

# Designing Randomized, Controlled Trials Aimed at Preventing or Delaying Functional Decline and Disability in Frail, Older Persons: A Consensus Report

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The discovery of effective interventions to prevent or delay disability in older persons is a public health priority. Most likely to benefit from such interventions are frail individuals who are not yet disabled and those with early disability who are at high risk of progression. In spite of this frail older persons have often been excluded from research on the assumption that they would not tolerate testing or benefit from treatment. The Interventions on Frailty Working Group developed recommendations to screen, recruit, evaluate, and retain frail older persons in clinical trials.

Specific recommendations are:

Eligibility screening should include a multistage process, to quickly exclude those who are too well and those who are too sick.

Inclusion criteria should target those most likely to benefit, be meaningful to clinicians, and reflect advancements in the frailty research area.

Disability outcome measures should include self-reported, objective, and proxy measures. Strategies to improve retention and compliance and to monitor their effectiveness should be an integral part of the study design.

Estimation of cost and sample size should contemplate high dropout rates and interference by competing outcomes.

Additional research is needed to refine criteria for screening frail older persons, identify objective measures of disability that are reliable and valid in frail older persons, and improve the informed consent process for high-risk participants, recognizing that research in this subgroup is essential to improving their health outcomes. *J Am Geriatr Soc* 52:625–634, 2004.

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Interventions that can prevent or delay disability in older persons are urgently needed. Randomized, controlled trials of exercise, comprehensive geriatric assessment,<sup>1,2</sup> and interventions targeting multiple risk factors have shown promising early results.<sup>3</sup> As understanding of aging improves and large observational studies are conducted in older populations, other targets for intervention are emerging (molecular and metabolic pathways, environmental risk factors, and organization of services) and need to be tested.

Despite this pressing need, guidelines for large-scale trials of interventions aimed at preventing or delaying disability in older persons have not yet been established. The basic elements of clinical trial design are well known,<sup>4</sup> but concerns specific to older individuals have hindered the conduct of clinical trials in this population. To facilitate such trials, American and Italian geriatricians and epidemiologists established the Interventions on Frailty Working Group.

Over a 6-month period, the Frailty Working Group convened subgroups to formulate recommendations on specific aspects of research design. The recommendations focus on preventing progressive disability, not disability caused by acute events such as stroke or hip fracture.<sup>5</sup> Although progressive disability is common, preventive approaches have rarely been studied. The concept of physical frailty was used to create a working definition of the population at high risk for disability onset or progression.

Physical frailty is an abnormal physiological state that can range from mild to severe stages. Although there is not yet a consensus definition, it is recommended that operational criteria to define physical frailty be based on impairment in the physiological domains most frequently cited in the frailty literature. These include mobility, balance, muscle strength, motor processing, cognition, nutrition (often operationalized as nutritional status or

**Table 1. Reported Components of the Frailty Syndrome**

Reference	Mobility	Strength	Balance	Motor Processing	Cognition	Nutrition	Endurance	Physical Activity
Winograd CH et al., 1988 <sup>59</sup>	X				X	X		X
Ory MG et al., 1993 <sup>60</sup>	X	X	X		X		X	
Pendergast DR et al., 1993 <sup>61</sup>		X	X	X			X	
Rockwood K et al., 1994 <sup>62</sup>					X			X
Tinetti ME et al., 1995 <sup>9</sup>	X	X						
Gill TM et al., 1996 <sup>63</sup>	X		X		X			
Campbell AJ et al., 1997 <sup>64</sup>		X	X	X	X	X	X	
Dayhoff NE et al., 1998 <sup>65</sup>		X	X					
Strawbridge WJ et al., 1998 <sup>66</sup>	X				X	X		
Chin APMJ et al., 1999 <sup>67</sup>						X		X
Vellas B et al., 2000 <sup>68</sup>		X				X	X	X
Brown M et al., 2000 <sup>69</sup>	X	X	X	X				
Fried LP et al., 2001 <sup>12</sup>	X	X				X	X	X
Saliba D et al., 2001 <sup>70</sup>	X							

weight change), endurance (including feelings of fatigue and exhaustion), and physical activity (Table 1). Physical frailty can be either detected clinically and is not yet associated with disability or clinically overt with clear manifestations of functional loss. Interventions for those with physical frailty might only target disability prevention, whereas interventions for those with clinically overt physical frailty might target delay or reversal of disability progression.

