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WHAT ARE THE OUTCOMES OF TREATMENT AMONG PATIENTS WITH SARCOPENIA?

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Abstract

Treatment outcomes for clinical trials of interventions on sarcopenia depend on the goals of the intervention, especially whether the treatment is considered therapeutic or preventive. Key issues regarding outcomes are the selection of a primary outcome and options for secondary outcomes. While clinical significance and face validity are key concerns when making this determination, other factors to be incorporated into the decision include measurement characteristics, feasibility and cost, risks of missing outcomes and options for alternative strategies to determine them. Primary should be highly responsive to changes in sarcopenia and clinically important. Like many problems of aging, functional abilities, especially mobility, may be the most clinically relevant states.

Treatment outcomes, like target populations, depend on the goals of the intervention, especially whether the treatment is considered therapeutic or preventive. For the purpose of clinical trials, key issues regarding outcomes are the selection of a primary outcome and options for secondary outcomes. While clinical significance and face validity are key concerns when making this determination, other factors to be incorporated into the decision include measurement characteristics, feasibility and cost, risks of missing outcomes and options for alternative strategies to determine them (1–4).

Primary outcomes for clinical trials of interventions on sarcopenia should be highly responsive to changes in sarcopenia and clinically important. As in the case of many problems of aging, functional abilities may be the most clinically relevant states. Measures of function among older adults have been clearly linked to other states highly valued by older adults and society, including survival, quality of life, use of health care, need for supportive services and caregiver burden. Among measures of function, performance-based and self report items are complementary but performance-based measures may be more reproducible and less vulnerable to bias. They are also considered by some to be more objective and are likely to be preferred by regulatory agencies. Among performance based measures of function, the best studied are those that assess lower extremity function and mobility. Such measures have demonstrated predictive validity for numerous critical health factors such as survival, health care use, future functional decline and quality of life (5–13). Performance measures of mobility have also repeatedly been shown to be sensitive to changes in strength (14). The most frequently used performance measures of mobility are described in Table 1, along with commonly used self report and professionally assessed measures.

Some of the challenges of using performance measures must also be noted. Missing data can be a real concern. Since data collection requires direct contact with the participant, outcomes will be missing in participants who drop out or become too ill or disabled to come in for testing. This form of missing data is considered “informative” since it is not random and such missing data will bias results. It is critical to develop alternative plans for data collection, perhaps during home visits. In some situations, proxy responses may be useful for defining the presence of serious mobility problems (15).

The form of the outcome measure is an important consideration. Dichotomous variables can define the presence of an important state that can be used to estimate treatment effects like number needed to treat. The 400 meter walk can be used as a dichotomous variable where mobility disability is defined as inability to complete the walk in 15 minutes (16).

Continuous forms of measures are likely to have better power with lower sample sizes than dichotomous variables, an attractive feature in early clinical trials. When using continuous measures, it is essential to assure that there is sufficient room on the scale to detect change in response to the intervention, both toward improvement and decline. If the target of the intervention is to promote recovery from mobility disability, there is a possibility that some participants could be initially nonambulatory and the performance measure would need to include measures of transfers and bed mobility. There are no widely accepted performance measures for the nonambulatory participant. Another challenge with continuous measures is to define clinically meaningful change (9). Table 2 provides a summary of evidence about meaningful change in performance measures.

Another challenge with function related outcome measures is that disability is known to fluctuate in older adults, especially related to transient acute illness and exacerbations of chronic illness (17). Some investigators have advocated using outcome criteria that account for persistence of disability over time. An example would be requiring at least two consecutive failed 400 meter walks several months apart in order to consider the outcome to have occurred. Another strategy that can account for fluctuation is to track “time in state” over the course of treatment. In this case, one might define “number of restricted activity days” over a period of months and compare rates in the treatment versus the control group. Studies of persons with sarcopenia related disability at entry to the study, for example after acute illness, could assess “time to independent ambulation” as an outcome. The latter measures require frequent monitoring but more recent technology such as hand held digital devices or accelerometers might be a convenient method for recording activity.

Another strategy to assess mobility frequently is to measure physical activity using devices like accelerometers. There are numerous forms of these devices now on the market. However, there are challenges in their use with older adults because 1) the conversion formulae used to convert the raw data to activity counts is proprietary and unproven, 2) most devices appear to underestimate the frequency of light or low MET activity and 3) all devices require participant cooperation to obtain reliable data (18–20).

Secondary outcomes could be considered in several classes. One set of outcomes might be mechanistically oriented to determine if the treatment worked in the way it was expected to work. In the case of sarcopenia, these might be the measures of muscle mass and strength.

Clearly all of the issues about the best ways to measure strength and mass come into play including validity, feasibility and reproducibility. In some cases, the measures of muscle could be even more detailed and include biopsy or more complex imaging techniques. Another set of outcome measures might focus on the more distal consequences of mobility disability including living situation, health care use, quality of life and survival. Measures of psychological state or life space might also be appropriate (21, 22). Self report measures of function, especially those related to mobility should be used to complement and confirm performance measures. While there are numerous forms of these measures, the 24 item survey developed for the FAST study, has been shown to be highly responsive to changes in physical performance (23). See Figure 2 for a recent analysis of change in physical performance and change in self report measures, derived from data from the LIFE study. Especially for studies of treatment of mobility disability, passively collected data on health care use, living situation and survival might be appropriate, as might professional assessment in the health care setting using instruments like the FIM (see table 1).

