this (Table 2).[3]

Table 2 Checklist for researchers and funders for effective and efficient research on developing complex interventions in geriatrics (adapted from Medical Research Council [3])

- Are the MRC framework phases of Development, Feasibility and Piloting, Evaluation and Dissemination sufficiently elaborated?
- Are stakeholders involved in the choice of the main research question and design of the research to ensure relevance and feasibility?
- Is the (existing) evidence provided and evaluated in an integrated and graded way? Is it based on systematic reviews and not solely on individual studies or clinical experience?
- Is the subtype of frail elderly, whom the intervention aims at, sufficiently described?
- Are all harms, benefits and costs identified?
- Is the context and environment, in which the evaluation is undertaken, sufficiently explored and the intervention adapted to this?
- What user involvement is going to facilitate in recruitment and carrying out the study?
- Is the study ethically sound and already judged on proportionality, with regard to the vulnerable patients involved, by the ethical review board ?
- What arrangements are put in place to monitor and oversee evaluation, feasibility, effectiveness and efficiency of the (evaluation of the) intervention?

Discussion

Developing and evaluating complex healthcare interventions is a high priority in geriatrics. This process is challenging, because it requires excellence in patient care and research, and rewarding, because it can improve patient care. This study illustrated that the MRC framework for the development and evaluation of complex interventions is a useful tool that describes, underlines, and supports this specific innovation technique. The framework successfully guided the development, evaluation, and reshaping of a fall prevention intervention. Moreover, in the past it also helped design an occupational therapy intervention for dementia patients and their caregivers that can be performed in the home that is currently the intervention that has the largest effect size on functional performance of all existing drug and non-drug interventions in dementia.[37,45] The framework is useful for complex geriatric interventions in general, particularly in the evaluation of geriatric syndromes.[46]

The use of the MRC framework eliminates the risk of evaluating unfeasible interventions and using designs that do not fit and maximizes the chance of developing a successful intervention and evaluation. In this way, resources are saved and the benefit:burden ratio of frail participants is maximized. Furthermore, for interventions that fail to demonstrate effectiveness, it is useful to move backward in the cyclical process. In this way, deficits in the development process or evaluation design can be determined, rather than abandoning the intervention altogether.

It was possible to refine a fall prevention intervention and evaluation using a number of methods and resources. Conducting in-depth interviews with patients and informal caregivers ensured that the intervention was appropriate and relevant to the needs of the target population. Furthermore, experts and independent specialists were involved (through expert meetings and Delphi studies, respectively) in all of the different domains of the intervention. Previous studies have found that expert groups provide valid representations of the opinions of the fields that they represent.[47]

The framework stresses the importance of piloting and process evaluation, and the publication of these data. The published literature on fall prevention interventions shows that it may impair the chances for future research, because only the negative RCTs of a complex intervention are published. For example, after the last negative trials on fall prevention in patients with cognitive impairment, no other interventions seem to have been attempted in these patients. To prevent such deadlocks, systematic methodological guidelines, such as the MRC framework, stimulate researchers to publish data on piloting and on careful process evaluations in conjunction with negative outcomes on complex interventions.

In conclusion, a fall prevention program for frail older fallers, including patients with cognitive impairment and their caregivers, was successfully developed and tested in a RCT. The cyclic evaluation and modeling process continues, leading to greater understanding of the components of the intervention, higher feasibility, and increasing the chances for optimal investment of research efforts.

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Qualitative study on the impact of falling in frail older persons and family caregivers: Foundations for an intervention to prevent falls

Abstract

Objectives: The primary aim of this study was to explore the impact of falling for frail community-dwelling older persons with and without cognitive impairments who have experienced a recent fall and their primary family caregivers. The secondary aim was to define components for a future fall prevention programme.

Methods: Grounded theory interview study, with 10 patients (3 cognitively unimpaired, 4 with mild cognitive impairment and 3 with dementia) and 10 caregivers.

Results: All patients described a fear of falling and social withdrawal. Caregivers reported a fear of their care recipient falling. Most patients were unable to name a cause for the falls. Patients rejected the ideas that falling is preventable and that the fear of falling can be reduced. Some caregivers rated the consequences of their care recipients' cognitive problems as more burdensome than their falls and believed that a prevention programme would not be useful because of the care recipients' cognitive impairment, physical problems, age and personalities.

Conclusion: Falling has major physical and emotional consequences for patients and caregivers. A fall prevention programme should focus on reducing the consequences of falling and on promoting self-efficacy and activity. The causes of falls should be discussed. The programme should include dyads of patients and caregivers because caregivers are highly involved and also suffer from anxiety. Before beginning such a programme, providers should transform negative expectations about the programme into positive ones. Finally, caregivers must learn how to deal with the consequences of their care recipients' falling as well as their cognitive impairment.

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Introduction

Falls are a major health problem in older persons; they lead to immediate effects such as fractures and long-term problems such as a fear of falling, disability and loss of independence.[1] Frail older persons are at an increased risk of falls.[2] The first three of the five components defining frailty (weakness, slow walking speed, low physical activity, self-reported exhaustion and weight loss) are risk factors for falling[2-3] cognitive impairment is an additional risk factor.[3] The annual incidence of falls in cognitively impaired older persons is 60%, which is twice the incidence in cognitively normal older persons.[4] About 25% of frail older persons are cognitively impaired.[5] In frail older persons falls often coexist with cognitive impairment.[6] However, quantitative and qualitative research on falling and the fear of falling have focused on non-frail older persons without cognitive impairments rather than on frail older persons both with and without cognitive impairments.[7-13]

In addition, little is known about the consequences of falling for informal caregivers, who are predominantly the family members of frail older persons. Caregivers of patients with dementia mainly deal with fall risk by controlling all of their care recipient's actions, often increasing the dependence of their care recipient.[14] A cross-sectional study showed that among frail community-dwelling older persons, falls are positively correlated with caregiver burden.[15] Caregivers of older persons who experienced recurrent falls and suffered from Parkinson's disease (PD) or stroke were concerned about possible future falls and felt unprepared for their caregiving role. These caregivers need more support and advice, especially about managing falls.[16-18]

Few fall prevention interventions have been effective in high-risk, frail, community-dwelling older persons without cognitive impairment. Furthermore, there currently is not a falls prevention intervention with proven effectiveness in frail community-dwelling patients with dementia.[12;19] In older persons with milder cognitive deficits only one intervention significantly reduced falls. However, the trial that evaluated the intervention also included cognitively unimpaired older persons and no sub-group analysis in relation to cognitive impairment was performed.[20] Evidence-based strategies to reduce the fear of falling in frail community-dwelling older persons, especially those who suffer from cognitive impairment, are lacking.[21]

Older persons with mild to moderate dementia are often good informants who are able to describe their subjective states and articulate their feelings, perspectives and experiences.[22] Therefore, there is no reason to exclude them from qualitative studies.

To provide adequate fall prevention and psychosocial support for frail community-dwelling older persons and their caregivers, in-depth knowledge of the impact of falling on both patients and caregivers is essential. Our primary aim is to explore the views, experiences, emotions and needs regarding falling in frail community-dwelling older persons with and without cognitive impairments who have experienced a recent fall, as well as in their primary caregivers. Our secondary aim is to define key components for a future fall prevention programme.

Methods

Sample

We drew a sample of patients and family caregivers from the geriatric outpatient fall clinic of the Radboud University Nijmegen Medical Centre in the Netherlands. Patients were eligible for participation in the study if they were community-dwelling, met the frailty criteria[2] and had fallen at least once in the month before their visit. Caregivers were eligible if they were the primary family caregiver, which was defined as the family member who was most involved in caring for the frail older person who experienced a fall; this caregiver assisted with at least one personal or instrumental activity of daily living and monitored the patient.

We used the method of purposive sampling, which involves a deliberate selection of subjects, to obtain a full view of the impact of falls on both patients and caregivers.[23] Patients differed in their level of cognitive functioning [indicated by their mini-mental state examination (MMSE) score]; this factor has been associated with a fear of falling and falls.[3;24] Patients with mild cognitive impairment (MCI) or dementia disagree and argue with their spouses about the causes of cognitive decline.[25] Half of the study participants were involved in care recipient-caregiver dyads. The remaining participants were not related to each other.

Participants (patients and caregivers) were informed about the study and received written consent material matched to the cognitive capacities of the patients. Before the interview, the researchers (MG and MF) answered participants' questions by phone. Patients' geriatricians (who were not involved in the study) and the researchers (MF and MG) judged all patients to be mentally competent to give informed consent. Ethical approval of this study was obtained from the Medical Ethical Committee Region Arnhem-Nijmegen.

Data collection

Two well-trained researchers (MG and MF) conducted the face-to-face interviews. The interviews were arranged at a time and place that suited the interviewees (home N=13, outpatient clinic N=7). Before the interview all interviewees gave their written informed consent. The interviews were audio-taped with the interviewees' permission and transcribed verbatim. Transcripts were anonymised and only two researchers (MG and MF) had access to the interviewees' names. The interviewees were told that they could stop the interview at any time and decline to answer questions without giving a reason. They were given the opportunity to discuss any concerns at the end of the interview and were asked to comment on the manuscript of their interview. The interviews lasted an average of 35 minutes (SD 14 minutes). An interview guide was used and included topics derived from the literature[9-10;14-15;26-27] and from daily practical experience. A panel of three experts (two in geriatrics and one medical psychologist) evaluated the validity of the two versions of the topic list. Topics were included when the majority of the experts agreed. After piloting the interview guide, several questions

were excluded or reformulated. The following topics were discussed within the interviews: the consequences (physical, emotional, behavioural and social) of falling for their daily lives, the cause of the falls and the expected impact of a fall prevention programme. The caregivers were asked about the same topics, but from the point of view of their personal experience with their care recipients' falling. A care recipient is a proxy with a fall problem the caregiver cares for.

Analysis

We used the qualitative method of the grounded theory: a constant comparative analysis to identify common themes and issues.[28] Findings that emerged from the first interviews were used to adjust the topics for subsequent interviews. Interviewees were included until the saturation point of qualitative data was reached. Transcripts of the first four interviews were independently read and analyzed by three researchers (MG, MF and LJ) using the principle of open coding of early data. The researchers decided on the preliminary code list and initial themes. Later interviews were coded by MF and MG using the code list; new codes were added when data were encountered that did not fit an existing code. In regular meetings, MF, MG and LJ confirmed the refinement of the themes and ensured that no themes had been overlooked and that the saturation point was reached. Atlas-ti (Atlas-ti (version 5.2) [computer software]. Berlin, Germany: ATLAS.ti Scientific Software Development GmbH) was used to manage the dataset and to allow for systematic searching and cross-referencing.

Results

Ten patients and 10 caregivers participated in the study. Tables 1 and 2 present the socio-demographic characteristics of the patients and caregivers, respectively. Table 2 also shows some characteristics of the caregivers' care recipients (CR). Interviewees were numbered (patients: P#1-P#10, caregivers: C#1-C#10) to allow for the identification of quotations. Reported quotations are translated literally into English. Patients and caregivers #6 through #10 are dyads, so P#6 through P#10 are the same persons as CR#6 through CR#10. All of the interviewees were able to understand the interview questions and to articulate their feelings, views and experiences. However, three cognitively impaired patients experienced difficulty describing falls in detail.

Table 1 Socio-demographic and health characteristics of patients (*n*=10)

Variables		*n*
Gender	Female	6
	Male	4
Age (years)	70-80	6
	81-90	4
Marital status	Married	7
	Widowed	2
	Divorced	1
Level of education (range 1-7[a])	1-3	3
	4-5	5
	6-7	2
MMSE-score (range 0-30[b])	15-20	2
	21-27	5
	28-30	3
Cognitive impairment	None	3 (P#1, P#5, P#10)
	MCI[c]	4 (P#3, P#4, P#6, P#9)
	Alzheimer's disease (CDR1[d])	2 (P#2, P #7)
	Vascular dementia (CDR1)	1 (P#8)
Number of falls in the past year	1-5	4
	6-9	3
	≥10	3
Relationship to caregiver	Mother	2
	Father	1
	Spouse	7

The mean age of the patients was 78.5 years (SD 4.3) and the mean age of the caregivers was 66.5 years (SD 4.3). Seven patients and eight care recipients suffered from MCI or dementia. The patients' mean MMSE score was 24.3 (SD 4.1, range 19-30) and the care recipients' mean score was 22.8 (SD 4.8, range 16-29). Patients reported physical consequences of their falls, including fractures and minor injuries such as soft tissue injuries and head wounds.

Emotions (patient and caregiver)

Both patients and caregivers described a constant fear of (the care recipient) falling; they also described a fear of unknown and serious consequences such as fractures and hospitalisations, regardless of their number of previous falls, gender and cognitive status. In addition, they all described fear of (the care recipient) being alone, in case of a fall accident. Some interviewees expressed fear related to not knowing the cause of the fall.

> P#6: I am afraid of falling again, especially when I am outside the house and I am alone. When I fall, then you never know, maybe I will fracture my hip.
>
> P#5: You don't understand what happened, or know what could happen; that frightens me.
>
> C#3: The biggest fear I have is that I enter the living room one day and she has been lying on the floor for a couple of hours with a fracture or worse.

Table 2 Socio-demographic and health characteristics of caregivers and their care recipients (*n*=10)

Variables		*n*
Caregivers		
Gender	Female	5
	Male	5
Age (years)	40-60	4
	61-80	3
	81-90	3
Marital status	Married	9
	Single	1
Relationship to care recipient	Son (in law)	3
	Daughter	2
	Spouse	5
Living together with care recipient	Yes	6
	No	4
Duration of care giving in years	<1	2
	2-5	3
	6-10	2
	>10	3
Level of education (range 1-7[a])	1-3	2
	4-5	3
	6-7	5
Occupational status	Retired	7
	Employee	3
Care recipients		
Gender	Female	6
	Male	4
Age	70-80	5
	81-90	5
MMSE-score (range 0-30[b])	15-20	4
	21-27	3
	28-30	3
Cognitive impairment	None	2 (CR#5, CR#10)
	MCI[c]	3 (CR#1, CR#6, CR#9)
	Alzheimers disease (CDR1[d])	3 (CR#2, CR#3, CR#7)
	Vascular dementia (CDR1)	1 (CR#8)
	Dementia not otherwise specified	1 (CR#4)
Number of falls in the past year	1-5	4
	6-9	2
	≥10	4

Notes table 1 and 2: [a] Education level was determined using Verhage's seven-point scale, where 1 denotes less than elementary school and 7 university education or higher.[35]; [b] MMSE= mini-mental status examination, lower scores mean greater disability; [c] MCI= mild cognitive impairment; [d] CDR= clinical dementia rating, range 0-3, higher scores mean greater disability.

Patients also described undirected fear, fear of losing independence and negative emotions such as frustration, anger and disappointment associated with falls and the awareness of limited physical capabilities. Several patients felt embarrassed when falling in public.

P#1: I can't attend birthday parties. It is too hot for me, I will collapse. I feel disappointed.
P#2: The fear stuck with me. I am sensitive to fear. I'm just frightened.
P#3: If I fracture my leg in a fall, before I know it I will be admitted to a nursing home.
P#4: I don't dare, there are many things I don't dare to do anymore, when we are with the two of us. I think it is annoying.
P#9: I always hope no one saw me; falling is embarrassing. *(He starts to cry.)*

Caregivers of cognitively impaired care recipients expressed feelings of stress, anger, helplessness and frustration when their care recipients refused to follow advice on fall prevention.

C#2: I feel helpless. I can't stand that. We don't control the situation; my mother-in-law *(care recipient)* doesn't listen to our advice.

Social consequences (patients)

Patients described social withdrawal and attributed this to their fear of falling and the loss of physical capabilities after falling. Patients recognized that they became (more) dependent on their caregiver after falling. One patient experienced social benefits from her fall, since she now receives more attention from her children.

P#1: I can't travel anymore because of my limited mobility. I injured my leg in a fall.
P#4: I stay at home more often and don't visit my friends anymore. I am afraid to fall when I go out.
P#5: My grandson is almost one year old. I still haven't seen his room. His room is upstairs; I am too anxious to fall when climbing the stairs.

Attributions (patients and caregivers)

Patients offered a wide range of explanations for their falls and often named several causes for one fall. Falling was ascribed to ageing, intrinsic factors (somatic origins and personal traits or habits) and extrinsic factors (poor lighting and loose carpets). However, all but one patient (P#1) said they could not name a cause for some or all falls. Patients described their falls as unexpected, uncontrollable and elusive.

P#2: In my opinion, falling is a vicious disease; I am overwhelmed by it.
P#4: There are a lot of people my age who fall.
P#5: I lost the feeling in my lower legs and then I collapsed.
P#7: I think my clumsiness must have been the cause. However, sometimes I stumble on a loose carpet.
P#9: Suddenly you fall, suddenly you black out. When you come round again, you wonder how this could happen. I can't do anything about it.

Caregivers ascribed the falls to ageing and intrinsic factors. Two caregivers mentioned intrinsic factors identified at the outpatient clinic. One caregiver ascribed the falls to an unknown origin, although she witnessed the fall (C#5). Caregivers described the falls as uncontrollable and unchangeable.

C#1: She *[care recipient]* fell that time, but sometimes I also fall. It will happen more often when you get older. I can't prevent her from falling.

C#6: If she stands up her blood pressure drops and that causes the fall, the doctor told us.

C#8: She takes a huge fall risk by keeping on doing things while she is too tired; she is too stubborn.

C#10: I think he falls because of his eye disease...macula something.

Care recipients and caregivers in dyads had incongruent ideas about the causes of falls. Caregivers attributed the falls to intrinsic factors while their care recipients either had no idea what caused the falls or mentioned an extrinsic factor (P#7).

Coping (patients and caregivers)

We observed three coping mechanisms with respect to falling in general: problem-focused coping, emotion-oriented coping and avoidance-oriented coping.

Both patients' and caregivers' problem-focused coping was reflected in actions taken to prevent future falls. Caregivers expressed strategies such as adaptations in the home environment, vigilance through frequent calls and/or visits, leaving the patient alone for as little time as possible, giving advice about posture and walking and promoting use of a walking aid.

C#2: I installed grab rails, I removed doorsteps and arranged for better lighting. I locked the door to the cellar.

C#3: When I am home, I check on her every half hour. I leave when she is safe in her chair. When I am at work, I call her every 45 minutes to check on her; during lunch break I rush home to check on her again.

C#5: At home, he uses a cane; I thought that would be safer.

C#6: I told her to stand up from a chair cautiously.

Strategies expressed by patients involved the use of walking aids, adapting their behaviour, developing new activities to compensate for activities they could not perform any more and talking about the problem with someone they trust.

P#1: Because I can't travel anymore, I started to read more papers and magazines to keep myself informed.

P#3: I decided to use a walking frame; it feels more secure.

P#10: When I get out of my car, I wait a moment and then I start walking, just to avoid falling.

The main problem-focused coping strategy for patients and one caregiver who were unsure what actually caused the falls was to use repeated searches until they arrived at an acceptable explanation for their accident. All patients came up with the same extrinsic cause, namely stumbling over an uneven pavement. Three cognitively impaired patients did not mention a search for an acceptable explanation. Some interviewees said that their coping was hindered by not having an explanation for their fall.

P#2: I still don't know why I fell. I thought that tile was the cause, but later on I think no, that wasn't the cause, I fell at a different location than where the tile was located. But in my mind, I think it must have been the tile. It is not clear, is it this, is it that, or is it a bit of both? Maybe if I knew more about it, I could deal with it; now I can't.

C#5: I don't know the cause. Sometimes I think it is because he walks so badly, sometimes I think it is something in his head.

Emotion-oriented coping in caregivers and patients was evident in thoughts reflecting acceptance of the fall problem and its consequences.

P#10: People get used to falling, they say. I will probably get used to it too.

C#1: Worrying is of no use, as it will not solve anything.

C#2: I accepted that she stays in her own home and at some point she will fall and then die.

Both patients and caregivers expressed avoidance-oriented coping methods. Patients' avoidance-oriented coping was reflected in their prevention of falls by avoiding certain situations or activities, denying falling and hiding their falls from their caregiver or others.

P#1: I just continue with my chores, thinking it (*falling*) will not happen.

P#2: I avoid going to places where there is no one to help me.

P#3: I have only fallen twice; all the other times I stumbled.

Caregivers concealed their worries and ignored the fall problem of their care recipients and the possible negative outcomes.

C#3: If I don't talk about it, the falls don't exist. I grit my teeth and just get on.

C#7: My wife doesn't know I worry a lot; I don't want to make her feel guilty.

Burden and rewards of care giving (caregivers)

Caregivers described caregiving in terms of objective and subjective burden and rewards. Objective burden refers to the amount of time spent on care giving and the nature of the care giving tasks that are performed. Caregivers describe tasks such as accompanying the care recipient to social activities or grocery shopping for them. Subjective burden refers to how the caregivers perceive the impact of the objective burden. Several caregivers mentioned that the possibility of their care recipient falling again resulted in a constant worry, vigilance and

reluctance to leave the care recipient alone. This reluctance was highly burdensome since it leads to social withdrawal.

C#2: We are on standby 24 hours a day. We take our cell phones everywhere. She *(mother-in-law)* might fall.

C#3: My husband and children hate it when I don't join them at parties. When I am at a party, I am constantly thinking about my mother. Therefore, I better stay home; I can check on her and I am more comfortable.

In addition, caregivers experienced subjective burden because of the awareness of their care recipient's dependency, role changes, fatigue and the feeling of being overwhelmed by duties.

C#3: After I *(daughter)* told her *(care recipient/mother)* not to go upstairs anymore, she said: 'Yes boss.' She makes me feel I am her mother; I hate it when she does that.

C#4: If something happens to me, he will be in trouble. It's quite a responsibility and hard to acknowledge.

Furthermore, caregivers mentioned that consequences of dementia or mild cognitive impairment such as forgetfulness, lack of understanding and communication problems were more burdensome than falls, and represented obstacles to care and fall prevention.

C#2: She not only falls regularly, but she is demented too, you know! Her Alzheimer's is the biggest problem.

C#8: I have the feeling I am met by a wall of incomprehension if I advise her not to climb the stairs anymore, but that's only because of her dementia.

Two caregivers experienced rewards of caregiving, including satisfaction from caregiving and a heightened sense of self-esteem. Only spouse caregivers mentioned caregiving as a sense of duty.

C#5: He often says to me: 'If you weren't here to support me, what would happen to me'. I get an energy boost and feel proud.

C#7: We are married in sickness and in health. Of course I care for her.

All caregivers emphasized that day care, home care, family support and respite care relieved the burden of caregiving by allowing them to be temporarily relieved of the responsibility of preventing their care recipients from falling.

C#3: Fortunately, from this week on a nurse from home care is with her during lunchtime. It provides me with some rest. I know the nurse prevents her from falling.

Fall prevention programme (patients and caregivers)

At the end of the interview, interviewees were informed about a future programme to support older persons and prevent them from falling. When asked what they expect from such a

programme, the first reaction of most patients was that they could not be helped: falling was considered inevitable and impossible to prevent. Furthermore, they felt that nothing could be done to reduce their fear of falling. Only one patient, cognitively unimpaired, had a positive view of fall prevention.

> P#1: To prevent people from falling is extremely important for older persons, but not for me. I now know what to do to avoid falling.
> P#3: They can't take my fear of falling away, they can't.
> P#5: To be able to get up after a fall by myself I need strength. They can't give me the strength in a course. I'd rather be told how not to fall, if that is teachable.

Most caregivers believed the programme would not be useful because of their care recipients' cognitive impairment, physical problems, age and personalities. One caregiver described the advantages of such a programme.

> C#1: My mother doesn't take to a thing quickly; she will tell the other participants how to deal with problems. Because of her memory problems, she is not teachable anymore.
> C#3: A fall prevention programme has no added value. My mother is not that athletic anymore. She is already 80 years old. With all her medical problems, such a programme is useless.
> C#6: My wife *(care recipient)* has fallen a couple of times, but I am old too; maybe it is useful for both of us. We may learn to avoid falls.

After insistence of the interviewers, patients and caregivers named issues that patients should learn in such a programme: awareness of the risk factors and consequences of falling, how to walk more safely, the best way to fall and stand up and how to feel more secure. Only one caregiver directly described an area with which he needed help.

> C#2: Situations that are normal to us can be dangerous for my mother-in-law; maybe we can learn how to make such situations safer.

Patients stressed that it would be helpful to contact other patients in the programme with similar experiences:

> P#2: Maybe my fellow sufferers can help me?

Discussion

This qualitative study is the first to examine the impact of falls on cognitively impaired frail older persons and primary family caregivers. Our findings shed new light on the impact of falls and fall prevention in frail older persons, especially for those suffering from cognitive impairment.

First, nearly all patients ascribed some or all falls to an unknown origin; this unawareness of origins was a source of fear and hindered coping. In two other studies that evaluated older

persons without cognitive disorders and post-stroke patients, only a minority did not know what caused their fall.[9; 17] The unawareness of the cause in this study is probably due to the cognitive problems of our patients. Only a few interviewees attributed falls to the causes identified in the outpatient clinic. No interviewee mentioned cognitive impairment as a cause. Several patients and one caregiver who did not know the actual causes of the falls tried to establish an acceptable cause through repeated searches. One way that people regain a sense of control in the face of a threatening event is through such a causal attribution.[29] Healthcare workers should make sure that both patients and caregivers understand the cause of the falls to avoid fear and promote successful coping.

Second, the study underlines that a fall prevention programme for frail older persons, especially those with cognitive impairments, should include dyads of patients and their caregivers. In this way, caregivers could be trained to function as co-therapists at home and to overcome the problems of limited learning ability in cognitively impaired patients. A study has found that the benefits of intervention programmes are better maintained when caregivers supervise the patients.[30] Training and individualised support for caregivers of patients with dementia reduced the caregiver burden.[30] Furthermore, caregivers and patients gain insight into each other's physical and mental capacities. They may be able to agree on the cause of the falls, although they did not report arguing with each other about the cause.

Third, caregivers rated the forgetfulness, lack of understanding and communication problems that arise from their care recipients' cognitive impairment as a higher burden than their falls. Cognitive decline is also felt to be an obstacle to care and fall prevention. This indicates that before inclusion of dyads in a fall prevention programme, the caregivers should learn how to deal with the consequences of their care recipient's cognitive impairment.

Fourth, patients, especially those suffering from cognitive impairment, and caregivers both expressed a fatalistic view on falls and a nihilistic expectation of fall prevention efforts. Patients described their falls as unexpected, uncontrollable and elusive, indicating a low level of self-efficacy. They stated that a fall prevention programme could not prevent falls and reduce the fear of falling. This is in contrast with research on cognitively unimpaired older persons, which revealed that the main barriers to participate in a fall prevention programme included denial of falling risk and the belief that no additional fall-prevention measures were necessary.[27] Caregivers described the falls as uncontrollable and unchangeable. In earlier research, caregivers of patients with dementia also expressed such fatalistic views of falls.[14] Caregivers attributed the falls to intrinsic factors (e.g., somatic origins and personal traits) and mentioned no extrinsic factors; similar attributions were seen from caregivers of PD patients as well.[16] Intrinsic factors are seen as less controllable than extrinsic factors since they are caused by physiological changes.[31] Since both patients and caregivers have a fatalistic view of falls and a negative attitude towards fall prevention, the chance that they will engage in and benefit

from a programme is low (a negative self-fulfilling prophecy). Therefore, it is important that the potential participants are well informed about the perceptions of falls, fall risk factors and the benefits of fall prevention, especially caregivers; such knowledge may promote a positive attitude towards fall prevention. Caregivers have an important role in fall prevention because they are trusted sources of information and they are in a position to engage the older person in prevention programmes and to motivate them to adhere to the programme.

Furthermore, our findings confirmed the consequences of falls in cognitively unimpaired older persons that are mentioned in the literature; these include a fear of falling and social withdrawal due to the fear of falling and physical limitations.[8-9;13;16;21;24] The coping styles found in our caregivers and patients were characterized by efforts to prevent falls and to avoid the problem; this resembles the coping styles of caregivers of patients with dementia and PD who fall.[14;16] and of older persons who fall.[8-9] Caregivers reported that the constant fear and worry that the care recipient would fall, which resulted in a reluctance to leave the care recipient alone, was highly burdensome. Similar findings have been reported in other caregiver populations.[15-16; 26]

Fall prevention programme

In addition to the issues named by interviewees, the programme should result in more awareness of the risk factors and consequences of falls, of how to walk, to fall and to stand up safely and how to feel more secure. Activity should be promoted; in addition to reducing the fear of falling, this may result in less social withdrawal. Providers should discuss the causes of falls with individual patients, promote patients' and caregivers' self-efficacy and help them to gain insight into each other's capacities.

