

## Special Article

# Functional Outcomes for Clinical Trials in Frail Older Persons: Time To Be Moving

Working Group on Functional Outcome Measures for Clinical Trials\*

ON January 10 and 11, 2007, a working group (\*see Appendix for listing of group members) met in Bethesda, Maryland, to discuss the subject of appropriate outcomes for trials designed to improve functional status in elderly people. In addition to the working group, representatives from the Food and Drug Administration (FDA) and the National Institute on Aging (NIA) participated in this meeting. The purpose of this special article is to describe the issues related to design and implementation of clinical trials with the intent of improving functional status of older people, with the ultimate outcome the approval of a specific drug by the FDA or widespread use of lifestyle interventions to delay or prevent functional declines associated with aging.

### CHALLENGES FOR RESEARCH IN THE GERIATRIC POPULATION

Aging is associated with a remarkable number of adaptive responses and changes. In particular, the loss of skeletal muscle mass (which has been termed sarcopenia) appears to be a universal phenomenon (1). It was thought that sarcopenia would predict late life events such as disability and loss of independence in much the same way that osteopenia is predictive of risk for a fracture. Although sarcopenia is strongly associated with functional capacity, frailty, and increased health care costs (2), the amount of skeletal muscle is certainly not the only predictor of functional outcomes with advancing age. A great many other variables are at play, including muscle quality, nutritional status, total body fatness, neurologic function, cardiovascular and pulmonary function, and multiple other comorbid conditions. What is clear, however, is that the functional capacity of an older person is highly predictive of mortality and many other important outcomes, such as loss of independence, nursing home admission, onset of dementia, and falls. Additionally, decline in functional status is the final common pathway of many chronic conditions, captures the overall impact of multiple, co-occurring conditions, and is an important indicator of quality of life (QOL). It has been estimated that, in a single year in the United States, the added costs of health care for the subset of older persons making the transition to a more dependant state (above estimated costs if they had not made the transition) was \$26 billion, just under one tenth of the total cost of personal health care for all people aged 65 years or older (3). There are, thus, compelling reasons to

develop evidence-based interventions to prevent or postpone functional decline among older persons.

It is generally recognized that geriatric patients have multiple comorbid conditions and, as a result, interventions that target single diseases may have limited efficacy in this population. For example, a hypertensive older patient may have diminished renal function, insulin resistance, and low levels of physical activity. Treating high blood pressure has clear benefits in preventing cardiovascular events and preserving renal function but may have a limited (or no) effect on risk of diabetes or reduced activity. Thus, conducting a clinical trial in older individuals is intrinsically more difficult than in younger adults and may lead to disease-specific improvements that have little impact on the day-to-day function of the individual. For this reason, it is crucial that the value of including an assessment of functional outcomes be considered in randomized controlled trials (RCTs) involving older persons. In addition, QOL measures have been used in a number of disease-specific clinical trials, but until all of the factors that contribute to QOL measures in the geriatric setting are understood, they may not be appropriate endpoints.

A substantial proportion of older persons with comorbidity and frailty are often excluded from clinical trials, thus the effectiveness of most new treatments for chronic diseases that typically affect older persons, particularly medications, has historically been established in individuals who are substantially healthier than average age-matched persons in the general population. As a consequence, when these new medications are used in older or frail persons, who often have the greatest need for new therapeutic agents, unexpected side effects commonly emerge and the benefits evidenced in the original trials may not occur or may not be relevant in this population. In these complex patients, it is critical to know if the intervention has improved, or at least slowed decline, in functioning.

### TURNING TO FUNCTIONAL OUTCOMES IN RCTs

In geriatric research and clinical practice, the problems arising from focusing on single diseases (one at a time) have been addressed for many years by the development of measures of functional status that may reflect the overall health status of an individual. One of the most important advantages of these measures is that they capture the effect of physiological changes that, although often interpreted as

signs of aging, clearly have detrimental consequences for the individual. The medical community recognizes some of these conditions, such as osteoporosis, as diseases, whereas others, such as sarcopenia or slow gait with resultant progressive functional decline, receive little consideration and are perceived as normal characteristics of older persons. For example, the concept of frailty has long been associated with advancing age but only recently has it been specifically defined and proposed as a medical syndrome (4). Physical performance is considered fundamental to identification of frail individuals, and an increasing body of literature provides evidence that this concept has a true biological basis that may be treatable (5,6). Important to this discussion, most definitions of frailty in older people include objective or self-report measures of functional status.

The powerful relationship between functional status and morbidity and mortality seen in older people in observational studies has stimulated considerable interest in conducting RCTs to evaluate the impact of interventions on functioning. To date, most RCTs using functional outcomes have tested nonpharmacological interventions such as exercise and strategies to improve nutritional status. Indeed, an important mandate of the NIA is to develop interventions that preserve functioning in older people (7).