The working group recognized that physical and cognitive problems play an important role in frailty and disability, but interventions in persons with dementia as the principal cause of disability progression were not addressed because they pose methodological and ethical challenges that are specifically addressed in the dementia literature.<sup>6</sup>

The working group concentrated on the methodology for disability prevention trials in frail older adults rather than on specific intervention strategies. The general principles outlined in this document should apply to a wide spectrum of interventions. Although current experience is limited mostly to exercise and comprehensive geriatric assessment, other disability prevention interventions (e.g., new drugs, changes in environment, organization of services, case management, surgery, prostheses, and nutritional supplementation) are likely to be tested in the future. The goal was to establish initial methodological guidelines for this new generation of trials with the hope of generating further development of this research area.

This article begins by discussing why frail older adults should be the central focus for preventing progressive disability. Then, how the emerging concept of physical frailty can be operationalized to identify older persons who, being at high risk of disability onset or already experiencing disability progression, are ideal subjects for cost-effective interventions is discussed. A discussion on inclusion and exclusion criteria, outcome measures, and matters related to follow-up, attrition, and reporting in medical journals follows. Finally, the special challenges encountered in studying frail older persons are delineated.

Throughout the text, matters that require more research are noted. Although the discussion refers to trials

with disability-related primary outcomes, many of the pitfalls addressed in this report apply to any trial involving older persons affected by comorbidity and physical and cognitive decline. Similarly, inclusion of disability-related outcomes in disease-specific trials—for example, in trials testing new interventions for congestive heart failure or chronic pulmonary disease—and consideration of other principles outlined in this document may expand the range of participants and the generalizability of the findings.

## IDENTIFICATION OF THE TARGET POPULATION

### Targeting Frail Older Persons

Late-life, progressive disability is thought to result from a generalized decline in multiple physiological systems, with exhaustion of functional reserves and vulnerability to a range of adverse outcomes including disability; geriatricians call this state frailty.<sup>7</sup> It is hypothesized that a rapid decline of functional status may follow even minor perturbations of physiological homeostasis in frail persons. The same perturbation would cause only negligible or transient illness in a healthy person. Interventions for disability prevention are considered most likely to be cost-effective when targeted to older persons who are progressing through this stage of expanding vulnerability. This is consistent with studies of geriatric evaluation units that showed the most benefit in high-risk groups,<sup>8</sup> but disagreement exists on criteria to define this target population, often referred to as “frail older persons.”

Recent efforts to define physical frailty as a clinical syndrome provide guidance. Although the biological mechanisms underlying physical frailty are still too poorly understood for practical application, the basic clinical features of the frailty syndrome are sufficiently well accepted to develop screening criteria (Table 1). Most authors focus on the following domains: mobility, such as lower-extremity performance and gait abnormalities; muscle weakness; poor exercise tolerance; unstable balance; and factors related to body composition, such as weight loss, undernutrition, and sarcopenia (loss of lean body mass). Although cognitive decline may be found in frail persons, it was considered that frailty resulting primarily

from reduced cognition was a distinct clinical entity. Additionally, it was recognized that a physically frail state may be clinically detected before disability, as well as a more advanced state of “clinically overt” physical frailty that has already determined some initial degree of functional disability. Studies showing that the individual components of these domains are associated with classical geriatric syndromes (e.g., falls, symptomatic depression, urinary incontinence, and functional impairment) and are strong and independent risk factors of disability and death support the validity of the above domains as critical elements of the frailty syndrome.<sup>9–11</sup>

In 1999, a group of investigators developed a conceptual framework of the frailty syndrome that combines the elements of the body composition and mobility domains into a pathophysiological pathway. In this pathway, sarcopenia and poor muscle strength, by limiting mobility and physical activity, reduce total energy expenditure and nutritional intake, which in turn cause weight loss and further sarcopenia.<sup>12</sup> Using data from the Cardiovascular Health Study, the elements of the pathway were operationalized as unexplained weight loss, poor grip strength, self-

reported exhaustion, slow walking speed, and low physical activity. After adjusting for significant confounders, participants with three or more of these characteristics were found to be at significantly increased risk of disability, hospitalization, and death.