Caregivers should be supported in order to reduce the caregiver burden, and they should be trained to supervise and motivate their care recipients. Since patients felt that contacting other patients with similar experiences would be helpful, a group format should be used.

Strengths and limitations

This study has some important methodological strengths. We followed quality guidelines for qualitative research with respect to purposive sampling, triangulation (interviewing both patients and caregivers), iterative analysis and multiple coding.[32-33] The sampling and data analysis achieved saturation. The manuscripts of the interviews were tested with interviewees (i.e., member checking), and the interviewees had no comments. This study also has some limitations. Our sample size was small, which is typical of qualitative research, and the results are not statistically valid for other populations. However, since the interviewees were broadly representative of patients and family caregivers at our outpatient falls clinic, our results may be generalised to other similar outpatient populations. We did not monitor the effects of the

geriatric consultation, which prevented us from discriminating the interviewees' direct fall-related experiences from those caused by the information they received. However, diagnostic labels can significantly influence a person's emotional responses, attributions and coping skills.[34]

Conclusion

The consequences of falls for frail community-dwelling older persons, including fear of falling and social withdrawal, are comparable to the consequences for non-frail, cognitively unimpaired, older persons. However, frail older persons, especially those suffering from cognitive impairment, could not name a cause for their falls; this inability is probably a major source of fear and hinders coping. A fall prevention programme should focus on reducing the consequences of falling, provide advice on walking and standing more safely and promote self-efficacy and activity. The causes of falls should be discussed.

We suggest that such a programme should include dyads of patients and caregivers. Through this approach, caregivers can be trained to provide supervision to the patients and function as co-therapists to overcome the problems of limited learning ability in cognitively impaired patients. The highly burdened caregivers can be more directly supported and their fear of their care recipient falling can be reduced. Furthermore, caregivers should also receive instruction about dealing with the consequences of both their care recipients' cognitive impairment and falling. However, before starting a fall prevention programme in frail older persons and their caregivers, providers should notice the dyads' attitudes towards fall prevention and try to transform nihilistic attitudes into positive ones; this transformation would promote uptake and improve the chances of success of such a programme.

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Determinants of caregiver burden and quality of life of informal caregivers of community-dwelling, vulnerable, older fallers

Abstract

Purpose: To identify determinants of subjective caregiver burden (CGburden) and the quality of life (CGQoL) of informal caregivers of community-dwelling, vulnerable, older fallers.

Methods: A cross-sectional study was conducted in 132 pairs of older fallers and their caregivers. CGburden and CGQoL were measured with the Zarit Burden Interview and the EQ-5D visual analogue scale, respectively. Potential determinants were measured in both caregivers and patients.

Results: A higher level of depression in caregivers (β=0.43), the caregiver being employed (β=4.72), and a higher fear of falling in patients (β=0.17) together explained 49% of the variance of CGburden. For CGQoL, 42% of the variability was explained by a regression model including the caregiver living with the patient (β=-16.64), a higher anxiety score of the caregiver (β=-1.51), a higher age of the patient (β=-0.41) and the patient attending day care (β=8.27).

Conclusion: CGburden and CGQoL of caregivers of older fallers are related to factors of both the patient and the caregiver. Anxiety and feelings of depression are the most important modifiable factors among caregivers. These findings can help to target caregiver support programmes.

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Introduction

More than one-third of community-living adults older than 65 years fall each year.[1] In older persons, falls and fall-related injuries are among the most common causes of decline in the ability to care for oneself and to participate in social and physical activities.[1] The risk of falls is high, especially in vulnerable, older fallers, and the highest risk group includes those who have cognitive impairments. Generally, such older patients do not make a satisfactory recovery from fall-related injuries.[2-4] Moreover, falling not only imposes a severe burden on patients but also on their relatives, particularly on those relatives who are directly responsible for care.[5-6]

In industrial countries, approximately 80% of help and care services to older persons is provided by informal caregivers (CG).[7] Providing care for older adults has been described as a stressful experience that may erode the physical and psychological health and quality of life of the caregiver.[7] The overall impact of physical, psychological, social and financial demands of care giving has been termed caregiver burden.[7] The concept of caregiver burden can be distinguished into objective burden, the caregiving tasks that are performed and the time spent on each task, and subjective burden, the caregivers' attitudes or emotional reactions to the caregiving experience, for example worry, anxiety and frustration.[8] It has been shown that caregivers of vulnerable older fallers experience more subjective caregiver burden (CGburden) than caregivers of vulnerable, older non-fallers.[5-6] However, the determinants of the CGburden in caregivers of vulnerable, older fallers are unknown.

In CGs of both the general population of older persons and in older persons suffering from chronic diseases, several determinants of CGburden have been identified, including the mental status, quality of life (QoL), mood, behavioral problems, disease duration, disease severity and disability of the care recipient, and the frequency at which CGs get a break from caregiving, the amount of care provided, and the duration of care giving.[5;7;9-11] Reducing CGburden may have positive effects on the fall risk in older persons because a prospective cohort study has shown that a higher CGburden score predicted more falls and fractures in patients with dementia.[6] The mechanism behind this increase in fall rate might include psychological burnout of the caregiver due to the high burden. This burnout could be so strong as to keep the CG from providing the patient with the necessary assistance.[6]

In addition to CGburden, another important factor related to caring for older persons is the caregivers' quality of life (CGQoL).[7;9;12] Despite earlier suggestions that CGburden and CGQoL are opposite sides of the same coin, research has indicated that these are distinct concepts, with CGburden being a determinant of CGQoL.[9] This result suggests that CGQoL can be improved even when burden is stable, and reducing burden may improve CGQoL.[9;13] In addition, it seems logical that an improvement in CGQoL may alleviate CGburden. In caregivers of older persons with and without chronic disease, the care recipients' QoL, mental status, mood, disease duration, disease severity and disability, and the CGs' perceived social support,

self-esteem and hours of informal care are known to be determinants of CGQoL.[9;11-12;14] Yet, up to now, no study has identified the factors that determine the CGburden and QoL of informal caregivers of community-dwelling, vulnerable, older fallers. Expanding the knowledge of these clinical correlates is important because it will enable clinicians to more quickly identify caregivers who are at risk of being overburdened or having a decreased QoL. Furthermore, the identified determinants could serve as targets for caregiver support. Caregiver support can directly benefit caregivers by facilitating management of caregiver distress. Moreover, it can also result in benefits to the patients by ensuring long-term informal care and reducing the fall risk of the patients. Our objective was to identify determinants of subjective caregiver burden and QoL of informal caregivers of community-dwelling, vulnerable, older fallers.

Methods

Study participants and recruitment

From January 2008 to September 2009, we recruited pairs of patients and their primary informal caregivers from the geriatric outpatient clinics of the Radboud University Nijmegen Medical Centre (RUNMC) and two non-university teaching hospitals (i.e., Canisius-Wilhelmina Hospital and Rijnstate Hospital/Alysis Zorggroep) in Nijmegen and Arnhem, the Netherlands, respectively. Patients were eligible if they a) fell at least once within six months before the visit to the outpatient clinic; b) were community-dwelling; c) were able to walk independently (use of a walking aid allowed); d) had a primary, informal caregiver; and e) were judged to be mentally competent by their geriatrician (who was not involved in the study) to understand the purpose and procedures of the study, to complete questionnaires and to give consent to participate. A fall was defined as an unexpected event in which someone came to rest on the ground, floor, or lower level.[15] The primary, informal caregiver was defined as the non-professional who 1) was most involved in caring for the older person who experienced a fall; 2) assisted with at least one personal or instrumental activity of daily living; and 3) monitored the patient. A pair was included when both the patient and the caregiver gave informed consent. The Medical Ethical Committee Region Arnhem-Nijmegen approved the study protocol.

Data collection

Caregivers and patients were sent self-administered questionnaires and a pre-addressed, reply-paid return envelope. The researchers phoned any participants who did not respond after three weeks to encourage them to complete the questionnaire.

Caregiver burden

The subjective caregiver burden was measured using the 12-item Zarit Burden Interview Short Form (ZBI). The responses to each item are on a 5-point Likert scale from 0 (never) to 4 (nearly always), with the sum score ranging from 0 (no burden) to 48 (highest burden). A score of ≥ 17 identifies caregivers who classify themselves as having a high burden.[16]

Quality of life of the caregiver

The QoL in caregivers was measured using the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions Questionnaire (EQ-5D-VAS).[17] The VAS assigns a global value to the current health status based on a 100-point scale, with 100 representing the 'best imaginable health state' and 0 representing the 'worst imaginable health state'. The EQ-5D-VAS scores of the caregiver (CGEQ-5D-VAS) were compared to the norm scores for the EQ-5D-VAS in the general Dutch population.[18]

Potential determinants in caregivers

The following potential determinants of burden and quality of life for caregivers were studied: age (in years), gender, employment status (yes/no), educational level (Verhage's seven-point scale, where 1 denotes less than elementary school and 7 indicates university education or higher)[19], relationship between the caregiver and the patient, anxiety (Hospital Anxiety and Depression Scale, anxiety subscale)[20], depression (Center for Epidemiological Studies-Depression scale)[21], fear that the patient would fall (yes/no), duration of care (in years), caregiving time (hours per week), and assistance from other informal caregivers (yes/no).

Potential determinants in patients

For the patients we studied, the potential determinants of burden and quality of life for the caregivers included age (in years), gender, household composition (living with other person/ living alone) , diagnosis of mild cognitive impairment (MCI) (yes/no) or dementia (yes/ no)[22-23], fear of falling (Falls Efficacy Scale-International)[24], multimorbidity (Cumulative Illness Rating Scale for Geriatrics)[25], cognitive status (Mini Mental-State Examination)[26], disability in (instrumental) activities of daily living [(I)ADL] (Groningen Activity Restriction Scale)[27], depression (15-item Geriatric Depression Scale-Short Form)[28], anxiety (Hospital Anxiety and Depression Scale, anxiety subscale), the quality of life score (EQ-5D-VAS) of the patient, and whether the patient receives professional home care (yes/no) and/or attends day care (yes/ no).

Analysis

Only data for complete pairs in which both the patient and the caregiver completed the questionnaire were included in the analysis. Descriptive statistics were used to depict the characteristics of the patients and their caregivers in the study sample. The association between CGburden and potential determinants in patients and caregivers was studied using linear regression analyses. These analyses were repeated with CGQoL as the dependent variable.

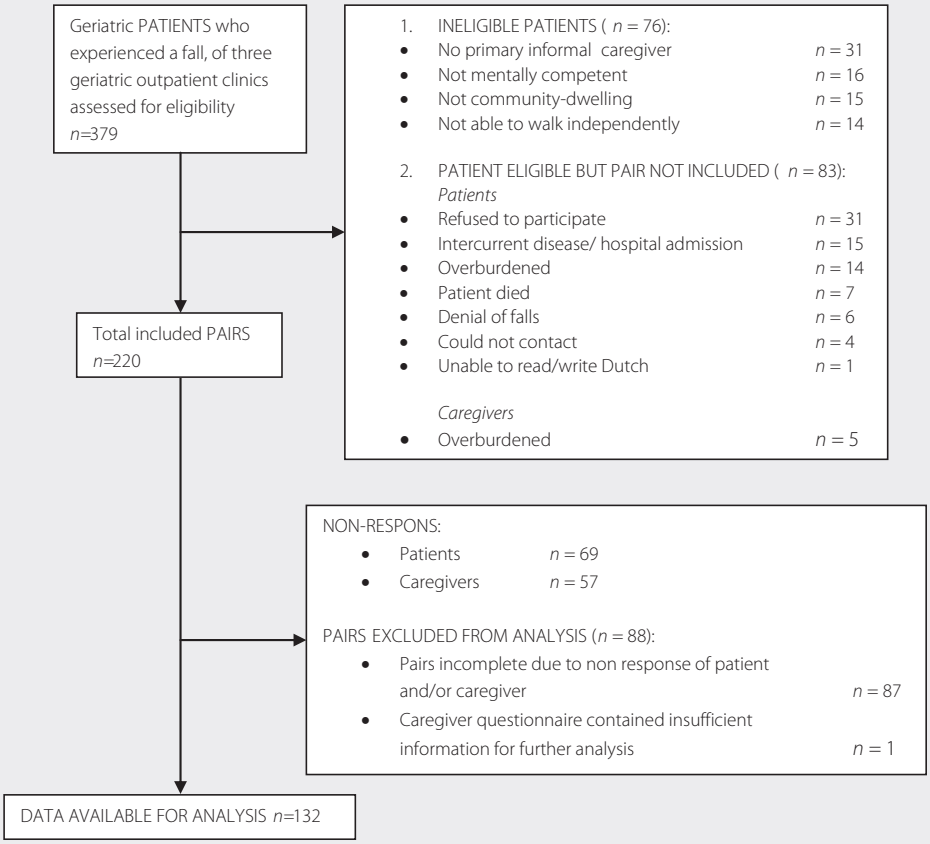
We first used forward selection to produce a multivariable linear regression model to identify the potential caregiver and patient determinants that explained CGburden and CGQoL. Overall, only variables with ≤15% missing values were included in these analyses. However, the result of such an multivariable analyses is usually not unique and alternative models may exist that perform almost as well. As a result, we calculated the percentage explained variance (R2) for all possible models and listed all models that had R2 values close to the R2 of the model that was selected by the forward procedure (R2 selection method). This approach allowed for the identification of a model with a high R2 that was most practical in clinical practice, i.e., that included determinants that are easy to obtain from taking patient or caregiver history or by administering standard questionnaires.

The forward regression method and the R2 selection method excluded all pairs with ≥ 1 missing value in any of the independent variables, even if those variables were not part of the selected model. Hence, we reevaluated each selected model on the dataset of all patients and caregivers that had no missing values for the variables in that particular model. The level of significance was set at a P value of less than .05. Results were presented with a β, and two sided 95% confidence intervals were calculated. Statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) and SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Figure 1 summarizes the recruitment of patients and caregivers. A total of 220 (58%) out of the 379 eligible pairs were recruited. Of these, 132 (60%) were included in the analysis. The main reasons for non-participation were refusal, intercurrent disease or hospital admission, and overburdening of the patient.

Figure 1 Caregiver and patient recruitment and follow-up flow diagram



The mean age of the caregivers in the sample was 68.3 years. Nearly 80% of the caregivers were female, and 47% lived with the patient (Table 1). Forty-five percent of the caregivers were daughters or sons (in law), 45% were spouses and 10% were related in another way to the patient. Seventy-eight percent of the caregivers were afraid that the patient would experience another fall. The median of the total caregiving time was 9.0 hours a week. A total of 43% of the caregivers were employed, and 52% were assisted by other informal caregivers.

Table 1 Characteristics of caregivers

Characteristics		
Age (years)		63.8 ± 13.6
Gender (female)		78 (59)
Living with the patient (yes)		62 (47)
Relationship to patient	Patient is father/mother (in law) Patient is spouse Other	60 (45) 59 (45) 13 (10)
Children (yes)		107 (83)
Children living at home (yes)		30 (23)
Employed (yes)		55 (43)
Educational level		5.0 [3.0]
Anxiety (HADS-A, range 0-21*)		3.0 [5.0]
Depression (CES-D, (range 0-60*)		5.0 [10.0]
Fear that the patient would fall (yes)		100 (78)
Duration of care (years)	≤ 2 years >2-6 years > 6 years	31 (36) 30 (35) 25 (29)
Caregiving time (hours per week)		9.0 [13.7]
Assistance of other informal caregivers (yes)		65 (52)

Notes: Data are presented as mean ± SD for normally distributed variables, median [interquartile range, IQR] for skewed variables, and N (percentages) for categorical variables; *Lower score is the more-favorable score; Abbreviations: HADS-A= Hospital Anxiety and Depression Scale, anxiety subscale; CES-D=Center for Epidemiological Studies-Depression scale.

The mean age of the patients was 79.8 years, 77% of whom were female and 44% of whom lived alone. The median number of falls among patients in the previous year was 2.5. The mean MMSE score was 25.6, and 53% suffered from MCI or dementia. The patients had a high level of multimorbidity (mean CIRS-G=12.1) and were moderately disabled in ADL and IADL (mean GARS=37.0). Patients also had a high level of fear of falling and low levels of anxiety and depression. The mean quality of life score (EQ-5D-VAS) of patients was 65.6 (Table 2).

Table 2 Characteristics of patients

Characteristics		
Age (years)		79.8 ± 7.3
Gender (female)		101 (77)
Number of falls in the previous year		2.5 [3]
Household composition	Living with other person Living alone	72 (56) 57 (44)
Multimorbidity (CIRS-G, range 0-64*)		12.1 ± 4.2
Cognitive status (MMSE, range 0-30†)		25.6 ± 3.5
Cognitive impairment	None MCI Dementia	58 (47) 37 (30) 29 (23)
Fear of falling (FES-I, range 16-64*)		34.4 ± 12.6
Disability in (I)ADL (GARS, range 18-72*)		37.0 ± 11.8
Anxiety (HADS-A, range 0-21*)		6.4 ± 4.1
Depression (GDS, range 0-15*)		4.5 ± 3.6
Quality of life (EQ-5D-VAS, range 0-100†)		65.6 ± 13.4
Professional home care (yes)		76 (59)
Attending day care (yes)		20 (16)

Notes: Data are presented as mean ± SD for normally distributed variables, median [IQR] for skewed variables, and N (percentages) for categorical variables; *Lower score is the more-favorable score; †Higher score is the more-favorable score; Abbreviations: CIRS-G=Cumulative Illness Rating Scale for Geriatrics; MMSE=Mini Mental-State Examination; FES-I=Falls Efficacy Scale-International; GARS=Groningen Activity Restriction Scale; HADS-A=Hospital Anxiety and Depression Scale, anxiety subscale; GDS=Geriatric Depression Scale-Short Form; EQ-5D-VAS=European Quality of Life-5 Dimensions Questionnaire Visual Analogue Scale.

Burden and quality of life of caregivers

The mean ZBI score was 10.5 (SD=7.6, median=9.0, interquartile range=11). Twenty percent of the caregivers experienced a high CGburden (ZBI≥17). The mean quality of life of the caregivers (EQ-5D-VAS) was 77.8 (SD=13.9, median=80, interquartile range=20). Forty-five percent of the caregivers had an EQ-5D-VAS score below the norm score for this age group within the general Dutch population (78.9).

Findings from univariable linear regression analyses

Univariable analyses revealed statistically significant associations between increasing caregiver burden (ZBI) and five caregiver determinants, including lower age (ß=-0.11; 95%CI=-0.21–-0.01; R2=0.04), being employed (ß=3.02; 95%CI=0.40–5.64; R2=0.04), higher levels of

anxiety (ß=0.74; 95%CI=0.46–1.02; R2=0.19) and depression (CES-D, ß=0.42, 95%CI=0.27–0.57; R2=0.21), and lower levels of CGQoL (ß =-0.13; 95%CI=-0.22–-0.03; R2=0.05). In addition, increased caregiver burden was also significantly associated with six patient determinants, including a more severe stage of cognitive impairment (ß=2.11; 95%CI=0.42–3.98; R2=0.05), the patient attending day care (ß=3.78; 95%CI=0.12–7.45; R2=0.03), increased fear of falling (ß=0.11; 95%CI=0.001–0.22; R2=0.03), anxiety (ß=0.37; 95%CI=0.05–0.69; R2=0.04), depression (ß=0.44; 95%CI=0.09–0.80; R2=0.05) and a lower level of the quality of life of the patient (ß=-0.14; 95%CI=-0.24–-0.04; R2=0.06).

Univariable regression analyses revealed statistically significant associations between a lower CGQoL and eight caregiver determinants and one patient determinant, including higher levels of caregiver anxiety (ß=-1.39; 95%CI=-1.93–-0.84; R2=0.18), depression (ß=-0.82, 95%CI=-1.10–-0.54; R2=0.22) and subjective caregiver burden (ZBI, ß=-0.42; 95%CI=-0.73–-0.10; R2=0.05), more invested care giving time (ß=-0.27; 95%CI=-0.47–-0.08; R2=0.06), a higher age (ß=-0.33; 95%CI=-0.57–-0.16; R2=0.10), living with the patient (ß=-7.13; 95%CI=-11.85–-2.42; R2=0.07), being unemployed (ß=7.26; 95%CI=2.51–12.01; R2=0.07), being the spouse of the patient (ß=5.67; 95%CI=2.03–9.30; R2=0.07) and more severe stages of the patient's cognitive impairment (ß=-3.94; 95%CI=-7.07–-0.80; R2=0.05).

Findings from the multivariable linear regression analyses

The determinant duration of care was excluded from these analyses because it had >15% missing values. Fifty-one pairs had ≥1 missing value in any of the potential determinants or the dependent variable and were excluded from the multivariable analyses. There were no statistically significant differences in the characteristics between the excluded patients and caregivers and the 81 pairs included in the analyses. When we further evaluated the selected determinants and models by including the complete dataset of all patients and caregivers that had no missing values for the variables in that particular model, results remained similar.

CGburden

The forward selection strategy resulted in a model with four variables that were significantly associated with an increased CGburden, including a higher depression score in caregivers, the caregiver being employed, more severe stages of cognitive impairment in patients and a greater fear of falling in patients (R2=0.54). Table 3 shows this model along with the four models with the highest R2 values, which have 2 and 3 variables. The other three models with 4 variables, also listed in table 3, had approximately the same R2 values as the model selected by the forward selection strategy. The depression score of caregivers was included in all models. The diagnoses of MCI and dementia that are required for the best four-variable model are not easy to obtain by taking patient history or administering standard questionnaires.

Based on this, we preferred the model with 3 variables, including caregivers' employment and depression score and the patients' fear of falling score because this may be the most useful model for clinical practice (R2=0.49).

CGQoL

Forward selection resulted in a model with four variables that were associated with a decrease in CGQoL (R2=0.42), including the caregiver living with the patient, a higher anxiety score in the caregivers, higher age of the patients and the patient attending day care. These variables are easy to obtain from taking patient history or administering standard questionnaires. As a result, we considered this model as the most useful for clinical practice. Table 4 shows this model along with the four models that had the highest R2 and include 2 and 3 variables. The other three models with 4 variables, which are also listed in the table 4, had approximately the same R2 values as the model selected by the forward selection strategy.

Discussion

This is the first study to examine the determinants of subjective caregiver burden and quality of life of informal caregivers of vulnerable older fallers. Explicit attention to caregivers of vulnerable older fallers is sorely needed because nearly 50% of the caregivers in our study had a quality of life score that was below the norm score in the general Dutch population.[18] Furthermore, 20% of the caregivers experienced a high level of caregiver burden.

Both caregivers' and patients' determinants, including fear of falling in patients, were associated with caregiver burden. In contrast, the quality of life of caregivers was mostly determined by the caregivers' own factors, including living with the patient, the relationship with the patient, employment, age, anxiety score, depression score, subjective burden, caregiving time and receipt of assistance from other informal caregivers. Only the severity of a patient's cognitive decline was a relevant patient factor in determining the quality of life of caregivers.

In our study, we confirmed that a negative association exists between CGburden and CGQoL in caregivers.[7;9;12] We also confirmed that a negative association exists between the QoL of patients and CGburden.[10] Furthermore, in contrast with findings from a former study among caregivers to dementia and nondementia care receivers, we could not confirm the negative association between respite care and CGburden.[9] Sending a patient to day care did not decrease caregiver burden. This discrepancy is due to the fact that the majority of patients attending day care are more severely cognitively impaired, which mediates the association between CGburden and attending day care. Furthermore, we expected that disability and morbidity would be determinants of both CGburden and CGQoL[9;11], however, we could not demonstrate such associations.

Table 3 Multivariable linear regression models with subjective caregiver burden as dependent variable (*n*=81)

Variables (β; 95%CI)				R^2
Models with 2 variables:				
Employed (5.28; 2.88 – 7.67)*	CES-D (0.45; 0.30 – 0.6)*			0.39
CES-D (0.4; 0.25 – 0.55)*	FES-I (0.19; 0.10 – 0.29)*			0.38
Living with patient (-4.39; -6.85 – -1.93)†	CES-D (0.43; 0.27 – 0.58)*			0.35
CES-D (0.40; 0.25 – 0.56)*	Cognitive impairment (2.67; 1.13 – 4.2)†			0.34
Models with 3 variables:				
Employed (4.72; 2.50 – 6.93)*	CES-D (0.43; 0.3 – 0.57)*	FES-I (0.17; 0.09 – 0.26)*		0.49
Employed (4.75; 0.246 – 7.04)*	CES-D (0.44; 0.3 – 0.58)*	Cognitive impairment (2.24; 0.82 – 3.66)†		0.46
Living with patient (-3.88; -6.16 – -1.61)†	CES-D (0.41; 0.27 – 0.55)*	FES-I (0.18; 0.09 – 0.27)*		0.46
CGAge (-0.13; -0.21 – -0.04)‡	CES-D (0.40; 026 – 0.55)*	FES-I (0.17; 0.08 – 0.26)*		0.44
Models with 4 variables:				
Employed (4.34; 2.2 – 6.48)*	CES-D (0.43; 0.3 – 0.56)*	Cognitive impairment (1.85; 0.51 – 3.18)‡	FES-I (0.15; 0.07 – 0.24)†	0.54‡
Employed (4.23; 1.95 – 6.5)*	Educational level (0.54; -0.12 – 1.2)	CES-D (0.45; 0.32 – 0.59)*	FES-I (0.18; 0.09 – 0.26)*	0.52
Employed (4.56; 2.35 – 6.78)*	CES-D (0.42; 0.28 – 0.56)*	FES-I (0.15; 0.07 – 0.24)†	PEQ-5D-VAS (-0.06; -1.32 – 0.02)	0.51
Employed (4.64; 2.43 – 6.85)*	CES-D (0.41; 0.27 – 0.55)*	FES-I (0.61; 0.07 – 0.25)*	Attending day care (2.2; -1.27 – 5.67)	0.51

Notes: * P ≤ .0001; † P ≤ .005; ‡ Model selected by forward selection. Living with patient, employed, and attending day care, no vs yes; cognitive impairment, 0=none, 1=MCI, 2=dementia. Abbreviations: 95%CI=95% confidence interval; CGAge=age of caregivers; CES-D=Center for Epidemiological Studies-Depression scale; FES-I=Falls Efficacy Scale-International; PEQ-5D-VAS=European Quality of Life-5 Dimensions Questionnaire Visual Analogue Scale of the patient.

Table 4 Multivariable linear regression models with caregiver quality of life as dependent variable (*n*=81)

Variables (β; 95%CI)				R^2
Models with 2 variables:				
Living with patient (-7.82; -12.82 – -2.81)†	CGHADS-A (-1.54; -2.16 – -0.92)*			0.35
Living with patient (-7.17; -12.2 – -2.15)‡	CES-D (-0.77; -0.18 – -0.46)*			0.34
CGAge (-0.29; -0.48 – -0.10)†	CGHADS-A (-1.56; -2.18 – -0.94)*			0.33
CGAge (-0.28; -0.46 – -0.09)†	CES-D (-0.79; -1.09 – -0.48)*			0.33
Models with 3 variables:				
Living with patient (-8.03; -12.95 – -3.12)†	CGHADS-A (-1.48; -2.09 – -0.87)*	Attending day care (-7.54; -15.02 – -0.06)§		0.38
CGAge (-0.31; -0.5 – -0.13)†	CGHADS-A (-1.49; -2.10 – -0.88)*	Attending day care (-0.83; -15.76 – -0.78)§		0.38
Living with patient (-10.17; -15.63 – -4.70)*	CGHADS-A (-1.57; -2.18 – -0.96)*	PAge (-0.37; -0.743 – 0.005)		0.38
Living with patient (-8.57; -13.56 – -3.58)†	CGHADS-A (-1.55; -2.16 – -0.94)*	Cognitive impairment (-2.97; -6.08 – 0.15)		0.38
Models with 4 variables:				
Living with patient (-10.64; -15.99 – -5.3)*	CGHADS-A (-1.51; -2.11 – -0.91)*	PAge (-0.41; -0.77 – -0.04)§	Attending day care (-8.27; -15.60 – -0.94)§	0.42¶
Living with patient (-8.45; -13.26 – -3.64)†	CGHADS-A (-1.55; -2.15 – -0.95)*	Fear that the patient would fall (6.56; 0.74 – 1.39)§	Attending day care (-8.4; -15.73 – -1.06)§	0.41
Living with patient (-9.82; -15.21 – -4.42)†	CGHADS-A (-0.90; -1.89 – 0.03)	CES-D (-0.44; -0.90 – 0.03)	PAge (-0.37; -0.74 – -0.01)§	0.40
CGAge (-0.32; -0.50 – -0.14)†	CGHADS-A (-1.56; -2.16 – -0.96)*	Fear that the patient would fall (6.33; 0.52 – 12.13)§	Attending day care (-9.11; -16.47 – -1.76)§	0.40

Notes: * P ≤ .0001; † P ≤ .005; ‡ P ≤ .01; § P < .05; ¶ Model selected by forward selection. Living with patient, fear that the patient would fall, and attending day care, no vs yes; cognitive impairment, 0=none, 1=MCI, 2=dementia. Abbreviations: 95%CI=95% confidence interval; CGAge= age of caregivers; CGHADS-A=Hospital Anxiety and Depression Scale, anxiety subscale in caregivers; CES-D=Center for Epidemiological Studies-Depression scale; PAge=age of patient.

