Preliminary Competition Guidelines

Nov 29, 2023

Version 1.0

PRELIMINARY COMPETITION GUIDELINES

XPRIZE Healthspan will be governed by Competition Guidelines to be published in 2024 following a 6 month **Public Comment Period**. The Preliminary Competition Guidelines summarize the high-level requirements and procedures of the competition. These Guidelines are based upon extensive research and consultation with experts including senior scientists, directors of aging research programs, basic biologists, geriatricians and preventive medicine clinicians, advocacy groups, government agencies, **clinical trials** specialists, and researchers across a wide array of relevant health-related fields. For the list of advisors, please see Appendix E.

XPRIZE will revise these Preliminary Competition Guidelines during the Public Comment Period, and may change the published Guidelines at any time during the course of the competition to provide additional information or to improve the quality of the competition. Unanticipated issues that arise or new technological advancements may require modifications to the Competition Guidelines. XPRIZE reserves the right to revise these Guidelines as it, in its sole discretion, deems necessary. All **registered teams** will be notified of the published Competition Guidelines in 2024, and of any revisions made to that document in a timely manner. Official updates will be communicated to team leaders by email.

For the most updated version of the Guidelines, check xprize.org/prizes/healthspan/guidelines.

Further details concerning the operation of the competition, such as exact dates and locations of events, recruitment requirements, safety considerations, effect size thresholds, specific **assessment measures**, and clinical trials manual operations protocols will be released in the **Rules & Regulations** and other documents that are forthcoming throughout the competition.

NOTE: **Bolded** items are defined in the Glossary.

Summary of updates in Guidelines:

1. None.

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1. COMPETITION OVERVIEW

XPRIZE Healthspan is a 7-year, $101M global competition to revolutionize the way we approach human aging. People around the world are living longer, but not necessarily in better health. To tackle this challenge, competing teams will develop and test therapeutics that target biological aging to improve function and extend healthy life. This radically collaborative effort will bring together top scientists, clinicians, policymakers, industry experts and non-governmental agencies to drive new science and create a future where healthy aging is made possible for all.

The **overall premise of $101M XPRIZE Healthspan** is that by targeting aging with a single or combination of **therapeutic treatments**, it may be possible to restore function lost to age-related degradation of multiple organ systems. Our objective is to incentivize hundreds of independent teams around the world to test this hypothesis in clinical trials using a variety of therapeutic treatments - including but not limited to drugs, biologics, gene therapies, devices, dietary or lifestyle approaches, administered alone or in combination.

Teams will be required to deliver their therapy in 1 year or less in persons aged 65-80 years who are free of major or life-threatening disease and disability. The winning team will demonstrate that their therapeutic treatment restores **muscle, cognitive, and immune function** by a minimum of 10 years, with a goal of 20 years. The prize awarding is based on the magnitude of functional improvement compared to controls observed in a 1 year period relative to the age-related declines expected over 10 years ($61M), 15 years ($71M), or 20 years ($81M) in a referent population.

The **overall premise of FSHD $10M Bonus Prize** is that aging with Facioscapulohumeral muscular dystrophy (**FSHD**) may accentuate the symptoms associated with muscular dystrophy, such as muscle weakness, and fatigue. Teams will be required to deliver their therapy in 1 year or less in clinical trials in persons with a genetically confirmed diagnosis of FSHD who are free of other major or life-threatening diseases.

Objectives

The XPRIZE Competition has four primary objectives it hopes to achieve:

1. Demonstrate that therapeutic treatments can restore functional ability typically lost during aging in humans.
2. Build consensus on methodologies to measure functional and biological aging.
3. Generate global interest in research and commercial implementation of healthspan extension, by inspiring and guiding individuals, companies, academic teams, and researchers to engage in this XPRIZE.
4. Stimulate public discourse and drive regulatory reform while educating the public, scientists, key stakeholders, and leaders.

Background

Global Challenge. Our global population is aging. In the last 100 years, public health measures like vaccinations, access to clean water and nutritional food, lower infant and maternal mortality, and trauma care, have more than doubled our expected lifespan. Yet at a population level, we have achieved these additional 20 years of lifespan by evading early death — not by extending the period spent in relatively good health, or ***healthspan***. According to the most recent World Health Organization reports, there is a 12-year gap between life expectancy and health-adjusted life expectancy in the United States (US). Globally people are living longer, but for an extended period with chronic disease, disability, and high healthcare costs.

This demographic shift will affect developed and developing countries alike. By 2040, China will be home to nearly half a billion people over 60. By 2050, Brazil's population of adults aged 65 and older is set to triple. By the same year, Japan's total dependency ratio will reach a turning point: there will be roughly as many working-age adults in the country as dependents, most of them retirees.

Economic Impact. Our global aging population brings great opportunity but also significant social and economic challenges due to a decline in the working-age population, increased health care costs, unsustainable pension commitments, and changing drivers of demand within the economy. For example: in the US, every 1% increase in healthcare spending leads to a 0.083% decrease in GDP growth rate. Further, a 10% increase in the fraction of the population over age 60 decreases the GDP per capita by 5.7%, primarily due to loss of labor supply. Globally, healthcare expenditure rose 4 to 10 fold over the last 15-20 years, and in China, healthcare expenditures exceeded the GDP growth rate. Meanwhile, in Brazil, pension and health expenditures already represent >50% of total public spending, accounting for ~20% of GDP, and are projected to reach 40% of GDP by 2050. Based on population projections in Japan from Fiscal Year 2020, total medical costs for their older persons are expected to increase from JPY 26.4 trillion in 2020 to JPY 28.5 trillion in 2030.

In contrast, successfully extending healthspan would net profound social and economic benefits. According to a 2021 report using US reference data, extending healthy life by 1 year would be worth US$38 trillion, and by 10 years, US$367 trillion.

Biological Aging Promise. Over the past few decades, remarkable progress has occurred in the science of aging. Studies have implicated genetic and biological pathways that modulate healthy lifespan in diverse species across great evolutionary distances, and demonstrated that aging-related pathways constitute an opportunity for intervention. Lifespan has been verifiably modulated by genetic interventions (such as disruption of the insulin/IGF-1 signaling pathway or by clearing the accumulating senescent cells in aging) and dietary interventions (such as caloric restriction and resveratrol) in multiple model systems. The US National Institute on Aging (NIA)-funded Interventions Testing Program has identified several new and repurposed drugs and supplements that prevent disease and extend lifespan in outbred mice. Newer gene therapies,

chemically-induced reprogramming, and vaccine or immunotherapies are now in development and show early promise in model organisms.

Hope for FSHD. FSHD is a type of muscular dystrophy characterized by muscle inflammation, degradation and replacement by fatty and fibrotic tissue, and impaired muscle function at ages much earlier than natural aging. For FSHD, the underlying genetics, molecular causes and pathobiology of FSHD has been increasingly understood but the gap to novel therapies remains large. Identification of the genetic causes has been established, with the truncated D4Z4 region on Chromosome 4 leading to derepression of a silenced transcription factor DUX4, and hypomethylation due to mutations in methylation genes (SMCHD1, DNMT3B, and LIRF1) being the genetic basis for FSHD1 and FSHD2 respectively. This leads to muscle inflammation, degradation and replacement by fatty and fibrotic tissue and impaired muscle function at ages much earlier than natural aging. Average age of symptom onset is 17-19 years and average age of diagnosis at 29-32 years, with age of onset correlated to allele size.

From Laboratory to Humans. Despite this promise, trials to demonstrate clinical efficacy in older individuals or those diagnosed with FSHD are hampered by numerous challenges. For example, modern conventional medicine is primarily focused on treating or preventing specific clinical diseases, like cancer or cardiovascular disease. Developing and testing therapeutics for single diseases — even for well-characterized clinical diseases — is arduous, with 12-17 years from research and development to regulatory approval for clinical use. There is no analogous testing or regulatory pathway for therapeutics that aim to target mechanisms of aging for the purpose of improved function and healthspan extension, which essentially brings this slow progress to a stand-still. The commercial and regulatory barriers have stymied scientific progress and left no standard of proof for our global community to judge the effects of therapeutics on aging or health. This lack of established regulatory pathways also makes it difficult to distinguish medicines that may legitimately improve healthy aging from untested commercial products. In addition, the lack of diversity of participants in the clinical trials hinders efforts to make certain that therapeutics are effective for all racial/ethnic groups.

Urgency. Between 2015 and 2050, the world's population of adults aged 60 or older is expected to nearly double from 12% to 22%. In addition to the doubling of the world’s older population, there will be much greater diversity as it relates to race/ethnicity. This underscores the urgency to find novel solutions for healthy aging. Failure to identify therapeutic treatments may lead to global economic strain, when older persons exit the workforce because of systemic mandates, age-related health concerns, caregiving responsibilities and mounting healthcare expenditures.

Core Problems

The following core problems are barriers that XPRIZE Healthspan will help us overcome:

Siloed Disease Treatments. Today, traditional medical practice and development of drugs or therapeutics predominantly focus on management and to a lesser extent on prevention and therapy of individual diseases viewed in isolation from other common disease processes. This is at odds with the lived experience of older adults, who often suffer from general functional declines resulting from the onset and progression of multiple concurrent disease processes or multimorbidity. The disease-centric reductionist model fails to recognize the multimorbidity so typical of aging, together with its multifactorial etiology, as well as the rich interconnected biology which underlies aging, the primary risk factor for most chronic conditions.

Fragmented Field. Academic investigators, biotechnology startups, clinicians, pharmaceutical companies, and other key stakeholders are insufficiently coordinated. No systematic frameworks or agreed-upon **endpoints** for trials or **biomarkers** exist, despite multiple task forces and research networks. This disconnect prevents the field from establishing and acting on needs.

Regulatory Barriers. No regulatory or well-established conceptual pathway for drug development or therapeutics testing exists for therapeutic treatments that target aging as a shared risk factor for multiple different diseases rather than the traditional focus on a single disease at a time. This, coupled with fragmentation within the field, leads to an undervaluing of therapeutics which could holistically intervene in the aging process and improve function, resilience, and health.

