Selecting Appropriate Clinical Trial Endpoints for Geroscience Trials: A Path Towards Consensus – Supplementary Documents

Includes

Supplement Table 1

Supplement Table 2

Supplement 3

Supplement 1 : Table 1. Expert views on endpoint elements or measures of a clinical trial of a treatment that may slow aging results of modified Delphi process.

Measure	Percent endorsing as a part of a Primary Outcome (%)	Percent endorsing as a Secondary outcome (%)	Percent Not Relevant (%)	Expectations for a Successful Intervention
Gait Speed	64.5	35.5	0	At least minimal improvement
Balance	25.8	74.2	0	Maintain or Improve
Performance test like short physical performance battery or timed-up-and-go test	48.4	48.4	3.2	At least minimal improvement
Performance on 6-minute or 400M walk test	64.5	61.3	0	Minimal to significant Improvement
Peak Exercise Capacity (VO2 Max)	38.7	35.5	0	At least minimal improvement
Voluntary Physical Activity	22.6	83.9	3.2	Maintain or Improve
Community Mobility (e.g. Life Space)	16.1	74.2	0	Maintain or Improve
Feelings of Tiredness/Fatigue	32.2	64.5	3.2	At least minimal improvement
Muscle Strength	45.1	54.8	0	At least minimal improvement
Muscle Mass	19.4	61.3	19.4	Maintain Current Level or Slower Decline
Short-term Memory	38.8	74.2	0	At least Slow decline
Executive Function	45.2	61.3	0	Maintain or Improve
Cognitive Fatigability	19.4	54.8	6.5	Maintain or Improve
Feelings of Vitality	19.3	64.5	9.7	Maintain or Improve
Activities of Daily Living	35.5	71	0	Maintain or Improve
Disability-free Life Years	45.2	51.6	3.2	Minimal to significant Improvement

Self-rated Health	29.0	64.5	6.5	At least minimal improvement
Quality of Well-Being (e.g. SF-36)	32.2	64.5	3.2	Maintain or Improve
Frailty (5-item Fried Frailty Phenotype)	38.7	54.8	6.5	At least Slow decline
A single panel of blood-based aging biomarkers	32.2	61.3	6.5	Maintain or Improve
Glucose Tolerance	29.0	51.6	19.4	Maintain or Improve
Ejection Fraction	9.7	51.6	38.7	At least Slow decline
Estimated Glomerular Filtration Rate	12.9	67.7	19.4	At least Slow decline
Response to a vaccine	25.8	54.8	19.4	At least minimal improvement

Supplement 2: Table 2. Expert views on the endpoint elements for health-related conditions of a clinical trial of a treatment that may slow aging results of modified Delphi process.

Health-Related Conditions	Percent endorsing as a part of a Primary Outcome (%)	Percent endorsing as a part of a Secondary Outcome (%)	Percent Anticipating that risk would be reduced
All-cause Mortality	48.4	45.2	71
Mortality secondary to age-related diseases	38.7	48.4	80.6
Fall/fractures	38.7	54.8	71
Common Age-related Cancers (Breast, lung, prostate, colorectal)	25.8	71.0	54.8
Ischemic Heart Disease	29.1	64.5	77.4
Stroke	29.1	64.5	74.2
Congestive Heart Failure	29.1	61.3	67.7
Chronic Obstructive Pulmonary Disease	12.9	64.5	48.4
Mild Cognitive Impairment/Dementia	41.9	51.6	83.9
Hospitalizations	29	61.3	71
Health Care Cost	6.5	74.2	58.1
Kidney Failure	25.8	54.8	54.8
A composite of some or all of the above	54.8	35.5	87.1

Supplement 3: Geroscience Outcomes Consensus Project Focus Group Moderator's Guide

WARM-UP AND EXPLANATION (10 minutes)

Introduction of Moderator & Thanks for Participating

Welcome and thank you for participating in this focus group discussion today. I'm _____ and I will be the moderator for this session. My role is to ask you questions and keep the conversation moving.

We are fortunate to have some help today. This is _____ and s/he will be the co-moderator for our session. S/he may ask some clarifying questions as they come up.

Purpose & Procedure

What we are doing here today is called a focus group. It is a small group discussion to find out your opinions on what outcomes or endpoints should be used for clinical trials of interventions that target the biology of aging to slow or prevent the emergence of health-related conditions or diseases. We are interested in hearing all of your ideas, comments, and suggestions. Please speak up -- even if you disagree with what somebody else is saying. Hearing from each of you is important.