An explanation for this might be that the patients in this study were only moderately disabled, which may have resulted in the factor cognitive impairment overruling the factor multimorbidity. Previous research from our group has revealed that caregivers feel that the consequences of dementia or MCI, such as forgetfulness, lack of understanding and communication problems, are more burdensome than falls or physical impairment.[29]

The identified determinants that are amenable to improvement or change could serve as targets for caregiver and patient support, including fear of falling, general anxiety level, and depressive symptoms in patients and anxiety, caregiving time and symptoms of depression in caregivers. Caregiver support will benefit caregivers by facilitating management of caregiver distress. These caregiver support practices will also benefit patients by ensuring long-term informal care and reducing their fall risk.

The multivariable models that were considered to be most useful in clinical practice may help healthcare professionals to identify informal caregivers who are at risk for a decreasing CGQoL or an increasing CGburden. Therefore, we recommend that any professional who is treating a vulnerable older faller should determine if the patient has a high fear of falling score (FES-I score), if the caregiver has a high depression score (CES-D score) and if the caregiver is employed to detect whether the caregiver has modifiable risk factors for a high CGburden. Identification of a caregiver who is at risk for a decreasing QoL can easily be accomplished using these three simple questions, the patient's age, if the caregiver is living with the patient, and if the patient attends day care, and by administering a questionnaire (HADS-A) to assess the caregiver's anxiety score. The FES-I, CES-D and HADS-A are short, standard questionnaires that are easy to incorporate into a geriatric assessment.

This study has several limitations. This research is based upon cross-sectional data. Consequently, any conclusions about prediction can only be understood in a statistical, and not a causal sense. Although duration of care is a known determinant of CGburden, this factor was excluded from the multivariable analyses due to missing values. Many caregivers stated that they had been caring for the patients their entire lives, others did not provide a number of years, and others simply wrote a question mark. Research on frail older persons, especially those with cognitive impairments, is known for its high level of missing data.[30] We phoned participants to recover as much missing data as possible; however, it turned out to be difficult for most of the participants, particularly patients, to answer the questions by phone. Finally, we stopped any effort to acquire missing data if we felt that our phone interviews overburdened our vulnerable older patients and/or busy caregivers. Despite the limitations, this study has several strengths. First, this is the first study that identified determinants for subjective caregiver burden and quality of life of informal caregivers of vulnerable older fallers. Second, we succeeded in collecting data in vulnerable, geriatric patients of whom more than 50% were cognitively impaired. Furthermore, these results are important for prevention purposes

because we may be able to help healthcare professionals to identify informal caregivers who are at risk for a burnout and identify targets for caregiver support. Healthcare professionals are vital to the process of recognizing caregivers who are at risk and providing caregiver support or referring caregivers to support groups. In summary, this study may contribute to improve evidence based and efficient history taking and geriatric assessments of both vulnerable older fallers and their informal caregivers.

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Studies with group treatments required special power calculations, allocation methods, and statistical analyses

Abstract

Objective: In some trials, the intervention is delivered to individuals in groups, for example groups that exercise together. The group structure of such trials has to be taken into consideration in the analysis and has an impact on the power of the trial. Our aim was to provide optimal methods for the design and analysis of such trials.

Study design and setting: We described various treatment allocation methods and presented a new allocation algorithm: optimal batchwise minimization (OBM). We carried out a simulation study to evaluate the performance of unrestricted randomization, stratification, permuted block randomization, deterministic minimization, and OBM. Furthermore, we described appropriate analysis methods and derived a formula to calculate the study size.

Results: Stratification, deterministic minimization, and OBM had considerably less risk of imbalance than unrestricted randomization and permuted block randomization. Furthermore, OBM led to unpredictable treatment allocation. The sample size calculation and the analysis of the study must be based on a multilevel model that takes the group structure of the trial into account.

Conclusion: Trials evaluating interventions that are carried out in subsequent groups require adapted treatment allocation, power calculation, and analysis methods. From the perspective of obtaining overall balance, we conclude that minimization is the method of choice. When the number of prognostic factors is low, stratification is an excellent alternative. OBM leads to better balance within the batches, but it is more complicated. It is probably most worthwhile in trials with many prognostic factors. From the perspective of predictability, a treatment allocation method such as OBM, that allocates several subjects at the same time, is superior to other methods, because it leads to the lowest possible predictability.

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1. Introduction

Group interventions, whether self-help or professionally conducted, are popular among patients and caregivers. They are used in the context of various, mainly, chronic, diseases; for example, exercise groups for obese teenagers, psychoeducational group interventions for the management of psychiatric disorders, or support groups for informal caregivers of elderly people with dementia.[1-3] Depending on the group's purpose and needs, a group intervention will be either open or closed. Open groups run on an ongoing basis and new members can join at any time during the group's existence, whereas closed groups do not allow newcomers to join once the group has commenced. In this article, we restrict ourselves to closed groups. Group interventions often help participants by providing an opportunity for social comparison.[4] The groups may include subjects that differ on factors affecting social comparison such as stages of disease or capability to express feelings and emotions.[4] This implies that the composition of a group may have a substantial impact on the outcome. A group with a majority of women, for example, may interact and react differently than a group with mainly men.[5] Not only are the subjects in a group likely to influence each other, but the leader, instructor, or therapist also may have an impact. This leads to a correlation within the groups and to extra variation of the treatment outcome between groups. These factors have to be taken into account in the statistical analysis and have consequences for the size of the trial (see sections 8 and 9). When the treatment outcome varies between groups, this increases the between group variance and therefore decreases the power of the trial. To reduce the differences between the groups, it may be useful to use treatment allocation methods that attempt to balance prognostic factors. Stratification and minimization are the commonly used methods to reduce imbalance on prognostic factors.[6] We describe the performance of these methods when used in an intervention trial with a closed group format in sections 6 and 7. It is important that prognostic factors are balanced over the treatment arms at the end of the trial, because imbalance on prognostic factors undermines the credibility of the trial.[7-9] Furthermore, it also decreases the power of the trial.[6,10] Minimization can handle more prognostic factors than stratification, but a disadvantage of minimization is that in certain circumstances it leads to predictability of the next allocation (see section 3).

However, when a treatment is given in a closed group format, a group can only start when the complete group has been enrolled. It is important to have parallel treatments in a clinical trial – ideally, groups should run simultaneously and should start in pairs, one in each treatment arm. In practice, this means that treatment allocation needs to be postponed till sufficient participants for two groups have been enrolled. In fact, postponement of the allocation is preferable because it may reduce loss to follow-up after allocation. When treatment allocation takes place for all participants of two groups at the same time, it is possible to further optimize the balance and to make the allocation unpredictable. For this purpose, we developed an allocation method called optimal batchwise minimization (OBM). We describe the method in section 4 and show to what extent it improves balance in sections 6 and 7.

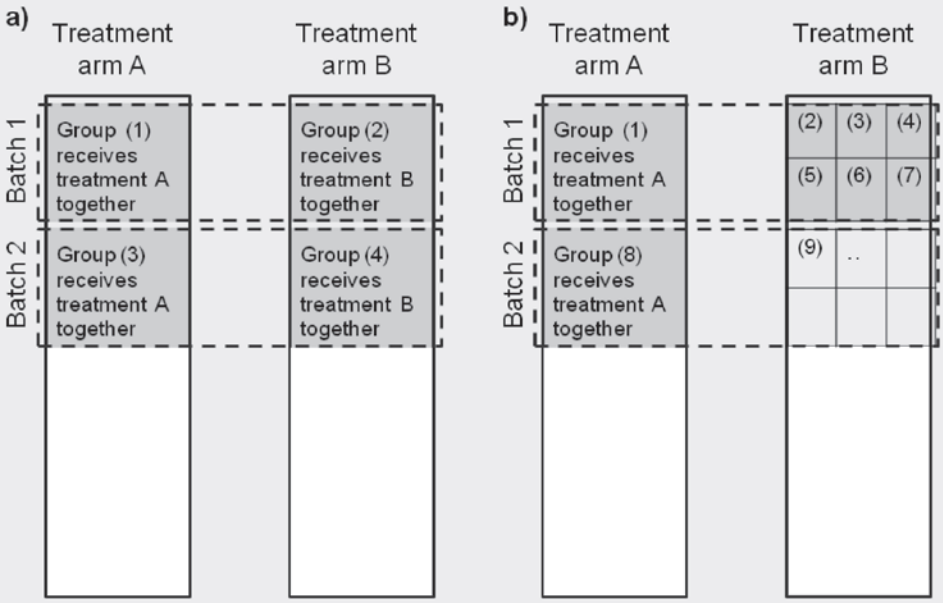
2. Terminology and examples

Fig. 1a shows the design of a trial that compares two treatments that are given in closed groups, for example a trial that compares two programs aimed at supporting juveniles with cancer. In treatment arm A, groups of 10 juveniles sit together and exchange experiences and get advice. In treatment arm B, not only the juveniles, but also their parents exchange experiences and get advice. The treatments are given in closed groups, so a group cannot start until all participants have been enrolled in the study. In this example, this implies that each time that a batch of 20 youths has been enrolled, two groups of 10 can be formed (one in each treatment arm). The illustration of the design (Fig. 1) shows each batch enclosed by dotted lines, and the groups nested within those batches are shown as gray squares. The group numbers, shown between brackets, will be discussed in section 8.

Fig. 1b shows the design of a trial that compares a group treatment (arm A) to an individual treatment (arm B). We are currently performing such a trial. It evaluates a fall prevention program aimed at reducing falls and fear of falling in community-dwelling frail older patients who have experienced a recent fall. The program consists of a closed group intervention of 10 two-hour sessions with both physical and psychological components. Balance and gait exercises are practiced under the guidance of a physiotherapist and a psychologist discusses feelings, emotions, and experiences associated with falls. Half of the patients receives the intervention in a closed group format and the other half receives usual individual care (controls). To ensure patient safety, each group consists of only six patients. Therefore, the batch size is 12. Each batch consists of six patients in treatment arm A and six patients in treatment arm B. The patients in treatment arm A receive the intervention as a group, whereas the patients in treatment arm B receive usual (i.e. individual) treatment and are therefore not part of a group and have no interaction with each other or with an instructor. We have attempted to illustrate this design in Fig. 1b by showing the intervention group (arm A) in an undivided square and the control group (arm B) in a subdivided square in which each participant is represented by a separate rectangle. The rectangles are intended to illustrate that the patients in arm B are treated individually.

Figure 1 a Design of a trial that compares two interventions that are delivered to individuals in closed groups

Figure 1 b Design of a trial that compares an intervention that is delivered to individuals in a closed group to an individual intervention



Notes: Diagram of the design of a trial with group treatments in both arms (a) and a trial that compares a group treatment to individual treatment (b). Each time a group treatment starts in one of the treatment arms a corresponding number of subjects in the other arm receives either group treatment (a) or individual treatment (b). These subjects constitute a batch and the study consists of a number of such batches.

As the fall prevention trial was fairly small with, 54 participants per treatment arm, we were worried that imbalances on important baseline variables would occur despite randomization and that this would undermine the credibility of the trial.[7-9] Hence, we planned to carry out stratification or minimization to minimize the risk of imbalances. In the next section, we will describe these methods in detail.

We selected baseline variables that could have an impact on the outcome of the study (prognostic factors) based on results of previous research. Earlier studies demonstrated that cognitive impairment and female gender are risk factors for falling. Additionally, a history of falls and age were known to be positively associated with falls.[11-12] We therefore considered age, gender, mini-mental status examination (MMSE) score,[13] and number of falls in the past year as prognostic factors that should be balanced between the two treatment arms. Each of

these factors was dichotomized, resulting in the following prognostic factors: gender (male vs. female), age (younger [≤ 80 years] vs. older [>80 years]), cognitive status (low MMSE score [15-23] vs. high MMSE score [24-30]) and number of falls in the past year (1 vs. >1).

3. Existing treatment allocation methods

Various methods have been developed for treatment allocation, as described below.

Unrestricted randomization: In unrestricted randomization, allocation is based on chance alone. In the case of two treatments with equal allocation, every subject has a probability of 1/2 of receiving one or the other, so the chance of correctly guessing the next allocation is 50%. Therefore, the predictability of the treatment allocation is said to be 50%. However, unrestricted randomization may lead to an imbalance of prognostic factors, and this may make the interpretation of the results of the study difficult. Furthermore, such imbalance may decrease the power of the trial.[6,10]

Randomization in permuted blocks: This randomization method[6] seems more suitable for trials that evaluate closed group interventions, especially when the size of the batch is used as block size. The predictability of the allocation for subjects that are enrolled when a new block has just started is 50%, but toward the end of the block it may increase to 100%, because if one knows all previous allocations, the last allocation in the block can perfectly be predicted. As is the case for unrestricted randomization, permuted block randomization also can result in imbalances on prognostic factors.

Stratified randomization: Stratified randomization[6] prevents imbalances, even for combinations of prognostic factors. In the fall prevention trial for example, stratified randomization aims to have balance for all possible combinations of the four prognostic factors mentioned in section 2. Each treatment arms should have half of the women over 80 with low MMSE and only one fall in the previous year. Likewise, the women over 80 with low MMSE and repeated falls in the previous year also should be equally distributed over the two treatment arms, and so forth. Balance is sought for all possible combinations of the prognostic factors. With four prognostic factors, the number of combinations is 2^4=16, and this divides the trial population into 16 different strata. When the number of factors increases, the number of strata increases exponentially, and this limits the number of variables that can be stratified for.[8,14] The predictability of the allocation with stratification is 50%.

Minimization: Minimization[6,15] makes it possible to balance treatment allocations for more prognostic factors. It is not aimed at balance within all strata, but at marginal balance. In the falls prevention trial, it seeks to arrange that each treatment arm has half of the women, half of the men, half of the over 80, half of the under 80, and so forth. It may still be the case, however, that the women over 80, or men over 80, or men under 80 and so forth are not equally divided over the treatments. Minimization does not necessarily lead to balance of the prognostic factors within the strata.

Minimization can be carried out in two ways: deterministically or with a random component. In deterministic minimization, each subsequent subject is allocated to the treatment that leads to the least imbalance. Deterministic minimization has the disadvantage that someone with knowledge of all previous allocations can predict the next allocation (high predictability)[10,15-16] and this may be an issue when all patients are enrolled or treated by a single investigator. When more investigators are involved that do not exchange information, predictability drops considerably. In minimization with a random component, each subsequent subject is allocated to a treatment such that there is a certain probability that the allocation will result in the least imbalance, for example with 75% chance.[6,15] If someone knows all previous allocations, the predictability is 75%. Because there is a 25% chance that an allocation will worsen the balance, minimization with a random component has a higher risk of imbalance over the treatment arms than deterministic minimization.

4. Optimal batchwise minimization (OBM)

The methods discussed above are all based on sequential treatment allocation: each time a subject is enrolled, a treatment is allocated. In trials that evaluate closed group interventions however, the group treatment will not start before a sufficient number of patients for a complete group is available, so it is possible to wait and carry out the treatment allocation once a whole batch is enrolled. In this situation, OBM can be used.

OBM is based on an algorithm that consists of three steps that are carried out for each consecutive batch of newly enrolled subjects:

1. Calculate the Sum of the Squared Factor Class Imbalances (SSFCI) for all possible allocations of the newly enrolled subjects.[6,15,17-19] We use the fall prevention study to illustrate the calculation of the SSFCI.

Each prognostic factor had two classes; man vs. woman, younger (≤ 80 years) vs. older (>80 years), low MMSE score (15-23) vs. high MMSE score (24-30), and one fall vs. recurrent falls in the past 12 months. $Diff_{man}$ denotes the difference between the numbers of men in the treatment arms. Similarly, $diff_{woman}$, $diff_{young}$, $diff_{old}$, $diff_{lowMMSE}$, $diff_{highMMSE}$, $diff_{onefall}$ and $diff_{recurrentfalls}$ denote the (absolute) differences between the numbers in the treatment arms for the other factor classes.

The SSFCI is then computed for each possible allocation as:
$SSFCI = diff_{man}^2 + diff_{woman}^2 + diff_{young}^2 + diff_{old}^2 + diff_{lowMMSE}^2 + diff_{highMMSE}^2 + diff_{onefall}^2 + diff_{recurrentfalls}^2$.

2. List all allocations with minimum SSFCI.
3. Randomly select one of the allocations with minimum SSFCI.

The algorithm is repeated for the complete enrollment of each batch. In the appendix, we present a SAS program and an R program (on the journal's website) that can be used to carry out OBM.

5. Evaluation of treatment allocation methods

We carried out a simulation study to compare the performance of unrestricted randomization, randomization in permuted blocks, stratification, deterministic minimization, and OBM. Our aim was to show that stratification, minimization, and OBM lead to substantially better balance than randomization in permuted blocks. We further aimed to evaluate the additional improvement of OBM vs. minimization.

The simulated trials differed in batch size, trial size, and the number of factors for which balance was sought. Trials with batches of 12 subjects had a total sample size of 48, 96 or 192 subjects. The trials with batches of 24 subjects had a total sample size of 96 or 192 subjects. For each simulated trial, balance was sought for 3, 6 or 12 factors with two classes per factor. We generated 1,00,000 trials for each combination of trial size, batch size, and number of factors. We carried out the five allocation methods in each trial and calculated the maximal imbalance of the trial (MaxI), the maximal batch imbalance (MaxBatchI), and the mean batch imbalance (MeanBatchI) as measures of performance for each method, as described below:

1. The MaxI is the maximum of the imbalances on the predictors in the trial.[16] Suppose that the treatment allocation in the fall prevention trial results in four more men in the intervention treatment arm than in the control arm. In addition, the treatment arm has six more women, but four fewer older patients, two fewer patients with low MMSE and two fewer patients with high MMSE, whereas the patients with and without recurrent falls and the younger patients are equally distributed over treatment arms. Then the imbalances are 4, 6, 4, 2, 2, 0, and 0, and MaxI is equal to the maximum imbalance of 6.

Of course, the importance of the imbalance depends on the size of the trial. A MaxI of six in a trial with two treatment arms of 24 patients each is more substantial than the same imbalance in a trial with 240 patients per treatment arm. Hence, we will present the relative MaxI (RelMaxI) by dividing the imbalance by the treatment arm size. For 6 of 24 the relative imbalance is 25%, whereas for 6 of 240, it is 2.5%. If all trial participants in a factor class were in one treatment arm only, then the imbalance would be 100%.

2. The MaxBatchI is the maximum of all factor class imbalances in the batches. Suppose a trial has five batches, and the MaxI in the factors in those batches is 0, 2, 4, 0 and 1, then MaxBatchI is 4.

In the fall prevention trial, MaxBatchI is the maximum of $diff_{man,i}$, $diff_{woman,i}$, $diff_{young,i}$, $diff_{old,i}$, $diff_{lowMMSE,i}$, $diff_{highMMSE,i}$, $diff_{onefall,i,}$ and $diff_{recurrentfalls,i}$ over all batches 1, 2, ,..,i, … $Diff_{man,i}$ is the difference in number of men between the treatment arms in batch i, $diff_{woman,i}$ is the difference in number of women, and so forth.

Again, the importance of the imbalance depends on the batch size. Therefore the relative MaxBatchI (RelMaxBatchI) is equal to the MaxBatchI divided by the number of participants in each treatment arm of the batch.

3. The MeanBatchI is the mean of all factor class imbalances in all batches: MeanBatchI is the mean of $diff_{man,i}$, $diff_{woman,i}$, $diff_{young,i}$, $diff_{old,i}$, $diff_{lowMMSE,i}$, $diff_{highMMSE,i}$, $diff_{onefall,i}$ and $diff_{recurrentfalls,i}$ over all batches 1, 2, ,..,i, …. MeanBatchI is converted to the relative MeanBatchI (RelMeanBatchI) in the same way that MaxBatchI is converted to RelMaxBatchI.

6. Results: Overall imbalance at the end of the study

Fig. 2 shows box plots of the RelMaxIs that were found in the simulated studies. For example, for studies with 48 patients and 3 prognostic factors, randomization led to a median RelMaxI of 25% of the treatment arm size (Fig. 2). So in half of the studies of this type, at least one of the prognostic factors had an imbalance of 25% or more at the end of the study, that is 6 subjects out of 24. Similarly, the lower and upper quartiles were 17% and 33%, so there was a chance of 75% that the imbalance exceeded 17% of the treatment arm size for at least one of the prognostic factors, and a chance of 25% that it exceeded 33%. The 95^{th} percentile was 46%, so in 5% of the simulated trials, the relative maximal imbalance exceeded 46% of the treatment arm size, that is 11 subjects. Finally, the maximum was 75%, so the imbalance never exceeded 75% out of 24 patients, or 16 subjects.

Figs. 2 and 3 illustrate that both minimization and OBM substantially reduced the risk of imbalances at the end of the study. When permuted block randomization was used and the trials had 192 subjects and 3 prognostic factors, the upper quartile of the RelMaxI was 24%, so there was a 25% chance of imbalances exceeding 24%, that is, an imbalance of 12 or more subjects. When the number of factors was larger, or when the trials were smaller, the upper quartiles were between 30% and 45%. The results for randomization with blocks of various lengths were similar to the results for unrestricted randomization (results not shown).

Figure 2 Relative maximal imbalance for a trial with 48 subjects

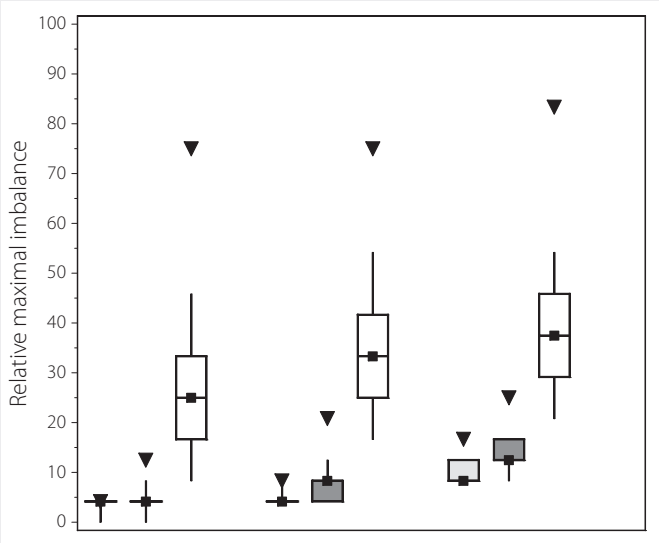
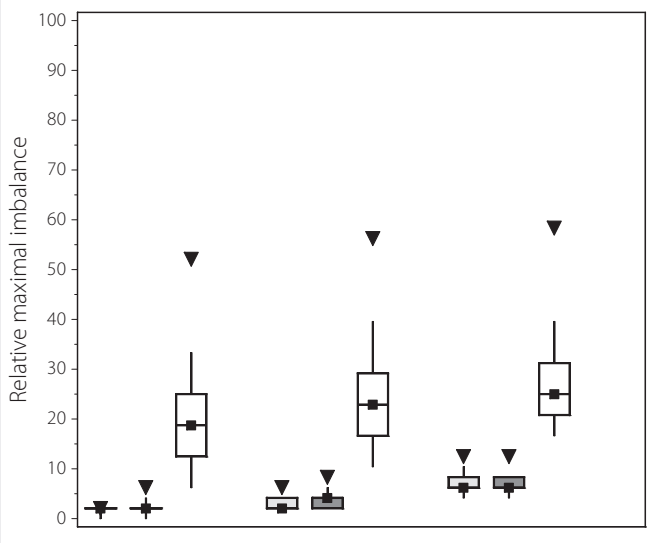


Figure 3 Relative maximal imbalance for a trial with 192 subjects



Notes: Box plots for the relative maximal imbalance RelMaxI when the group sizes are 6 (Fig. 2) and 12 (Fig. 3). The bold horizontal bars indicate the medians, the ends of the boxes indicate the quartiles, the whiskers go up to the 5th and 95th percentiles, and the triangles represent the maximum. For each combination of number of factors and number of batches. The light gray, dark gray and white boxes correspond to OBM, deterministic minimization, and permuted block randomization, respectively.

For minimization and OBM, the RelMaxI almost never exceeded 20%. The difference between OMB and minimization was modest. The largest difference was observed with 12 prognostic factors and a trial size of 48, when the upper quartiles differed by approximately 5%.
The global results, including the results for the medians were similar to those for the upper quartiles. Stratification was only practical for three prognostic factors (eight strata) and led to similar results as minimization (not shown).

7. Results: Imbalance in the batches

Figures 4-7 show box plots of the imbalance in the batches resulting from OBM, deterministic minimization, and randomization in permuted blocks. The RelMeanBatchI for OBM never exceeded 20% for trials with batches of 12 subjects (Fig. 4) and never exceeded 10% for trials with batches of 24 subjects (Fig. 5). In general, the imbalance observed with minimization was higher by a factor 1.3 when three factors were used and higher by a factor 1.7 - 2 for more than three factors. Imbalance remained below 30% in trials with batches of 12 subjects and did not exceed 20% for trials with batches of 24 subjects.

Figure 4 Relative mean batch imbalance when the batch size is 12

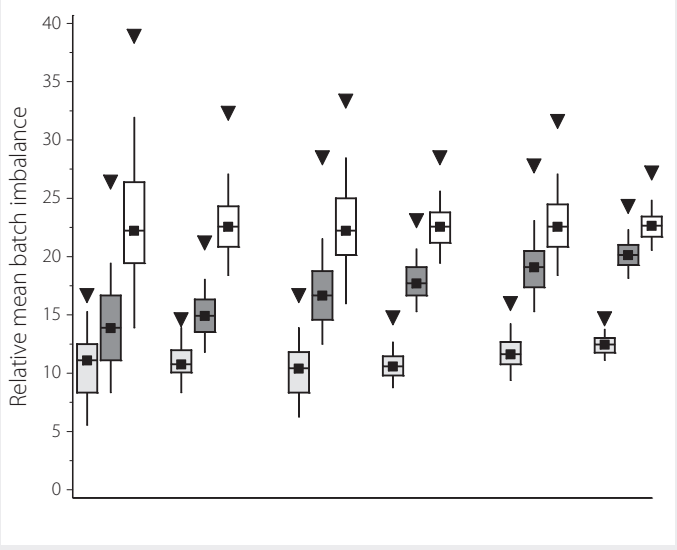
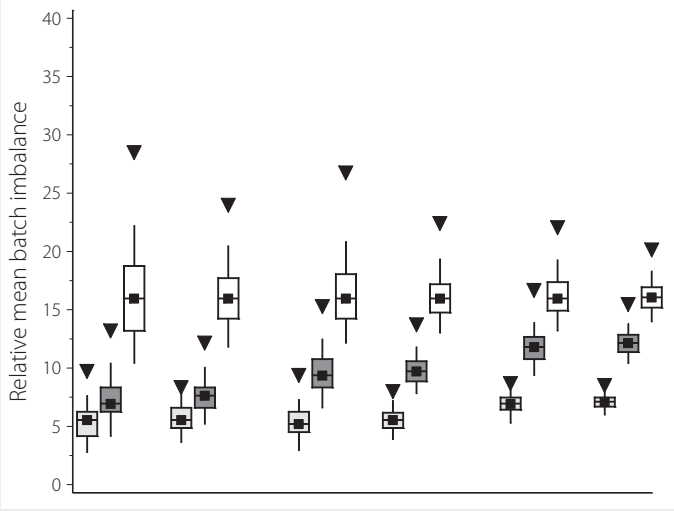


Figure 5 Relative mean batch imbalance when the batch size is 24



Figs. 6 and 7 show the RelMaxBatchI. For trials with up to 6 factors and batches of 12 or 24 subjects, the upper quartiles of imbalance for OBM never exceeded 35% and 20%, respectively. For trials with 12 prognostic factors and batches of 12, the upper quartiles of RelMaxBatchI were between 35% and 50%. When the batch size was 24, the upper quartile was approximately 25%. For minimization, the upper quartiles were a factor 1.3 - 2 higher.
In all cases, permuted block randomization led to substantially larger batch imbalance.