Long Treatment Timelines. Clinical trials on health- and life-span typically take many years of effort and to prove the concept that a treatment would extend healthspan remains difficult and may be expensive to measure. The establishment of biomarkers of aging that reliably predict **benefits** for clinical aging conditions, alongside new approaches to trial design, are all critical components required to accelerate the discovery of therapeutic treatments which may improve function and prevent declines in health before onset of overt clinical disease or disability.

Lack of Personalized Options. Because therapies are developed to treat the average person, individual response is highly variable and multiple drugs are often administered simultaneously to treat *one* age-related condition. A shift is needed toward testing paradigms that allow matching treatments to an individual's unique biology, together with important heterogeneity between individuals in their social and economic circumstances, environmental conditions, physical and functional status, as well as personal care preferences, especially in older adults who are more likely to manage more than one condition or prescription medication. Nonetheless, efforts to target biological aging as a shared risk factor, irrespective of individual circumstance, through interventions that would be broadly accessible and affordable could represent the first and ultimately potentially transformational opportunity to impact healthspan at the population level.

Safety & Feasibility. Older adults tend to be more vulnerable to all stressors, especially those that

are new, including medications. As a result, when new medications are prescribed, a variety of factors, including dosing and pharmacokinetic/pharmacodynamic responses that differ from younger adults, predispose older adults, especially those who are frail and living with multiple chronic conditions, to experience a higher risk of **adverse events**, including loss of function. For this and many other reasons, drug and therapy development often excludes older individuals. Yet this exclusion makes it difficult to evaluate the risk-to-benefit ratio prior to taking some therapeutic treatments to market.

Disparities in Access. Even when effective therapeutics exist, they can be costly and out of reach for many individuals. This is the case in the US, for instance, with gene therapies for sickle-cell anemia projected to cost in excess of US$2.7 million per patient, and modern weight management drugs like the GLP-1 agonist (semaglutide) at US$900 - $1350 per month. Such costs may put undue financial burden on those who most need access. Therefore, **accessibility**, affordability, and practicality of the therapeutic treatment will be factors for decision rubrics considered at each milestone. The XPRIZE Healthspan will not, however, reject outright novel therapeutics based solely on the projected costs of development, should that therapeutic be approved for use, as many factors may drive market cost not foreseen during the competition.

Design and delivery considerations will be encouraged that improve access, from scalability of manufacturing and distribution, to ease of dosing, clear instructions, easy-to-open product packaging, and temperature stability and shelf-life. We are particularly keen to develop therapeutic treatments that can improve aging equitably so that vulnerable populations throughout the globe may benefit.

Diversity, Equity, and Inclusion. Diversity, inclusion, and representation matter to our global societies, science, and clinical research, yet are notable barriers in science. By diversity we refer to the inclusion of persons from all geographic, racial, ethnic, socioeconomic, educational, biologic sex, gender identity, sexual orientation, ability, or age. The global reach and diversity of XPRIZE Healthspan will be measured by: 1) the number of countries and geographic locations of our competing teams; 2) the diversity of our competing investigators and trainees, interns, and staff; 3) the diversity of the communities served by the teams' proposed clinical research centers. Because this is a global competition, we cannot mandate recruitment and retention targets for minority populations as these will vary by geographic location and recruitment **catchment areas**. However, we will proactively support best practices to help teams build diverse and inclusive scientific communities and research participant recruitment.

Imagine a world where widely accessible, safe therapeutics are available to improve function, enhance resilience, and extend healthspan — for all.

2. PRIZE FUNDING & PURSE DISTRIBUTIONS

At time of prize launch (29 November 2023) this competition has raised a total of US$141 million from private individuals and foundations across the world. The funding and its uses break down as follows:

(1) **Healthspan Prize Purse** totaling US$101 million (distributed as indicated below).

(2) **FSHD Bonus Prize Purse** of US$10 million (distributed as indicated below).

(3) Operations budget for all testing, validation and verification, and seven years of operations plus conferences is US$30 million.

(1) HEALTHSPAN

MILESTONE-PRIZE AWARDS:

First $10M Milestone Prize: After 2 years, up to 40 of the registered teams (as selected by the **Judging Panel**) will each receive a $250,000 award (**total of $10M**) to support their ongoing work. The remaining teams are invited to continue in the competition. This award is determined by the judges based upon evidence and materials submitted by teams.

Second $10M Milestone Prize: After 3 to 4 years, up to 10 of the registered teams (as selected by the Judging Panel) will each receive a $1M award (**total of $10M**). The remaining teams are invited to continue in the competition. This award is determined by the judges based upon evidence and materials submitted by teams.

GRAND-PRIZE AWARDS:

10 Year Functional Improvement: Any team who conclusively demonstrates, to the satisfaction of the Judging Panel, a functional improvement of at least **10 years** in all three systems (muscle, cognition, and immune), compared with controls, through a therapeutic treatment lasting 1 year (or less) is eligible to win **$61 Million** of the purse. This purse is paid out only if no team achieves the award at the 15 year or 20 year functional restoration level.

15 Year Functional Improvement: Any team who conclusively demonstrates, to the satisfaction of the Judging Panel, a functional improvement of at least **15 years** in all three systems (muscle, cognition, and immune), compared with controls, through a therapeutic treatment lasting 1 year (or less) is eligible to win $**71 Million** of the purse. This purse is paid out only if no team achieves the award at the 20 year functional restoration level.

20 Year Functional Improvement: Any team who conclusively demonstrates, to the satisfaction of the Judging Panel, a functional improvement of at least **20 years** in all three systems (muscle, cognition, and immune), compared with controls, through a therapeutic treatment lasting 1 year (or less) is eligible to win $**81 Million** of the purse.

(2) FSHD BONUS PRIZE

A bonus purse totalling $10,000,000 will be awarded to the First Place Team on the FSHD Bonus Prize. The best team who conclusively demonstrates, to the satisfaction of the FSHD Judging Panel, an improvement of at least **10 years** in muscle function, compared with controls, through a therapeutic treatment lasting 1 year (or less) is eligible to win the **$10 Million** bonus prize purse.

Please see Section 6 for more information on judging criteria for both tracks.

3. HEALTH AND SAFETY OVERVIEW

Safety is our top priority. Developing and testing therapeutics carries a variety of risks for h**uman subjects** and for animals used in preclinical testing. XPRIZE works with an array of best-in-class professionals to evaluate the appropriate balance of risk and benefit, but each team must secure their own institutional and federal regulatory approvals, data safety monitoring plans, medical oversight, and risk minimizing plans. We will work closely with judges and local officials to ensure the safety of all participants and teams during testing. **Safety stands as the most critical aspect of all testing rounds of this competition.**

Competitors should see Appendix A for guidance on minimum human subjects safety measures for finalist teams, but further details will be released in the **Rules & Regulations**. XPRIZE reserves the right to adjust the Competition Guidelines and Rules & Regulations based on the latest scientific and legal information available at the time to ensure environmental safety and minimized risk to human subjects and animals. XPRIZE reserves the right to disqualify teams who are found to be operating in an unsafe or unethical manner, whether at central or regional testing sites or at their own facilities.

XPRIZE acknowledges the possibility that therapeutics may carry risks of adverse events. Although we believe solutions can come from anywhere, prior to advancing to later stages in the competition, teams will be assessed on their understanding of the inherent risks to human participants in their respective clinical trials. Specifically, teams' risk-benefit analysis plans, regulatory approvals, and plans to assure and monitor participants' safety will be reviewed. Due to the nature of XPRIZE Healthspan testing, teams may be required to obtain insurance coverage as required by their institutions or clinical trials centers. Details will be provided in the **Competitor Agreement** (pending release, 2024).

Competition entries must minimize harm and ensure safety of participants, animals, and communities. All teams must comply with the following requirements:

- Teams will comply with all relevant environmental, health, and safety regulations.
- Teams must ensure compliance with institutional and national regulatory standards for research involving human subjects, and animal testing if used, obtaining all relevant approvals prior to start of studies.
- Teams must obtain any necessary regulatory approvals for drug, device or biologic procurement, development, distribution, and administration as it pertains to their tested solution. Such approvals must be filed with XPRIZE Healthspan administrators and reviewed by judges prior to testing.
- Teams must ensure that therapeutic treatments will not pose more than a minimal risk to trial participants or teams.

4. COMPETITION STRUCTURE

Competing teams will innovate across all aspects of early-stage therapeutic development and testing — from preclinical research and development or epidemiologic evidence, to clinical trials testing in persons 65-80 years of age. The competition consists of two parallel testing and awarding tracks: XPRIZE Healthspan and XPRIZE FSHD Bonus Prize.

XPRIZE Healthspan is a 7-year $101M incentivized competition that will include two milestone prizes awarded in recognition of research and development and proof-of-concept testing phases, and will culminate in final adjudication of the Grand Prize based on testing interventions in a diverse cohort of individuals aged 65-80 years.

FSHD Bonus Prize will focus on Facioscapulohumeral Muscular Dystrophy (FSHD) with a $10M bonus prize based on testing interventions in genetically confirmed FSHD individuals aged 50-80 years.

Teams may register to compete in one or both tracks. Refer to Section 2 for details about all **prize purses**. An independent Judging Panel will be assembled to evaluate each stage and adjudicate the winning team(s) based on **Finals Testing** criteria.