The work of these investigators<sup>12</sup> demonstrates that aggregating measures from the domains of physical function and body composition provide initial screening criteria for the frailty syndrome that have predictive validity in identifying older persons with intrinsic vulnerability. With improved knowledge of the mechanisms underlying physical frailty, more specific diagnostic criteria will likely be developed. For example, executive function and multiple task coordination, chronic inflammation and the associated hormonal changes, the response to different types of stress, and primary impairments in energy metabolism have all been shown to predict late-life disability and may be used in future screening criteria for physical frailty.<sup>13,14</sup>

The major pitfalls in designing and conducting clinical trials of disability prevention in frail older persons are discussed in the following section of this report and are outlined in Table 2.

**Table 2. Major Challenges and Recommendations Involving Randomized Controlled Trials of Disability Prevention in Frail Older Persons**

Challenges	Recommendations
Standard criteria for physical frailty are lacking	Operationalize variables in the domains of mobility, nutrition, and body composition. Justify the specific criteria used in the trial
Enrolling the most appropriate study population may be complex and expensive	Use a multistage selection process: 1) Exclude the “robust.” 2) Identify those who are frail. 3) Identify subset according to specific domains of physical frailty
Excessive exclusions may reduce generalizability	Design studies with the idea of enabling participation. The principal exclusion criteria should be factors that prevent participation Avoid exclusions for comorbidity Ascertain the level of cognitive impairment incompatible with participation in specific interventions
Inclusion and exclusion of frail older persons from trials raise ethical concerns	Make explicit the procedures used for consenting participants. Provide multiple methods to explain the study to the participants and involve a surrogate when needed. Discuss ethical issues when reporting results
Assessing disability through self-report may be problematic	Limit self-report to primary outcomes that are “hard” measures of disability such as activity of daily living disability, mobility disability Standardize disability questions and responses and provide continuing, intensive training to interviewers Collect objective measures of physical function and proxy information in parallel Make the outcome less sensitive to random fluctuations (e.g., defining disability as “lasting more than 3 months” or targeting “multiple falls”) Include mortality in the primary outcomes
The mechanism by which the intervention prevents disability may be unclear	Use as secondary outcomes physiological or functional measures that are in the theoretical pathway between the intervention target and the disability outcome
Improvements in functional status may not translate into well-being and quality of life	Use secondary outcome measures that assess perceived well-being and factors, such as somatic symptoms, that are important for quality of life in frail older persons Consider global impression
Avoid attrition and competing morbidity	The expected mortality and dropout rates should be incorporated into sample size calculations Adherence rates can be improved by designing interventions feasible by most, allowing flexible time-frame for follow-up interviews, providing a comfortable environment, prioritizing safety, providing transportation, establishing a good relationship with family or caregivers, preplanning alternatives to full clinic visits (e.g., shorter home visits, telephone calls)

## Inclusion Criteria

It is recommended that trials target persons aged 70 and older, because the prevalence of physical frailty is low at younger ages. Inclusion criteria should identify a population that is at high risk of developing disability and likely to benefit from the intervention and is recognized using simple criteria that are feasible in a screening program or clinical practice. If measures that are not realistic for practicing physicians define the study population, then the findings of the trial are unlikely to be applied in the real world.

To recruit a frail population, a multistage process is recommended. The first stage involves a quick and inexpensive exclusion of those who have characteristics generally incompatible with physical frailty (e.g., engage in regular, vigorous exercise). Depending on the nature of the trial, subjects who have advanced disability or end-stage disease may also be excluded, because they have already developed the outcome or because they are unlikely to respond to treatment.

Within the population selected by Stage 1, Stage 2 identifies subjects who are most likely to be frail based on the domains that were described above. It is recommended that the domains of mobility, muscle strength, nutritional intake, weight change, balance, endurance, fatigue, and physical activity be focused on. These domains are easy to assess, are generally agreed-upon features of the frailty syndrome, and are strong, independent predictors of disability. The application of these domains, including selection of cutoff points that define meaningful thresholds, should be adapted to the goals of the specific trial. Performance-based measures of lower-extremity function capture composite information on strength, balance, and mobility and have been proposed to screen older individuals at high risk of disability.<sup>15</sup> Screening for physical frailty based on the five criteria proposed earlier can provide a more-inclusive approach.<sup>12</sup>

Staging of physical frailty, based on severity within selected domains, permits the targeting of participants according to their position on the spectrum of physical frailty and disability risk. In general, those who have the greatest likelihood of receiving benefits from a specific intervention should be selected based on clinical experience or preliminary data. For example, in a home-based intervention program aimed at preventing functional decline, one study enrolled participants who were considered frail according to specific criteria but were still able to walk and scored 20 or more on the Mini-Mental State Examination (MMSE).<sup>1</sup>

Finally, if the trial intervention targets a particular characteristic of physical frailty, in Stage 3, a subset of subjects with that specific characteristic may be identified. For example, in a trial on nutritional supplementation, the investigator may want to select, from among the frail persons identified, those who have signs of poor nutrition or report inadequate nutritional intake. A combination of Stages 1, 2, and 3 is probably appropriate for most trials.