Figure 6 Relative maximal batch imbalance when the batch size is 12

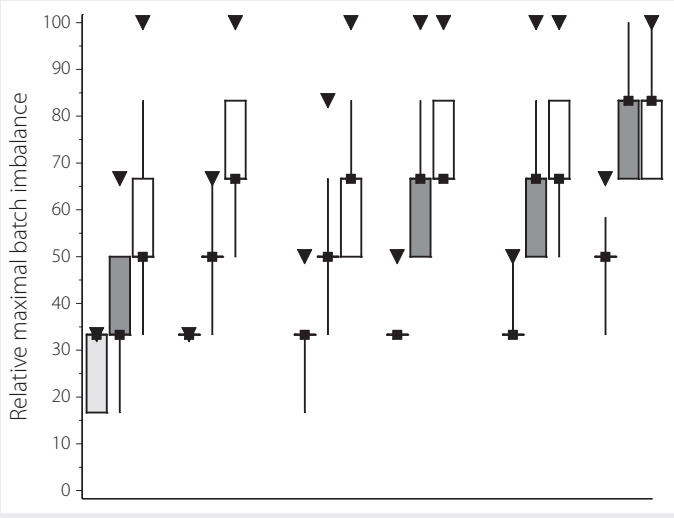
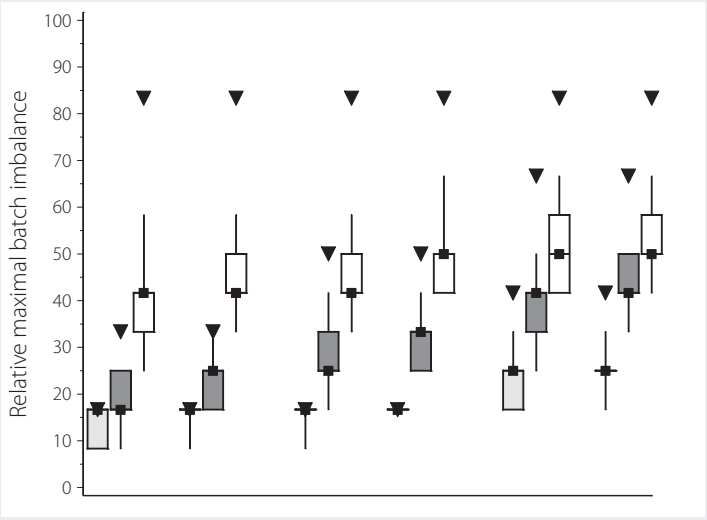


Figure 7 Relative maximal batch imbalance when the batch size is 24



Notes: Box plots for the relative mean batch imbalance (RelMeanBatchI) and the relative maximal batch imbalance (RelMaxBatchI) when the group sizes are 6 (Figs. 4 and 6) and 12 (Figs. 5 and 7). The bold horizontal bars indicate the medians, the ends of the boxes indicate the quartiles, the whiskers go up to the 5th and 95th percentiles, and the triangles represent the maximum. For each combination of number of factors and number of batches, the light gray, dark gray and white boxes correspond to OBM, deterministic minimization, and permuted block randomization, respectively.

The results for unrestricted randomization were similar (not shown). Stratification was only practical for three prognostic factors (eight strata) and led to similar results as minimization (not shown). Because the number of batches did not affect the outcome, we did not show the results for trials with 8 batches of 12 subjects.

8. Analysis methods

As we explained in the introduction, the group structure of the intervention needs to be taken into account in the analysis. To do so, a "batch" variable has to be created. All patients in a given batch have the same batch number. For example, there were 12 patients per batch in the fall prevention trial, so all 12 patients in a given batch would have the same batch number. Fig. 1 gives an example of the batch numbers. The numbers can be arbitrary, as long as different batches have different numbers.

Furthermore, a "group" variable is required. In the trial that evaluated support to juveniles with cancer (see section 2), every youth received treatment in a group, and each of these groups

should have its own unique number. In Fig. 1a, group numbers are shown between brackets. The group numbers are arbitrary, as long as different groups have different numbers.

When the treatment is given in a group format in only one arm of the trial, such as in the fall prevention trial, every subject in the other arm constitutes his own group and must be assigned his own unique group number. Fig. 1a illustrates this. Patients in treatment arm A received the intervention in a group format, so all six patients in a given group have the same group number. Patients in treatment arm B received individual treatment and so every patient has his own group number.

If unrestricted or permuted block randomization is used to allocate the treatments, the outcome of the trial should be evaluated in a mixed model (multilevel model) with group as a random factor and treatment and batch as fixed factors. If stratification, minimization, or OBM are used for treatment allocation, the prognostic factors should be included as additional fixed variables. Variables that are expected to correlate with the outcome of the study should always be included as variables in the analysis, because they will increase the power of the analysis, even if they are not used as actors in the stratification, minimization, or OBM.[20,21]

When stratification, minimization, or randomization was used in the fall prevention trial, the fixed variables would be treatment arm, batch, gender, history of falls, age, and MMSE. "Group" would be the random factor.

9. Trial size

The trial size for a study of an intervention that is delivered to individuals in groups is most easily calculated in a stepwise fashion. First, calculate the number of subjects that would be required if the treatment arm ratio were 1:1 and a t-test were carried out for the analysis. Next, if both treatments are given in a group format, the actual study size can then be calculated by multiplying this number by the design factor:

$1+\lambda_A(k_B-1)ICC + \lambda_A(k_B-1)\ ICC$ (1)

Here, λ_A and λ_B are the proportion of the subjects that are in arms A and B, respectively. The group sizes in the two arms of the trial are k_A and k_B, respectively. ICC is the intra class correlation, that is, the quotient of the between batch variance and the total variance. The derivation of the formula is shown in the appendix that will be available online.

When group B has no closed groups, as in the fall prevention trial, $k_B=1$. In that case, the formula simplifies to:

$1+\lambda_B(k_A-1)ICC$ (2)

As can be seen from the formulas, the group structure leads to an increase in trial size. Adjustment for baseline covariates may then allow for a reduction in trial size by a factor $1-\rho^2$, where ρ is the correlation between the baseline and follow up measurements.[20]

In the falls trial for example, the fall rate was expected to drop from 0.5 to 0.3 per year, with a standard deviation of 0.4. Based on a t-test, a total of 128 patients would then be required for 80% power and two-sided testing at α=0.05. The ICC was thought to be 0.05. When we now use formula 2, with k_A=6 and λ_B=0.5, we find that the study should have [(1+0.5(6-1)0.05]128=144 participants. Furthermore, we expected a correlation of 0.5 between the number of falls before and after start of treatment and so the inclusion of the number of falls before treatment as a covariate resulted in a reduction of trial size to a trial size of at least (1-0.5^2)144= 108 subjects, that is nine batches.

If the treatment ratio were six to four, so that each batch had 10 subjects of which six received the group treatment and four received individual treatment, λ_B would be 0.4. Formula 2 would then lead to a trial of [1+0.4(6-1)0.05]128= 141 subjects. Adjustment for the number of falls before start of the treatment leads to (1-0.5^2)141= 106 subjects. As each batch consist of 10 subjects, this would lead to a trial of 11 batches, with a total of 110 subjects

10. Discussion and conclusion

We described methods for the design, the analysis, and the sample size determination of trials evaluating interventions that are delivered to individuals in closed groups. The group structure of the trial requires multilevel analysis and has an impact on the power of the trial.

Furhtermore, we developed and described OBM - a new allocation method for trials evaluating interventions that are delivered to individuals in groups that are subsequently assigned to randomization. We compared the performance of unrestricted randomization, permuted block randomization, stratification, deterministic minimization, and OBM and found that the latter two methods have considerably less risk of imbalance than unrestricted randomization and permuted block randomization. When stratification is feasible, that is, when the number of factors does not exceed three, also stratification has considerably less risk of imbalance than unrestricted randomization and permuted block randomization. We used the maximal imbalance (MaxI) to quantify the imbalance at the study level. As we mentioned before, a large imbalance on one or more prognostic factors, that is a large MaxI, may lead to questions about the interpretation of the results of the study. Therefore, maximal imbalance is a suitable primary outcome measure to evaluate the performance of the treatment allocation methods.[7-9]

On the batch level, OBM leads to less imbalance than minimization. However, the exact impact of the imbalance is difficult to estimate. Although it has been speculated that the composition of a group may have a substantial impact on the outcome, to our knowledge there is no quantitative information about the extent of the impact. Most likely it will vary substantially, depending on the nature and the constitution of the groups. Furthermore, between-group differences lead to an increase of the variance and therefore decrease the

power of the trial, but it is difficult to quantify the strength of this relationship. Most likely, the extra variance because of imbalance is proportional to the size of the imbalances but how large the impact is will depend on many factors such as the strength of the relation between the prognostic factors and the outcome, the number of prognostic factors, the batch size, and the correlation between those factors.

We have evaluated OBM in trials with up to 12 factors, whereas the batch sizes were 12 or 24. The results mainly depended on the number of factors and a small additional simulation also showed that for other batch sizes the imbalance on the batch level was similar (results not shown).

We did not evaluate minimization with a random component, because the results would lie between permuted block randomization and deterministic minimization. When a random component is used, the chance that each allocation is optimal has to be chosen beforehand and it will lie between 50% and 100%. A chance of 50% would correspond to unrestricted randomization whereas a chance of 100% would imply deterministic minimization. Accordingly, the results for random component minimization lie between those for randomization and deterministic minimization. As the chance of an optimal allocation becomes closer to 100%, the results are more similar to deterministic minimization.

We used SSFCI for the minimization and OBM algorithms because, to our knowledge, it is the most commonly used method for minimization. Patient allocation based on the SSFCI was originally developed by Taves, Pocock, and Simon, is well known and has shown excellent performance.[16-19,22-24] However, other approaches also could be used. For example a weighted SSFCI would be an option. In the fall prevention study, this would lead to SSFCI = $w_1*diff_{man}^2+ w_2*diff_{woman}^2+ w_3*diff_{young}^2+ w_4*diff_{old}^2+ w_5*diff_{lowMMSE}^2+ w_6*diff_{highMMSE}^2+ w_7*diff_{onefall}^2+ w_8*diff_{recurrentfalls}^2$. The weights w_1, w_2, w_3, … w_8 reflect the relative importance of the factors classes. In principle, all approaches that have been developed for minimization[6,10,15] can be used for OBM.

From the perspective of obtaining overall balance, we conclude that minimization is the method of choice. When the number of prognostic factors is low, stratification is an excellent alternative. OBM leads to better balance within the batches, but it is more complicated. It is probably most worthwhile in trials with many prognostic factors. From the perspective of predictability, a treatment allocation method such as OBM, that allocates several subjects at the same time, is superior to other methods, because it leads to the lowest possible predictability.

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Studywise minimization: A treatment allocation method which improves balance between treatment groups and makes allocation unpredictable

Abstract

Objective: In randomized controlled trials with many potential prognostic factors, serious imbalance among treatment groups regarding these factors can occur. Minimization methods can improve balance, but increase the possibility of selection bias. We described and evaluated the performance of a new method of treatment allocation, called studywise minimization, that can avoid imbalance by chance and reduce selection bias.

Study design and setting: The studywise minimization algorithm consists of three steps: 1. Calculate the imbalance for all possible allocations. 2. List all allocations with minimum imbalance. 3. Randomly select one of the allocations with minimum imbalance. We carried out a simulation study to compare the performance of studywise minimization with three other allocation methods: randomization, biased coin minimization and deterministic minimization. Performance was measured, calculating maximal and average imbalance as a percentage of the group size.

Results: Independent of trial size and number of prognostic factors, the risk of serious imbalance was the highest in randomization and absent in studywise minimization. The largest differences between the allocation methods regarding the risk of imbalance were found in small trials.

Conclusion: Studywise minimization is particularly useful in small trials where it eliminates the risk of serious imbalances without generating the occurrence of selection bias.

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1. Introduction

In most clinical trials, randomization is applied as a method for treatment allocation and this usually leads to balance of important prognostic factors among treatment groups. Balance improves the accuracy and precision of the results, and thus it increases the credibility and the acceptance of the results.[1-2] However, occasionally substantial imbalances among randomly allocated treatment groups may occur, particularly in small trials or trials with many prognostic factors.[2-3] When this happens, statistical adjustment by means of analysis of covariance may be considered.[4] Nevertheless, this approach has several disadvantages.

First of all, from a strictly statistical point of view, adjustment is not required. Because of the randomization, a properly designed and conducted clinical trial will result in an unbiased estimate of the difference among the treatment groups, even when prognostic factors are imbalanced. Adjustment that is based on observed imbalances and that has not been specified before the start of the study, is even undesirable, because the statistical analysis of a clinical trial should not be adapted once results are known.[5]

Second, the results of the adjusted analysis can only be correctly interpreted if the analysis model fits the data. For example, when analysis of covariance is used, the relationship between the covariate and the outcome should follow a straight line in each treatment group and those lines have to be parallel. Often this is unclear, and especially when the study is small and the imbalance large, these assumptions may be difficult to verify.

Finally, whatever adjustment method is used, unbalanced covariates lead to loss of power. The reasons are twofold: first, imbalance causes collinearity between the treatment effect and the covariates, and second, adding covariates lowers the number of degrees of freedom. The latter will be irrelevant in large trials, but it can have an impact in small trials.

A better method to prevent imbalances is the use of stratified randomization[6] that aims to achieve balance for each combination of the prognostic factors. However, the number of combinations grows exponentially as the number of factors increases. Therefore, an important disadvantage of this method is that only a limited number of factors can be included.

For a trial with many potential prognostic factors, minimization may be a better choice.[7-10] It aims to achieve balance for each prognostic factor separately and not for combinations of factors. Consequently, it can cope with more factors.

Minimization consists of two steps. First, an algorithm determines for each study participant which treatment assignment would lead to the best balance among the treatment groups. In deterministic minimization, the participant is then allocated to that treatment. In biased-coin minimization (minimization with a random component), the participant is allocated that to treatment with a certain probability, for example with an odds of 3:1. Deterministic minimization leads to better balance, but in some situations (e.g., single-center trials, open trials), it makes the treatment allocation predictable and this may influence the investigator.

This enhances the possibility of selection bias. Unfortunately, the biased coin approach cannot completely avoid unpredictable allocations either: as the odds are further away from 1:1, the chance of imbalances decreases, but the predictability increases.[11] For a more detailed discussion we refer to Rosenberger and Kalish.[3,12]

Although minimization leads on average to balanced prognostic factors, we found serious imbalance in a pilot study that we conducted (see section 2: Example). This led us to devise a new minimization method, called "studywise minimization". It can be used in trials in which all participants are included before the study starts, for example in phase I clinical trials, pilot trials and other studies for which the inclusion period is so short that start of the study can be postponed until all participants are enrolled. Studywise minimization optimizes balance among treatment groups and thus avoids loss of power. The predictability of this method, and therefore the possibility of selection bias, are lower than in other minimization methods.

In this article, we describe the studywise minimization method and evaluate its performance.

2. Example: Pilot evaluation of a dementia training programme

The motive to develop the studywise minimization method was a serious imbalance that we found in a small pilot study. This pilot study was set up in preparation for a randomized controlled trial aimed at evaluating a dementia training program (DTP) for general practitioners (GPs) and primary care nurses (PCNs). The DTP is a complex educational intervention that consists of workshops, a coaching program, access to an Internet forum and a computerized clinical decision support system on dementia diagnostics. We expect the DTP to improve diagnosis, management and collaboration in primary dementia care. For the pilot study, 20 dyads of GPs and PCNs were recruited; half of them were allocated to the intervention group, receiving DTP, and half to the control group receiving no training at all.[13] Previous research demonstrated that younger and female GPs have a more positive attitude toward dementia and better knowledge of dementia diagnosis and management.[14] Practice nurses are more used to collaborate with GPs than district nurses. Therefore, we considered sex, age and nurse affiliation to be potential prognostic factors.

A biased-coin minimization procedure with odds 3:1 was used, based on three factors, each with two classes: GP sex (man vs. women), GP age (< 45 years vs. ≥ 45 years) and nurse affiliation (district vs. practice). The procedure resulted in an allocation with approximately equal distribution of the age and nurse affiliation classes, but the sex balance was poor and might have acted in favor of the intervention: 1 of the 6 male GPs and 9 of the 14 female GPs were in the intervention group. This example illustrates that minimization may occasionally result in a poor balance. In contrast, when we retrospectively applied studywise minimization, the maximal imbalance of the factors was one.

3. Studywise minimization

Measuring imbalance

Minimization is aimed at optimalizing the balance; so to perform minimization measurement of imbalance is required.

For each factor class (e.g. factor sex, with classes men and women) the imbalance is the difference between the numbers of patients in the treatment groups that are in that class. The overall imbalance then can be defined and calculated in various ways:

1. The *quadratic imbalance* is the sum of the squared class imbalances. This type of imbalance is used in the variance method of minimization.[8-9,15] This method is well known, has shown excellent performance,[16-19] and is easy to execute.[15]
2. The *maximal imbalance* is the maximum imbalance among the class imbalances. The balance of a trial is usually presented in a baseline characteristics table, that is a frequency table that for each treatment shows the percentages of the patients in each factor class. When the imbalance on one or more of those characteristics is large, i.e. when the maximal imbalance is large, questions may arise. It is, therefore, a suitable primary outcome measure to evaluate the performance of the treatment allocation methods.
3. The *average imbalance* is the mean of the class imbalances.

The calculation of the three measures of imbalance is demonstrated below. As an example, we consider a trial with factors sex (man vs. women) and age (young, middle, old). $Diff_{man}$ is the difference between the number of men in the groups. Similarly $diff_{woman}$, $diff_{young}$, $diff_{middle}$ and $diff_{old}$ are the differences between the numbers of women, the young, the middle aged, and the old, respectively. The imbalances then are:

$$Imbal_{quadr} = diff_{man}^{2}+diff_{woman}^{2}+ diff_{young}^{2}+ diff_{middle}^{2} + diff_{old}^{2}$$
$$Imbal_{mean} = (diff_{man}+diff_{woman}+ diff_{young}+ diff_{middle} + diff_{old})/5$$
$$Imbal_{max} = \max (diff_{man}, diff_{woman}, diff_{young}, diff_{middle}, diff_{old})$$

Studywise minimization algorithm

The studywise minimization algorithm consists of three steps:

1. Calculate the imbalance for all possible allocations. Because the number of allocations is more than a million when the group sizes are larger than nine, it becomes impractical to consider all possible allocations and the imbalance may be calculated for a random selection of allocations only.
2. List all allocations with minimum imbalance.
3. Randomly select one of the allocations with minimum imbalance.

In this algorithm, step 1 limits the use of the method to trials in which all participants are enrolled before the start of the study, step 2 generates optimal balance, and step 3 reduces

the risk of selection bias. In step 2, the studywise minimization algorithm used quadratic imbalance in this study, that is, in step 2, all allocations for which the sum of the squares of the factor class imbalances is lowest were selected.
The Appendix (available online) contains a SAS and an R program that carries out the minimization.

4. Evaluation of the performance of studywise minimization

Design

We carried out a simulation study to compare the performance of four treatment allocation methods: (unrestricted) randomization, biased-coin minimization, deterministic minimization and studywise minimization. All minimization methods used the quadratic imbalance and the odds of the biased coin minimization were 3:1. For studywise minimization, we investigated all possible allocations when the number of patients in the trial was 12 or less. For larger trials, we took a random sample of 5,000 allocations.
The simulated trials had two groups of 6, 12 or 24 subjects and 3, 6 or 12 factors with two classes per factor. The probability that a patient was in one of the two factor classes varied between 20% and 80%.
For each combination of trial size and number of factors, we generated 1,000 trials. In each trial, we carried out the four allocation methods and calculated the maximal and average imbalance of each method as measures of performance. The maximal imbalance as a percentage of the group size was the primary outcome.

Results

Figures 1 and 2 show the maximal and the average imbalance, respectively, presented as a percentage of the group size. For example, in a trial with groups of six, the largest class imbalance is three and the maximal imbalance is 50%. For each factor, the probability that a subject was in either of the two factor classes was 50%. The lines connect the medians (p50), the ends of the boxes indicate the quartiles (p25 and p75), the whiskers indicate the 10th and 90th percentiles (p10 and p90), and the triangles represent the maximal imbalance (p100). For each combination of trial size and number of factors, the black, dark gray, light gray and white symbols correspond to studywise minimization, deterministic minimization, biased-coin minimization and unrestricted randomization, respectively.

Maximal imbalance for trials with three factors

In all situations, the risk of imbalance was highest for unrestricted randomization. For six subjects per group, 10% of the trials resulted in maximal imbalances of at least 67% (p90). For 12 or 24 subjects per group, this percentage dropped to 42% and 29%, respectively.

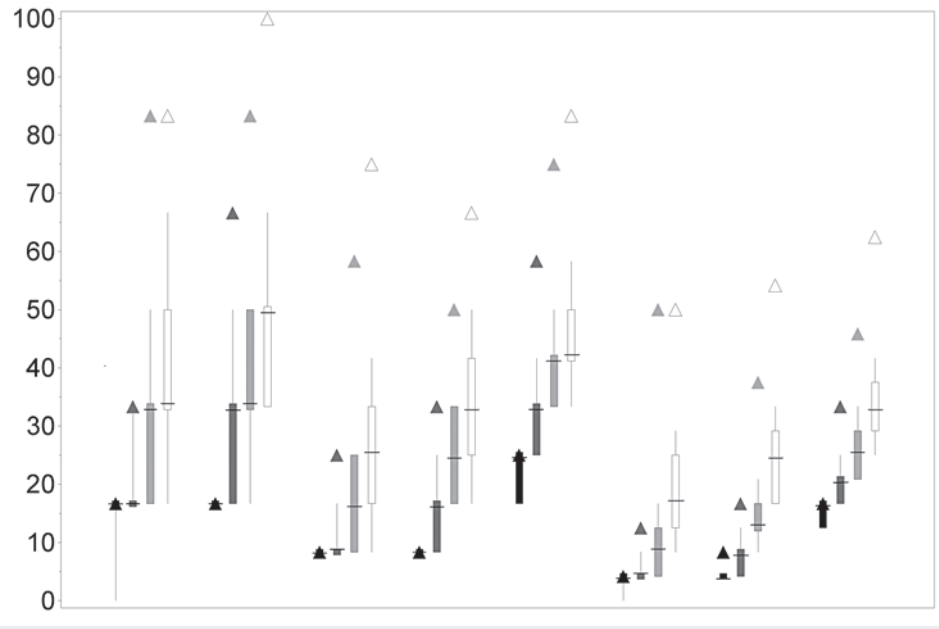
For biased-coin randomization in trials with group sizes of 6, 12 or 24, 10% of the trials had maximal imbalances of at least 50%, 25%, and 17%, respectively. For deterministic randomization, these figures were 33%, 17%, and 8%. Studywise minimization lead to maximal imbalances that never exceeded one patient, because the imbalances were 17%, 8%, and 4% for trials with 6, 12, and 24 subjects per group, respectively.

Maximal imbalance for trials with more factors

Trials with more factors showed the same pattern of improving balance when the next treatment allocation method was used. Even for rather extreme situations, such as six factors in a trial with two groups of six subjects, the largest maximal imbalance was 17%, that is one subject.

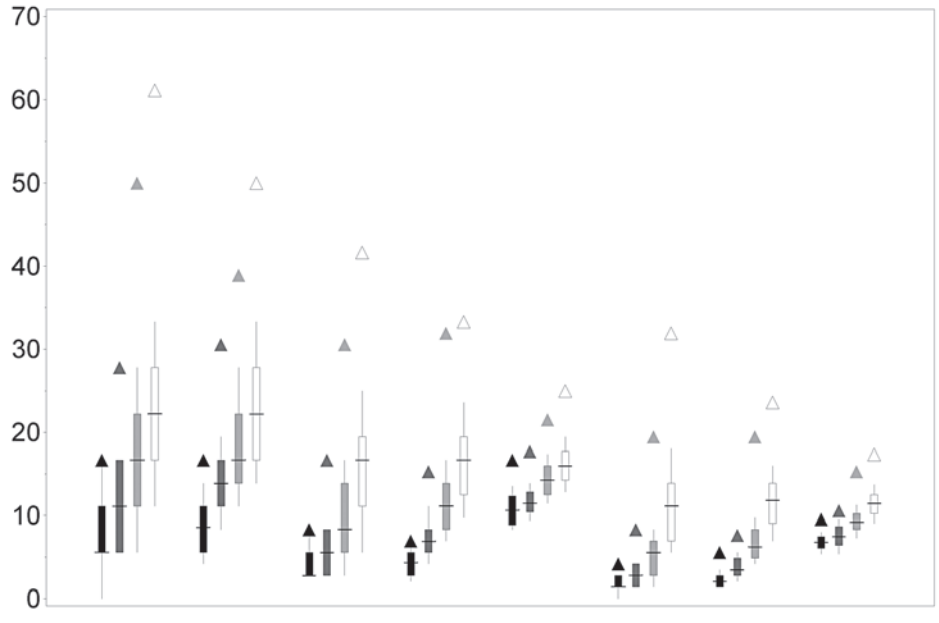
For trials with 12 factors and two groups of 12 or 24, the largest maximum imbalances were 25% and 17%, respectively. When the number of factors and the trial size increased, differences in risk of imbalance among the allocation methods slightly decreased.

Figure 1 Box plot of the maximal imbalance, as a percentage of the group size



Notes: The whiskers indicate the 10th and 90th percentiles, and the triangles represent the maximal imbalance. The black, dark gray, light gray, and white symbols correspond to studywise minimization, deterministic minimization, biased-coin minimization and unrestricted randomization, respectively.

Figure 2 Box plot of the average imbalance, as a percentage of the group size



Notes: The whiskers indicate the 10th and 90th percentiles, and the triangles represent the maximal imbalance. The black, dark gray, light gray, and white symbols correspond to studywise minimization, deterministic minimization, biased-coin minimization and unrestricted randomization, respectively.

Average imbalance

Figure 2 demonstrates that the average imbalance shows a similar pattern. The figures only show the results when the odds of subject distribution in either of the two classes of a factor were 1:1. However, the pattern of the maximal and average imbalance was similar when the odds were varied (data not shown).

5. Discussion and conclusion

We studied the performance of various treatment allocation methods in trials with study sizes varying from 12 to 48 participants and the number of factors ranging from 3 to 12. Although a trial with 24 or 48 patients and 12 factors may be rather unrealistic, the simulation results give an impression about the performance of the methods in extreme cases. In all combinations of trial size and number of factors, the risk of imbalance among treatment groups regarding potential prognostic factors, was the lowest in studywise minimization, and thus it performed better than randomization, biased-coin minimization and deterministic minimization. We only

reported the results when quadratic imbalance was used. However, when we used maximum imbalance or average imbalance, the results were similar (data not shown).

Because studywise minimization never exceeded a maximal imbalance of one, it totally eliminated the occurrence of serious imbalance. It, therefore, diminished the risk of loss of power, which is especially important in small trials. The differences in risk of serious imbalance between studywise minimization and the other three allocation methods studied, decreased when the trial size increased. This combination of findings demonstrate that studywise minimization is particularly useful for treatment allocation in small trials. For larger trials, minimization is a justifiable choice. It will result in adequate balance in most of the trials. This study showed that when biased coin or deterministic minimization are used, 90% of the trials with 48 subjects and 6 factors would have maximum imbalance of at most 21% and 13%, respectively. Furthermore, minimization is more feasible in larger trials, because it does not require the enrollment of all patients before allocation can take place.

An another important advantage of studywise minimization is the unpredictability of treatment allocation. The chance that an investigator correctly guesses the treatment is 50%, which is the same as for unrestricted randomization. Consequently, selection bias is considerably reduced compared with other minimization methods.

In conclusion, studywise minimization showed an excellent performance with regard to creating balance of potential prognostic factors among treatment groups and reducing the possibility of selection bias compared with other minimization methods. The fact that the enrollment of all patients is required before allocation can occur, makes the method less feasible for large trials. We, therefore, advocate the use of studywise minimization, especially in small, one-center or open trials.

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6

Multifactorial fall prevention for pairs of frail community-dwelling older fallers and their informal caregivers: A dead end for complex interventions in the frailest fallers

Abstract

Objective: To assess whether a multifactorial fall prevention program was more effective than usual geriatric care in preventing falls and reducing fear of falling in frail community-dwelling older fallers, with and without cognitive impairment, and in alleviating subjective caregiver burden in caregivers.

Design, setting and participants: A randomized, two parallel-group, single-blind, multicenter trial conducted in 36 pairs of frail fallers, who were referred to a geriatric outpatient clinic after at least one fall in the past six months, and their informal caregivers.

Intervention: Groups of five pairs of patients and caregivers received ten twice-weekly, two-hour sessions with physical and psychological components and a booster session.

Measurements: The primary outcome was the fall rate during a six month follow-up. Additionally, we measured fear of falling and subjective caregiver burden. Data on the secondary outcome measures were collected at baseline, directly after, and at 3 and 6 months after the last session of the intervention.