Self-report measures of disability have been used in successful clinical trials (8,9) but, stimulated by the need to evaluate functioning in a standardized manner free of the influence of diverse environmental factors, clinicians and epidemiologists have turned to objective performance measures as outcomes. These measures evaluate many different domains of function, such as upper extremity function and flexibility, but the most methodological work, by far, has been done on assessments of lower extremity functioning and mobility. These tools include such measures as the Short Physical Performance Battery (SPPB), usual gait speed, the "Get Up and Go" test, the 6-minute walk test, and stair climbing power.

The SPPB and gait speed measurement were the two functional tests that were seen by the working group as being closest to being ready for pharmacological trials. Extensive work on the SPPB has demonstrated excellent reliability (10); predictive validity for a large number of adverse outcomes, including mortality, nursing home admission, hospitalization, and new onset of disability (11–15); and sensitivity to clinically important change (10). As an outcome, the SPPB has been shown in prospective studies to be related to important risk factors such as depression (16) and anemia (17) and to be responsive to an exercise intervention in an RCT (Lifestyle Interventions and Independence for Elders [LIFE] Study). Levels of clinically meaningful change have been established for the SPPB and gait speed (18). A wide range of relationships between the SPPB and biological, medical, and social factors supports the validity of this measure. These include significant associations with brain white matter volume and white matter signal lesions (19,20); inflammatory markers and d-dimer (21–23); insulin-like growth factor 1 (IGF-I) (24); diabetes and hip fracture (23); falls and loss of mobility with social repercussions (inability to leave home or need for nursing home care) (25); self-reported disability and function (26); and history of manual

work, especially associated with high physical stress (27). Simple gait speed assessment has been shown to capture nearly all of the predictive value of the SPPB (13); it is quicker to perform and has many associations and predictive abilities similar to those of the SPPB (28–31). The 6-minute walk has undergone extensive methodological evaluation (32). It assesses function but also has a major component that is related to exercise tolerance and endurance, a consideration in deciding if it will be responsive to an intervention. Longer walks have been incorporated into observational studies and clinical trials in congestive heart failure (33) and many forms of lung disease (34–36). A variant, called the long distance corridor walk, has been developed to have greater sensitivity among high-functioning older adults (37,38). Leg power (power = force  $\times$  speed) has been demonstrated to strongly relate to functional status in very old and frail men and women (39,40), and strategies to improve muscle power may have a strong effect on functional improvements (41). Leg power (weight of an individual  $\times$  speed of climbing) can be estimated from the speed at which an individual can climb stairs as well as from time to perform repeated chair rises (42).

Despite the growing evidence of the excellent psychometric properties of physical performance measures, a number of issues remain unresolved. For example, there is not a clear consensus on the method of selection of the most appropriate test of functional status according to the specific pharmacological or lifestyle intervention and the targeted goal of improving function, preventing functional losses, or ameliorating frailty in older persons. For objective performance tests, most of which are administered in a standardized setting, we are just beginning to understand what constitutes clinically meaningful change for commonly used tests (18), and the relationship between standardized test results and patient-reported improvement needs further elucidation. Although the number of RCTs in older cohorts continues to grow (43), there is a great need to accumulate clinical trial experience across a variety of interventions and cohorts to refine clinical trial methodology that uses functional outcomes.

#### COMMON GOALS BETWEEN FDA AND GERIATRICS COMMUNITY

Why has experience in this critical area been slow to accrue? Why have we been unable to communicate to the FDA the relevance and possibility of translating the functional approach for pharmacologic research? One of the important goals of the January meeting was to begin a dialogue between the FDA and persons with experience in measurement of functional status in older people. Because older persons are at the greatest risk of loss of functional independence due to weakness, loss of balance, and low functional reserve, they are the most appropriate subset of the population for interventions such as anabolic therapies to improve strength and function. It is known that exercise interventions that increase muscle strength are highly effective in improving gait speed and spontaneous physical activity among older people. However, the efficacy of specific drugs to improve functional outcomes has not been

documented. For example, testosterone is highly effective at increasing muscle size and strength in older men (44), but the effects of these changes on functional capacity or mobility are unknown. With new drugs specifically aimed at addressing these kinds of problems in development, and with many nearly ready for human testing, it is imperative that guidelines for functional assessment be developed that are acceptable to both the geriatric community and the FDA.