COMPETITION STAGES & MILESTONES

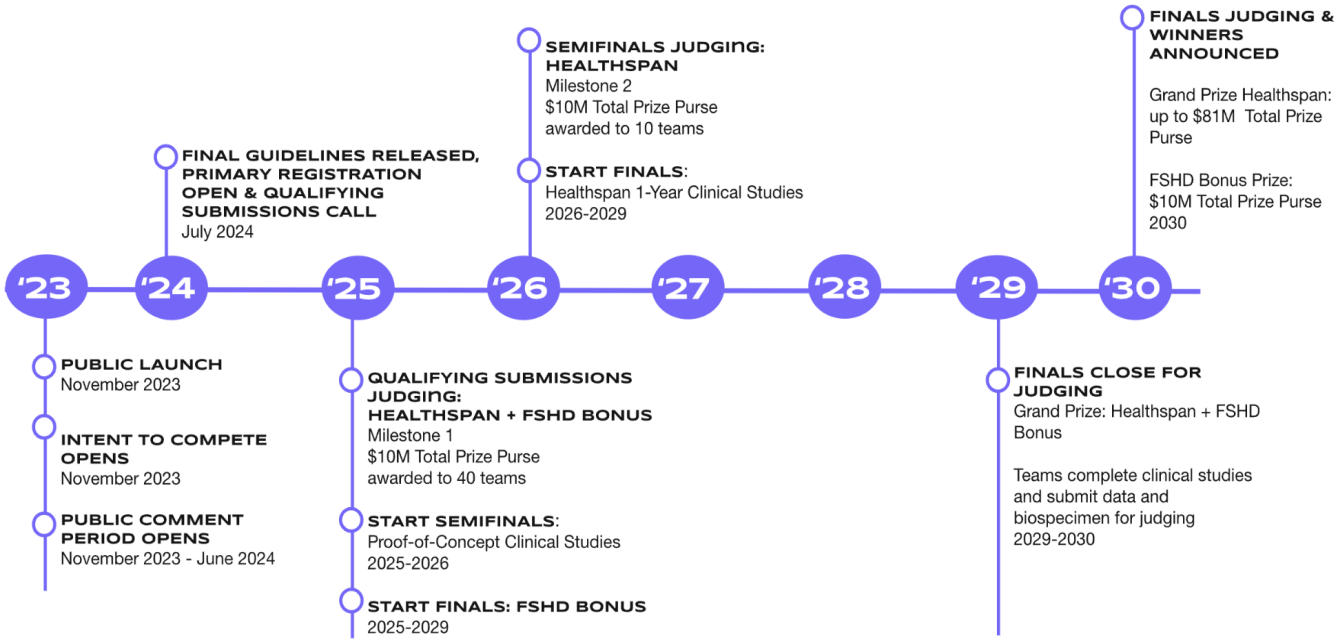
Competition Milestone dates may be subject to change. The following tables are intended to provide an overview of major competition milestones.

XPRIZE Healthspan will take place over 7 years with 2 milestones along the way. Following deliberation with the **Judging Panel**, XPRIZE will directly notify all teams who are selected for awarding of each milestone prize. The FSHD Bonus Prize will follow the same general timeline. An additional 12 months will be devoted to amplifying the impacts of XPRIZE Healthspan and sharing data banked in the common **XPRIZE Healthspan Data Coordinating Center**.

Table 1. Competition Summary Table

XPRIZE Healthspan	FSHD Bonus Prize
• Intent to Compete • Team Registration & Qualifying Submission • Semifinals: Proof of Concept Clinical Studies • Finals: 1 Year Clinical Study Testing • Finals: Judging Period • Scaling & Impact	• Intent to Compete • Team Registration & Qualifying Submission *(no Semifinals)* • Finals: 1 Year Clinical Study Testing Period • Finals: Judging Period • Scaling & Impact

FIGURE 1. Competition Timeline



Milestone 1. Qualifying Submission - Research & Development

To be eligible to compete and win a Milestone 1 award, teams must establish necessary preclinical and research and development data guiding the therapeutic treatment. Teams are required to submit a proposal for their therapeutic treatment and participation in the prize, including data and evidence of progress to date, regulatory requirements, and pathway to achieving testing in clinical studies in participants aged 65-80 years. Submissions are due on January 31, 2025. Specific evaluation criteria and Qualifying Submission forms will be released in early 2024. All teams may continue in the competition, but up to 40 teams will be chosen as Semifinalists and share a Milestone 1 prize purse of $10,000,000 (e.g., $250K each for 40 awarded teams).

Note, Semifinals will not be conducted in FSHD Bonus Prize; teams will advance from Qualifying Submission to Finals Testing (1 Year Clinical Studies) for FSHD following qualifying submission.

Milestone 2. Semifinals Testing - Proof of Concept Clinical Studies

Proof of Concept Trials of up to 60 days to show feasibility of approach, safety, and early estimates of effect in two of the primary target areas (muscle, cognitive, immune function) that suggest next stage phase II trials are warranted. Teams will be responsible for submitting regulatory and human subjects safety approvals, data and safety monitoring reports, evidence of target engagement or pharmacodynamic / pharmacokinetic response (if necessary for novel drugs), or to submit drug labeling for repurposed agents, or comprehensive instructions provided to human subjects for dietary / lifestyle / behavioral interventions. Teams must provide evidence that it will be feasible to enroll and retain participants meeting their Inclusion and Exclusion Criteria in proposed trials. Up to 10 teams will be chosen as Finalists and share a Milestone 2 award of $10,000,000 (e.g., $1M each for 10 awarded teams).

Note, Semifinals will not be conducted in FSHD Bonus Prize; teams will advance from Qualifying Submission to 1 Year Clinical Studies Finals Testing for FSHD following qualifying submission.

Finals Testing - 1 Year Clinical Studies

To be eligible to win the Grand Prize, teams must recruit participants and conduct prospective clinical studies with a 1 year (or less) intervention or therapeutic treatment period in persons aged 65-80 years without major life-threatening conditions or disability. To be eligible to win a Grand Prize, teams must demonstrate their therapeutic solution can restore muscle, cognitive and immune function (all three) using clinical protocols with detailed information appended to the Rules & Regulations document. Prior to the start of Finalists' trials, the assessment measures and specific adjudication criteria for awarding will be made available and teams must prespecify all design criteria that may impact outcome or awarding. Data must be recorded in a central XPRIZE Healthspan determined database. A pre-specified set of biospecimens will be collected in research participants at repeat timepoints using standard operating procedures; these will be held in

regional or central biobanks. XPRIZE will support operations and analyses for data and biomarker determination used for judging of the Grand Prize. Teams can collect additional data and or biomarkers as needed for their study as long as it does not impede validity of measures needed for Judging.

For awarding, the magnitude of the improvement across all three systems compared with controls will be indexed against expected declines over 10 years, 15 years, or 20 years in a referent **population**. Please see Section 6 and subsection Finals Judging for details.

Table 2. XPRIZE Healthspan and FSHD Bonus Prize Detailed Timeline
(November 2023 – December 2030)

Date	Event or Activity	Details & Requirements
INTENT TO COMPETE		
November 29, 2023	Official Competition Launch	Team Pre-Registration Opens, Preliminary Competition Guidelines Released
November 2023 to June 2024	Public Comment Period	Comments may be sent to healthspan@xprize.org
PRIMARY REGISTRATION & QUALIFYING SUBMISSIONS		
July 2024	Published Official Competition Guidelines	Published Competition Guidelines and Application for Qualifying Submission released **$500 Intent to Compete Fee** (Will be rolled over to Primary Registration Fee) Competitor Agreements available (see Team Registration)
July 2024 - December 2024	**Primary Registration Period**	**Primary Registration Deadline: January 1, 2025, USD $1000. Signed Competitor Agreement required with payment (see Team Registration)**
August 2024	Teams and Biomarker Summit	In-person and/or virtual meetings
December 2024		Detailed Qualifying Submission Deadline for Judging and Milestone 1 Award (see Competition

	Qualifying Submission Deadline	Stages)
March 2025	Qualifying Submission Judging (Healthspan and FSHD Milestone 1 Awards)	Independent Judging Panel reviews submitted qualifying materials for both XPRIZE Healthspan and FSHD Bonus Prize
March 2025	Teams and Biomarker Summit Semifinalist Teams Announced	In-person and/or virtual meetings Up to 40 Healthspan Teams will share Milestone 1 prize purse (see Prize Purses) Qualified FSHD Teams will advance to Finals (there are no Semifinals or Milestone Awards for the FSHD Bonus Prize)
SEMIFINALS, PROOF OF CONCEPT STUDIES		
March 2025	Semifinals Discretionary Late Registration Open	Late Registration Fee, **USD $10,000** See Team Registration for details
February 2026	Data Submission for Healthspan Semifinals Testing and Judging (Milestone 2 Award)	Independent Judging Panel reviews submitted qualifying materials for XPRIZE Healthspan
April 2026	Semifinals Submission Judging (Milestone 2 Award)	Independent Judging Panel reviews submitted qualifying materials XPRIZE Healthspan
May 2026	Teams and Biomarker Summit Finalist Teams Announced	In-person and/or virtual meetings Up to 10 Healthspan Teams will share Milestone 2 prize purse (see Prize Purses)
FINALS, 1 YEAR CLINICAL TRIALS		
January 2026	Finals Discretionary Late-Registration Open	Late Registration Fee of **USD $100,000** to support ad hoc Judging Panel review and onboarding costs
June 2027	Finals Discretionary Late-Registration Closes	Last competition entry period closes
2027 - 2029	Teams Summit & Interim	In-person and/or virtual meetings to foster

	Reporting	collaboration opportunities and align resources and assessment measures
January 2030	Initiate Finalists Study Close-Out	Prepare finalist teams for clinical studies close-out and Finals judging procedures
April 2030	Data Submission Deadline for All Finalist Teams	Final data and specimen submissions XPRIZE Healthspan teams Final report submission from XPRIZE FSHD Bonus Prize teams
September 2030	Finals Judging	Independent Judging Panel review submitted finals materials XPRIZE Healthspan and FSHD Bonus Prize
November 2030	**Final Award Ceremony and Winners Announced**	**The winning teams from XPRIZE Healthspan and FSHD Bonus Prize announced**
2030 - 2031	Post-Competition Scaling and Impact	Analyses continue and impact reporting continue for 1 year post-prize

5. HOW TO COMPETE: TEAM REGISTRATION

Taking part in an XPRIZE competition is an exciting and challenging journey that requires a significant commitment of time, expertise, and resources. XPRIZE will frame and guide parameters for the final testing demonstration through clinical trials; each team will be responsible for the total costs of their participation in the competition, including R&D, general operations, and travel among other costs.