## Exclusion Criteria

Exclusion criteria are meant to remove from the selected frail population those who cannot participate in the full trial. It is critical to minimize exclusions, because exces-

sively restrictive criteria may compromise generalizability of the results. The true challenge of this area of research is to design studies that enable a broad spectrum of frail older persons to participate, with the guiding principle of limiting exclusions to those essential to the integrity of the study. In many clinical trials, comorbidity has been the main reason for excluding older persons. It is recommended that traditional exclusion criteria (such as comorbidity and poor cognitive function), which in the past have excluded large numbers of frail older persons, should be avoided or, at least, minimized.

A practical approach to exclusions is to consider the cognitive and physical performance required for participating in the trial, rather than explicitly listing all possible health conditions that should be absent. This method improves generalizability of the trial findings and substantially reduces the cost of recruitment by not automatically excluding subjects with mild forms of disease.

If a certain level of cognitive function is required for the intervention, subjects whose cognitive function is below this level or who are reasonably expected to cross this threshold during the period of the trial should be excluded. The global cognitive level and the performance in specific domains of neuropsychological functions required for trial participation are highly specific for the type of intervention. Complex pharmacological regimens can be administered even to cognitively impaired individuals if adequate supervision is provided. The cognitive requirement for different exercise regimens is unknown and should be identified in pilot studies. In general, cognitively impaired patients are often able to participate in exercise programs,<sup>16</sup> whereas their participation in behavioral interventions is more questionable.

Inability to consent is not an absolute criterion for exclusion. Many frail older persons lack full capacity for consenting, which may raise ethical or legal dilemmas, but although frail older persons are entitled to special protection, excessive safeguards may halt the development of new care strategies that may improve their health and quality of life (QoL). Comprehension of the purpose, design, conduct, and potential risks and benefits of the study should be promoted by using short, simple consent forms and techniques of communication that minimize the effect of perceptual barriers.<sup>17</sup> Long consent documents should be avoided because they are unlikely to be understood and therefore will fail to meet the goals that they are intended to achieve.<sup>18</sup> The understanding of some key concerns should be verified, and a lack of understanding should lead to a more formal assessment at time of enrollment and closer monitoring during the study follow-up. Tests of frontal lobe function, such as executive function, word fluency, and attention skills, best predict capacity for rational decision-making.<sup>19,20</sup> The word-list learning test (immediate and delayed recall) from the Consortium to Establish a Registry for Alzheimer's Disease battery, the Trail-Making Test Part A, and test of conceptualization are recommended.<sup>21–23</sup> These neuropsychological tests predict an individual's capacity to choose from among alternatives and engage in complex, sequenced, and planned actions.<sup>19,24</sup> In contrast, global measures of cognitive status, such as the MMSE and the Clinical Dementia Rating, are less informative.<sup>19</sup> A number of brief instruments to assess decision-making

ability in cognitively impaired elderly persons have recently been reviewed.<sup>25</sup>

If a proxy decision is deemed necessary, investigators should also attempt to obtain some form of assent from the participant, together with the surrogate consent from a proxy. Surrogate judgment should be based on the participant's previous preferences or, if unknown, on his or her best interest. A legally appointed representative or a next of kin is the most appropriate surrogate decision-maker. For participants who are able to consent at enrollment, designation of proxy surrogates should be discussed early in the study, as potential background for future surrogate consenting.<sup>26</sup> The consenting process should be fully disclosed in reporting clinical trials in frail older persons, avoiding generic, template statements such as "informed consent was obtained from all participants."<sup>27</sup>

Physical functioning may be used for determining inclusion, but subjects who lack specific physical abilities required for the trial may need to be excluded. Examples are sensory impairments, symptoms triggered by the testing procedures or interventions (e.g., exercise causing chest pain), or inability to perform required study activities. Even if inclusion criteria are met, persons with a trajectory of irreversible physical decline, such as those affected by certain neurological conditions or rapidly progressive cancers, should be excluded.