We are going to record our discussion because everything that is discussed is important to us, and we want to make sure we do not miss any comments. This group is one of four we're planning on this topic. Your responses will be reported with those of the other three groups. Nevertheless, all your comments are confidential, and they will be used only for research purposes. Nothing you say will be connected to your name. Also, if any questions make you uncomfortable, you do not have to answer them. We ask that you keep all of the information you hear from the other participants confidential as well.

If you are joining from a location with background noise, please mute yourself when you are not speaking. We have a lot of things to talk about -- so sometimes I may change the subject or move ahead. Just stop me if you want to add anything.

Introduction and Ice Breaker (5 minutes)

To get us started, we would like each person to introduce themselves and tell what your background and what institution you are affiliated with (if you are).

Section A: What Do We Expect to See with a Successful Geroscience-Inspired Intervention. (Loose Target: 45 min)

There is tremendous interest in the geroscience hypothesis – that targeting aging biology can improve human health and slow the emergence of age-related health conditions. Let's say there is an intervention that in animal models extends life span and preserves function. In early phase human studies, it was safe and well tolerated. The investigators are now planning a 5-year study to see if the intervention works. They are especially interested in outcomes that reflect how a person feels, functions, or survives, because these are the dimensions important to the FDA's regulatory framework.

1. What kinds of data would you want to see the study team collect that would help you decide whether the intervention slows the aging process in humans?

Probe: What dimensions of health or well-being do you see as being relevant?

Probe: In its guidance, the FDA emphasizes outcomes related to how a person feels, functions, or survives. Does this suggest any other assessments that might be made?

2. If the investigators have the resources to include all the assessments you all just discussed, are they equivalent in your mind? Or would you consider some to be more important than others? Why?

Probe: What about from the perspective of a participant or a regulator?

Section B: In preparing the study protocol, the investigators are faced with the challenge of specifying a "primary endpoint" for the study. (Loose Target: 25 minutes)

For those not familiar with the term, the primary endpoint is the focus of the study design. The intervention will be judged according to whether the endpoint significantly differs between the treatment group and the control group at the end of the study.

3. Given what we just discussed, what do you think a convincing primary endpoint would look like?

Probe: Is it a single event like death is it a combination of multiple-disease events, is it an important change in physical and or cognitive function, the avoidance of disability, or maybe a combination of things?

Probe: If the endpoint is a combination of measures should they be evaluated as co-primary endpoints or combined into a composite endpoint or index?

4. To what degree do you think the endpoint selection depends on the intervention being tested? Is there an endpoint that could be used universally, or would it always be tailored?

Probe: What should be kept in mind when tailoring the endpoint?

Section C: Specific Alternatives: The literature provides a number of examples of proposed primary outcomes for geroscience-inspired trials, let's discuss a few of them. (Loose Target: 25 minutes)

5. There is a planned study called the TAME study which seeks to test whether the drug metformin reduces the rate of onset of 5 age-related health conditions– dementia, heart failure, most kinds of cancer, coronary heart disease, stroke or death. If the intervention (metformin) significantly reduced the rate of onset of these in aggregate, would this be convincing evidence that aging had been slowed?

Probe: What if the statistical result was only due to reductions in coronary heart disease and heart failure, would you feel the same way?

6. In gerontology, the term frailty is commonly assessed in one of two ways. Let's talk about each one in turn.
a) There is the frailty phenotype developed by Dr. Linda Fried and colleagues which assesses weight change, walking speed, grip strength, feelings of fatigue and physical activity to classify people as frail or not. Would the prevention of frailty be a suitable endpoint for the trial we've been talking about?

Probe: If not, is there a way to make it more suitable?

Probe: If yes, can you elaborate and also consider what might be some objections that could be raised?

b) There is a way of thinking about frailty popularized by Dr. Kenneth Rockwood which defines frailty based on the number of health problems a person might have at a given time. A person with more health problems would be frailer than a person with fewer health problems. Would differences in frailty at the end of a study be suitable endpoint of the trial we've been talking about?

Probe: If not, is there a way to make it more suitable?

7. Are there any other endpoints you can think of that might be appropriate that have not been discussed so far?

Closing

We've reached the end of our questions. Is there anything else that you'd like to share today?

Please be on the lookout for information from Elizabeth Owens regarding the surveys that will be provided via a link that will be generated based off information discussed in the focus groups. She will also be providing more information regarding the stipend as well. Thank you very much for your input today and we appreciate your time.