XPRIZE competitions are driven by multidisciplinary teams of innovative groups and individuals, composed of subject matter experts, enthusiasts, start-ups, student teams, and all problem-solvers in between; a winning idea can come from anywhere. However, given the nature of the competition and resources required to develop therapeutics and conduct clinical trials, we anticipate that most of our teams will come from federally- and philanthropically-funded academic teams and institutions, private research institutes, for-profit biotechnology and pharmaceutical companies, or other established organizations.

Teams and individuals are encouraged to collaborate and combine skills during the competition. Teams may recruit additional experts and are permitted to add new members to their team at any time throughout the competition. Teams may also merge with other teams at any time during the competition, especially to add technical and subject matter expertise to their roster. Teams must notify XPRIZE 10 days before a merger. In the case of mergers, teams must determine which legal entity will remain in the competition and assign one Team Leader. Additional details regarding team mergers are provided in the Competitor Agreement.

To support team collaboration, XPRIZE will host informational sessions and facilitate team summits, and may suggest that teams merge to form a more robust or interdisciplinary team. These sessions will allow teams to get to know each other and receive important competition updates. All **Interested Teams** are encouraged to join, but participation in these sessions is not mandatory.

How to Register a Team

To participate, all teams must first create a Team Account and log in to the Prize Operations Platform (POP). POP is an online platform through which teams will register for the competition and complete all required activities. All teams must appoint a Team Leader, who will be responsible for maintaining communications with XPRIZE. Teams are expected to maintain their POP profiles throughout the competition, ensuring their profile shows the most recent team information, including an active email address.

Teams may register to compete in either XPRIZE Healthspan, FSHD Bonus Prize, or both. Progress and success in one track do not imply commensurate progress or success in the other, and vice versa, however, there may be synergy between tracks.

To remain eligible to compete, teams must complete the registration form, submit a Competitor Agreement, and pay a registration fee by the appropriate Registration Deadlines. Teams must complete all required activities within each respective track throughout the duration of the competition.

Teams may register and advance through the qualifying submission round with more than one candidate therapeutic treatment if they define their screening approach *a priori*. This screening must be used to identify a distinct therapeutic treatment (drug, biologic, device, gene therapy, or dietary or lifestyle intervention, alone or in combination; see Therapeutic Treatments) to test for Finals.

Teams may decide that they possess more than one idea and wish to submit multiple entries. Multiple simultaneous competition entries are permissible, but 1) each entry must represent a distinct therapeutic treatment, and 2) each distinct therapeutic treatment must be submitted by a unique contact Principal Investigator. Please refer to the Competitor Agreement for more details.

As of the date of submission of the Competitor Agreement, each Team must own, or hold appropriate license rights to, all technologies, methods, resources, and Intellectual Property included in the Team's submission. Please refer to the Competitor Agreement for more details.

Any person or entity can participate in the Competition, no matter their citizenship or nationality, unless prohibited by US law—see Sanctions Programs and Country Information | US Department of the Treasury. If a Team has a Team Member who is ordinarily a resident in such destinations, it will be up to the team to obtain a license of authorization issued under US Law. Government entities are not allowed to compete.

Registration Submission

Each team will complete a Registration Submission. The Registration Submission activity will be assigned to teams in POP automatically upon creating a team profile. This submission will be used to obtain an initial landscape of competitors, and to support the facilitation of collaboration opportunities between teams. The aggregate information from these submissions may be shared to support team collaboration opportunities. XPRIZE Healthspan will not distribute specific details about any team without permission.

The Registration Submission will ask about the following:

- Team composition (e.g., number of expected team members)
- Proposed solution focus areas (e.g., device, biologic, etc.)
- In what areas of technical or subject matter expertise is your team seeking support?
- Is your team open to collaboration opportunities?

Registration Submissions are due by the standard registration deadline of each competition track but it is recommended to complete the submission sooner.

XPRIZE encourages teams to begin designing their technologies at the earliest opportunity in preparation for the Qualifying Submissions of their respective track(s).

Registration Fees

Registration fees are required as a simple qualifier to ensure competitors can obtain the appropriate resources to fully compete in the prize. All fees collected go toward supporting post-prize efforts, including **Alumni Network** development and prize impact work. Team Registration must take place by the registration deadlines below.

Registration Fee: USD $500 for Intent to Compete, $1000 for teams to register and sign a Competitor Agreement ($500 from Intent to Compete will be applied toward registration)

Registration Dates:

- Intent to Compete: November 29, 2023 - June 30, 2024
- Primary Registration: July 1, 2024 - December 31, 2025
- **Discretionary Late Registration**: January 1, 2025 to Finals testing start

XPRIZE has sole discretion to register and qualify additional teams across XPRIZE Healthspan and FSHD Bonus Prize from the close of their respective registrations until the Discretionary Late Registration deadline. Teams that register during this period must meet all preceding registration and submission requirements and pay a late registration fee between USD $10,000 (Discretionary Late Registration after Milestone 1) and $100,000 (Discretionary Late Registration after Milestone 2). *XPRIZE strongly encourages teams to register before the regular registration deadline. There is no guarantee late registration will be granted to a team.* Potential teams should contact XPRIZE directly for more details.

If teams are unable to fund the registration fee, please inquire with XPRIZE Healthspan for hardship allowances or considerations.

Competitor Agreement

To be considered to advance to subsequent stages of the competition, all registered teams are

required to sign the Competitor Agreement to acknowledge the terms expected of teams upon entering the competition. This document contains vital information detailing the requirements teams must meet to remain eligible for the competition. Competitor Agreements will be signed when a team makes their registration fee payment. The Competitor Agreement will be available for teams to peruse before signing.

6. HOW TO WIN: EVALUATION CRITERIA FOR FINALS

Finals Testing Framework

NOTE: XPRIZE Healthspan is intended to be a radically collaborative effort, and that begins with Public Comment. Content below is subject to change based on feedback from teams, stakeholders, regulatory officials, community members, and advisors. This preliminary Finals Testing Framework was informed by a panel of Scientific and Technical Advisors (Appendix E). Further details will be found in updated Competition Guidelines and Rules & Regulations that will be released following the public comment period (November 2023 to June 2024).

Teams will conduct 1 year clinical studies to determine if their therapeutic treatment improves muscle, cognitive, and immune function. The **Population, Interventions and Control, Outcome for Grand Prize, and Time (PICOT)** format is used below to frame the trial requirements. Teams will define the elements and **protocols** of their Finals study design, including sample size estimates. PICOT elements are summarized briefly below and linked to subsequent sections. Protocols, statistical plans, and testing location(s) (Clinical Centers) will be reviewed by XPRIZE during **Finalist Verification**.

Population. XPRIZE Healthspan's primary eligibility criteria are persons who are aged 65-80 years, free of major or life-threatening disease and disability. Participants may have some evidence of functional decline, which would improve the likelihood of observing an improvement in function over 1 year. **FSHD Bonus Prize** competitors will recruit persons aged 50-80 years with a genetically confirmed diagnosis of FSHD. See Participant Enrollment and Retention.

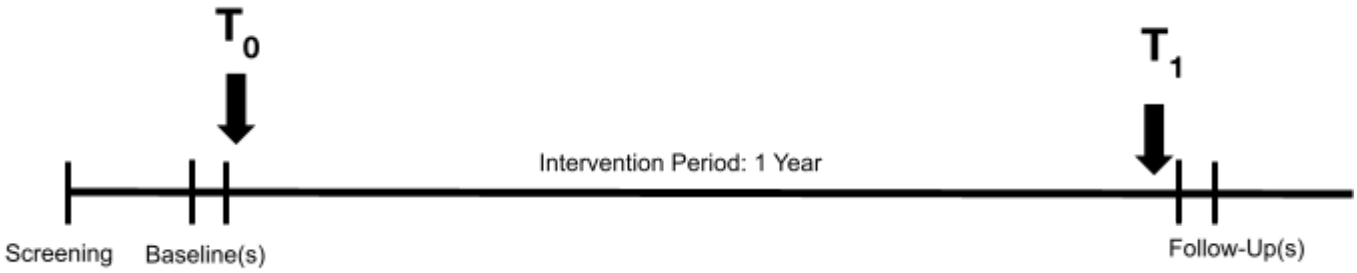
Interventions. In the context of XPRIZE Healthspan, "therapeutic treatments" refers to drugs, biologics, devices, gene therapies, nutritional supplements, dietary interventions, lifestyle interventions or other approaches - alone or in combination. This list is not exhaustive. Frequency and duration of treatment or therapeutic combinations during the 1 year treatment period are at teams' discretion per their therapeutic intervention and study design. See Therapeutic Treatments. When possible, assignment to treatment arms should be masked.

Control. Teams are encouraged to identify the trial design that best suits their therapeutic treatment; however, whether parallel group designs, n-of-1, or adaptive approaches are used, the design must include defined and sufficient controls to minimize confounding and bias results. An alternative could involve a multi-arm trial with common controls, consistent measurement intervals

and measurement protocols to ensure uniformity. When possible, assignment to treatment arms should be masked.

Outcome. The outcomes are changes in assessments of muscle, cognitive, and immune function relative to control, and supported by safety, accessibility / scalability, and biomarkers data. Determinations of specific assessments will be made by a panel of experts (Appendix E) following a period of public comment (November 2023 to June 2024). See Outcomes and Endpoints for more information on potential outcome measures. Data analyses will be performed by central adjudication and data collated by the XPRIZE Healthspan Data Coordinating Center. Teams will be notified when the final outcome measures are selected. **FSHD Bonus Prize** outcomes are based solely on FSHD Bonus Prize criteria, including muscle function as defined by the FSHD Judging Committee.