## MEASURING OUTCOMES

### Primary Outcomes

Most traditional randomized, controlled trials are powered on discrete outcomes, such as death, incident diseases, or disease recurrences. These events can be ascertained according to accepted criterion standards, but they may not be the most important outcomes for frail, older persons. Moreover, death may be problematic for some studies, due to sample size considerations. Functional status is by far the most important factor affecting QoL and healthcare utilization in old age.<sup>28</sup> Therefore, trials targeting older populations should consider using a functional measure as one of the main outcomes, regardless of the therapeutic intervention. Unfortunately, disability has proved difficult to define operationally. Obtaining valid, discrete outcomes in the domain of physical disability requires more time and resources than traditional ascertainment of disease-related events. An example is the assessment of mobility disability or disability in activities of daily living (ADLs). Self-report is the usual method and consists of asking participants to report whether they have difficulties or need help in performing basic ADLs or mobility-related tasks, such as dressing or climbing stairs, respectively. Although the reliability of self-reported ADL disability is considered high, data on reliability are limited in frail older patients.<sup>29</sup>

Although ascertainment appears simple, a number of pitfalls may threaten reliability or validity of self-reported measures.

1. Studies have shown that the threshold of physical ability below which older individuals perceive difficulty varies widely between individuals and can be influenced strongly by factors that change over time in older

persons, such as social environment, economic status, cognition, and depression.<sup>30</sup>

2. Participants may become unable to provide self-reports of functional status.
3. Although specific disease events, such as a myocardial infarction or the diagnosis of cancer, may mark irreversible changes in health, reversible conditions may also cause disability, creating fluctuation and recovery over short time periods.<sup>31</sup> However, disability may also be considered an incident event. In fact, persons who become disabled and recover fully are more likely to develop permanent disability than persons who have never been disabled. Furthermore, the probability of recovery is lower in older and frailer individuals.
4. For some frail persons, the response to disability questions more accurately reflects what caregivers allow them to do than their actual capacity (perceived ability vs actual performance in daily life).

Several strategies can improve the reliability, validity, and comparability of disability measures over time and avoid loss of study outcomes.

1. Disability questions should be standardized, crafted, detailed, and made easy to understand in the context of day-to-day life. Whether the participants' responses should assess potential capability or current behaviors should be specified. Whether disability is defined as perceived difficulty or as need for help should be decided, because only a small percentage of older persons who perceive difficulty in performing ADLs actually receive help in executing those tasks. Interviewers should be trained to work with frail and sensory-impaired older persons. Interrater and test-retest reliability should be determined in subjects similar to those enrolled in the full study.
2. Given that functional status may fluctuate over short periods, operational requirements for the duration of disability (e.g., transient, long-lasting, permanent) should be stated explicitly in the study protocol. Examples are any new disability, transient disability (that resolves within a certain time period), or persistent disability (that lasts over a defined time period or more). Follow-up intervals must enable detection of the desired outcome.
3. Objective, performance-based measures of physical function may be collected in parallel with self-reported measures of disability. Performance-based measures of physical function obtained under standardized conditions are highly reliable, have strong predictive validity, and are somewhat sensitive to change,<sup>10,32,33</sup> but performance at the time of assessment may not represent the usual performance of the tested individual.<sup>34</sup> Additionally, the relationship between self-report and objective ability is unclear, either because the instruments to measure objective ability assess rudimentary skills and the effect of cognitive function or because those that mimic traditional ADLs have been validated mostly in the rehabilitation setting.<sup>35,36</sup> Also, in many frail older persons, performance-based measures cannot be obtained, although methods for scoring those who are "unable" (e.g., attributing worst possible score) have

been proposed.<sup>11</sup> Thus, self-reported and objective tests of disability should be considered complementary.

4. Predefined methods of assessing the primary outcome through proxy should be used for participants who cannot be evaluated with other methods. Existing data on validity and reliability of proxies' responses, although limited, suggest that older people tend to overestimate their abilities, that family members tend to underestimate their older relative's capacity, and that agreement between proxy and older participants varies across different health measures.<sup>37</sup> Thus, to detect change over time, data from proxy informants should be collected from the beginning of the trial, at least for primary outcome measures. Criteria for selection of the most appropriate proxy informants should be developed. These criteria should ensure that the selected proxies spend a minimum amount of time per week with the participants, have opportunities to observe their behavior in performing daily life tasks, and have the ability to judge and report on this behavior. Limited data suggest that relatives who live in the same household are the best source of proxy information, followed by other relatives, friends, and healthcare professionals.<sup>38</sup> Ideally, the selected person should act as a proxy informant over the entire study period, but loss of proxies due to illness is not uncommon, and whenever possible, a secondary proxy should be identified. When the use of proxies is not equally distributed between treatment arms, combining information from the participants and proxies may bias the trial findings. This possibility can be tested formally and the effect of this potential bias reduced by introducing into the analytical model a dichotomous dummy variable that is set to 1 for proxy observation.