Results: Directly after the intervention and at the long-term evaluation, the rate of falls in the intervention group was higher than in the control group, although these differences were not statistically significant (RR = 7.97, P = 0.07 and RR = 2.12, P = 0.25, respectively). Fear of falling was higher in the intervention group, and subjective caregiver burden did not differ between groups.

Conclusion: Although we meticulously developed this pairwise multifactorial fall prevention program, it was not effective in reducing the fall rate or fear of falling and was not feasible for caregivers, as compared to regular geriatric care. Future research initiatives should be aimed at how to implement the evidence-based principles of geriatric fall prevention for all frail fallers rather than developing more complex interventions for the frailest.

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Introduction

The high need for prevention of falls and associated injuries in community-dwelling older persons raises urgent questions for research and care innovation. Especially in frail older persons with cognitive impairments, as they have the highest risk of falls and of the associated fear of falling,[1-4] and are less likely to achieve a satisfactory recovery from a fall-related injury.[1;5;6] Falls also result in a high burden on the fallers' informal caregivers, including high levels of stress and fear related to potential falls of the care recipient.[4;7;8] Thus, the need for effective strategies to reduce falls and fear of falling in community-dwelling frail older persons, including those with cognitive impairment, and to increase support for their informal caregivers is substantial. The preponderance of evidence suggests that multifactorial interventions are effective in reducing falls in high risk community-dwelling older persons.[4;9] However, the exact target group and intervention context still have to be defined, as an important number of multifactorial interventions showed a lack of effect in the frail community-dwelling older fallers with the highest risk for falling.[4;9-11] Furthermore, older persons with cognitive impairments were excluded from most trials evaluating multifactorial interventions.[4;9] To our knowledge, there has not been any prospectively evaluated multifactorial fall prevention intervention proven to reduce the fall rate in frail community-dwelling patients with dementia or mild cognitive impairment (MCI).[9] In frail cognitively impaired community-dwelling older persons, evidence-based strategies to reduce fear of falling are lacking too.[12;13] In addition, it is unknown whether fall prevention interventions alleviate the caregivers' high subjective burden related to recurrent falls of their care recipients.

To compensate for the lack of data on effectiveness of fall prevention programs in the frail community-dwelling populations with or without cognitive decline, we developed[14] and evaluated a fall prevention program to reduce the fall rate and fear of falling in these patients and to alleviate subjective caregiver burden. Here, we report the results of the randomized controlled trial (RCT) that evaluated this program and present full details of the intervention.

Methods

From January 2008 to September 2009, we recruited pairs of patients and their primary informal caregivers from the geriatric outpatient clinics of the Radboud University Nijmegen Medical Centre (Nijmegen) and two non-university, teaching hospitals (i.e., Canisius Wilhelmina Hospital and Rijnstate Hospital in Nijmegen and Arnhem, the Netherlands, respectively). Patients were eligible if they a) fell at least once in the six months prior to the visit to the outpatient clinic; b) were able to walk 15 meters independently (use of a walking aid allowed); c) had a primary informal caregiver; d) were community-dwelling; e) had a life expectancy of > 1 year and f) were frail. Patients were excluded if they were awaiting nursing home admission or had a MMSE of <15.[15]

Frailty was defined as the presence of two or more of the widely accepted frailty indicators,[16] in addition to the fact that all patients fell at least once in the previous six months. A fall was defined as an unexpected event in which the individual came to rest on the ground, floor, or lower level.[17] The primary informal caregiver was defined as the non-professional who was most involved in caring for the patient who experienced falls, assisted with at least one personal or instrumental activity of daily living and monitored the patient at least two times a week. The researchers obtained written informed consent from both the caregiver and patient.

Intervention

A small-group training environment was chosen for this intervention, with groups including a maximum of five pairs of patients and caregivers. The instructors of the program were a geriatric psychologist and a geriatric physiotherapist. The program, comprising ten twice-weekly, two-hour sessions and a two-hour booster session six weeks after the initial ten sessions, included both physical and psychological components (Table 1).

Randomization and procedures

Treatment allocation, carried out by an independent statistician, was based on a minimization algorithm that balanced for the minimization factors: gender, MMSE score (15-23 vs. 24-30), age (≤ 80 vs. >80), and number of falls in the past 12 months (1 fall vs. >1 fall). Half of the pairs received usual care of the geriatric outpatient clinic, and half of the pairs received the intervention in addition to usual care. The instructors, patients and caregivers were aware of the treatment assigned; the assessors (MR and MF) were blinded. If the patient withdrew or was lost during follow-up, both the patient and caregiver left the study. In cases in which a caregiver withdrew or was lost during follow-up, the patient continued with the trial.

Outcome assessment and measures

The primary outcome in this study was the fall rate. Falls were registered daily using a pre-addressed, reply-paid two-weekly fall registration calendar throughout the whole course of the trial.[18] Data on the secondary outcome measures were collected at baseline (T0), directly after (T1), and at 3 (T2) and 6 months (T3) after the last session of the intervention.

We assessed the following patient's characteristics: age, sex, history of falls, household composition, use of walking aids, multimorbidity (Cumulative Illness Rating Scale for Geriatrics[19]), cognition (MMSE[15]), dementia[20] or MCI[21] diagnoses (diagnosed by the geriatric team), number and type of drugs used, and handgrip strength with a Jamar-type hand-held dynamometer (Sammons Preston, Inc.).

Table 1 Brief overview of the components and targets of the fall prevention program

Psychological teaching and training components	Physical training component
Introduction of the program, participants and instructors Expectations and aims	Getting out of bed (safely and efficiently)
Individual expectations and aims Individual causes of falls Causes of falls in general Ageing and falls	Rising from a chair (safely and efficiently)
Home safety Emotions concerning falls Fear of falling; the vicious cycle Limitations and abilities: acceptance	Walking (safely and efficiently, with a walking aid if applicable)
Fear of falling; the vicious cycle Impulsiveness; risk behavior Impact of falls on the caregiver	Rising from a chair and walking (safely and efficiently, with a walking aid if applicable)
Activity pattern Stop-think-go	ADL-based circuit training (outdoors if possible)
Methods/aids to prevent falls	Getting up after a fall (safely and efficiently)
Experiences and emotions associated with the practice of getting up after a fall Asking for assistance	ADL-based circuit training (outdoors if possible)
Evaluation methods/aids for preventing falls Coping	Getting up after a fall (safely and efficiently)
Physical activity Caring for significant others	ADL-based circuit training
Falls Evaluation of the individual aims and goals Individual effects of the program Evaluation of the program	ADL-based circuit training; elements at the request of the participants

Note: for more details see part C of this thesis.
Caregivers received training in serving as a co-therapist at home, and in strategies to sustain their own autonomy. Considering the heterogeneity of the group, the program was tailored to each participant by adapting the facultative components of the program (see Table 1 and, for a more detailed description, part C of this thesis).

As secondary outcomes, we assessed fear of falling (Falls Efficacy Scale-International[22]), anxiety [Hospital Anxiety and Depression Scale, anxiety subscale (HADS-A)[23]], depression (15-item Geriatric Depression Scale-Short Form[24]), disability in (instrumental) activities of daily living [(I)ADL] (Groningen Activity Restriction Scale[25]), mastery (5-item Pearlin Mastery Scale[26]), and perceived health-related quality of life (HRQoL) [European Quality of life-5 Dimensions Visual Analogue Scale (EQ-5D-VAS)].[27]

Additionally, we collected gait, dynamic balance, mobility, and activity performance parameters at baseline, T1, and T3. To quantitatively analyze gait, patients walked at their preferred velocity on an electronic walkway (GAITRite®). Balance during walking was measured with a wireless device, which was attached to the trunk, with two angular velocity sensors measuring trunk sway (SwayStar®). The secondary outcome measures were gait velocity, stride-length variability [stride length coefficient of variation (CV); CV = (Standard Deviation/Mean)*100], and medio-lateral trunk sway (i.e., roll angle and roll velocity (90% range)). Overall mobility was assessed with the timed up and go test.[28] The intensity of daily activities performed [LASA (Longitudinal Aging Study Amsterdam) physical activity questionnaire[29]] as well as the mean daily physical activity (using an accelerometer with activity log) were measured. Patients wore the accelerometer on seven consecutive days.

The caregiver characteristics that were assessed were: age, sex, relationship with the patient, employment status, and fear of the care recipient falling (yes/no). Caregiver outcomes were subjective caregiver burden (12-item Zarit Burden Interview Short Form[30]), depression (Center for Epidemiological Studies-Depression scale[31]), anxiety (HADS-A), objective caregiver burden [total caregiving time (hours per week), based on the number of caregiving tasks performed (from a pre-defined set of 16 ADL, HDL and IADL tasks[32])], and average time per task during the week preceding the completion of the questionnaire and EQ-5D-VAS.

Statistical analysis

In our pilot study of a cohort of 43 patients, who were seen in our outpatient clinic between January and July 2007, the rate of falls (FR) showed some extreme outliers. Therefore, in the power calculation, we truncated the rate of falls at 12 per year [truncated fall rate (FRT)]. The mean and standard deviation of the logarithm of the FRT in this group were 1.2 and 0.8, respectively. To reach clinical relevance, we assumed that the intervention would require an effect of approximately 0.5 SD, which is generally considered to represent a substantial effect.[33] For α=0.05 (two-sided) and β=0.20 and an attrition rate of 15%, the total required sample size was 160 pairs. In the analyses only the first 5 falls per 1.5 months for each patient were used in the analysis (maximum 24 falls in 3 months) to avoid over-weighting outliers who frequently fell.

Direct efficacy was evaluated at the end of the intervention. For long-term efficacy, we used the sum of the assessments at T2 and T3 in the analysis of the fall rate and the mean of these assessments in the analysis of the secondary outcome measures.

To compare the fall rates between the groups, a linear model with a negative binomial distribution and logarithmic link function was used. Secondary outcomes were analyzed using a linear model. In all models, group allocation and the minimization factors were the independent variables as well as the baseline value. For the analysis of the long-term efficacy,

the random factor "patient" was included to account for the repetition of the measurements at T2 and T3. The results of the primary analysis were compared with the results of a per-protocol analysis. Intervention pairs included in the per-protocol analysis had attended ≥ 6 sessions. The level of significance was set at a *P* value of less than .05 (two-sided). All statistical analyses were performed using SPSS statistical software version 16.0 (SPSS Inc., Chicago, Illinois).

Results

We evaluated 813 patients for eligibility and recruited 36 pairs of patients and caregivers, which is 13% of the 282 eligible patients. No falls in the previous six months (74%) and absence of a primary informal caregiver (21%) were the two major factors that resulted in non-eligibility. The overburdening of patients (22%) and caregivers (11%), and patients' intercurrent diseases and associated hospital visits (19%), were major factors in the refusal of participation of eligible pairs. Immediately following randomization, three patients in the control group ended participation in the trial before baseline measurements were collected. These patients and their caregivers were not aware of the treatment allocation and were not included in the analyses.

Table 2 and table 3 show the characteristics and baseline outcome measure data of patients and caregivers respectively. The mean age of the patients in the sample was 78.3 years, nearly 70% were female and 60% lived alone. Twenty-four percent had fallen once in the prior year (non-recurrent faller) and 76% had fallen multiple times (recurrent faller). Forty-eight percent suffered from MCI or dementia. The mean MMSE score was 25.8. The patients had a high level of multimorbidity (mean CIRS-G 13.8) and were moderately disabled in ADL and IADL (mean GARS 36.3). No relevant differences were found between the two groups with regard to baseline characteristics and outcome measures.

None of the patients had missing values on the primary outcome measures before death (n = 2) or being lost for follow-up (n = 4). There was no relevant difference between the intervention and control groups in term of number of days of follow-up (199 days vs. 177 days, respectively).

At T1 and at the long-term evaluation, the rate of falls in the intervention group was higher than that in the control group, although these differences were not statistically significant (T1: 4.32 vs. 0.52 falls per patient per year, RR = 7.97, 95% CI = 0.86 – 73.4; *P* = 0.07 and long-term: 4.94 vs. 1.17 falls per patient per year, RR = 2.12, 95% CI = 0.6 – 7.56; *P* = 0.25). During the 7 months of follow-up, 10 intervention patients (56%) and 6 control patients (40%) fell at least once, of whom, 6 (33%) and 1 (7%), respectively, fell at least twice.

Table 2 Characteristics and baseline outcome measure data of patients

Characteristics		Intervention *n*=18	Control *n*=15
Age (years)		78.3 ± 6.9	78.3 ± 7.2
Gender (female)		14 (78)	9 (60)
Number of falls in the previous year		3.0 ± 1.75	5.07 ± 6.41
Non-recurrent fallers (1 fall in the previous year)		5 (28)	3 (20)
Recurrent fallers (>1 fall in the previous year)		13 (72)	12 (80)
Household composition	Living alone	8 (44)	8 (53)
	Living with other person	10 (56)	7 (47)
Use of a walking aid (yes)		8 (44)	10 (67)
CIRS-G (range 0-64*)		14.0 [3]	13.0 [8]
MMSE (range 0-30†)		26.1 ± 3.6	25.4 ± 3.4
Cognitive impairment	None	11 (61)	6 (40)
	MCI	6 (33)	7 (47)
	Dementia	1 (6)	2 (13)
Use of >4 different medications (yes)		11 (61)	10 (67)
Use of psychoactive medication (yes)		5 (28)	5 (33)
Handgrip strength (kgf)		28.9 ± 5.6	25.4 ± 5.7
Outcome measures at baseline			
FES-I (range 16-64*)		32.8 ± 11.1	35.4 ± 11.0
HADS-A (range 0-21*)		7.7 ± 4.8	6.57 ± 3.7
GDS (range 0-15*)		4.7 ± 4.0	4.5 ± 3.4
Mastery (range 5-25†)		13.5 ± 4.7	15.4 ± 2.4
GARS (range 18-72*)		34.7 ± 11.5	38.3 ± 10.1
EQ-5D-VAS (range 0-100†)		71.9 ± 16.7	64.9 ± 17.8
Gait & balance analysis	Velocity (cm/s)	81.0 ± 29.9	68.5 ± 22.9
	Stride length CV (%)*	3.4 [3.3]	4.3 [3.6]
	Roll angle (deg)*	3.6 [2.3]	4.2 [2.3]
	Roll velocity (deg/s)*	23.5 [25.6]	24.4 [14.8]
TUG (sec)		14.9 [8.8]	14.8 [9.7]
LAPAQ (kcals/day)		529.0 [559.6]	193.1 [588.1]
Mean daily activity		54.2 ± 30.3	40.2 ± 21.6

Notes: Data are presented as mean ± SD for normally distributed variables, median [IQR] for skewed variables, and N (percentages) for categorical variables; *Lower score is the more favorable score; †Higher score is the more favorable score; CIRS-G= Cumulative Illness Rating Scale for Geriatrics; MMSE= Mini-Mental State Examination; FES-I= Falls Efficacy Scale-International; HADS-A= Hospital Anxiety and Depression Scale, anxiety subscale; GDS= Geriatric Depression Scale-Short Form; GARS= Groningen Activity Restriction Scale; EQ-5D-VAS= European Quality of Life-5 Dimensions Questionnaire Visual Analogue Scale, 100 representing the 'best imaginable health state' and 0 representing the 'worst imaginable health state'; TUG= timed up and go test, which was performed as quickly and safely as possible.; LAPAQ= LASA physical activity questionnaire.

Table 3 Characteristics and baseline outcome measure data of caregivers

Characteristics		Intervention *n*=18	Control *n*=15
Age (years)		67.3 ± 13.1	64.3 ± 14.3
Gender (female)		9 (50)	10 (67)
Living with the patient (yes)		10 (55)	7 (47)
Relationship to patient	Married/unmarried partners	10 (55)	9 (60)
	Child	5 (28)	6 (40)
	Other	3 (17)	0
Employed (yes)		5 (28)	5 (33)
Fear of the care recipient falling (yes)		18 (100)	12 (80)
Outcome measures at baseline			
ZBI (range 0-48*)		5.2 [4.5]	6.0 [11.0]
CES-D (range 0-60*)		3.0 [6.5]	3.0 [17.0]
HADS-A (range 0-21*)		2.5 [3.8]	3.0 [8.8]
Total caregiving time (hours per week)		8.0 [13.1]	10.5 [8.0]
EQ-5D-VAS (range 0-100†)		84.5 [15]	84.0 [18]

Notes: Data are presented as mean ± SD for normally distributed variables, median [IQR] for skewed variables, and N (percentages) for categorical variables; *Lower score is the more favorable score; †Higher score is the more favorable score; ZBI= Zarit Burden Interview Short Form; CES-D= Center for Epidemiological Studies-Depression scale; HADS-A= Hospital Anxiety and Depression Scale, anxiety subscale; EQ-5D-VAS= European Quality of Life-5 Dimensions Questionnaire Visual Analogue Scale, 100 representing the 'best imaginable health state' and 0 representing the 'worst imaginable health state'.

Directly after the intervention, there were no statistically significant differences in any of the secondary outcome measures between the intervention and the control group (Table 4). At the long-term evaluation, the patients in the intervention group experienced more fear of falling, anxiety, and depression than the patients in the control group (Table 4, $P = 0.038$, $P = 0.003$, $P = 0.002$, respectively). Sense of mastery was higher in the intervention group compared to the control group (Table 4, $P = 0.002$). There were no differences between the two groups in any of the gait and balance parameters measured at the long-term evaluation. The analysis of secondary outcome measures in caregivers did not yield significant differences between the two groups directly after the intervention or at the long-term evaluation (Table 5). For the per-protocol analysis, 3 intervention pairs group were excluded. Per-protocol results were similar to the results of the primary analysis (data not shown).

Table 4 Mixed linear regression analyses of secondary outcome measures in patients

	Direct follow-up			Long-term follow-up*		
Instrument/ Outcome measure	Intervention	Control	Regression Coefficient (95% CI)	Intervention	Control	Regression Coefficient (95% CI)
FES-I‡	1.78 ± 8.51	-3.62 ± 8.59	4.81 (-2.11 – 11.72)	6.68 ± 6.98	-1.06 ± 8.73	7.69 (0.48 – 14.9)‖
HADS-A‡	-0.76 ± 3.42	-2.82 ± 2.93	2.34 (-0.32 – 4.99)	0.83 ± 2.70	-2.77 ± 2.2	3.41 (1.34 – 5.49)¶
GDS‡	-0.27 ± 1.91	-0.54 ± 1.68	0.10 (-1.46 – 1.67)	1.47 ± 2.23	-1.33 ± 1.97	2.36 (0.98 – 3.73)¶
Mastery§	-0.27 ± 4.18	-2.00 ± 2.67	0.93 (-2.14 – 4.18)	1.14 ± 1.94	-2.05 ± 2.10	2.55 (1.07 – 4.02)¶
GARS‡	-0.90 ± 7.61	-1.27 ± 3.32	-0.41 (-4.85 – 4.03)	3.03 ± 11.01	-1.09 ± 6.96	1.24 (-6.81 – 9.28)
EQ-5D-VAS§	-4.07 ± 12.18	4.25 ± 16.38	-6.04 (-15.93 – 3.84)	-10.54 ± 17.19	9.19 ± 15.64	-12.86 (-28.30 – 2.58)
Velocity (cm/s)†	2.49 ± 18.84	3.23 ± 16.65	2.86 (-8.06 – 13.78)	-3.79 ± 21.46	5.64 ± 6.8	-4.80 (-20.77 – 11.16)
Stride length CV (%)†‡	-0.85 ± 4.22	-2.05 ± 4.42	0.70 (-1.28 – 2.68)	-0.31 ± 4.55	-0.27 ± 2.44	1.24 (-1.88 – 4.36)
Roll angle (deg)†‡	0.18 ± 0.76	-0.61 ± 0.98	0.80 (-0.01 – 1.60)	-0.24 ± 1.51	-0.01 ± 1.20	-0.57 (-2.61 – 1.48)
Roll velocity (deg/s)†‡	3.21 ± 11.81	-5.35 ± 10.55	4.7 (-3.53 – 12.93)	1.07 ± 9.42	-1.75 ± 4.19	1.03 (-8.64 – 10.71)
TUG (sec)†	-1.12 ± 3.1	-2.44 ± 7.15	0.14 (-2.73 – 3.01)	0.52 ± 5.3	-0.78 ± 5.0	0.06 (-4.56 – 4.68)
LAPAQ (kcals/day)†	66.23 ± 436.89	164.15 ± 316.34	-77.52 (-444.91 – 289.86)	223.20 ± 1008.47	115.46 ± 338.33	516.28 (-249.13 – 1281.69)
Daily activity†	-16.36 ± 16.66	-4.20 ± 12.03	-10.68 (-26.93 – 5.57)	-14.67 ± 17.61	-19.17 ± 19.10	5.99 (-8.69 – 20.68)

Notes: Data presented are the unadjusted changes over time (follow-up minus baseline) in the raw mean score ± SD, unless otherwise indicated. The crude regression coefficients and corresponding 95% confidence intervals (95% CI) present the difference between the intervention and control groups in change scores; *Long-term indicates T2 and T3 averaged, except for the variables only measured at T3.; †These variables were not measured on T2, long term change is calculated as T3 minus baseline; ‡Negative mean changes indicate a favorable change in the outcome measure; §Positive mean changes indicate a favorable change in the outcome measure; ‖$P < .05$; ¶$P < .01$.

Table 5 Mixed linear regression analyses of secondary outcome measures in caregivers

	Direct follow-up			Long-term follow-up*		
Instrument/ Outcome measure	**Intervention**	**Control**	**Regression Coefficient (95% CI)**	**Intervention**	**Control**	**Regression Coefficient (95% CI)**
ZBI‡	1.21 ± 3.41	-0.69 ± 2.25	1.42 (-1.02 – 3.86)	1.94 ± 2.97	0.14 ± 4.99	1.58 (-2.07 – 5.23)
CES-D‡	-0.33 ± 3.31	-0.86 ± 3.53	0.06 (-2.39 – 2.50)	1.00 ± 2.87	-2.05 ± 6.40	2.73 (-0.32 – 5.78)
HADS-A‡	0.33 ± 2.09	0.69 ± 1.65	-0.39 (-1.95 – 1.18)	0.53 ± 1.75	0.05 ± 1.38	0.52 (-0.85 – 1.92)
Total caregiving time (hours per week)	NA†	NA	NA	-2.07 ± 15.96	-3.37 ± 14.39	0.03 (-8.99 – 9.05)
EQ-5D-VAS§	-2.67 ± 11.16	-2.77 ± 9.79	-1.02 (-7.69 – 5.66)	-7.21 ± 11.27	-2.77 ± 11.91	-7.03 (-15.63 – 1.57)

Notes: Data presented are the unadjusted changes over time (follow-up minus baseline) in the raw mean score ± SD, unless otherwise indicated. The crude regression coefficients and corresponding 95% confidence intervals (95% CI) present the difference between the intervention and control groups in change scores; *Long-term indicates T2 and T3 averaged; †NA = not available. Total caregiving time was not measured at T1; ‡Negative mean changes indicate a favorable change in the outcome measure; §Positive mean changes indicate a favorable change in the outcome measure.

Discussion

This multifactorial fall prevention program for pairs of patients and their caregivers was not effective in decreasing falls in community-dwelling frail older fallers (of whom some had cognitive impairment). At long-term follow-up, the rate of falls in the intervention group even showed a tendency to be higher than that in the control group. The program was not effective in decreasing fear of falling in patients or subjective caregiver burden in caregivers. In fact, fear of falling was higher in the intervention patients, an effect that was accompanied by higher anxiety and depression scores in this group. In favor of the intervention, the participants of the fall prevention program experienced a higher level of mastery.

To evaluate the lack of effectiveness of this intervention, we examined three main factors that determine an intervention's effects: content, process, and choice of the target group.[34]

The intensity and duration of the physical therapy in our intervention, may not have been sufficient to reduce the fall rate.[35] However, increasing intensity likely conflicts with the frailty of these patients. The intervention patients' increased awareness of their risk of falls and consequences of falls may have resulted in the increased feelings of fear of falling. The increased awareness may have also caused the increase in anxiety and depression in the intervention patients. Overall, 74% and 91% of patients had scores that were below the clinically relevant cut-off scores that are indicative of depression (GDS score ≥ 6[36]) and anxiety disorder (HADS-A score > 10[37]), respectively. More importantly, the intervention patients developed a higher sense of mastery, which may help them actively address their fall problem. The lack of changes on outcome measures in the informal caregivers may indicate that the program was not optimally adjusted to their situation.

By evaluating the process; that is the way in which the intervention content was applied, we identified several strengths. The intervention was built on psychological theories.[14;38-39] We included mechanisms to maximize uptake and to facilitate habit formation, for example, via homework exercises. Furthermore, the intervention was advertised as a movement course with the aim of stimulating independence, because older adults are more likely to engage in fall prevention strategies when interventions are couched in terms of preserving independence.[40]

Focusing the intervention on caregivers had a major drawback. The majority of the caregivers were unable to participate, as the course was provided during working hours. Former trials have suggested that introducing the caregiver as a co-therapist may result in the increased effectiveness of interventions in cognitively impaired subjects; however, this trend was not confirmed in the current trial in the frailest fallers.[41;42]

The choice of the target group is the third construct that must be considered. The preliminary analysis of the results of a questionnaire study among the non participating pairs revealed that the intervention and assessments were likely too burdensome for patients due to numerous

health problems and their dislike to leave house. Furthermore, the instructors mentioned that the target group was quite heterogeneous, with patients who were afraid of falling and needed to be activated as well as impulsive patients who needed to be controlled. In addition, the intervention group was also heterogeneous with regard to cognition, which was reflected in problems with holding the attention of cognitively impaired participants. Thus, a group format seems to be unsuitable in this population.

We conclude that this multifactorial fall prevention program is not suited for reducing falls and fear of falling in community-dwelling frail older fallers, including patients with cognitive impairments. Furthermore, one could conclude from our results that improving fall-related outcomes in this vulnerable group is beyond intervention, because programs are overly intensive for frail, sometimes cognitively impaired, older persons.

The current study, although presenting negative results, has an important message for medical directors, funding agencies and policy makers concerning the development and evaluation of fall prevention programs in frail older subjects, including the frailest with cognitive defects, and their caregivers. Developing even more complex and specialized fall prevention interventions is not effective or feasible for these patients and caregivers. Currently, the greatest added value can be reached by focusing on the implementation of basic geriatric practice principles, id est geriatric comprehensive fall assessment and drug review, for all fallers.

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How to perform a preplanned process evaluation for complex interventions in geriatric medicine: Exemplified with the process evaluation of a complex falls-prevention program for community-dwelling frail older fallers

Abstract

Complex interventions are difficult to develop, document, evaluate, and reproduce. Process evaluations aid the interpretation of outcome results by documenting and evaluating each process step in detail. Despite its importance, process evaluations are not embedded in all evaluations of complex interventions.

Based on literature, we structured the process evaluation for trials on complex interventions into 3 main components: (1) the success rate of recruitment and quality of the study population, (2) the quality of execution of the complex intervention, and (3) the process of acquisition of the evaluation data.

To clarify these process evaluation components and measures, we exemplified them with the preplanned process evaluation of a complex falls-prevention program for community-dwelling frail older fallers and their informal caregivers. The 3 process evaluation components are operationalized, results are presented, and implications discussed. This process evaluation identified several limitations of the intervention and effect study, and resulted in multiple recommendations for improvement of both the intervention as well as the trial.

Thus, a good quality process evaluation gives a detailed description of the most important components of a complex intervention, resulting in an in-depth insight in the actually performed intervention and effect analysis. This allows us to draw the appropriate conclusions on positive or negative trial results, and results in recommendations for implementation, or adjustment of the intervention or effect evaluation, respectively.

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Introduction

Complex interventions are defined as interventions comprising multiple components acting independently or interdependently, and are therefore difficult to develop, document, evaluate, and reproduce. Such complex interventions are very often applied for treatment and prevention of geriatric syndromes, as these are mostly multifactorial by cause.[1] The UK Medical Research Council (MRC) published a framework in which the development and evaluation of complex interventions is comprehensively guided.[2] This framework emphasizes the importance of performing a process evaluation alongside the effect evaluation, however, little information is provided on how to perform such a process evaluation.