Time. The therapeutic treatments for both tracks will be evaluated in a 1 year intervention window. Randomization coincides with time point T_0. Judged follow-up testing corresponds with time point T_1, 1 year (12 months) after T_0. Midpoint data collection (e.g., 3 months, 6 months) for primary outcome measures may be required. Safety monitoring, adverse event tracking, patient-reported outcomes, and adherence measures will also be assessed during the intervention based on a schedule determined prior to Finals, but not used as primary outcomes for award adjudication. Frequency and duration of treatment or therapeutic combinations during the 1 year period is at teams' discretion per their therapeutic intervention and study design.



Reminder: Further details will be found in updated Competition Guidelines that will be released following the public comment period (November 2023 to June 2024) and Rules & Regulations.

FINALS PARTICIPANT ENROLLMENT AND RETENTION

Overview of Participant Enrollment

Participants in the finalists trials must be 65-80 years of age. Potential participants with treatable diseases such as hypertension or diabetes will need to have those diseases managed successfully to within acceptable limits prior to enrollment. Research participants may have evidence of some non-disabling, mild, age-related decline in function or health, which may increase the likelihood of measurable improvements with a 1 year therapeutic treatment time frame. Specific eligibility criteria are described in Appendix B, as are example recruitment and monitoring guidelines (Appendix C).

Based on the known natural history of FSHD, enrollment for **FSHD Bonus Prize** is suggested to begin at a younger age (50 years) in participants with genetically confirmed FSHD (via D4Z4 Repeat Units or D4Z4 region methylation level) without other comorbidities.

Participant Recruitment

Enrollment of participants in Finalists' trials will be performed by a team's Clinical Center or, if needed, an XPRIZE independent clinical testing center. An estimate of the number of participants enrolled and randomized will be provided by teams. The Judges Panel will review sample size calculations and power analyses and evaluate the feasibility of achieving the specified sample size. The sample size required will be for teams to determine based on estimated therapeutic effects. It is anticipated that 40-200 total participants will be required to achieve the large effects required to win the Grand Prize.

Participant recruitment targets should strive for balance in sex (ideally, 50% female, but 40-60% balance is acceptable with accommodation for intersex individuals) and also in ethnic and racial composition reflective of the geographic region. Teams should proactively incorporate best practices to build diverse and inclusive research participant recruitment strategies, and XPRIZE Healthspan will actively seek additional support to incentivize diversity.

Run-In Period (Optional)

At the competing team's discretion, a run-in period may be used to evaluate safety concerns or potential responses to a therapeutic, or to detect poor adherence or retention; justification and specific protocols for run-in should be reviewed and approved by Judges.

Monitoring Retention

Adherence to treatment and control conditions is important to minimize bias in the outcomes of the trials. Adherence to scheduled clinic visits and the corresponding windows surrounding assessment dates will be systematically monitored by the **XPRIZE Healthspan Data Coordinating Center** and contained in regular reports for interim review and judging.

THERAPEUTIC TREATMENTS

Therapeutic Treatments Description

The competition is designed to incentivize the development and testing of novel therapeutic treatments. In the context of XPRIZE Healthspan, therapeutic treatment categories can refer to the following:

- Medicinal drugs - can be investigational new drugs or repurposed drugs or medicines already prescribed for other indications
- Biologics - such as vaccines, immune modulators, monoclonal antibodies, blood and blood components, allergenics, and recombinant protein therapeutics
- Devices - such as novel medical therapeutic devices, game-based devices, digital health devices, and devices to deliver specific exposures
- Gene and cell-based therapies
- Electroceuticals and magneceuticals
- Nutritional supplements and nutraceuticals
- Dietary or lifestyle intervention approaches
- Other innovative interventions
- Varied combinations of the above

This list is not exhaustive. Also, the therapeutic treatments can be proposed for use alone or in combination. Our Judging Panel will review therapeutic treatments from teams' Qualifying Submissions for safety, feasibility, and appropriateness for testing within the competition. In each case the teams must demonstrate adequate preclinical evidence, *in-vivo* testing in mammals, safety and tolerability in humans, and feasibility for use of solution in clinical trials and by the general population if approved for market in future trials. Please refer to Section 3 and Appendix A for human subjects safety information.

FINALS TESTING OUTCOMES AND ENDPOINTS

The main outcome for Grand Prize adjudication is operationalized as the change in assessments of muscle, cognitive, and immune function - all of which are affected by aging - relative to control. Each of these functional domains are multifaceted. We expect that each functional domain will be evaluated based on a set of appropriately validated assessment measures; examples are given below and a definitive set will be provided to teams in the **Rules & Regulations** for Finals testing. For example, for the purposes of this prize muscle function represents a functional domain that is inclusive of measurements such as exercise capacity, walking speed, and strength, among other possible measures. Similarly, cognitive function will be assessed based on a specific set of neuropsychological assessments, and immune function based on immune cell and/or protein counts or phenotyping, circulating cytokines, or response to vaccine.

The specific assessment measures will be determined following a public comment period (see Competition Stages and Milestones for timeline) in consultation with scientific and technical advisors (Appendix E), independent investigators, potential teams, and regulatory officials. The same instruments will be used in all Finals clinical studies, with repeat assessments at baseline and 1 year follow-up. Assessors, data collectors, and similar team staff and investigators should be masked to treatment conditions during evaluations to whatever extent is possible.

The measures must be supported by critical evaluation of test-retest reliability, feasibility of use, and quality of existing data. The measures should be meaningful to the general population and predictive of future risk of clinical outcomes relevant to healthspan, like hospitalization, incident disease, disability, or mortality. Each of the assessment measures will also need to have established normative data per decade in older adults and, ideally, normative data on longitudinal change that can be used to evaluate anticipated population-level change per decade. All teams will be required to include the specific assessment measures detailed in the *to be developed* **Rules & Regulations** clinical protocols for Finals Judging.

Example Specific Assessment Measures

Muscle Function. Example measures of muscle function include:

- 6 minute walk test or 400 meter corridor walk distance
- Cardiopulmonary Exercise Testing (CPET) to assess VO2 peak
- Stair climbing power
- One repetition max (1RM) or knee extensor strength
- Muscle mass measurements by deuterated creatine (D_3Cr) or muscle volume by MRI
- Grooved pegboard test
- Short Physical Performance Battery (SPPB)
- Other

Cognitive Function. Example measures of cognitive function include:

- Montreal Cognitive Assessment (MoCA)
- Digit Symbol Substitution Test (DSST)
- Logical Memory Test (Delayed Paragraph Recall)
- Alternative tests appropriate for culture and language that test global cognition, psychomotor speed, working memory, and short and long-term memory
- Other

Immune Function. Example measures of immune function include but are not limited to:

- Pro-inflammatory and anti-inflammatory cytokine panels
- Naïve to memory T cell ratio
- Percentages and absolute values of T cell subsets in blood (CD4, CD8, gamma/delta T cells and differentiation states thereof)
- Percentages and absolute values of other immune cells in blood (B cells, NK cells, NKT cells, DCs etc.)
- CD4+/CD8+ T cell ratio
- Subsets of cells (e.g. NK, CD8+ T cells) expressing cytotoxicity profiles (e.g., GZK, PRF1)
- Differential white blood cell counts (WBC)
- Lymphocyte to granulocyte ratio
- Antibody response to a vaccine or test challenge
- *In vitro* assays of immune cell function including cell-mediated responses to a vaccine or test challenge
- Evidence of chronic viral burden influencing immune function (e.g., CMV, EBV, HIV)
- Other

FSHD Bonus Prize Outcome

In FSHD, there is an asymmetric and progressive muscle weakness and a disease pathology characterized by fat infiltration and ultimately fibrosis associated with the loss of muscle mass. Current treatments in FSHD are focused on showing reduced fat infiltration in muscle and corresponding improvements in muscle function. Muscle-related endpoints that have been tested in FSHD clinical trials include:

- Muscle fat fraction
- 6 minute walk test
- Gait speed
- Grip strength
- Knee extensor maximum voluntary contraction (MVC)
- Timed up and go
- Revised Upper Limb Module
- Reachable workspace
- Other

Additional Assessment Measures and Judged Criteria

Safety, Tolerability, Scalability.

We will evaluate adverse events, tolerability (e.g., patient reported and study drop-out), and feasibility to scale-up testing and use (e.g., accessibility, ease of administration). See Appendix A. Adverse Events will be reported by sites to the XPRIZE Healthspan Data Coordinating Center based on common reporting criteria set by regulatory authorities and prize guidelines. Additional measures will be based on self- and proxy-report, clinical assessments, standardized questionnaires, and laboratory assays. Protocol deviations that impact participant privacy and safety will also be evaluated. Long-term safety is an important issue, but given the nature of the prize, safety monitoring for prize adjudication is restricted to the 1 year follow-up period, though XPRIZE will remain in contact with all Finalists through an XPRIZE Alumni Network. Long-term monitoring is the sole responsibility of the competing teams, as is safety during the competition.

Biomarkers and Clinical Risk Factors.

Judges may consider additional biologic measures, biomarkers of aging, and clinical risk factors (e.g., cardiometabolic, renal, bone, and anthropomorphic measures) that are predictive of major age-related chronic diseases. Biospecimens or circulating/excreted drug levels may also be used to evaluate adherence if needed and depending on the therapeutic. However, these measures will not be included in the functional domain scores. Biomarker Summits to discuss biomarkers of aging will be held annually during the Competition - all Competing Teams will be invited to participate.

FINALS JUDGING

In order to win XPRIZE Healthspan, teams will measure changes in muscle, cognitive and immune function. The magnitude of functional improvement observed in the treatment group(s) relative to control will be used for awarding based on pre-specified thresholds that will be provided to teams prior to Finals testing. Awards will be indexed against the expected 10, 15, and 20 year declines in established referent populations for each domain. Judging will proceed in two parts:

(1) **Improvement in Function Relative to Control** (hypothetical examples in **Figure 2,** next page). The Judges will evaluate the change in function during the 1 year clinical trials with therapeutic treatment relative to control for each assessment measure. To be eligible for the Grand Prize, the changes in function measured in the treatment group will be significantly greater than the changes in function observed in controls in all three domains (not corrected for multiple comparisons; see Power and Statistical Considerations).