Another potential outcome measure is the occurrence of falls. Each year, falls affect one-third of persons aged 65 and older; in 10% of cases they produce serious injuries.<sup>39</sup> Falls contribute indirectly, through shared risk factors, and directly to ADL disability, nursing home admission, and chronic pain. Most falls occur in older persons with reduced neuromotor function and loss of compensatory ability, which are hallmarks of the frailty syndrome. Several clinical trials, primarily those testing multifactorial interventions, have shown that falls can be prevented.<sup>3,39,40</sup> The experience from these trials highlights the challenges in assessing falls as a primary outcome.

Obtaining high-quality reports of falls is resource intensive. Older persons may forget falls, and fall ascertainment based on long-term recall is incomplete. For community-dwelling older persons, the criterion standard for tracking falls requires asking participants to mail a follow-up card weekly or monthly, soliciting nonresponders, and characterizing each event by directly visiting the participants.<sup>3,41</sup> If this resource level cannot be sustained, less-complex and -expensive methods based on standard questionnaires are available.

There are clear advantages to using multiple falls instead of any falls as an endpoint. Isolated falls are stochastic events, whereas falling multiple times is usually associated with underlying neurological or musculoskeletal decrements and is a stronger predictor of negative health outcomes.<sup>42–44</sup> Falls associated with major injuries and falls

caused by syncopal episodes should also be considered separately.

Frail older persons have limited life expectancy and may die during the study. Depending upon sample size considerations, investigators should consider including mortality, the ultimate expression of loss of autonomy, among the primary outcome measure. Even when mortality is not a primary outcome measure, mortality should be monitored carefully, because those who die are no longer eligible for the primary outcome. In many cases, mortality and the primary outcome are correlated or, in technical terms, censoring from mortality is "informative." If not properly accounted for, informative censoring can bias the result of the trial. Analytical methods can reduce the bias of informative censoring,<sup>45</sup> but only if the amount of censored data is small, which is unlikely in trials of frail older persons. As will be discussed later, analogous considerations hold when the censoring events are dropouts.

It is good practice to analyze disability and mortality separately and jointly, because no intervention would be judged useful if it prevented disability but, at the same time, reduced survival.

### Secondary Outcomes

Secondary outcomes are recommended to (1) capture information on the causal pathway between the target of the intervention and the risk of disability, which may improve understanding of the mechanism by which the intervention is effective, and (2) investigate whether the treatment influences well-being, directly or through changes in disability status. When possible, secondary outcomes in both these domains should be obtained.

The first type of measure adds scientific validity to the study findings. For example, in a multifactorial intervention to reduce the risk of falling, one study collected data on risk factors for falls such as polypharmacy, poor balance, and gait before and after the intervention. The study found that a smaller percentage of the intervention group than of the control group still had a specific risk factor at reassessment. Based on these data, it was suggested that risk-factor modification could explain, at least in part, the preventive effect of the intervention.<sup>3</sup> In a hypothetical trial aimed at preventing mobility disability by improving muscle strength, it would be wise to include tests of muscle strength and lower-extremity performance as secondary (or intermediate) outcomes. If the intervention group develops fewer events of new disability than the placebo group and shows improvement in muscle strength and physical performance, the validity of the finding is stronger, and insight is gained into the mechanism of disability prevention.

The development of new techniques specifically designed for the frail, older person is an important area of research. For example, new methods for measuring isokinetic muscle strength and total power are needed, because current methods are difficult and somewhat hazardous for frail older persons.

The second type of outcome measure addresses the problem that, because frail older persons may have serious comorbidity and somatic symptoms, positive changes in functional status may not have a meaningful effect on perceived QoL. This uncertainty underlies the

recommendation that changes in perceived QoL should be directly measured and not inferred in frail older persons. There are two approaches to this task: directly questioning the participants concerning well-being and health-related quality of life (HRQoL) and assessing global change ratings from the perspective of the participant, significant other, or healthcare provider.