Clinicians and researchers are facing the challenge of developing and testing new drugs that can reduce the burden of disease and disability in the expanding population of older persons. They have been aware for a long time that targeting a specific disease and evaluating disease-specific outcomes would only address a portion of the problems that older people face [e.g., (45)]. They have also realized that taking this approach would effectively exclude from clinical trials the truly frail elderly who are most in need of these new treatments (46). On the other side, the FDA is facing the challenge of addressing, on a case-by-case basis, proposals for strategies to prove efficacy for a growing number of drugs that target age-related conditions that cannot be strictly defined as disease. This often requires the use of functional outcomes, mostly in the area of mobility or physical function, which are not disease specific and which may be influenced by many other factors beyond the studied intervention. There is clearly a lack of communication and missed opportunities on both sides. Increasing interactions and collaboration can result in a win-win situation if both sides recognize common needs and goals and try to learn from each other.

For example, researchers and clinicians in the geriatric field should be open to the notion that screening criteria and relevant outcomes for drug trials may be different from those used in trials testing the efficacy of behavioral interventions. There are many reasons for this, but perhaps the most important is that whereas behavioral interventions (e.g., smoking cessation, exercise, dietary changes) have a low likelihood of causing severe side effects, this possibility is much higher in drug interventions. Therefore, the choice of the study population, the type of outcome, and the minimal size effect that is considered clinically important can be markedly different. Pharmacological interventions that lead to a drug approval will have to demonstrate both a specificity of effect through a defined mechanism and a significant impact on the life and well-being of the individual, with an acceptable safety profile. The beneficial effects must be large enough to outweigh the potential risks of prescribing another drug for a frail older person already in need of multiple medications to control multiple comorbid diseases.

In contrast, the FDA should recognize that age-related conditions that are currently not labeled as diseases (such as sarcopenia and frailty) pose a substantial burden to older persons and should be considered as suitable targets for intervention. The need for a shift in paradigm is exemplified by comorbidity. There is clear epidemiological evidence that a large proportion of older persons are affected by multiple concurrent diseases. To eliminate confounding variables, increase precision, and ensure specificity of effect, clinical trials often exclude individuals with comorbidity. The consequences are that drug efficacy is tested in patients

who are substantially healthier, on average, than age-matched individuals in the general population with the same condition and that a preponderance of patients who will be using these drugs in practice are excluded from most clinical trials. New designs, methods, and measures should be created that enable frail older persons to participate in these trials without excessive risk. In individuals with comorbidity and frailty, for whom an outcome that assesses a single disease is simply not adequate, the shift to the more general measures of function is essential. Making the transition to the new methodology of functional assessment in drug trials will be a challenge for the FDA and researchers alike.

The lack of communication (and the critical need for more information and research) is evident in the prior work that has been done to create and validate measures of physical functioning and frailty. Although most geriatricians and aging researchers may be convinced that sufficient evidence already exists to justify the use of these instruments in clinical trials, none of this prior work has been guided by criteria established for the use of outcomes in clinical trials testing pharmacological interventions. For example, more research is required on how a one-point improvement on the SPPB is perceived by older individuals and how it affects their well-being and daily life. In addition, it is unclear whether these patient-specific metrics are homogeneous across the entire range of SPPB scores. Indeed, the most appropriate functional outcome for specific clinical trials is not always apparent. Whereas strength improvements may be an immediate consequence of an anabolic therapy, the selection of a specific measure of functional status that is the best benchmark by which to judge clinical efficacy is not clear.

### Summary

This is an exciting time with great potential for discovering therapies to improve functional capacity and decrease the high prevalence of frailty and disability in older people. The FDA will need to consider how best to incorporate the geriatric perspective into its mission. Cooperation between aging researchers, pharmaceutical companies, and regulators will be required to establish guidelines for outcome measures for the coming generation of clinical trials in frail older persons. Ultimately, all stakeholders have the same goals: reducing the burden of chronic disease and disability in older persons while avoiding harm.

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FDA representatives participated in and contributed to this meeting, but this document should not be construed as an FDA policy statement.

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#### APPENDIX: WORKING GROUP ON FUNCTIONAL OUTCOME MEASURES FOR CLINICAL TRIALS

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## GERIATRIC CLINICIAN/EDUCATOR

The Donald W. Reynolds Department of Geriatric Medicine at the University of Oklahoma Health Sciences Center is seeking board certified or eligible, fellowship trained geriatricians for positions as clinician educators. These positions are supported by Reynolds endowed chairs for clinician educators, and carry with them a requirement of clinical service, education and educational program development, and scholarly pursuits. Although the positions are non-tenured, individuals are appointed to the chairs for a minimum of three years, and presuming continued outstanding performance, have the option of renewal for three or more years.

Specific positions that are available for July 1, 2008 include medical director of a VA based home care program and involvement with long-term care facilities in the community.

**Interested applicants should submit a letter of interest with curriculum vitae to:**

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