(2) **Magnitude of Improvement Relative to Expected Decline in Referent Population** (hypothetical examples in **Figure 3**, next page). If all three domains show a statistically significant difference compared with control, the team is eligible for awarding. For the tiered awarding, the magnitude of the observed changes will be indexed against expected functional changes per 10 years, 15 years, or 20 years in a sex-stratified referent population.

Preliminary Rationale for Longitudinal Declines in Function. Our current referent cohort examples were derived from literature and well-characterized cohort studies with longitudinal assessment of older adults (unpublished, pending comment). Our in-development models suggest that while cross-sectional declines in function with age are non-linear, longitudinal changes in the 60-80 year age-range are “quasi-linear” but the rate of change is sex-specific. If the assumptions in our initial modeling hold for all to-be-determined assessment measures, then it is possible to compare the changes in 1 year (relative to control) with the magnitude of the quasi-linear longitudinal rate of change in a sex-stratified referent cohort (see **Figures 2 and 3**, next page). **We invite public discussion regarding assumptions and actively seek additional referent cohorts for indexing.** While cohorts with well-characterized longitudinal data such as the Baltimore Longitudinal Study on Aging (BLSA) may or may not be an ideal referent cohort for a given team’s recruited population, referent data considerations will be vetted during the public comment and judging. Projected rates of decline for each functional measure and thresholds required for change will be provided to teams within the forthcoming **Rules & Regulations.**

Figure 2. Improvement in Function Relative to Control

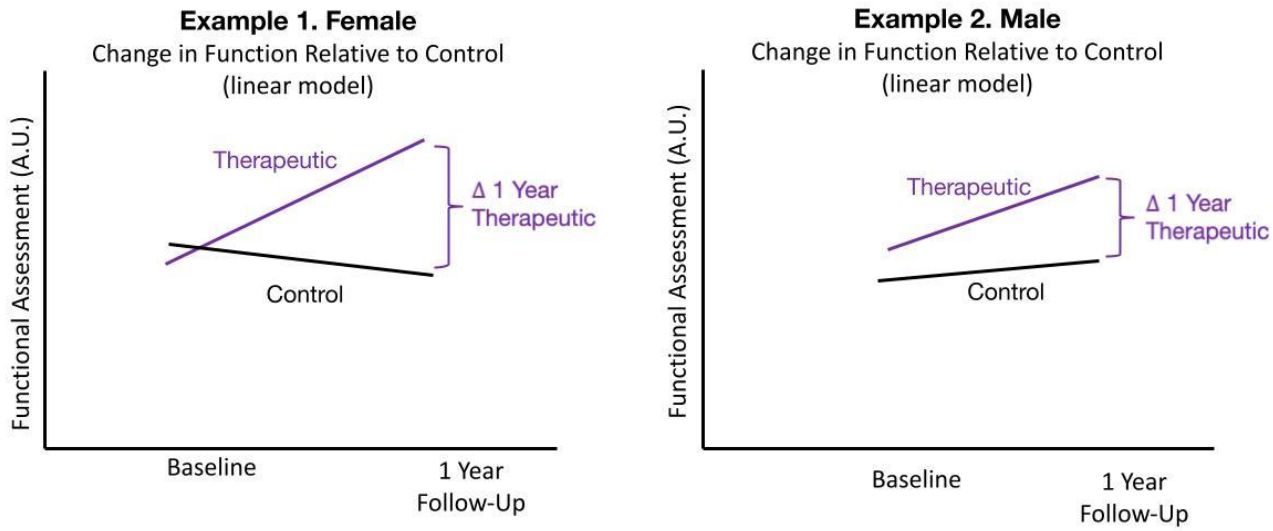
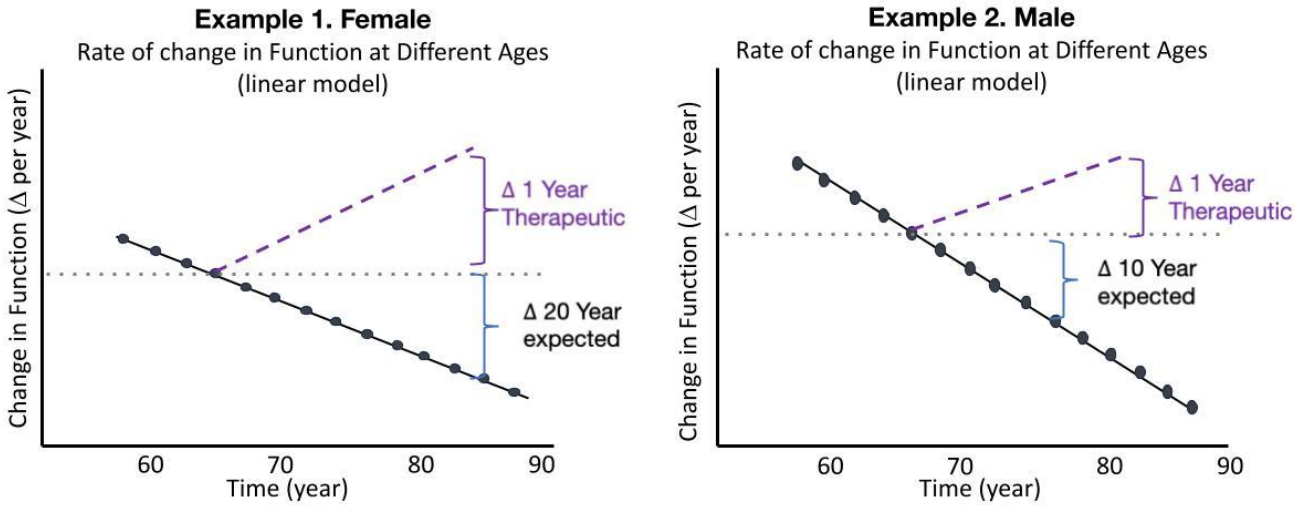


Figure 3. Magnitude of Improvement Indexed to Expected Decline in Referent Population



Example assumes men and women have linear rate of change in function with age

Domain-level scoring will be determined following the public comment period and additional modeling using selected functional measures. However, an example of a potential scoring system using binary semi-quantitative determinations is provided below to illustrate the judging concept. A domain score could be based on a fixed number of measurements (e.g., 3 assessment measures) per functional domain. Teams will first demonstrate that their therapeutic improves each measure relative to control, then the judging team will evaluate the effect sizes against referent data. For each assessment measure, the following logic could be applied:

- if test value improves relative to control = 1, else 0
- if 1, then magnitude test value > magnitude 10 yr declines in referent = 10, else 1;
- if 10, then magnitude test value > magnitude 15 yr declines in referent = 15, else 10;
- if 15, then magnitude test value > magnitude 20 declines in referent = 20, else 15.

Points will be tallied per domain. To be awarded the full $81M Grand Prize, teams must score in the 20 Year category in all 3 domains. An example judging score card is shown in Table 3, and is used for illustrative purposes only and subject to change.

Table 3.

Judging Card	10 Year ($61M)	15 Year ($71M)	20 Year ($81M)
Muscle Score:	Score 20 – 44	Score 45 - 59	Score ≥ 60
Cognitive Score:	Score 20 – 44	Score 45 - 59	Score ≥ 60
Immune Score:	Score 20 – 44	Score 45 - 59	Score ≥ 60
Non-Scored Judge Considerations: 1) Safety, Tolerability, Accessibility of Therapeutic 2) Biomarkers and Clinical Risk Factors 3) Legal / Ethical Considerations			

FSHD Bonus Prize Criteria. Based on current available information in the literature, the winning team of the FSHD Bonus Prize should show:

- a 10% reduction in muscle fat fraction relative to control
- AND a 25% improvement in at least three of the functional muscle tests listed in the FSHD-specific outcomes section. One of the functional endpoints can be a novel, validated clinical outcome measure that has been designed using AI or other novel approaches. See Appendix F for FSHD Bonus Prize criteria.

Notwithstanding the foregoing, prior to any part of the FSHD Bonus being provided directly from the Sponsor to such Bonus Winner, the Sponsor must: (i) be provided with key data, methodology, breakthroughs, and limitations regarding the research of the Competing Teams by the FSHD Bonus Judging Panel; (ii) be provided with the Competing Team Summary Reports; and (iii) have decided to approve the Bonus Winner selected by the FSHD Bonus Judging Panel.

POWER & STATISTICAL CONSIDERATIONS

Statistical and Analytical Plans

Teams are required to submit their own detailed statistical and data analysis plans prepared as a separate document early during the competition, which will be reviewed and approved by the XPRIZE **Advisory Board**. XPRIZE will not create plans for teams but will review them as outlined in the Rules and Regulations. If a team does not have a biostatistician (highly recommended) a list of consultants will be provided by XPRIZE. If the statistical plan does not meet the rigor required for Finals Testing, the XPRIZE Judges Panel may discontinue a team's involvement.

The XPRIZE Healthspan analytical approach is governed by rigorous principles of clinical trial design. Teams should undertake extensive and careful planning prior to initiating data collection. We encourage teams to be creative and innovative in their clinical trial design with the expectation that they will provide a strong justification of the statistical approach given the therapeutic. Some key analytic features of successful clinical trials include *a priori* sample size calculations, detailed randomization and stratification schema, bias minimization, control of Type I and Type II error, and intent-to-treat analyses, with potential attrition and loss to follow-up addressed. We will not require adjustments for multiple comparisons for the outcome measures. Research questions, hypotheses, and interim monitoring rules should be pre-specified.

Statistical Hypotheses

The primary null hypothesis of each of the trials performed in consideration for the Finals Testing in XPRIZE Healthspan is that the change in muscle, cognitive, or immune function is the same between treatment and control. In order to be considered for the Grand Prize, teams must show a statistically significant improvement in the treatment group relative to control. Depending on trial design this could be a time-control group, standard of care, or the participant may serve as their own control.