Process evaluations aid the interpretation of outcome results by documenting and evaluating each process step in detail. This is of great value for both positive and negative trial results. A process evaluation may increase insight into why a successful intervention works, how it can be optimized, and provide insights to aid dissemination and implementation.[2] Next, it may also explain discrepancies between expected and observed outcomes, or explain lack of effectiveness, which is of great value for future studies. Process evaluations aid in making the distinction between "failure to demonstrate underlying efficacy or effectiveness" (ie, the evaluation failed) and "good evidence of lack of efficacy and effectiveness" (ie, the intervention failed).[3] Both may have various causes, for example, failure of the evaluation may be due to inappropriate outcome measures or insufficient power, and failure of the intervention may be because of an incorrect intervention theory, or unsuccessful implementation. Without this information, accurate conclusions cannot be drawn on (lack of) efficacy or effectiveness of the intervention. Therefore, process evaluations should be conducted to the same high methodological standards and reported just as thoroughly as the clinical trial and its outcomes. However, currently process evaluations are not embedded in all evaluations of complex interventions, and when present, process evaluation components differ per study, or studies assess only a single aspect. Possible explanations are a lack of standardized measurement instruments for evaluating intervention processes, and that these evaluations may be time-consuming and considered of less interest than effect analyses. Especially in geriatrics, the burden on frail older persons because of additional measurements is an important consideration that may hinder process evaluation planning. Although, for complex interventions in heterogeneous frail populations in-depth insight in the process is highly relevant and has to be carefully planned before trials start.

This article presents a systematic and comprehensive guide for the development and application of a process evaluation for complex interventions in geriatrics, based on components used in previous studies on complex interventions. We then demonstrate and clarify this guide by applying it to the process evaluation of a complex falls-prevention program for community-dwelling frail older fallers and their informal caregivers; the "Carthage-Phoenix Study".[4]

Process evaluation components for complex interventions

Previous process evaluations

We performed a literature search revealing previous studies performing process evaluations for complex interventions. Several studies performed a feasibility analysis of the intervention, studying barriers and facilitators to fine-tune the intervention or improve implementation.[5;6] Measures determining feasibility include performance of the program according to protocol (timing and duration of assessments, number and type of protocol deviations), nature of recommendations and referrals from assessments, participants" compliance with referrals and recommendations (self-reported compliance), and opinions about the program (benefit and satisfaction experienced by participants, acceptability of the program, recommendations for implementation).[5;7;8] Barriers and facilitators may be assessed at different levels, ie, the intervention itself, the professional, the participant, or the social , organizational, economical or political context.[7;9] In some studies, the process evaluation includes identification of the characteristics of individuals attracted to the program.[10] Often cited components follow the evaluation of fidelity, dose delivered, dose received, reach, recruitment, and context,[9;11;12] or some of these components.[13] These components provide a comprehensive evaluation of the intervention itself, however, this overlooks the importance of the evaluation of the research trial itself, which is of great influence on the assessed efficacy or effectiveness. A framework was proposed, to determine the strength of evidence, based on the study design, methodological quality and statistical precision, the magnitude of the measured effects, and the relevance of these effects measured in relation to the implementation context.[3] Integration of the process and outcome evaluation also importantly aids in the explanation of the results, and thereby may improve knowledge on underlying pathways.[7]

Components of process evaluations for complex interventions

Based on these literature findings, we structured the process evaluation for trials on complex interventions into 3 main components: (1) the success rate of recruitment and quality of the study population, (2) the way the complex intervention was carried out, and (3) the process of acquisition of the evaluation data (Table 1). Each process component can be assessed by several measures and multiple variables.

Table 1 Process-evaluation components and related process measures of a multi-component intervention

Process components	Process measures
Study population	1. Recruitment and selection rate 2. Barriers and facilitators in recruitment and selection process 3. Follow-up: Attrition rate 4. Barriers and facilitators for follow-up
Multiple components	1. Quality of delivery of the interventional components 2. Barriers and facilitators for delivery of interventional components 3. Adherence to interventional components 4. Barriers and facilitators for adherence to interventional components 5. Experience of participants and instructors with interventional components
Evaluation data	1. Outcome measures: Coverage of interventional components 2. Completeness of data collection 3. Barriers and facilitators for data collection

The evaluation of the selection of the study population aims to determine the success rate of the selection process of this population, ie, reach, generalizability of the sample and barriers and facilitators for inclusion. This incorporates identifying characteristics of individuals participating in the intervention and refusing participation, and assessing motivations for (or refusal of) participation and adherence. Especially in a heterogeneous population, insight into the quality of the recruitment, presence of selection bias, and barriers and facilitators for recruitment, are highly valuable and can be used to improve recruitment in next stages of the cycle of development and implementation of a new complex intervention.

The evaluation of the intervention itself aims to determine whether the intervention was delivered as intended (fidelity) and was feasible, to identify successful components of the intervention and recommendations. Especially for complex interventions this is an important but difficult part of the process evaluation. The intervention may be intended to be delivered tailor-made, therefore successful delivery cannot simply be assessed with "performance according to protocol". In addition, participants may mention contradictory strengths and weaknesses, and reveal different beneficial components. Conclusions on revisions should therefore be prepared carefully. Adherence, motivation to participate or reasons for dropout may be diverse, and should be closely assessed, to be able to approach each (category of) participant appropriately.

Investigation of the process of acquiring the evaluation data aims at determining whether the appropriate outcome measures were selected to measure effect of the intervention, and whether they were sufficiently sensitive to change and close enough to the intervention.

This part also assesses completeness of the data collection. The characteristics of missing data often reveal important characteristics of the intervention and the trial. Missing data can bias results, when persons with and without outcome data are different, and can reduce generalizability and limit power.[14] So it is highly relevant to indentify, how much data are missing, characterize missing data, and to assess why data are missing.

Methods of process evaluations

Process evaluations can use both quantitative and qualitative methods. Quantitative methods may be easier to apply, and require relatively straightforward analyses and interpretation. Qualitative methods may be more difficult to obtain and use, although it gives insight into the underlying mechanism by answering "why" and "how" questions, as well as collecting diverse perspectives of participants. By triangulation of the data collected from different sources, an accurate image of all aspects of the process can be derived. In designing the process evaluation plan, the choice of methods is strongly influenced by considerations of feasibility, including the limitations of available resources, burden and acceptability of methods, and the likelihood of obtaining information of the same quality through alternative methods. Especially in a geriatric population, the burden-benefit ratio must be carefully weighed and when cognitive impairment is present, outcome measures may require verification by caregivers.

Example: Process evaluation of a complex fall-prevention

We preplanned a process evaluation for our newly developed fall-prevention program, based on the components described previously. Table 2 shows the variables operationalizing the process components for our study. Because of the frailty of our population, we tried to assess as many variables as possible with simple questionnaires or registration forms. In addition, we performed short semistructured interviews among participants and instructors to gather information about their experiences and thoughts.

Table 2 Preplanned process variables collected for the process analysis of a multi-component falls-prevention program study in frail older persons

Process measures	Process variables
1. Recruitment and selection rate 2. Barriers and facilitators in recruitment and selection process 3. Follow-up: attrition rate 4. Barriers and facilitators for follow-up	1. a. Number of eligible persons in screened population; b. Number of participants from the sample of eligible persons; c. Number of participants versus aimed number 2. a. Difference in baseline characteristics between nonparticipating and participating eligible persons; b. Motivation of nonparticipating and participating eligible persons; c. Experience with recruitment and selection 3. Number of participants completing follow-up versus number started 4. Reasons for drop-out and motivation for continued participation
1. Quality of delivery of the interventional components 2. Barriers and facilitators for delivery of interventional components 3. Adherence to interventional components 4. Barriers and facilitators for adherence to interventional components 5. Experience of participants and instructors with interventional components	1. a. The part of each component and the complete intervention delivered by instructors; b. Satisfaction with delivery 2. Reasons for diverging from, or applying (planned) components 3. a. Number of sessions followed; b. intervention components (partly) followed; c. Compliance to individual recommendations; d. Homework adherence 4. Motivation for (lack of) attendance and compliance 5. a. Perceived benefit; b. Strong and weak aspects of the interventional components (structure and content), and the total intervention
1. Outcome measures: coverage of interventional components 2. Completeness of data collection 3. Barriers and facilitators for data collection	1. Average number of outcomes per component 2. Number and characteristics of missing data 3. a. Feasibility of outcome measures; b. Reasons why data were missing; c. Reasons why participants were excluded from analysis 4. Comparison of qualitative and quantitative effectiveness data

Intervention

The fall-prevention program is a group program developed for pairs of frail older fallers and their informal caregivers, primarily aimed at fall risk reduction and reduction of fear of falling. The intervention has both physical and cognitive components, specifically tailored to this frail patient group. Physical training took place in an "activities of daily living" based circuit that simulates daily living conditions, and aimed at training of balance, strength, coordination and functionality. Cognitive training handled fear of falling, impulsiveness, uncovering and accepting limitations and abilities. The intervention is described in detail in a previous publication.[15]

Table 3 shows the most important findings of the process evaluation per process measure. Following we describe the implications of these findings, and how the process evaluation facilitates adaptation of the intervention and study.

Implications study population

Results from the process analysis of the study population indicate that the information supply for potential subjects needs adaptation, to ensure and increase understanding of the intervention content and structure of the program. This will increase insight into potential benefits of the program, and therefore acceptance of the burden of the program, which may increase successful recruitment. Moreover, the group actually selected may have been too frail to participate and benefit. The current intervention seems more appropriate for a less frail group of older persons with a high risk of falls. For this frail population, adaptations of the program should reconsider location, timing and duration, with a special consideration to caregiver availability.

Implications multi-component intervention

Process data on the complex intervention show that adherence and compliance were moderate. Inclusion of participants should specifically address appropriateness for group participation, including physical and cognitive aspects, and availability. In addition, more emphasis should be placed on the importance and benefit of homework exercise. The intervention should be prolonged to ensure that the increased insight results in behavioral change, and to overcome negative effects of the increase in insight.

Implications outcome measures

The process analysis of the outcome measures indicate that these measurements did not fully match the intervention. Heterogeneous effects could be expected, and even contradictory findings between different persons might be expected, such as both increased and decreased activity, which would result in lack of change in overall group analysis. Effectiveness ultimately

Table 3 Most important findings from the pre-planned process analysis of a multi-component falls-prevention intervention study in frail older fallers

Process components	Findings per process variable*
Study population	1. a. A total of 813 patients were screened; b. Of the 282 eligible patients, 241 participants (85.5%) declined participation; c. Recruitment objective was not reached (22.5%) 2. a. Compared with nonparticipating eligible patients, participants were younger, experienced fewer falls, had a higher comorbidity score, showed a lower frequency of dementia, attributed falling more to extrinsic causes, had less frequent employed caregivers, and less frequent caregivers who experienced fear that the patient would fall; b. Most important barrier for participation was the burden of participation, because of the frequency and timing of the sessions, distance to facility, comorbidity or other obligations. In addition, caregiver participation was an important barrier; c. Recruitment was complicated and time-consuming. None of the participants could express their expectations or give a clear description of the content of the intervention before the start. 3. Dropout was 27.7% and 55.6% in the intervention and usual care groups respectively. 4. Dropout was due to co-morbidity and mortality.
Complex intervention	1. a. All components were applied, and the program could be delivered tailor-made; b. The intervention components were feasible and satisfactory. 2. Barriers for delivery were absence of one or more of the pairs, or moderate cognitive or severe physical impairment of one of the participants in a group. 3. a. Five pairs (21.7%) followed fewer than 5 sessions (out of 10); b. All participants received all components that were applicable for them; c. Most patients (90%) followed personalized recommendations, although some only at the end of the intervention; d. Most patients (90%) continued to exercise at home, although at moderate frequency (mean: 6 times a week, 15 minutes a time) 4. Reasons for low attendance of pairs were unavailability of the caregiver on a specific day, previously planned obligations, and health issues (severe illness, too severe hearing impairment for group participation, and hip fracture of the caregiver). Barriers for homework exercise performance were physical impairment, fatigue, or not recalling homework exercise.

	5. a. All participants indicated to have benefited from the intervention, which was in line with the judgment of the instructors. Perceived benefits were diverse, including increased insight in fall risk and limitations, increased coping, decreased fear of falling and increased physical activity; b. Both training in pairs and training in a group were considered very valuable; it was enjoyable and educational, learning from other pairs, sharing experiences, feeling supported, and being able to practice together. Participants desired to receive a higher number of sessions, up to 30 sessions, and/or a longer follow-up, to be able to practice more, receive more information, and achieve behavioral change. Insight into personal limitations and capacities was increased in all participants. However, increased insight was confronting for participants, resulting in negative feelings or rejection of the intervention content. For some caregivers, increased insight led to an increase in time and load invested. Information and training were considered very useful, although, when a fall did occur, it proved difficult to stay calm and implement intervention. Some participants refused to use aids to decrease fall risk, afraid people might condemn them, or because of the wish to stay independent. Some caregivers refused to act as trainer, to avoid conflict or because they believed the patient would not change.
Evaluation data	1. Participants could roughly be divided into 2 groups; the "fearful" and "high risk behavior/denial" groups. The heterogeneous nature of the group resulted in different aims and thus different results for each individual. Not all goals that were listed by the participants were assessed in the measurements, eg, level of acceptance, insight in limitations, ability to get up after a fall. 2. None of the patients had intercurrent missing values on the primary outcomes measure before death or loss to follow-up otherwise. The frequency or causes of dropout or missing data on secondary outcome measures did not differ between the treatment groups. 3. a. Measurements were considered long, but not too burdensome. Questionnaires were easy to understand and measurements easy to follow; b. Visiting the hospital for measurements was considered burdensome, in most cases because of intercurrent disease or lack of transportation; c. Reasons for exclusion from analysis were missing data owing to disease. 4. Perceived benefit was not in accordance with quantitative benefit. Participants indicated more effects of the intervention than were assessed quantitatively. Some changes became apparent only after questioning in interviews, probably because participants had adjusted their standard and were no longer aware of the achieved change.

Notes: *Numbers in the second column "Findings per process variable" refer to numbers in Table 2.

may be assessed at the individual level, for example, goal attainment scaling may be of high value for tailor-made complex interventions. In addition, some of the goals were not assessed at all, such as being able to get up after a fall or acceptance or increased insight in limitations and abilities, although the intervention trained specifically on these aims. Thus, all possible goals should be reviewed before start of the intervention, adjusting outcome measures to anticipated goals. Perceived benefit assessment should consider an individual frame shift, which may result in no longer acknowledging improvement because one adapted to the new situation. Socially desirable answers should also be evaluated, since these may result in a too positive intervention evaluation.

In conclusion, the process evaluation identified limitations of the intervention and effect study, and resulted in multiple recommendations for improvement of our fall intervention. Therefore, the intervention was not implemented in its present form. We both adapted the program to an individual, home based program for the group of frail older fallers, who could not participate in the group intervention, and we adapted the recruitment, so a less frail group could be selected for the ongoing group intervention. Outcome measures will be adapted to more closely represent the individual aims in this heterogeneous population. Pilot studies with these adaptations included are currently being performed.

In general, future complex intervention studies, especially in heterogeneous groups, should perform a preplanned process evaluation alongside the effect evaluation. The study population and the intervention itself, but also the data collected for the evaluation should be conscientiously evaluated, resulting in an in-depth insight in the actually performed intervention and effect analysis. This prevents inappropriate conclusions from being drawn on efficacy or effectiveness, and results in comprehensive recommendations for appropriate adjustment of the intervention or effect evaluation. It gives detailed information on the barriers and facilitators for this and similar interventions, and experiences from participants and instructors, which would otherwise remain unidentified. This results in more efficient adaptation and development of complex interventions, and aids implementation.

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The overall aim of this thesis was to develop and evaluate a falls-prevention intervention for frail community-dwelling older persons with and without cognitive impairment. We will begin this chapter with a short report on the principal findings of the randomized controlled trial (RCT) that was used to evaluate the intervention. Subsequently, we will reflect on the phases of the MRC framework that guided the development and evaluation of the intervention. For each part of the study, we will provide a summary. Following the summary, we will discuss strengths and limitations and give recommendations for future falls-prevention research in frail older persons and for studying complex interventions for frail older persons.

Principal findings

The primary aim of the study was to determine the effectiveness of the intervention on the falls rate. A secondary aim was to determine the intervention's effect on subjective caregiver burden.

Although we meticulously developed this pairwise multifactorial falls-prevention program, it was not effective in decreasing the fall rate in patients or the subjective caregiver burden in caregivers. In favor of the intervention, the participants of the program experienced a higher level of mastery and, despite the negative effects on several outcomes, were positive about the program.

Discussion and conclusions of the Carthage-Phoenix study following the phases of the MRC framework

Development phase

The research activities in this phase helped us identify the best available evidence and appropriate theories and to model the process, intervention, evaluation and outcomes.

In an early stage of the development phase, the project team targeted the intervention to not only falls reduction but also to decrease of fear of falling. Elements of cognitive-behavioral therapy that have been shown to be effective in older patients without cognitive impairments with fear of falling [1] and in cognitively impaired patients with general anxiety disorder [2] were included in the intervention. Intervention components to achieve decrease of fear of falling:

- questioning and testing notions, assumptions, evaluations and beliefs concerning falls and fear of falling.
- exploring new methods to prevent falls and effective ways to cope with falls and fear of falling.
- facing activities that may have been avoided, for example, walking up or down stairs.
- setting realistic goals for increasing activity.

In addition to the psychological component, we included a physical component. Physical training took place in an "activities of daily living"-based circuit that simulates daily living conditions and was aimed at training balance, strength, coordination and functionality. The elements of these two interacting components of the intervention were based on a literature review, non-participatory professional observations, Delphi studies and consultations with experts. By performing this extensive research, we ensured that the intervention would be state-of-the-art.

In this early stage, the project team also decided to include caregivers in the intervention. This decision was based on three arguments:

1. A caregiver with a positive attitude towards falls-prevention could motivate a patient to join and adhere to the program.
2. Caregivers could serve as co-therapists to overcome the problems of limited learning ability in cognitively impaired patients.
3. Limited research revealed that informal caregivers of frail older fallers experience more caregiver burden than caregivers of frail, older non-fallers.[3] By including the caregiver in the intervention, caregivers could be supported as well. Consequently, the intervention should also reduce subjective caregiver burden on the informal caregivers of frail older fallers.

In this developmental phase, we carried out a series of studies that were directed at shaping the complex falls-prevention intervention and at allowing adequate scientific evaluation of the results. Here we will discuss the major findings, strengths and limitations of these preparatory studies.

The first step in providing adequate falls-prevention and psychological support for frail community-dwelling older fallers and their caregivers was aimed at acquiring in-depth knowledge of the impact of falling on both patients and caregivers. Because such knowledge is essential, we conducted a qualitative study.

Chapter 2: Qualitative study on the impact of falling in frail older persons and family caregivers: Foundations for an intervention to prevent falls

The primary aim of this qualitative study was to explore the views, experiences, emotions and needs regarding falling in frail community-dwelling older persons with and without cognitive impairments who have experienced a recent fall, as well as in their primary caregivers. Our secondary aim was to define the key components for a future falls-prevention program.

This grounded theory interview study included ten patients (three cognitively unimpaired, four with mild cognitive impairment and three with dementia) and ten primary informal

family caregivers. The consequences of falls for frail, community-dwelling, cognitively healthy and cognitively impaired older persons, including fear of falling and social withdrawal, are comparable to the consequences for non-frail, cognitively unimpaired older persons. However, frail older persons, especially those suffering from cognitive impairment, could not name a cause for their falls; this inability is a major source of fear and hinders coping. Caregivers reported fear of their care recipients falling. Patients rejected the ideas that falling is preventable and that the fear of falling can be reduced. Some caregivers rated the consequences of their care recipients' cognitive problems as more burdensome than their falls and believed that a prevention program would not be useful due to the care recipients' cognitive impairment, physical problems, age and personalities.

Strengths: The use of in-depth interviews with patients and caregivers ensured that this intervention was appropriate and relevant to the needs of the target population. We followed quality guidelines for qualitative research with respect to purposive sampling, triangulation (interviewing both patients and caregivers), iterative analysis and multiple coding.[4;5]

Implications for the intervention and the evaluation: Reducing the consequences of falling, promoting self-efficacy and activity, discussing the causes of falls, and educating caregivers to deal with the consequences of their care recipients falling as well as their cognitive impairment were considered active components for the intervention. This research also revealed that caregivers are highly involved and that they suffer from fear when thinking about potential falls of their care recipients. The data confirmed that caregivers are highly burdened.

These results further shaped the intervention. Based on practical experience with the target group and the necessity of transforming negative expectations about the program into positive ones, we developed a multistage recruitment process for the RCT that included multiple methods for explaining the study to the participants and their caregivers. Furthermore, to avoid attrition that might be based on negative expectations toward the intervention, we adopted recommendations from the existing literature regarding the engagement and the adherence of older people in activities to prevent falls, as well as recommendations from aging research in general[6;7]. Recommendations regarding the type and number of outcome measures and for lowering attrition rate in randomized controlled trials (RCTs) in frail older persons were also followed. The recommendations included the following:

- Flexible time frame for follow-up visits: The actual assessment date should be within a month of the anniversary of the assessment date.[8]
- Tailor-made intervention: The interventions should be tailored to the specific situation, needs and values of each patient. That this is especially important is shown by the fact that a review of the literature, as well as our group's research, indicates that there are two groups of fallers: fearful individuals who avoid activity[9;10], and impulsive individuals with a lack of insight.[11;12] Both types of patients should be addressed in the interventions.

- Realistic goal-setting: To tailor the intervention to a specific dyad, intervention instructors should help patients and caregivers set realistic goals. This could be problematic because this qualitative research showed that neither patients nor caregivers could easily name components that should be included in a future falls-prevention intervention.
- Providing a comfortable environment: The facilitator should provide positive feedback, should incorporate time for coffee during the sessions; the course venue should be easily reachable, and travel costs of the participants should be reimbursed.
- Providing a safe environment: To ensure patient safety, a maximum of six dyads will be included.

Limitations: The caregivers who could be included were all family caregivers (children or spouses); we did not include non-familial caregivers such as friends or neighbors. We believe this will have only minor effect on the generalizability of our results. Co-residence has been shown to be more important than the kinship tie in determining the pattern of caregiving.[13] Thus, we designed our study so that half the caregivers included in it lived with their care recipients and half did not. In addition, informal care for older persons is predominantly provided by family caregivers.[14] The majority of the patients of our geriatric outpatient clinic have family caregivers.

Chapter 3: Determinants of subjective caregiver burden and the quality of life of informal caregivers of community-dwelling, vulnerable older fallers

The intervention also aimed to reduce subjective caregiver burden; therefore, the objectives of this cross-sectional study included identifying determinants of subjective caregiver burden and the quality of life of informal caregivers of community-dwelling, vulnerable, older fallers.

We included one hundred thirty-two pairs of vulnerable older fallers who had been referred to a geriatric outpatient clinic after at least one fall in the past six months and their caregivers. This study revealed that explicit attention to caregivers of vulnerable older fallers is sorely needed; nearly 50% of the caregivers had quality-of-life scores that were below the norm score in the general Dutch population.[15] Furthermore, 20% of the caregivers experienced a high level of subjective caregiver burden.

Both caregivers' and patients' determinants, including fear of falling in patients, were associated with subjective caregiver burden. In contrast, the quality of life of caregivers was strongly determined by the caregivers' own factors, including living with the patient, the relationship with the patient, employment, age, anxiety score, depression score, subjective burden, caregiving time and receipt of assistance from other informal caregivers. Only the severity of a patient's cognitive decline was a relevant patient factor in determining the quality of life of caregivers. The identified determinants that are amenable to improvement or change

and could serve as targets for caregiver and patient support include fear of falling, general anxiety level, depressive symptoms in patients and anxiety, caregiving time and symptoms of depression in caregivers.
The multivariable models developed in this study may help healthcare professionals identify informal caregivers who are at risk for decreasing quality of life or increasing caregiver burden. Based on these models, we recommend that any professional treating a vulnerable older faller determine whether the patient has a high fear of falling score (FES-I score)[16], whether the caregiver has a high depression score (CES-D score)[17] and whether the caregiver is employed, to detect whether the caregiver has modifiable risk factors for a high caregiver burden. These three determinants together explained 49% of the variance of caregiver burden. Identification of a caregiver who is at risk for decreasing quality of life can easily be accomplished using three simple questions involving the patient's age, whether the caregiver is living with the patient, and whether the patient attends day care and by administering a questionnaire (HADS-A)[18] to assess the caregiver's anxiety score. These three determinants explained 42% of the variance of caregivers' quality of life. The FES-I, CES-D and HADS-A are short, standard questionnaires that are easy to incorporate into a geriatric assessment.

Strengths: This was the first study that identified determinants for subjective caregiver burden and quality of life of informal caregivers of vulnerable older fallers. The results are also important for prevention purposes because they may permit healthcare professionals to identify informal caregivers who are at risk for a burnout. The design of this study was guided by the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) statement.[19]

Implications for the intervention and the evaluation: We used the determinants that are amenable to improvement or change as targets in our intervention and as outcome measures in the RCT. The finding that fear of falling was negatively associated with caregiver burden strengthened us in our decision to target the intervention to both fall reduction and decreasing fear of falling. The high number of cases with missing values resulted in prespecification of alternate data collection strategies.

Limitations: This research is based upon cross-sectional data. Consequently, any conclusions about prediction can only be understood in a statistical and not a causal sense. The patients were indicated as vulnerable instead of frail. We were unable to check all the frailty criteria[20] because this study was a postal survey. We believe the patient population of this study to be frail because they all fell, had a high level of multimorbidity, were moderately disabled; furthermore, many of them had professional home care and more than fifty percent suffered

from MCI or dementia. The majority of the study patients' characteristics were comparable to those of the 43 patients seen in our outpatient fall clinic, all of whom were frail and all of whom were included in the descriptive analysis. We believe these results are representative for the population of community-dwelling frail older fallers of our geriatric outpatient clinic. Research on frail older persons, especially those with cognitive impairments, is known for its high level of missing data.[21] In this study, 39% of the subjects had ≥1 missing value. There were no statistically significant differences between the characteristics of the patients and caregivers, who were excluded due to missing values, and those of the pairs included in the analysis. In addition, when we further evaluated the selected determinants and models by including the complete dataset of all patients and caregivers that had no missing values for the variables in that particular model, the results remained similar.

The development phase also includes the planning of strategies for treatment allocation, blinding, recruitment, adherence and analysis. *Chapter 4* provides methods for the design, analysis and sample size determination of trials that evaluate interventions that are delivered to individuals in closed groups, i.e., groups that do not allow newcomers to join once the group has commenced, like our falls-prevention intervention.

Chapter 4: Studies with group treatments required special power calculations, allocation methods, and statistical analyses

Not only are the subjects in a group likely to influence each other, the leader, instructor or therapist may also have an impact. This influence may lead to correlations within groups and to additional variation in treatment outcome between groups. These factors must be taken into account in the statistical analysis and have consequences for the size of the trial.

Allocation methods for trials in which the intervention is delivered in closed groups: Various allocation methods, unrestricted randomization, randomization in permuted blocks, stratified randomization and minimization are described. These methods are all based on sequential treatment allocation: each time a subject is enrolled, a treatment is allocated.

In closed group trials, the group treatment does not begin until a sufficient number of patients for a complete group are available. In a clinical trial, it is important to use parallel treatments; ideally, groups should run simultaneously and should start in pairs, one in each treatment arm. The group of subjects allocated between the two arms of the trial at the same moment is indicated as a batch. The batch structure of these trials makes it possible to make treatment allocation completely unpredictable simply by postponing the allocation until all subjects in a batch have been enrolled. In addition, the balance can be optimized by investigating all possible treatment allocations for that batch and selecting a 'best' one: Optimal Batchwise Minimization (OBM).

The OBM algorithm consists of the following three steps:
1. Calculate the imbalance for all possible allocations within a batch.
2. List all allocations with minimum imbalance.
3. Randomly select one of the allocations with minimum imbalance.

The simulation study that evaluated the performance of unrestricted randomization, stratification, permuted block randomization, deterministic minimization and OBM revealed that stratification, deterministic minimization and OBM had considerably less risk of imbalance of prognostic factors than unrestricted randomization and permuted block randomization. From the perspective of obtaining overall balance, we conclude that minimization is the method of choice. When the number of prognostic factors is low, stratification is an excellent alternative. OBM leads to better balance within the batches, but it is more complicated. OBM is probably most worthwhile in trials with many prognostic factors. From the perspective of predictability, a treatment allocation method like OBM that allocates several subjects at the same time is superior to other methods because it leads to the lowest possible predictability. Both the *analysis* and *sample size calculation* must be based on a multilevel model that takes the group structure of the trial into account. The group structure of these trials necessitates a larger sample size than in a non group structure trial.

Strengths: This is the first study that describes methods for the design, analysis and sample size determination of trials that evaluate intervention delivered to individuals in closed groups. Because group interventions, whether self-help or professionally conducted, are popular among patients and caregivers, this study may help researchers to evaluate such interventions in a methodologically sound manner.

Implications for the intervention and the evaluation: Because our falls-prevention intervention is a closed group intervention and we had to deal with a high number of prognostic factors, we used OBM for treatment allocation and multilevel models for the sample size calculation and for analysis in the RCT.