A number of instruments are available to assess HRQoL in general and for specific health dimensions. Although not considered the criterion standard, the Short Form-36 (SF-36) has gained rapid acceptance as a HRQoL measure and has been recommended as the optimum outcome measure across a range of ages, participant characteristics, and illness conditions.<sup>46</sup> The information derived from the full SF-36, and from its shorter versions, could be used as primary outcomes in clinical trials involving frail older persons as an alternative to the discrete measures described above. A study has shown that a single outpatient comprehensive geriatric assessment, coupled with an intervention to improve primary care physician and patient adherence with recommendations, significantly improves the scores of several SF-36 subscales.<sup>47</sup> Unfortunately, little methodological work on the psychometric properties of the SF-36 has been done in older persons, and validity and reliability have been tested mostly in younger populations. The few studies that evaluated the SF-36 measurement properties in older persons have shown low internal consistency and poor reliability and concurrent validity, especially in persons with multiple health problems associated with cognitive and physical impairments.<sup>48,49</sup> According to some authors, the SF-36 also fails to address the full effect of pain and other somatic symptoms that are independent of effects on functional status, critical predictors of QoL in older persons.<sup>50</sup> Thus, until more data are available on which domains best discriminate QoL in frail older persons, and new specific instruments are created, the use of the SF-36 in this population is justified but should be coupled with a comprehensive instrument assessing the global burden of somatic symptoms.

Little is known about how changes in physical function affect perceived QoL at different ages. For example, the minimal improvement in performance-based measures that older persons perceive as beneficial and is therefore clinically meaningful needs to be determined. Trials of acetylcholinesterase inhibitors in dementia faced similar problems. Although the treatment produced significant improvements in memory tests, whether these score improvements translated into better daily life for the patients and their family was questioned. This problem led to the development of the Clinical Global Impression Scale and the Clinician Interview-Based Impression, which are tools for coding how physicians perceive changes of the patients' behavior in several aspects of daily life during the trial.<sup>51,52</sup> An analogous instrument, a clinical global assessment of physical frailty and changes over time in frailty severity, could be useful in conducting clinical trials in frail older persons. Until such an instrument is developed, we are limited to subjective measures of perceived QoL.

Depending on the aims of the study, additional secondary outcomes related to healthcare costs and resource utilization may be used. The problem of obtaining

such information in frail older persons is beyond the scope of this report.

### Attrition

The ideal clinical trial follows all participants until the end of the study. In reality, censoring due to multiple causes hampers all clinical trials in frail older persons. For example, the effectiveness of rehabilitation after hospital discharge in frail older women was studied recently. Of 142 women who were eligible and accepted enrollment, 29 dropped out after 1 year of follow-up.<sup>53</sup> Another study performed a trial of exercise intervention aimed at improving physical function in community-dwelling older persons. Of 119 participants enrolled in the study, only 87 completed the 9-month trial.<sup>54</sup> Not only are dropouts frequent, but many also occur for reasons directly related to the primary outcome, a phenomenon defined as "informative censoring." For instance, patients more likely to decline would also be those most likely to die, to enter a nursing home, or to become cognitively impaired and lost to follow-up. These losses can jeopardize the validity of the study.

The potential bias introduced by informative censoring can be reduced by appropriate statistical techniques,<sup>55</sup> but every imputation method assumes a model for the missing data. Therefore, the study design should provide for collection of the reasons for withdrawals. Statistical procedures to evaluate the effect of informative censoring are available, even in some commercial statistical packages,<sup>56</sup> but no statistical technique can fully eliminate the bias from informative censoring.

Investigators who study frail older persons should be conservative in determining sample size and should implement retention strategies to maintain a dropout rate at 20% per year or lower, especially in the intervention group. Because of dropouts, studies enrolling frail, older persons are considerably more expensive than those conducted in healthy middle-aged persons. To reduce the potential effect of dropout bias, the analysis of the clinical trial data from frail older persons should include an intention-to-treat approach.

Comorbidity, exhaustion, and respondent burden are the major reasons why frail study participants drop out during follow-up. There are strategies that can reduce the effect of these factors.