For awarding, the magnitude of the observed improvement in each of the three domains must be equal or exceed established 10, 15, or 20 year expected declines observed in well-defined referent populations in each functional domain (see Finals Judging). These effect sizes will be provided to teams and described in the **Rules and Regulations** and will be made available during the primary registration period.

Rates of all adverse events will be reported for treatment and controls. Serious adverse events will also be reported.

Analysis Datasets

Teams that qualify for the Finals will be required to enter data into a centralized data repository via the **XPRIZE Data Coordinating Center**. Finalist teams will be trained on how to enter their trials

data. Several datasets will be prepared by the XPRIZE Data Coordinating Center for each of the Finalist teams. These may include, screening, baseline, monitoring, analysis, public use, and special use datasets.

Safety Analyses

Adverse events will be coded using a standardized medical dictionary, to be determined prior to Finals (e.g., Medical Dictionary for Regulatory Activities (MedDRA)). Safety data will be regularly monitored by the Competing Teams and their regulatory and safety oversight committees to identify any issues related to participant safety and trial conduct. This includes adherence to safety alert protocols set by the teams.

Both serious adverse events and selected adverse events of interest will receive special focus as safety requirements for XPRIZE Healthspan. Rates of serious adverse events and (non-serious) adverse events (per person-years) and rates of participants with at least one event (percent) will be reported. Reports will include physician-based determination of the relationship of events to therapeutic administered and actions taken. Adverse events will be tallied overall and by organ system.

Tabulation of Individual Response Data

No data will be publicly reported at the level of an individual to protect confidentiality.

WINNERS ANNOUNCEMENTS

Following Finals Testing in each track, the Judging Panel will convene to review and discuss the results and determine the winners of the Grand Prize and the FSHD Bonus Prize. The winning team(s) will be announced in a Final Award Ceremony.

POST-PRIZE IMPACT

The awarding of this XPRIZE marks the recognition of an audacious breakthrough with the potential to put humanity on a course to realize the vision where healthy human aging is made possible and accessible to all. To realize this potential, XPRIZE will work with partners to address some of the most pressing innovation barriers - from regulatory hurdles, through access to investment, to therapeutic delivery and accessibility opportunities. Scaling impact activities will be offered to competing teams throughout the competition, while Finalists teams will receive additional support following the awarding of the XPRIZE Healthspan.

Alumni Network

By registering to compete in an XPRIZE competition, teams will automatically be enrolled into the XPRIZE Alumni Network. This **Alumni Network** will allow XPRIZE to communicate with and support competitors after the competition is completed. The objectives of the Alumni Network are to monitor post-prize impact; to support and scale team solutions; to create opportunities for networking among alumni and with XPRIZE's partnership ecosystem; to provide continuing education for competitors; to invite and engage alumni in various conferences and events. At any point in time, where a competitor no longer wishes to be an alumnus of XPRIZE, they may opt out of the Alumni Network.

7. ROLES & RESPONSIBILITIES

COMPETING TEAMS

GOOD STANDING. Teams must register their intent to compete on the XPRIZE Prize Operations Platform (POP), sign the Competitor Agreement, and pay the registration fee ahead of the deadline in order to be eligible for an award. Each team must specify a legal entity (i.e. individual or corporation). At milestones where prize money is awarded, XPRIZE will pay the award to the specified legal entity. XPRIZE Healthspan will refer to competing teams that progress through the competition using the following **team definitions**:

- **Interested Team**: A team or individual that is interested in participating in the competition and has created a profile in the XPRIZE POP system.
- **Registration in Progress**: A team that has completed registration but has not yet paid the fee and signed the Competitor Agreement.
- **Registered Team:** A team that has paid the required registration fee, signed the Competitor Agreement, and is eligible to submit a Qualifying Submission for the Judging Panel's review.
- **Qualified Team:** A team that has been selected by the Judging Panel from the pool of Registered Teams based on the strength of their Qualifying Submission.
- **Semi-finalist Team:** A team that has successfully completed the necessary technical submission and is approved by the Judging Panel to advance in the competition.
- **Finalist Team:** A team that has successfully completed Semifinals Testing and is approved by the Judging Panel to participate in Finals Testing and compete for the Grand Prize. This requires conducting prospective clinical trials using a common XPRIZE Healthspan **Data Management System** and submitting biological specimens for biomarker testing.

FUNDRAISING. All costs of competing in XPRIZE Healthspan and FSHD Bonus Prize are the responsibility of the competing team.

SAFE AND ETHICAL BEHAVIOR. Teams are responsible for maintaining the health and safety of their teams and the environment in which they are working over the course of their participation in the prize. Teams must comply with all laws and regulations which apply to their participation in the prize. XPRIZE reserves the right to expel teams who do not uphold reasonable standards of safety and ethics.

ADVISORY BOARD

A. **SELECTION OF ADVISORS.** XPRIZE will appoint a panel of topical experts and big-picture thought leaders to serve as the "**Advisory Board**" (AB) for the Competition. The AB will

remain in place throughout the Competition to advise XPRIZE regarding the scientific and other elements of the Competition.

B. **INDEPENDENT ADVISORY BOARD.** The AB will be independent of XPRIZE and all teams and team members. No Advisor, nor any member of the Advisor's immediate family, shall participate, nor have any financial or other material interest, in XPRIZE, the Sponsor(s), and/or any team or team member. All members of the AB shall promptly disclose to XPRIZE any such current, former, or expected future conflict of interest with XPRIZE, the Sponsor, or any team or team member.

C. **ROLE OF ADVISORY BOARD.** The duties and responsibilities of the AB may include, but not be limited to: (i) assisting with the establishment of qualifications for prospective Judges; (ii) recommending members of the Judging Panel; (iii) assisting with development of testing protocols and judging criteria; (iv) and providing input toward the development of these Competition Guidelines.

JUDGING PANEL

A. **SELECTION OF JUDGES.** XPRIZE will propose Judging Panel candidates to the AB for its review and consideration. The AB will recommend the candidates it believes are best suited to serve on the Judging Panel. XPRIZE will secure the Judging Panel based on the AB recommendations.

B. **INDEPENDENT JUDGING PANEL.** The Judging Panel will be independent of XPRIZE, the Title Sponsor, any other Sponsors, and all teams and team members. No Judge, nor any member of Judge's immediate family, shall participate, nor have any financial or other material interest, in XPRIZE, the Sponsor(s), and/or any team or team member. All members of the Judging Panel shall promptly disclose to XPRIZE any such current, former, or expected future conflict of interest with XPRIZE, the Sponsor, and/or any team or team member.

C. **ROLE OF JUDGING PANEL.** The duties and responsibilities of the Judging Panel will include, but not be limited to: (i) evaluating teams' compliance with the Competitor Agreement as they relate to prize operations, these Competition Guidelines, and the Rules & Regulations for the purposes of the Competition; and (ii) the awarding of points and selection of teams that will proceed to each subsequent round of the competition.

D. **GROUNDS FOR JUDGING PANEL DECISIONS.** Official decisions made by the Judging Panel will be approved by a majority of the Judges that vote on each such decision after

careful consideration of the testing protocols, procedures, guidelines, rules, regulations, criteria, results, and scores set forth in the Competitor Agreement, these Competition Guidelines, Rules and Regulations, and all other applicable Exhibits to the Competitor Agreement. If any vote of the Judges results in a tie, then the Judging Panel shall determine, in its sole and absolute discretion, the mechanism to settle the tie. Similarly, if one or more teams are tied at any stage during the competition, the Judging Panel shall have the sole and absolute discretion to settle the tie.

E. **DECISIONS OF JUDGING PANEL ARE FINAL.** The Judging Panel shall have sole and absolute discretion: (i) to allocate duties among the Judges; (ii) to determine the degree of **accuracy** and error rate that is acceptable to the Judging Panel for all competition calculations, measurements, and results, where not specified in the Rules & Regulations; (iii) to determine the methodology used by the Judging Panel to render its decisions; (iv) to declare the winners of the competition; and (v) to award the prize purses and other awards. Decisions of the Judging Panel shall be binding on XPRIZE, teams, and each team member. XPRIZE and teams agree not to dispute any decision or ruling of the Judging Panel, including decisions regarding the degree of accuracy or error rate of any competition calculations, measurements, and results. Teams shall have no right to observe other teams' testing or evaluation, or to be informed of other teams' calculations, measurements, and results, unless such information is made publicly available by XPRIZE.

COMPETITION PARTNERS

Achieving global impact requires global action. XPRIZE strives to cultivate networks of partners to support the competition from design conception through the awarding of the prize and beyond. Partners may include individuals, government entities, businesses, non-profit organizations, coalitions, or other groups. Partners may provide industry and technology knowledge as well as in-kind or discounted services and products to directly support XPRIZE and teams throughout the competition. As applicable, XPRIZE will connect teams with partner-provided resources. Collaboration with competition partners is encouraged, but optional.

8. INTELLECTUAL PROPERTY

As of the date of submission, each Team must own, or hold appropriate license rights to, all technologies, methods, resources, and Intellectual Property included in its submission.

Teams will retain ownership of their Intellectual Property on any technology or data integration techniques and processes they bring to the competition, and which they develop as part of their competition entry. All details relating to team technology, innovations, or methods submitted to XPRIZE at the submission deadlines will remain strictly confidential unless clearly and specifically noted. Please refer to the Competitor Agreement for more details.

XPRIZE will adhere to national or international regulations regarding ownership of the data and insights produced as part of the competition. XPRIZE will retain ownership of data collected during the course of the competition for Semifinals and Finals judging via the XPRIZE Healthspan Data Coordinating Center and Prize Operations Platform (POP) for alumni. These data and insights will only be released following the conclusion of the competition. Please see the Competitor Agreement for additional details on Intellectual Property.