Cognitively impaired patients

To ensure that cognitively impaired patients could benefit from the program and that the evaluation was tailored to this group, we employed several measures. These included the following:
1. Repeating important information several times in several ways during the program.
2. Including caregivers who could serve as co-therapists.
3. Choosing outcome measures that were applicable to cognitively impaired patients.

Using the information from the development phase, we designed the draft intervention and evaluation; these were tested in the feasibility and piloting phases.

Feasibility and piloting phase

Pilot study (chapter 1)

In this phase, we tested the feasibility of the recruitment process, intervention and baseline measurements in four pairs of patients and caregivers.

Strengths: In the pilot study, we paid special attention to the burden the intervention and evaluation posed on the participants and attempted to maximize the benefit: burden ratio. The assessment was not overly burdensome for patients or caregivers.

We derived an accurate image of the feasibility of both the intervention and the evaluation by triangulation of data collected from different sources. We used observations of the interventions by independent researchers, project team meetings, an expert meeting, literature reviews, consultations with a biostatistician, focus groups with patients, instructors and caregivers, and questionnaires administered to the same groups.

Implications for the intervention and the evaluation: It was necessary to reduce the number of exercises and psychological components due to the low functional and cognitive levels of the patients. A basic set of components and several additional components were established so that the intervention could be tailored to each individual participant. The presence of caregivers was of additional value. However, the caregivers felt burdened by the requirement to attend each session; therefore, it was decided that they could be replaced by another caregiver in case of prior obligations. Otherwise, the content and organization of the intervention were not changed.

The patients in the pilot study used a falls calendar to register their falls. It is known that falls calendars provide more valid data than retrospective methods; however, they are burdensome and the response rate may be low.[8] In the pilot study, we noted that the caregivers had to remind the patients to fill out the calendar. Furthermore, the patients indicated that if they were asked to continue to fill out the calendar over a longer period of time they would probably forget to do so.

A pilot study performed alongside the RCT to evaluate an automated call system using the Touch Tone Data Entry (TTDE) system to detect falls [fall telephone (FT)] in our frail population revealed that the fall telephone is a feasible, reliable and valid method to assess falls in frail older persons, including those with cognitive impairment.[22] The FT was also a convenient and reliable instrument to monitor falls in patients with Parkinson disease.[23] For our RCT, the FT was not yet available. Therefore, we continued using the time-intensive method of pre-addressed, reply-paid two-weekly fall registration calendars, with follow-up for non-response and characterization of each fall by contacting the patients by telephone.[8]

At the start of the pilot study, one dyad dropped out because of hospitalization of the patient. Older adults are more likely than younger adults to experience health and functional problems that limit data collection.[21] Before the start of the trial we calculated an attrition rate of 15%.
To identify as many eligible patients as possible, the project team decided to recruit patients from other geriatric outpatient clinics as well as from the falls clinic. Two other neighboring hospitals were also recruited to participate in the study. Anticipating a multicenter trial, we confirmed at an early stage that we could recruit our target population from those hospitals.

Limitations: Although the pilot study was not performed in a randomized controlled design and we did not test the long-term effectiveness of the intervention, we believe that the results were highly valuable for further shaping the intervention and the evaluation.

In addition to the above-mentioned factors, we focused on methodological aspects of designing and evaluating pilot studies. We developed a new treatment allocation procedure that we call studywise minimization.

Chapter 5: Studywise minimization: a treatment allocation method that improves balance between treatment groups and makes allocation unpredictable
In order to carry out small pilot studies using a randomized controlled design, a methodological innovation of the allocation procedure was deemed necessary. In randomized controlled trials with many potential prognostic factors, serious imbalance among treatment groups regarding these factors can occur. Minimization methods can improve balance; however, these methods may make the treatment allocation predictable, and this predictability may influence the investigator. This enhances the possibility of selection bias. This problem frequently occurs in small one-center trials such as pilot studies or phase-I-clinical trials.
Therefore, we developed a new allocation strategy called studywise minimization. It can be used in trials in which all participants are included before the study starts.

The studywise minimization algorithm consists of the following three steps:
1. Calculate the imbalance for all possible allocations.
2. List all allocations with minimum imbalance.
3. Randomly select one of the allocations with minimum imbalance.

We carried out a simulation study to compare the performance of studywise minimization with three other allocation methods: randomization, biased coin minimization and deterministic minimization.
Independent of trial size and number of prognostic factors, the risk of serious imbalance was the highest in randomization and absent in studywise minimization. Studywise minimization

therefore diminished the risk of loss of power, which is especially important in small trials. The differences in risk of serious imbalance between studywise minimization and the other three allocation methods studied decreased when the trial size increased. This combination of findings demonstrates that studywise minimization is particularly useful for treatment allocation in small trials. For larger trials, minimization is a justifiable choice, especially because it does not require enrollment of all patients before allocation can take place.
Another important advantage of studywise minimization is the unpredictability of treatment allocation. The chance that an investigator correctly guesses the treatment is 50%, the same as for unrestricted randomization. Consequently, selection bias is considerably reduced compared with other minimization methods.
Studywise minimization is particularly useful in small trials, where it eliminates the risk of serious imbalances without generating selection bias.

Implications for the intervention and the evaluation: This allocation strategy will be very valuable in the design of pilot studies, especially studies of heterogenic geriatric populations that are characterized by many prognostic factors. The procedure has already proved its value in geriatric research in a pilot study of a trial evaluating a dementia training program for general practitioners and primary care nurses.[24]
The rigor with which we carried out the development, feasibility and piloting phases of the study was necessary in order to turn the combined patient-caregiver falls-prevention intervention into a flexible, tailor-made, theory-and-consensus-based falls-prevention intervention with well defined program goals based on the currently available literature and ready for evaluation in a large-scale RCT.

Evaluation phase
This phase comprised an effect evaluation *(chapter 6)* and a process evaluation *(chapter 7)*. We begin this section by presenting our newly developed systematic and comprehensive guide for the development and application of a process evaluation for complex interventions in geriatrics. We then describe the results of the RCT, followed by a reflection on these results and on the methodological aspects of the RCT.

Chapter 7: How to perform a preplanned process evaluation for complex interventions in geriatric medicine: Exemplified with the process evaluation of a complex falls-prevention program for community-dwelling frail older fallers
For complex interventions in heterogeneous frail populations, in-depth insight into the process is highly relevant, and the interventions must be carefully planned before trials start. Complex interventions are difficult to develop, document, evaluate, and reproduce. Process

evaluations aid the interpretation of outcome results by allowing documentation and evaluation of each process step in detail. Despite their importance, process evaluations are not embedded in all evaluations of complex interventions; even when present, process evaluation components may differ or studies may only assess a single aspect.
Based on the existing literature, we structured the process evaluation for trials of complex interventions into 3 main components: (1) describe the success rate of recruitment and quality of the study population; (2) critically evaluate the quality of execution of the complex intervention; (3) monitor the process of acquisition of the evaluation data. Each of these process components can be assessed by several process measures and process variables.
Thus, a good-quality process evaluation, such as the evaluation that can be performed using this guide, gives a detailed description of the most important components of a complex intervention, resulting in an in-depth insight in the actually performed intervention and effect analysis.

Strengths: This is the first process evaluation guide for complex interventions in geriatric medicine. A process evaluation performed according to this guide allows researchers to draw appropriate conclusions regarding positive or negative trial results and results in recommendations for implementation or adjustment of the intervention or effect evaluation, respectively.

Implications for the evaluation: We performed a process evaluation for our falls-prevention program based on this guide. Because of the frailty of our population, we tried to assess as many variables as possible with simple questionnaires or registration forms. In addition, we conducted short semi-structured interviews with participants and instructors to gather information about their experiences and thoughts.

Chapter 6: Multifactorial fall prevention for pairs of frail community-dwelling older fallers and their informal caregivers: A dead end for complex interventions in the frailest fallers
A randomized, two parallel-group, single-blind, multicenter trial was conducted in 36 pairs of frail fallers who were referred to a geriatric outpatient clinic after at least one fall in the past six months and their informal caregivers. The objective of this study was to assess whether our multifactorial falls-prevention program was more effective than the usual geriatric care in preventing falls and reducing fear of falling in frail community-dwelling older fallers with and without cognitive impairment and in alleviating subjective caregiver burden in caregivers. The intervention comprised ten twice-weekly, two-hour sessions with physical and psychological components and a booster session. The sessions were conducted with groups of five pairs of patients and their informal caregivers.

The primary outcome was the fall rate during a six month follow-up. We also measured fear of falling and subjective caregiver burden. Data on the secondary outcome measures were collected at baseline, directly after the intervention and at 3 and 6 months after the last session of the intervention.
Directly after the intervention and at the long-term evaluation, the rate of falls in the intervention group was higher than in the control group, although these differences were not statistically significant (RR = 7.97, $P = 0.07$ and RR = 2.12, $P = 0.25$, respectively). Fear of falling was higher in the intervention group, and subjective caregiver burden did not differ between groups. In addition, the analysis of secondary outcome measures in caregivers did not yield significant differences between the two groups. In favor of the intervention, the intervention patients experienced a higher level of mastery.
Although we meticulously developed this pairwise multifactorial falls-prevention program, it was not effective in reducing the fall rate or fear of falling and was not feasible for caregivers, as compared to regular geriatric care.

Why was the intervention not effective?
An intervention may fail to show effectiveness in two ways: 1) "failure to demonstrate underlying efficacy or effectiveness" (i.e., the evaluation failed) and 2) "good evidence of lack of efficacy and effectiveness" (i.e., the intervention failed). To evaluate the lack of effectiveness of this intervention, we used a model that examines three main factors that determine an intervention's effects; these factors are content, process and choice of target group.[25] We also used the results of our process evaluation *(chapter 7)*.

Content analysis refers to analysis of all the components that are considered part of the multifactorial intervention and are integral to its success.[25] Examining the content of our intervention, we conclude that the intensity and duration of the physical therapy it included was insufficient to reduce the fall rate. Evidence suggests that to be successful, physical therapy must persist for several months and be progressive.[25] However, the provision of physical therapy of increasing intensity is problematic because of the frailty of these patients; furthermore, it conflicts with the need to alleviate the caregiver burden because it is necessary for caregivers to support the patients during the exercises.
The intervention patients' increased awareness of their risk of falls and of the consequences of falls may have resulted in the increased feelings of fear of falling.
The intervention did not reduce subjective caregiver burden. This may indicate that the program was not optimally adjusted to the caregivers' situation. It is possible that the program created some extra burden for caregivers, as evidenced by the observation that the included caregivers felt burdened to attend each session. However, the qualitative analyses revealed

that the caregivers felt supported by the intervention. Overall, the outcome measures may not have been suited to reflect these benefits of the program.

Process analysis refers to evaluation of the way in which intervention content is delivered to maximize uptake by the individual. We believed that training caregivers to function as co-therapists at home could overcome the problems of limited learning ability in cognitively impaired patients. Although a previous trial that introduced the caregiver as a co-therapist seemed to result in increased effectiveness of interventions in cognitively impaired subjects, this trend was not confirmed in our trial in the frailest fallers.[26] Moreover, focusing the intervention on caregivers had a major drawback. The majority of the caregivers, and therefore pairs, were unable to participate because the course was provided during working hours.

Target group reflection: Although frailty according to the criteria of Fried et al. was one of the inclusion criteria, the high age, high level of multimorbidity, high percentage of patients with MCI or dementia, and the high prevalence of intercurrent disease and mortality during follow-up also support the idea that a group of frail, old, vulnerable patients was indeed sampled. The analysis of the results of a questionnaire study undertaken with the non-participating pairs and the results of the RCT and process evaluation revealed that the intervention and assessments were likely too burdensome for our frail patients due to numerous health problems and their dislike of leaving their homes. The instructors mentioned that the target group was quite heterogeneous; it included patients who were afraid of falling and needed to be activated as well as impulsive patients who needed to be controlled. The intervention group was also heterogeneous with regard to cognition; this was reflected in problems with holding the attention of cognitively impaired participants.
A subgroup analysis showed no benefit of the intervention in either the group of cognitive healthy patients or the group of patients with MCI or dementia. The subgroup analysis was not specified a priori; the two groups were very small, and we did not apply the criteria necessary for the credibility of a subgroup analysis.[27]

Outcome measures: The process analysis of the outcome measures indicated that these measurements did not fully match the intervention. Heterogeneous effects, even contradictory findings between different persons such as increased activity in some and decreased activity in others, might be expected, and this could result in lack of change in the overall analysis of the group and failure of the evaluation. In addition, some of the goals, such as being able to get up after a fall and acceptance or increased insight into limitations and abilities, were not assessed at all despite the fact that the intervention focused specifically on these aims. Effectiveness ultimately may be assessed at the individual level, for example, goal attainment

scaling may be of high value for tailor-made complex interventions. Thus, all possible goals should be reviewed before start of the intervention and outcome measures should be adjusted to anticipated goals. Perceived benefit assessment should consider an individual frame shift (i.e., 'response shift') that may result in no longer acknowledging improvement because an individual adapted to the new situation.

One can conclude that the most likely primary reason the falls-prevention program showed no effectiveness on the most important outcome measures is that the intervention failed. However, the evaluation also failed to reveal the benefits of the intervention that were mentioned in the qualitative analysis, which was obtained from focus groups, interviews and questionnaires among participants and instructors.

Additional methodological aspects of the RCT

The CONSORT guidelines for randomized trials guided the design and report of this trial.[28]

Recruitment: The recruitment objective was not reached; only 22.5% of the eligible patients participated. The most important barrier to participation was the burden of participation; this burden was caused by the frequency and timing of the sessions, the distance to the facility, multimorbidity, or other obligations.

Allocation: The optimal batchwise minimization method performed well. No relevant differences were found between the two groups with regard to baseline characteristics and outcome measures.

Blinding: The trial was observer blind; double blinding was impossible given the type of intervention under study. In a fairly high number of cases, treatment assignment was revealed to the assessor during follow-up visits despite the fact that the assessors explicitly asked the participants not to mention to the assessor whether they attended the program or not. This shows how complicated research can be in frail patients who may or may not exhibit cognitive impairment and are not easy to instruct. However because our primary outcomes were assessed using a written falls calendar and through questionnaires that were completed by the participants before each follow-up visit, they were not significantly influenced by the state of knowledge of the assessor.

Follow-up: Although the Prevention of Falls Network Europe (ProFaNe) recommends a follow-up time of 12 months in falls-prevention trials because an intervention may have a delayed effect[29], our study applied a maximum follow-up of six months. Although six months represent a fairly short period, a longer follow-up would not have benefited our trial. With a longer follow-up, the short-term effects of the intervention, which are highly important for frail older persons, would probably be lost and the effects of competing morbidity and mortality might be unacceptably high.[8] (Even with our six-month follow-up, ten pairs dropped out due to

intercurrent disease and mortality.) Furthermore, a delayed effect could not be the cause of lack of effectiveness on the fall rate at 6 months. It is more likely that the intervention is simply not effective.

Implications for the implementation phase: The process evaluation was essential for analyzing why the intervention was not effective and why the recruitment rate was low. The process evaluation helped us adjust the intervention and the effect evaluation.

Comparison with other studies

Patient effects

Cognitively impaired frail older persons: To our knowledge, no prospectively evaluated multifactorial falls-prevention intervention has been proven to reduce the fall rate in frail community-dwelling cognitively impaired patients[30;31]; this accords with our results. The only published study that specifically investigated the effectiveness of a multifactorial intervention in patients with cognitive impairment in the community also demonstrated lack of effectiveness.[32] However, in a post hoc analysis of a trial that evaluated a small subgroup of older fallers with Mini-Mental State Examination (MMSE) scores of ≤ 27 (dementia or mild cognitive impairment diagnoses were unknown) who were not living alone, the rate of falls was lower in the intervention group (home-based, individual multifactorial falls-prevention program) compared to the usual care group (rate ratio 0.45).[33] Unfortunately, we could not validate these results; however, they strengthened our belief that the support of informal caregivers is necessary for effective falls-prevention in cognitively impaired older persons.

Frail older persons without cognitive impairment: Although several single-component falls-prevention interventions (exercise, psychotropic drug withdrawal, vitamin D supplementation, cataract surgery, cardiac pacemaker insertion) were effective in reducing risk of falling [31], the preponderance of evidence suggests that multifactorial interventions are the most effective prevention strategy in reducing falls in high risk community-dwelling older persons.[31;34] Most of the effective trials included multiple factor risk assessment, withdrawal or minimization of psychoactive and other medications, PT or exercise and home safety modification. The first two factors are already part of the assessment and management of fall risk factors that are performed according to the guidelines [31] at our geriatric outpatient clinic. Our intervention comprised even more components than physical therapy and home safety modification, yet it was not effective.

Fear of falling: An intervention aimed at reducing fear of falling that also used cognitive behavioral components reduced fear of falling in older persons.[1] However, cognitively impaired older persons were not included, and the included patients were less frail than ours.

Caregiver effects

This was the first falls-prevention study that included informal caregivers. Two interventions aimed at geriatric patients with cognitive deficits and their caregivers decreased subjective caregiver burden and caregivers' sense of competence.[26;35] We could not confirm this result in the caregivers of the frailest fallers.

Implementation phase

As mentioned earlier, the effect evaluation and the process evaluation identified limitations of the intervention and resulted in multiple recommendations for improvement of our fall intervention program. Therefore, the intervention was not implemented in its present form.
However, we have published an appendix (see Appendix A) in which the intervention is described in detail so that other researchers can easily copy our intervention. A full description of the intervention that allows any planned variation and facilitates further publications is essential for successful dissemination. To our knowledge, this is the first falls-prevention intervention that has been presented in published form in such an easily accessible way.

Conclusion and discussion of the MRC framework

The MRC framework for the development and evaluation of complex health care interventions defines complex interventions as interventions that include several components such as different organizations from which the intervention is delivered, heterogeneity of the target population (patients with different multi-morbidity problems, fearful patients, patients with lack of insight, and different types of caregivers), different target populations for one intervention (intervention directed at patients and caregivers), the inclusion of different approaches (psychological and physical, for example) in one intervention and the performance of different activities (as is usual in tailor-made interventions). As indicated our intervention fulfils these criteria, and the MRC framework proved to be highly valuable for the development and evaluation of our falls-prevention intervention.
As described earlier, the sequence of studies that were carried out before the randomized controlled trial was conducted led to several aspects that were critical for the final outcome, and these studies shaped both the intervention and the evaluation.
The major strength of the MRC framework is the systematic way in which it proposes developing the best intervention, evaluation and implementation methods. The framework can be used flexibly. In our description of the framework and its application *(chapter 1)*, we did not intend to be prescriptive but to help researchers, funders and decision makers in geriatrics in making appropriate methodological and practical choices.

We believe the MRC framework can be highly valuable in geriatrics. Geriatric medicine focuses on diagnosing and treating geriatric syndromes and their underlying multiple causes and contributing factors in a heterogeneous population of patients with a high level of multimorbidity, thereby taking the social system of the patient into account. Complex interventions are generally considered most powerful in geriatric patients.[36] The MRC framework has already proved its value in the development of an occupational therapy program for patients with dementia and their caregivers [26] and in a physiotherapy program for patients with Parkinson's disease.[37]

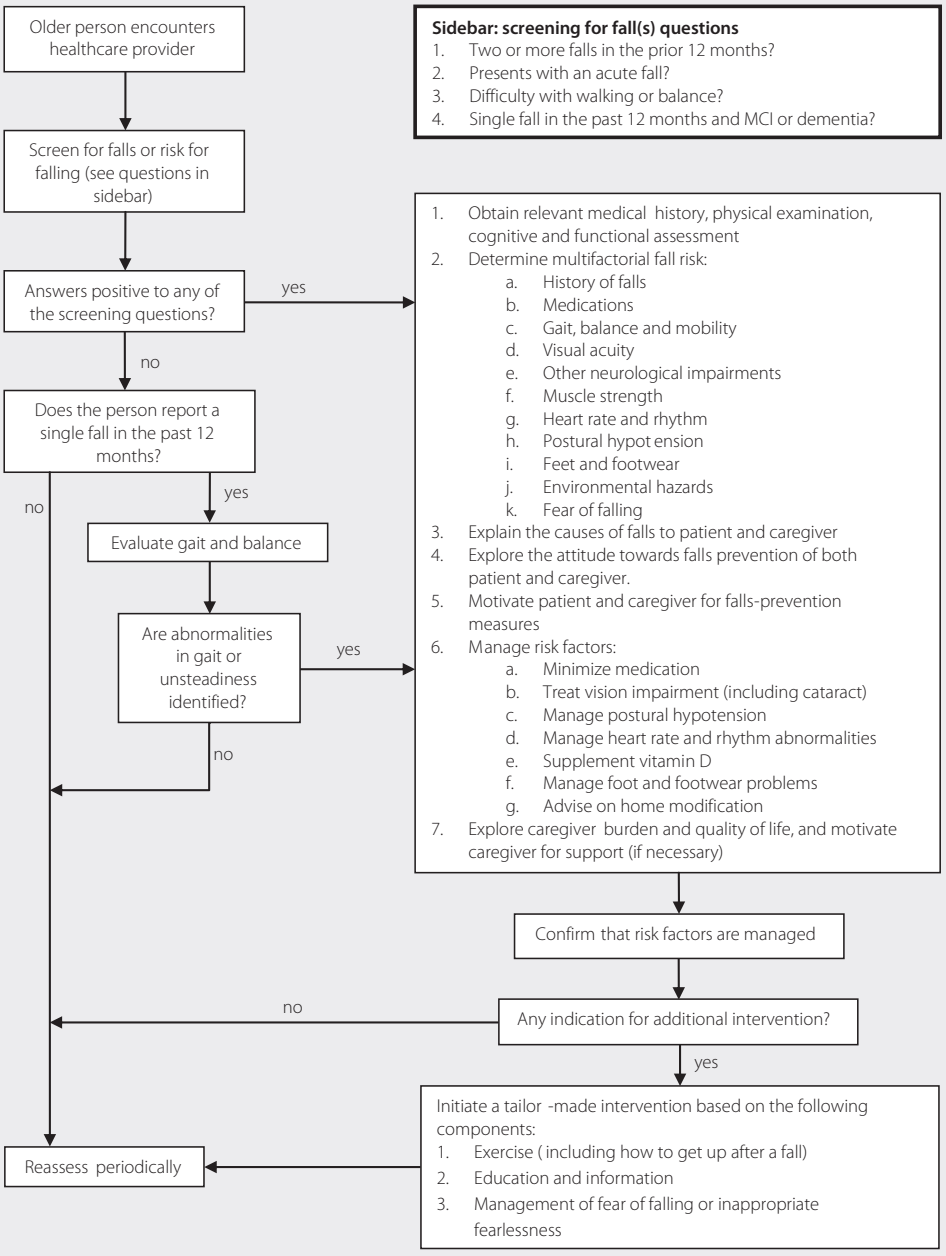
The clinical applicability of the MRC framework is not obvious; this is related to the fact that there is often a lack of funding for studies of the first phases of the framework. Research funding agencies should be prepared to support developmental studies before large-scale evaluations are undertaken; furthermore, they should use the framework to assess whether developmental research sufficiently addresses the challenges of the framework phases and the criteria directly related to each phase. Using the MRC framework avoids the risk of evaluating unfeasible interventions by using designs that do not fit and maximizes the chances of successful intervention and evaluation. In this way, resources are conserved and the benefit:burden ratio for participants is maximized. For interventions that fail to show effectiveness, instead of writing off the intervention, it is useful to move backward in the cyclic process to determine deficits in the process of development or evaluation design.

Recommendations for falls-prevention in community-dwelling frail older persons with and without cognitive impairment and future falls-prevention research in this group

Figure 1 is based on a recently published algorithm intended for use in a clinical setting for assessment and intervention to reduce falls in community-dwelling persons 65 years of age and older. [30] Based on the research described in this thesis, we adjusted and extended the figure.

We suggest that all patients with 1) two or more falls in the prior 12 months, 2) an acute fall, 3) difficulties with walking or balance, 4) a single fall in the past 12 months *and* with MCI or dementia or 5) a single fall in the past 12 months with gait/balance abnormalities and their primary informal caregivers should receive a basic package of risk assessment and management. This risk assessment and management package is described in the gray box in figure 1. In the original algorithm and in falls-prevention research, the interventions mentioned under the heading 'manage risk factors' are indicated as additional interventions.

Figure 1 Algorithm for the prevention of falls in community-dwelling older persons (based on the algorithm of the Panel on Prevention of falls in older persons of the American and British Geriatrics Societies)[30]



First fall risk factors and the level of fear of falling should be determined. To promote effective coping, the cause(s) of the fall(s) should be clearly explained to patients and caregivers. Our research revealed that few patients and caregivers attributed falls to causes identified in the outpatient clinic. The attitude towards falls-prevention of both patient and caregiver should be explored, and patients and caregivers should be motivated for falls-prevention. This improves adherence and uptake of falls-prevention measures. Next, the identified risk factors should be managed, taking the physical condition and cognitive status of the patient into account. For example, cardiac pacing or cataract surgery may be contraindicated. Caregiver burden and quality of life should be explored. If necessary, the caregiver should be motivated to seek caregiver support. In a follow-up consultation, management of the risk factors should be checked. Research has indicated that interventions in which investigators only offered advice or referral to existing community or health care sources were not effective.[31]

Additional interventions

Subsequently, all possible indications for additional interventions should be explored. Indications could be gait, balance or mobility problems, a need for supplementary information, a high level of fear of falling, inappropriate fearlessness or a patient's continuing to fall despite firm risk management. The possible components of additional intervention place high demands on the patient; for example, exercise requires training. Patients should be reassessed periodically. If after assessment, management of risk factors and possibly an additional intervention a patient still experiences fall accidents, the algorithm may need to be reapplied because a change in risk factors may have occurred.

Non-frail, cognitively healthy patients can participate in falls-prevention interventions, including complex interventions, with proven effectiveness. Complex refers to interventions that are aimed at improving multiple risk factors, those that target both patients and caregivers, those that are held at a course venue (not at home), and group interventions. Frail and/or cognitively impaired patients, the majority of the geriatric population, should be offered either a non-complex intervention or no additional intervention. 'Non-complex' is used to describe a tailor-made intervention that is carried out at home, focuses on limited risk factors, and preferably includes the participation of an informal caregiver who can function as a co-therapist. Our research indicated that the average geriatric patient is too frail for a complex multifactorial falls-prevention program.

We believe that developing even more complex and specialized fall-prevention interventions is not effective or feasible for community-dwelling frail patients with or without cognitive impairments and their informal caregivers. Currently, the greatest added value can be obtained by focusing on the implementation of basic geriatric practice principles, i.e., geriatric

comprehensive fall assessment and risk factor management for all fallers, including those with cognitive impairment.

Future falls-prevention research should be focused on the following:

1. Assessing the effectiveness of firm risk factor assessment and management (as indicated in the gray box in figure 1) in patients with cognitive impairment.
2. Assessing the effectiveness of an additional, non-complex tailor-made intervention at home with the informal caregiver as co-therapist in frail patients with and without cognitive impairment.

Recommendations for studying interventions for frail older persons

Based on the studies described in this thesis, several recommendations can be made regarding research on interventions for frail older persons with and without cognitive impairment. We strongly advocate the use of the MRC framework for the development, evaluation and implementation of such interventions. Before designing an intervention to reduce a specific health problem, one should explore whether the problem is also a problem for patients and their informal caregivers. Qualitative research is an excellent way to explore a health problem, its impact and possible participants' attitudes towards a future intervention, even in cognitively impaired older persons. Older persons with mild to moderate dementia are often good informants who are able to describe their subjective states and articulate their feelings, perspectives and experiences.[38] To avoid a negative attitude towards the intervention, one should motivate patients and their caregivers to adhere to the prescribed program before the intervention starts. Interventions should be tailor-made and adapted to an individual's specific abilities. With cognitively impaired patients, including the caregiver as a co-therapist may be useful.

In research concerning frail older persons, several methodological aspects are important. Strategies to reduce missing values and attrition should be employed because older adults are more likely than younger adults to experience health and functional problems that limit data collection.[21] Prespecification of alternative data collection methods could be useful. The burden:benefit ratio of measurements must be carefully weighed; when cognitive impairment is present, outcome measures may require verification by caregivers. Goal attainment scaling may be of high value for tailor-made complex interventions. Furthermore, a process evaluation should be preplanned.

In conclusion, we believe intervention studies in geriatrics should move towards tailor-made interventions with evaluations based on achieving realistic individual goals.