1. Because frail older persons may be affected by multiple impairments, they may be less willing or able to come to the clinic, participate in the intervention, or take specific medications. In addition, older persons have more contacts with physicians and more hospital admissions, which increase the probability of being prescribed a competing therapy or of stopping study participation. Ways to approach this problem are to expand the sample size and perform frequent follow-up visits, offer home-assessment visits, and predetermine a brief "essential" assessment as an alternative to the full protocol. Another alternative is to prolong the study follow-up, thereby allowing time for the anticipated number of events or effect size to occur. The problem with this approach is that the short-term effects of the intervention, which may be important for frail, older persons, would probably be lost, and the toll of competing morbidity

and mortality may be unacceptably high. It is recommended that large-scale interventions of disability be powered on short-term outcomes but also examine long-term intervention effects. Especially in an older, frail sample, an initial favorable effect may diminish over time because of competing endpoints and decreased efficacy of the intervention. A third approach is to exclude older persons who are too ill. For example, a run-in period before randomization may exclude those who would drop out early, but investigators must carefully consider that a run-in period before randomization selects a different population than if everyone were included and will thus strongly affect the generalizability of the trial results. In general, a long, complex enrollment phase selects individuals who are not severely frail.

2. Feelings of exhaustion are a hallmark of physical frailty. Thus, frail, older persons are more likely to miss appointments because they are too tired or because nobody will accompany them to the clinic. The rule is “reach out for the participants and enable them to participate.” In order not to lose these participants, a window of 1 month before and after the anniversary assessment date is recommended. When a participant is too exhausted to come to the clinic, a brief, prestandardized home-based or telephone assessment should be offered. Provision of transportation may be a good strategy to increase adherence; some authors have suggested that studies of frail older persons may not be feasible if adequate transportation is not provided.<sup>57</sup> Building strong, trusting relationships between investigators, participants, their families, and their primary care physicians is probably the most effective strategy to promote adherence. Maintaining a low turnover in project staff is essential. Working with frail, older persons can be stressful, and staff members may occasionally require counseling and support. Calling participants regularly and sending birthday and get well cards between scheduled visits may be important to maintain contact. One should recognize that frail, older persons might miss a follow-up evaluation but still be willing to return for future assessments. Creative ideas for improving retention add to the quality of the study and represent an important area for research.

## REPORTING RESULTS IN SCIENTIFIC JOURNALS

Most medical journals require that authors provide a Consolidated Standard of Reporting Trials (CONSORT) checklist and flow diagram when reporting a randomized, controlled trial.<sup>58</sup> The intent is to identify explicit methodological and ethical components of the trial, allowing the reader to evaluate the quality of the findings. Understandably, the CONSORT guidelines do not address issues pertaining to special populations. Thus, in addition to the CONSORT checklist, the following seven methodological and ethical items that are critical for trials performed in frail older persons are proposed.

1. State the definition of physical frailty adopted by the trial and justify the choice.

2. Describe how expected rates of drop-out were factored into sample size calculations.
3. Present details on losses at each stage of the trial, including eligibility screening, enrollment, consenting, and study implementation in the study flow chart, to weigh the effect of competing morbidity and mortality. Given the study population, discuss the generalizability of the findings.
4. Discuss consent strategies. Describe how the ability of the participants to give informed consent was assessed and how the consent was obtained if the participant had impaired decision-making capacity or was vulnerable to exploitation. A template statement should be avoided.
5. Describe missing data according to study arm and demographic characteristics, reasons for missing data, and analytical methods for managing missing data.
6. Describe strategies to minimize exclusions, to enhance compliance with intervention, and to reduce missing follow-up visits and dropouts, and briefly describe their acceptability and effectiveness.
7. Report whether the effect of treatment on well-being and QoL was ascertained.

## CONCLUSION

The planning of interventions to prevent disability in frail older persons requires a conceptual shift from the traditional approach to clinical trials. In the attempt to detect the pure effect of an intervention, many traditional trials have selected a “clean” study population through the use of numerous inclusion and exclusion criteria. In the case of frail, older persons, such an approach may fail to evaluate the intervention in the most clinically relevant group in which such intervention is needed. In addition, this approach is not feasible with frail older persons because it would enroll such a small percentage of the reference population that the generalizability of the findings would be questionable. The challenge therefore is to design studies that allow participation of persons with physical frailty, while implementing strategies to enhance participation and avoid excessive risk.

There is a great need for methodological developments in this area, including improved statistical methods for managing competing events and missing data, improved screening criteria for frailty that are widely accepted by the scientific community, a consensus on appropriate methods of consenting older persons who have cognitive or physical problems, and validation of objective measures of disability that capture behaviors that are essential in daily life. It is necessary to convince investigators that excluding frail, older persons because of concerns about comorbidity, heterogeneity of response, and safety not only limits the generalizability of the findings, but also fails to target those who most need and would probably benefit most from interventions for disability prevention.

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