Next steps in research in the area of outcome measures include the following.

1. Develop standardized approaches to default and proxy responses when performance based data is missing.
2. Agree on performance measures for nonambulatory participants to be used in studies of mobility disabled persons in whom treatment is designed to hasten recovery.
3. Develop low burden methods to track mobility frequently in order to assess time in state, time to recovery and physical activity.
4. Agree on the best ways to measure muscle and strength!

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Figure 1.
Model of Sarcopenia and Disablement for use in Designing Clinical Trials

Figure 2.
Magnitude of improvement and decline in self-report measures for each unit of change in gait speed: data from the LIFE study (unpublished)

Table 1

Instruments used to Screen and Classify Mobility from Brack, Rosano and Studenski Mobility in press (24)

Instrument type	Instrument name, references	Items	Range	Comments
Self report	Rosow-Breslau	Walk 1/2 or 1/4 mile, climb stairs	Ambulatory to vigorous	Used as single items
	SF-36 physical function	10 items, many directly related to mobility, from walk 1 mile to walk across a room	Ambulatory to vigorous	Score 0–100 US adult mean 84.2 older adult mean 52.0 insensitive at lower levels of mobility
	Long term cue survey Mobility modifications	Waiting inside and bed/chair transfers Self-report of changing the way one waits one half mile of climbs stairs	Nonambulatory to ambulatory Ambulatory	Used as single items Used as single items
	Avlund mobility	Fatigue and need for help in sis mobility activities from transfer to stairs and walking outside	Nonambulatory, ambulatory and vigorous	Scores 0–6
	Self reported disability scals from the FAST study	Perceived difficulty with 24 activities. many are mobility related	Nonambulatory, ambulatory and vigorous	Each item is rated on a five level ordinal scale from no difficulty to cant do
Professional assessment	Barthel mobility items	Walking (or wheeling).transfers, stairs	Non ambulatory, ambulatory and vigorous	Mobility items integrated into total score
	Functional Independence Measure (FIM)	Transfers and locomotion (walk, wheelchair, stairs)	Nonambulatory, ambulatory and vigorous	7 level scoring of need for assistance with items. Mobility items are integrated into total score
	MDS	Bed mobility, transfers, locomotion (includes wheelchair mobility) walking	Nonambulatory to ambulatory	Used as single items
Performance	Short Physical Performance Battery (SPPB)	Timed walk, chair rises, tandem stands	Ambulatory	Score 0–12 Scores of 10–12. 7–9 and 4–6 associated with increasing risk of poor outcomes
	Gait speed	Timed walk, varying distances, instructions. procedure s	Ambulatory	Healthy older adult > 1.0 meter/sec Slow <0.6 meter/sec Very slow < 0.4 meter/sec
	Timed up and go	Time to rise from chair. walk 10 feet, turn, walk back and sit down	Ambulatory	<10 seconds- normal, < 20 seconds- able to move in community >30 seconds- needs assistance for mobility
	Six minute walk	Distance covered in 6 minutes	Ambulatory to vigorous	Healthy older adult mean >500 meters older adults in

Instrument type	Instrument name, references	Items	Range	Comments
	Health ABC	Waiting endurance: 400 meter walk time	Ambulatory to vigorous	assisted living < 300 meters More sensitive among apparently vigorous older adults than 6 minute walk. Usual time should be less than 6 minutes
		Expanded SPPB: longer tandem stands, one foot stand, narrow walk time		Supplements SPPB by expanding differentiation among healthy older adults. Useful for persons with scores of 10–12 on SPPB score range 0–4

Table 2

Overall Recommendations for Criteria for Meaningful Change and Sample Size Estimates based on Responsiveness Index (9)

Performance Measure		Recommended Criterion for Meaningful Change (Δ)	Estimated Standard Deviation of Change for Stable Subject (Δ)	Number Needed per Group 80% Power in a between Group Comparison (N)
10-foot gait speed:	small meaningful change	0.05 m/s	0.11 m/s	77
	substantial meaningful change	0.10 m/s	0.11 m/s	21
10m gait speed:	small meaningful change	0.05 m/s	0.15–0.16 m/s	142–161
	substantial meaningful change	0.10 m/s	0.15–0.16 m/s	37–42
4m gait speed	small meaningful change	0.05 m/s	0.12 m/s	90
	substantial meaningful change	0.10 m/s	0.12 m/s	23
SPPB score	small meaningful change	0.5 point	1.48 points	138
	substantial meaningful change	1 points	1.43 points	35
6-minute distance	small meaningful change	20 m	45–53 m	71–115
	substantial meaningful change	50 m	45–53 m	13–20