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Contents of the multifactorial falls-prevention program for frail older fallers and their informal caregivers

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Background

This program is designed as a treatment for frail, older persons who fall, following diagnostic assessment at the geriatric outpatient clinic. Existing effective falls-prevention programs are not feasible for this frail population, which requires a specific approach because of the presence of physical and cognitive impairments. The program was developed following the Medical Research Council Framework (MRC) for developing and evaluating complex interventions. The development phases have been described in detail elsewhere. (Faes et al, JAGS 2010).

Target population

Geriatric outpatients are eligible for the prevention program if they have experienced at least one fall in the last six months, live independently or in a care home, are able to walk 15 m independently (use of a walking-aid permitted), and have an informal caregiver. Patients participate in dyads together with their primary informal caregiver. The primary informal caregiver is defined as the non-professional who is most involved in caring for the patient and assists with at least one personal or instrumental activity of daily living.
Patients with (mild) cognitive impairment are not excluded unless their Mini-Mental State Examination score is below 16 (range 0-30). A lower score indicates a cognitive impairment that is too severe for this group program. In addition, patients with a severe hearing impairment are not able to participate.

The falls-prevention program

Aims of the falls-prevention program

The primary aims of the program are to:

- Reduce the fall frequency in patients
- Reduce the level of fear of falling in patients

Secondary aims for the patients are to:

- Improve quality of life
- Improve mood
- Increase the level of activity and performance of activities of daily living (ADL)
- Improve gait and balance parameters

Secondary aims for the caregivers are to:

- Decrease caregiver burden
- Improve well-being
- Improve quality of life
- Improve mood

Key aspects and preconditions

The program is a multifactorial intervention and consists of ten sessions given twice weekly for five weeks and a booster session six weeks after the initial ten sessions. Each session lasts two hours. The structure of each session is the same so that participants know what to expect from the session (see Box 1). The program consists of several components, both psychological and physical (in accordance with the bio-psycho-social model). These components work in complement, and the combination and interaction of these components is a key aspect in this program. Box 2 gives a brief overview of these components, which are described more extensively below along with their rationales.

There are two instructors for each session: a physiotherapist and a psychologist with cognitive behavioral skills and experience in coaching groups. Experience with the specific patient population is a requirement because some of the participants will have a cognitive impairment or (severe) multiple morbidities. The presence of two instructors is necessary to ensure the participants' safety. The physiotherapist leads the components that are primary physical, and the psychologist leads both the educational components and the discussions. Participants have an active role during all aspects of the program, discussing problems and solutions within the group.

A second key aspect of this program is that caregivers actively participate in the program. Consequently, they can aid patients during the session and, more importantly, also help them at home and stimulate them to practice at home. Moreover, caregivers learn how to provide adequate support to the patients during the physical program, and they gain insight into the limitations and abilities of the patients. Caregivers also participate in the physical program to experience what the patients experience.

During the educational parts of the sessions and the conversations, the participants and instructors are seated in a semicycle. This promotes eye contact and interaction between participants. The caregiver sits beside the patient to provide support. Especially in groups of frail older persons, it is important that a patient has a person next to him/her whom he/she trusts and may fall back on. However, in some cases this arrangement may be disturbing to the group, for example when there is too much talking between the patient and caregiver, or because a negative interaction between the patient and caregiver exists. In those cases, the caregiver and patient are separated.

The patient-caregiver interaction is an important aspect in determining whether the program will be successful. Instructors need to be aware of their interaction and respond appropriately to this dyad, or 'system', during the program and address both the patient and caregiver as separate entities and as a whole to be able to achieve change.

The program is delivered in groups of a maximum of six dyads to enable the participants to learn more by recognition, based on shared experiences and similar needs. Participants may

identify with one another, thereby increasing acceptance. However, to ensure the participants' safety and to be able to provide enough individual attention, the group should not exceed six dyads. Considering the heterogeneous nature of the group, an important aspect of the program is that it is tailored for each participant. The components can be used and adapted according to the needs and limitations of the participants.

To ensure that participants adapt the way they move and behave, and to promote fitness and strength, they receive homework exercises. Participants receive an intervention booklet to note their individual aims, homework and progress, and to collect brochures handed out in the sessions.

Because the participants of the program are frail, there are high demands on the facility. It should be easily accessible, without stairs, have a toilet nearby (preferably a toilet for the disabled), and have easy parking at the entrance. In addition, the acoustics should be good because participants may have (mild) hearing problems.

The program was advertised as a movement course with the aim to stimulate independence in the patients, since research suggested that older adults are more likely to engage in fall prevention strategies when the interventions are couched in terms of preserving independence rather than preventing falls.

Box 1 Structure of each session

1 Agenda for this session	To provide structure for the participants, the agenda for the session is listed on a flipchart and briefly explained at the start of each session.
2 Key points of previous session and questions (not in session one)	Repetition is an important aspect of the learning process, especially in participants with cognitive impairment. Repetition promotes habit formation, which is essential for behavioral change. Therefore, in each session the key aspects of the previous session are discussed, and participants have the opportunity to ask any remaining questions.
3 Falls	Participants note the falls that occur during the program. Should a fall have occurred, the causes and consequences of the fall for both the patient and caregiver are discussed.
4 Homework from previous session (not in session one)	The purpose of the homework is to practice at home and to stimulate reflection on important issues. By discussing the homework, its importance is emphasized. Participants are encouraged to share experiences and answer each other's questions. It is very motivating for participants to receive positive feedback on their efforts and on participating in the discussion. When participants did not complete their homework, the reasons for this should be explored and solved, preferably together with the other participants.
5 Education, conversation, and practice	This part differs for each session; see Box 2.
6 Homework for next session (not in session ten)	The individual homework assignments for the next session are discussed and noted in the intervention booklet. The importance of performance of the homework assignments is emphasized.
7 Questions or remarks	Participants have the opportunity to ask questions or make remarks concerning this session. The instructor stimulates other participants to reply to the questions or remarks because this improves information uptake.
8 Individual learning points	The instructor asks the participants to identify and note their individual learning points, facilitating repetition of the key points.
9 Summary and closing of the session	The instructor summarizes the learning points of this session based on the answers of the participants and the content of this session. Instructors thank everyone for their attention and active participation and remind participants of their homework and of the date and time of the next session.

Box 2 Brief overview of the components and targets of the falls-prevention program for frail older persons and their caregivers

Psychological component	Physical component
Introduction of the program, participants and instructors Expectations and aims	Getting out of bed (safely and efficiently)
Individual expectations and aims Individual causes of falls Causes of falls in general Ageing and falls	Rising from a chair (safely and efficiently)
Home safety Emotions concerning falls Fear of falling; the vicious cycle Limitations and abilities: acceptance	Walking (safely and efficiently, with a walking aid if applicable)
Fear of falling; the vicious cycle Impulsiveness; risk behavior and the vicious cycle Impact of falls on the caregiver	Rising from a chair and walking (safely and efficiently, with a walking aid if applicable)
Activity pattern Stop-think-go	Activities of daily living (ADL)-based circuit training (outdoors if possible)
Methods/aids to prevent falls	Getting up after a fall (safely and efficiently)
Experiences and emotions associated with the practice of getting up after a fall Asking for assistance	ADL-based circuit training (outdoors if possible)
Evaluation methods/aids for preventing falls Coping	Getting up after a fall (safely and efficiently)
Physical activity Caring for significant others	ADL-based circuit training
Falls Evaluation of the individual aims and goals Individual effects of the program Evaluation of the program	ADL-based circuit training; elements at the request of the participants

Components

Below, the components and their rationales are discussed in more detail. Although the boxes suggest a fixed program, this is only a guideline that can and should be adapted to the needs of the dyads. Consequently, the components may be discussed in different sessions, and the emphasis on various components will differ in each group.

Session 1

1. Introduction (different from the other sessions)

Welcome	Instructors welcome the participants. It is important to realize that all participants experience participation in such a program in their own way and that they may be nervous or scared. Instructors try to reassure/relax participants.
Introduction of the instructors	Instructors briefly introduce themselves, giving some information about their background.
Intervention booklets	Program documents are handed out and explained. The first pages of the intervention booklet contain practical information concerning the instructors, the rules that apply to the group, directions to the facility and contact information. Behind each tab, there is session-specific information and blank pages to take notes.
Group rules	Group rules are discussed. Instructors emphasize the importance of asking questions and discuss the confidentiality within the group.
Introduction of the participants	Participants introduce themselves. They are encouraged to give some information regarding their personal situation and their fall history. Instructors ask participants to name the cause(s) of their fall(s). Older persons who are convinced that the cause of their fall is extrinsic (in the environment) are less likely to adapt their behavior to reduce their fall risk. Instructors respond to and, where necessary, adapt these attributions during the program.

2. Education, conversation and practice

Expectations and aims	The instructors introduce the topic of "expectations and aims" and ask the participants what they hope to learn and achieve during the program. Instructors guide the participants in setting realistic goals.
Homework	After the introduction and guidance by the instructors, the participants draw up a list of expectations and goals as homework.
Getting out of bed (safely and efficiently)	Getting out of bed is practiced with each participant. The manner in which participants currently get out of bed is demonstrated and discussed, and suggestions are made individually to increase safety and efficiency. This may include teaching the caregiver how to support the patient in this task. After the exercise, participants receive the folder "Getting out of bed".
Homework	Participants practice getting out of bed safely and efficiently a few times a day (depending on the abilities and endurance of the patient) with their caregiver. Patients receive photo material with supporting text on the correct performance of the exercise.

3. Closing the session (see Box 1; items 6-9)

Session 2

1. Introduction (see Box 1; items 1-4)
2. Education, conversation and practice

Individual expectations and aims	Participants explain their expectations and aims. Instructors guide the participants to set realistic goals and discuss what it takes to achieve these goals. Similarities between the participants' aims are discussed.
Individual causes of falls	Instructors explain that falling is a common and serious problem that can have multiple causes. The group discusses causes of the participants' falls. Unawareness of the cause of a fall could be a source of fear and could hinder the coping process. The instructors help both patients and caregivers understand the causes of the falls.
Causes of falls in general	Situations with a high fall risk are discussed, with intrinsic and extrinsic risk factors being distinguished, both indoors and outdoors. The group collectively thinks of solutions and methods for fall risk reduction. Instructors ensure that all major causes are discussed. Participants receive additional brochures on "Causes of falls" and "Home safety".
Aging and falls	Many older persons consider falling a normal part of aging. It should be emphasized that falling is not normal but is rather pathological and preventable. Many older persons of comparable age do not experience falls. The reasons for this difference are discussed. Emphasis is on knowing your limitations, acceptance of these limitations, and keeping active within these limitations.
Rising from a chair (safely and efficiently)	Participants practice and receive instructions regarding how to safely and efficiently rise from a chair and sit down again. Caregivers are instructed on how to support the patient. First, this is practiced in a chair with armrests, depending on the ability level of the dyad; it is then practiced in a chair without armrests. Participants receive the brochure "Rising from a chair; safely and efficiently".
Homework	Participants practice with their caregiver rising from a chair safely and efficiently a few times a day (dependent upon the abilities and endurance of the patient) at home. In addition, strength, balance, and endurance are bolstered by squatting with chair support (Brochure: "Quadriceps training"; frequency and intensity dependent on the abilities and endurance of the patient). Patients receive photo material with supporting text on both exercises.

3. Closing the session (see Box 1; items 6-9)

Session 3

1. Introduction (see Box 1; items 1-4)
2. Education, conversation and practice

Home safety	The "Home safety" brochure, handed out in session two, is discussed in detail.
Homework	Participants use the brochure to check the safety in their home and to check on the need for adjustments.
Emotions concerning falls	Falls have a high impact on older persons. Thirty percent of older persons develop a fear of falling after experiencing a fall. This often results in feelings of helplessness and fear of losing independence. Both the patient and caregiver may develop anxiety and depression. These consequential feelings are discussed, and participants are asked whether they recognize and identify with these feelings and how they feel after experiencing a fall. The group discusses which feelings are functional and realistic and which feelings should be adjusted. To support this discussion, the beliefs and preconceived opinions on falls are discussed as well.
Fear of falling; the vicious cycle	As a result of fear of falling, older persons may restrict their activities, which results in deconditioning and an increased risk of falling. This fear of falling vicious cycle is discussed with the participants to increase insight and to raise awareness. The relevance of performing activities to stop and reverse this negative cycle is highlighted.
Limitations and abilities; acceptance	There is an important balance between a person's limitations and abilities. People should not perform activities beyond their ability, but also should not avoid activities that they are capable of performing. Participants discuss negative and positive consequences of avoidance and of performing activities beyond their abilities.
Walking (safely and efficiently, with a walking aid if applicable)	Participants walk around the room, using their walking aid if necessary. Each participant receives instructions on how to walk as safely and efficiently as possible. Emphasis is on the proper use of a walking aid.
Homework	Continue the homework from session two. Additional instructions are provided and the intensity and frequency are adapted, if necessary.

3. Closing the session (see Box 1; items 6-9)

Session 4

1. Introduction (see Box 1; items 1-4)
2. Education, conversation and practice

Fear of falling; the vicious cycle	The fear of falling vicious cycle is reproduced by the participants. Both the negative consequences of the fear of falling and positive consequences of a decreased fear of falling are discussed.
Impulsiveness; risk behavior and the vicious cycle	In addition to the fear of falling vicious cycle, the impulsiveness vicious cycle is discussed. Cognitive impairment, overestimation of personal abilities or not willing to accept limitations may lead to high-risk behavior (performing activities one should not be performing). This mechanism is explained and discussed.
Impact of falls on caregiver	Falls also have a high impact on caregivers. Caregivers share the feelings they experience when the patient falls. It is discussed to what extent these feelings are realistic and which feelings should and can be modified.
Homework	Patients note the activities they perform in the following days in detail to increase insight into behavior and activities associated with falls and the fear of falling.
Rising from a chair and walking (safely and efficiently, with a walking aid if applicable)	Patients walk around the room, using their walking aid if necessary. Each caregiver receives instructions on the best position relative to the patient and how to support the patient to walk as safely and efficiently as possible. Walking is combined with rising from different types of chairs, to practice switching between tasks, handling different situations, and repeat rising from a chair safely and efficiently.
Homework	Continue the homework from session two. Additional instructions are provided and the intensity and frequency are adapted, if necessary.

3. Closing the session (see Box 1; items 6-9)

Session 5

1. Introduction (see Box 1; items 1-4)

2. Education, conversation and practice

Activity pattern	Patients´ daily activities are discussed, in which possible high-risk or activity avoiding behavior is identified and possible solutions are discussed.
Stop-think-go (STG)	Following the impulsiveness vicious cycle, the stop-think-go method is introduced as a method to decrease high-risk behavior. Instructors emphasize the benefits of carefully over thinking and planning tasks and activities before performing them. Planning should also take into account planning moments to take a break from activities. Participants will be regularly reminded of the stop-think-go method during the ADL-based circuit training.
Activities of daily living (ADL)-based circuit training	Participants practice multiple elements combined in an ADL-based circuit. Elements include balance, strength, endurance, coordination, planning, dual-task performance and use of the STG method. Caregivers are observed and then instructed on how to support the patient in different situations and with complex tasks. In addition, each patient's capacity to perform dual tasks is evaluated and discussed.
Homework	Continue the homework from session two. Additional instructions are provided and the intensity and frequency are adapted, if necessary.

3. Closing the session (see Box 1; items 6-9)

Session 6

1. Introduction (see Box 1; items 1-4)

2. Education, conversation and practice

Methods/aids to prevent falls	Previously, individual causes of the patients' falls and possible methods/aids to prevent falls were discussed. In this session, the use of the suggested methods/aids is evaluated. Reasons for not applying the suggested method/aid are discussed and, where necessary, new solutions are suggested. Specifically, embarrassment concerning the use of such methods/aids is discussed. In session eight, these methods/aids will be evaluated again.
Getting up after a fall (safely and efficiently)	Participants demonstrate how they get up after a fall. The instructor then demonstrates how to get up after a fall as safely and efficiently as possible. Both patient and caregiver practice getting up after a fall following the advice of the instructor.
Homework	Continue homework from session two. Additional instructions are provided and the intensity and frequency are adapted, if necessary. In addition, patients receive balance exercises on reaching, including supporting photo material with text (brochure "Reaching").

3. Closing the session (see Box 1; items 6-9)

Session 7

1. Introduction (see Box 1; items 1-4)

2. Education, conversation and practice

Experiences and emotions associated with the practice of getting up after a fall	Experiences and emotions associated with the practice of getting up after a fall are discussed.
Asking for assistance	Many older persons have difficulty asking for assistance. However, because this may decrease high-risk behavior, asking for assistance is an important aspect of fall risk reduction. The group discusses feelings and experiences associated with asking for assistance (patients) or being asked for help (caregivers). Success stories and benefits are emphasized.
ADL-based circuit training outdoors	The outdoor circuit is introduced by the instructors first so that participants know what to expect. Safety during the circuit has priority, and, if necessary, a (wheel) chair is brought along to use for patients to rest. Then, participants practice how to deal with high fall risk situations outside. Emphasis is on the appropriate use of a walking aid (if applicable) and efficient support by the caregiver.
Homework	Continue homework from session two with the additional reaching exercises. Additional instructions are provided and the intensity and frequency are adapted, if necessary.

3. Closing the session (see Box 1; items 6-9)

Session 8

1. Introduction (see Box 1; items 1-4)

2. Education, conversation and practice

Evaluation methods/aids for preventing falls	Evaluation of the methods/aids suggested in sessions two and six. If applicable, the reasons for not using the method should be discussed and other solutions should be sought.
Coping	The coping strategies of the participants are explored. Avoidance-oriented coping strategies are discouraged. A problem-focused coping strategy is encouraged to increase the level of self-efficacy.
Getting up after a fall (safely and efficiently)	Participants demonstrate how they get up after a fall. The instructor provides additional advice if necessary. Both the patient and caregiver practice getting up after a fall following the advice of the instructor.

3. Closing the session (see Box 1; items 6-9)

Session 9

1. Introduction (see Box 1; items 1-4)

2. Education, conversation and practice

Physical activity	The vicious cycles of fear of falling and impulsiveness are repeated, and the benefits of regular physical activity and negative consequences of inactivity are discussed. Participants establish a plan to permanently increase their activity, for example, by participating in a group activity nearby.

The dyads are separated; caregivers engage in a conversation with the psychologist, and patients practice with the physiotherapist.

Caring for significant others	The caregivers carry on a conversation regarding the positive and negative aspects of caring for their significant other.

ADL-based circuit training	Participants practice multiple elements combined in an ADL-based circuit. Depending on the level and abilities of the dyad, variations are applied to the circuit or the tasks during performance of the circuit such as increasing the frequency and difficulty. The caregivers join in at the end of the exercise so they can see how the patients perform on the circuit.

3. Closing the session (see Box 1; items 6-9)

Session 10

1. Introduction (see Box 1; items 1-4)

2. Education, conversation and practice

Falls	The group discusses whether the frequency of falls or the risk of a fall has been reduced by this program and what other changes have been established. Explanations for (lack of) change are discussed.
ADL-based circuit training	Circuit: elements at the request of the participants or as identified by the instructor.
Goals and expectations	At the start of the program, each participant has set individual goals. It is evaluated to what extent these goals were reached and what requires additional attention. Reasons for not reaching a goal are discussed, and additional suggestions are made.
Evaluation of the program	The program is summarized and evaluated, including positive and negative aspects of the program and overall opinion of the program and instructors. Adherence to homework assignments and advice is evaluated, and perceived benefit is discussed.

3. Closing the session (items 7, and 8 (Box 1) and closing session as below)

Summary and closing of the session	Instructors thank everyone for their active participation and hand out certificates to all participants. Instructors remind participants of the date and time of the booster session, which takes place six weeks after session ten. Instructors emphasize that although the program is over, participants should continue to put what they have learned into practice.

Booster session

The booster session monitors the progress and/or deterioration of the dyads and gives additional training and suggestions if necessary. Instructors and participants discuss to what extent the dyads have adapted their daily behavior to include what they have learned in the program. Barriers to changing behavior are discussed and solved when possible.

DI

DI

Nederlandse samenvatting

Meer dan 30% van de zelfstandig wonende ouderen van 65 jaar en ouder valt elk jaar. Ongeveer 10% van de vallen resulteert in ernstig letsel, zoals een heupfractuur. Kwetsbare ouderen hebben een verhoogd risico op vallen. Kwetsbaarheid, of frailty, is een biologisch syndroom van verminderde reserve en weerstand tegen stressoren door cumulatieve schade aan fysiologische systemen. Dit veroorzaakt een verhoogde vatbaarheid voor ongewenste gezondheidsuitkomsten, onder andere vallen. Kwetsbare ouderen die vallen hebben vaak ook cognitieve stoornissen.

Valincidenten en de hiermee geassocieerde letsels, zijn de meest voorkomende oorzaken van het verlies van zelfstandigheid en verminderde deelname aan sociale activiteiten. Hierdoor hebben valincidenten ook grote gevolgen voor de mantelzorger.

Complexe, multifactoriële valpreventie-interventies blijken effectief te zijn in het voorkomen van vallen bij niet-kwetsbare ouderen. Op dit moment bestaat weinig wetenschappelijk bewijs voor het effect van valpreventie bij de groeiende groep van kwetsbare zelfstandig wonende ouderen, met en zonder cognitieve stoornissen. Onderzoekers betrekken deze ouderen vaak niet in wetenschappelijk onderzoek door de multimorbiditeit en cognitieve stoornissen binnen deze groep.

Er bestond een grote behoefte aan een valpreventie-interventie voor deze groep ouderen.
Derhalve was het overkoepelende doel van het onderzoek, het ontwikkelen en evalueren van een valpreventiecursus voor kwetsbare, zelfstandig, wonende oudere patiënten, met en zonder cognitieve stoornissen, van de polikliniek geriatrie, die in de tijd voor hun polikliniekbezoek gevallen waren. Het primaire doel van het onderzoek was het vaststellen van het effect van de cursus op de valfrequentie van de patiënten. Het secundaire doel was het vaststellen van het effect van de cursus op de valangst van de patiënten en op de belasting van hun primaire mantelzorgers.
Voor het ontwikkelen en evalueren van de valpreventiecursus is gebruik gemaakt van het raamwerk voor de ontwikkeling en evaluatie van complexe interventies in de gezondheidszorg van de Britse Medical Research Council (MRC raamwerk).

Hoofdstuk 1 geeft een beschrijving van de vier fases van het MRC raamwerk en het gebruik van dit raamwerk wordt geïllustreerd door de beschrijving van de toepassing ervan bij de ontwikkeling en evaluatie van de valpreventiecursus.

Fase 1 Ontwikkelfase: *Hoofdstuk 2* beschrijft de kwalitatieve interviewstudie met als doel het verkennen van de meningen, ervaringen, emoties, en behoeften ten aanzien van vallen van patiënten en mantelzorgers. Het definiëren van componenten voor de valpreventiecursus was het tweede doel. De patiënten, met name degenen met cognitieve stoornissen, konden geen oorzaak van hun valincidenten geven, wat een belangrijke bron van angst was en de coping bemoeilijkte. Patiënten waren van mening dat vallen niet te voorkomen is en valangst niet te verminderen is. Veel mantelzorgers vonden de problemen die voortkwamen uit de cognitieve stoornissen van hun naasten meer belastend dan de, vaak zeer ernstige, valincidenten van hun naasten. Mantelzorgers beschouwden een valpreventiecursus als nutteloos door de cognitieve stoornissen, fysieke problemen, leeftijd en persoonlijkheden van hun naasten. De resultaten van deze studie zijn gebruikt om de valpreventiecursus verder vorm te geven.
Op basis van literatuuronderzoek, consultatie van experts in de vorm van focusgroepen en een Delphi vragenlijstronde en bovenstaande kwalitatieve studie, werd door de onderzoeksgroep besloten de valpreventiecursus te richten op het koppel van patiënt en mantelzorger. Verder werd besloten dat de cursus uit 10 sessies zou bestaan, met zowel psychologische als fysieke componenten en aandacht voor de mantelzorger. Een psycholoog en fysiotherapeut leidden de sessies.
Hoofdstuk 3 beschrijft een cross-sectionele studie naar de determinanten van mantelzorgerbelasting (gemeten met de Zarit Burden Interview) en kwaliteit van leven (gemeten met de EQ-5D-VAS) van 132 mantelzorgers van kwetsbare ouderen die vallen. Mogelijke determinanten werden gemeten bij zowel de mantelzorgers als de patiënten. 50% van de mantelzorgers had kwaliteit van leven scores die lager waren dan die van de Nederlandse normpopulatie. 20% van de mantelzorgers was overbelast. Een hogere depressiescore van de mantelzorger ($\beta = 0.43$), een betaalde baan van de mantelzorger ($\beta = 4.72$) en een hogere valangstscore van patiënten ($\beta = 0.17$) verklaarden 49% van de variantie van mantelzorgerbelasting. 42% van de variabiliteit in kwaliteit van leven van de mantelzorgers werd verklaard door een hogere angstscore van de mantelzorger ($\beta = -1.51$), een hogere leeftijd van de patiënt ($\beta = -0.41$) en het feit dat een mantelzorgers samenwoont met de patiënt ($\beta = -16.64$). Deze determinanten fungeerden als aanknopingspunten voor het ontwikkelen van de mantelzorgercomponent van de cursus.
De cursus werd in gesloten groepsverband gegeven, dat wil zeggen dat er geen nieuwe leden meer kunnen instromen als een groep eenmaal begonnen is. De deelnemers in de groep zullen elkaar beïnvloeden, maar ook de docent zal invloed op de deelnemers hebben. *Hoofdstuk 4* beschrijft hoe met deze factoren rekening dient te worden gehouden bij de powerberekening, statistische analyse en toewijzing van behandeling binnen een trial. Een nieuwe methode, genaamd Optimal Batchwise Minimization (OBM), van toewijzing van behandeling voor trials waarin een interventie op basis van een gesloten groep geëvalueerd wordt, wordt beschreven.

Fase 2 Toepasbaarheidsfase: In deze fase testten we de toepasbaarheid van de rekruteringsmethode, interventie en meetinstrumenten in 4 koppels van patiënt en mantelzorger. In deze fase is het uitvoeren van een pilotstudie belangrijk. Om kleine pilotstudies gerandomiseerd uit te kunnen voeren hebben wij een nieuwe methode van toewijzing van behandeling ontwikkeld, genaamd Studywise Minimization. Deze methode, beschreven in *hoofdstuk 5*, is te gebruiken voor kleine studies met veel prognostische factoren en waarbij de deelnemers geïncludeerd zijn voordat de studie start.

Fase 3 Evaluatiefase: *Hoofdstuk 6* beschrijft de resultaten van de gerandomiseerde, enkelvoudig geblindeerde, multicenter studie naar de effectiviteit van de valpreventiecursus. De primaire uitkomstmaat was valfrequentie, secundaire uitkomstmaten waren valangst van patiënten en mantelzorgerbelasting van mantelzorgers. Op basis van OBM werden 18 patiënt-mantelzorger koppels ingedeeld in de valpreventiecursusgroep en 18 in de controlegroep (usual care). 48% van de patiënten had een mild cognitive impairment of dementie. Direct na de interventie en op de langere termijn (3 en 6 maanden) was de valfrequentie in de interventiegroep hoger dan in de controlegroep, maar dit verschil was niet statistisch significant (respectievelijk, RR = 7.97, P = 0.07 en RR = 2.12, P = 0.25). Valangst was hoger in de interventiegroep en er was geen verschil in mantelzorgerbelasting tussen de groepen.
In *hoofdstuk 7* wordt een beschrijving gegeven van een gestructureerde procesevaluatie voor complexe interventies. Met behulp van deze procesevaluatie is de valpreventiecursus geëvalueerd, wat ook gerapporteerd wordt in dit hoofdstuk. Samenvattend kan gesteld worden dat er geen verschil tussen de valpreventiecursusgroep en controlegroep in de belangrijkste uitkomstmaten was omdat de interventie niet effectief was, ondanks de nauwgezette ontwikkeling.

Fase 4 Implementatiefase: Aangezien de cursus niet effectief was, is deze niet geïmplementeerd.

Een complexe multifactoriële valpreventiecursus is niet geschikt voor kwetsbare ouderen. Ondanks de negatieve resultaten toont deze studie aan dat toekomstig onderzoek naar valpreventie voor kwetsbare ouderen, met en zonder cognitieve stoornissen, gericht moet zijn op de implementatie van de basale geriatrische principes, namelijk een uitgebreide geriatrische analyse van het valprobleem en een medicatiereview. Verder dient de effectiviteit van een recent ontwikkelde, aangepaste valpreventiecursus, die niet complex is, die in de thuissituatie gegeven wordt en op maat gesneden is voor de individuele patiënt geëvalueerd te worden.
Demonstratiefilmpje van de valpreventiecursus: kijk op youtube met als zoektermen valpreventie geriatrie (http://www.youtube.com/watch?v=xEjcqTQ1XiQ).

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