9. APPENDICES

APPENDIX A. ASSESSMENT OF SAFETY

Specification of Safety Parameters

Safety management in XPRIZE Healthspan and FSHD Bonus Prize is intended to achieve four objectives: 1) to minimize the occurrence of adverse events, especially those related to interventions proposed by Competing Teams; 2) to effectively communicate adverse events as they relate to the Competing Teams; 3) to identify when XPRIZE Healthspan interventions should be suspended because of concerns for participant safety; 4) and to determine, in consultation with Data and Safety Monitoring Committees, regulatory boards, and medical safety officers overseeing Competing Teams trials, when and if a team solution should be considered for judging after having been suspended temporarily or permanently.

Each Competing Team's Principal Investigator will have primary responsibility for the safety of participants as it relates to their study protocol, and good clinical practice which includes local safeguards related to Covid-19 or other infectious disease. The Competing Team will engage their own Data and Safety Monitoring Committee or similar study monitoring committee according to their local regulations. For example, a team competing in the United States will be required to have their own **Institutional Review Board** (IRB) assigned to their clinical trial. This committee / board will have responsibility for monitoring study data for evidence of adverse events attributable to participation in clinical trials. Reports from this committee will be submitted for judging as part of the XPRIZE Healthspan competition.

The XPRIZE Healthspan will not directly provide medical care to participants. Instead, participants will receive medical care from their personal health care provider. Clinical Centers engaged in XPRIZE finals clinical trials should be overseen by trained and certified staff, who hold valid, up-to-date licenses, if required of their position. Study personnel for each team should also have current Research, Ethics, Compliance and Safety training (e.g., Collaborative Institutional Training Initiative (CITI) Program, CITI-Canada Program, or a similar country-specific program). The Competing Team is responsible for engaging a clinical study medical officer or designated clinic staff who will review all health assessments, vital signs, medical history, medication / therapeutic treatment use, and blood tests. All Clinical Centers should have on-call access to a study physician and post contact numbers for emergency services as required by their local regulatory requirements. Participants should be clearly informed of specific study procedures for contacting Clinical Center staff outside of scheduled interactions, for both urgent and non-urgent health concerns and in the event that adverse events arise.

Clinical Site Monitoring

Clinical Site monitoring may be conducted to ensure that the rights and well-being of human subjects are protected, that the reported data submitted for Judging are accurate, complete, and verifiable, and that the conduct of the trial is compliant with the currently approved protocol and all of its amendment, and with applicable regulatory requirement(s). Each Clinical Center is expected to perform internal quality management of study conduct, data collection, documentation and completion based on individualized quality management plans.

Safety Oversight

The Clinical Center's and Competing Teams are responsible for their study Safety Committee and safety oversight, reviews of masked study data related to the overall safety of study participation, and safety reports for their trial specific Data and Safety Monitoring Committee or Regulatory Oversight Committees as related to participant safety issues that may arise. The Competing Teams and Clinical Centers, not XPRIZE, are ultimately responsible for all clinical practice-related issues and the clinical safety of all study participants.

APPENDIX B. EXAMPLE INCLUSION AND EXCLUSION CRITERIA

Inclusion/Exclusion Criteria for Human Subjects Enrolling in 1 Year Finals			
Criteria	**Inclusion**	**Exclusion**	**Assessment**
Age	Age range 65-80 years		Participant Self-report
Functional status and risk predictors	Suggested to include at least one of the following: Short Physical Performance Battery ≥ 9 - <11 and/or Montreal Cognitive Assessment (MoCA) >20 – MoCA ≤25 (or similar questionnaire by judges review) and/or BMI 28-39 kg/m2	Dependent on walker or wheelchair; severe difficulty or inability to perform activities of daily living independently (amputee ok as long as able to walk without walker or wheelchair) Diagnosed Alzheimer's Disease or related dementia or other cognitive impairment that interferes with daily life or independent living	Screening in clinic
Unintentional Weight loss		Unintentional weight loss (≥10%) in past 6 months BMI < 17.5 kg/m^2	Self-report Height and weight at screening visit
Orthopedic status		Severe orthopedic disease (e.g., awaiting joint replacement surgery within the next six months)	Self-report
Comorbidity / health status		Uncontrolled resting hypertension (e.g., ≥150mmHg systolic and/or ≥90 mmHg diastolic)	BP measurement
		Myocardial infarction, stroke, or hospitalization for heart failure in the past 6 months	Self-report with medical record verification if needed
		Severe chronic obstructive pulmonary disease (or other pulmonary condition) requiring chronic steroid use or oxygen	Self-report
		Known active rheumatologic or autoimmune disease (e.g., rheumatoid arthritis, lupus, Crohn's disease) or current	Self-report and Medication log

treatment with immunosuppressive agents such as oral prednisone or TNF-alpha inhibitors	
Chronic infection (HIV, tuberculosis)	Self report or screening lab
Recent or recurrent exacerbation of gout	Self-report
Severe congestive heart failure (NYHA class 4)	Self-report
Severe hearing or vision loss or speech disorder	Self-report from phone screener and assessor input
Terminal illness with life expectancy less than 24 months	Self-report
Abnormal kidney function (eGFR <30 ml/min/m^2)	Self-report or Metabolic panel
Any evidence of significant liver dysfunction (e.g., elevated transaminases or a Child-Turcotte-Pugh Classification score >5)	Self report or screening lab
Major vitamin deficiencies according to published guidelines for the participants' geographic region	Self report and Medication Log
Type 1 Diabetes Mellitus or uncontrolled Type 2 Diabetes Mellitus (Hgb A1C > 7.5% for people aged 65-75 and >8.5% for people over 75)	Self- report, or screening lab and Medication Log
Megaloblastic Anemia or untreated severe anemia (e.g., Hb < 10 g/dl)	Self-report or screening lab (CBC)
Current drug abuse or excessive alcohol use/alcoholism (>14 drinks/week - drinks defined as: beer-12 ozs, wine -5 ozs, liquor-1.5 ozs) or a diagnosis of Substance Use Disorder with abstinence of less than one year.	Self-report
Cancer (except for non-melanoma skin cancer and prostate cancer) requiring medical, surgical or radiation treatment in the past 2 years; any history of stage 4 (metastatic) cancer	Self-report
Severe uncontrolled psychiatric disorder in the past year (e.g., bipolar, schizophrenia) – which precludes the ability to safely	Self-report

		carry out participation in a clinical trial and/or give informed consent	
		Parkinson's, MS, or other serious neurological disorder likely to affect mobility over the next 4-6 yrs	Self-report
		Diagnosis of Alzheimer's or dementia and/or taking a prescribed AD medication	Self-report; medication log
Medication / supplement use		Use of medications that may interfere with therapeutic effectiveness or increase risk for drug-drug interaction	Self-report, Medication Inventory, screening lab
Research participation	Willing to provide informed consent	Current participation in another intervention study	Self-report
		Residence outside of the study site or planning to move out of the area during the study period	Self-report
		Other conditions that would make participation unsafe or inappropriate	PI discretion

APPENDIX C. RECRUITMENT, RETENTION, AND WITHDRAWAL

Below are general guidelines for recruitment and retention for Finals 1 Year Clinical Studies. Teams are encouraged to use their own recruitment and retention methods, but must submit data necessary to construct a CONSORT checklist to the XPRIZE Data Coordinating Center to support XPRIZE Healthspan study monitoring, impact reporting, and to aid the Judging Panel in determining the Grand Prize awardee if needed.

Other Exclusion Criteria Related to Retention

Included among the exclusion criteria outlined in Appendix B are several that serve to identify individuals for whom retention may be compromised. These include criteria related to severely impaired function, life expectancy, and stability. At the Competing Team's discretion, a run-in period may be used to evaluate potential negative responses to a therapeutic, safety concerns, or to detect poor adherence or retention; justification and specific protocol for run-in should be reviewed and approved by Judges.

Participant Recruitment

It is the responsibility of each Competing Team and their selected Clinical Centers to meet their recruitment and enrollment goals as stated in approved local protocols. The goal of each team's Finals Testing protocols should be to enroll approximately 40-200 total participants. Recruitment goals are based on local catchment areas but should strive for sex balance (ideally, 50% female, but 40-60% balance is acceptable, with accommodation for intersex individuals) and also in ethnic and racial composition reflective of the geographic region.

Responses to Recruitment Problems

If Clinical Centers encounter difficulties in recruitment, the XPRIZE Healthspan Executive Committee (see Appendix G) may be notified of the recruitment shortfall, and provide suggestions tailored to the needs of the Clinical Center. If recruitment continues to fall short despite invigorated recruitment activities and targeted strategies aimed at improving recruitment yields, the other Clinical Centers may be asked to assist as secondary trial sites.

Participant Retention, Withdrawal, or Termination

Monitoring Retention

Adherence to scheduled clinic visits and the corresponding windows surrounding these visits is systematically monitored by the **XPRIZE Healthspan Data Coordinating Center** and contained in regular reports for interim review and the Judging Panel. In interim reports from Clinical Centers, recent participant attendance and completeness of data collection may be reviewed. Problems

with retention will be noted, and retention strategies can be continuously refined by Competing Teams.

Participant Withdrawal or Termination

Participants who choose to withdraw from clinical trials conducted by Competing Teams for XPRIZE Healthspan or FSHD Bonus Prize will be asked for the reasons leading to this decision, which will be tallied and reported to the Judging Panel. In a similar manner, participants who refuse to continue their assigned study therapeutic (but who continue to be followed for data assessments) will also be queried and responses will be tallied. Primary analysis and definition of success will be on an intention to treat basis.

Premature Termination or Suspension of Study

If the Competing Team, study investigators, regulatory agency, or the funder terminates or suspends the trials conducted for consideration of XPRIZE Healthspan competition, participants of that trial should be notified according to procedures approved by the local study monitoring committee and regulatory boards.

FSHD participant recruitment and withdrawal

Recruitment of participants in FSHD Bonus Prize will follow those laid out for XPRIZE Healthspan, but all trials will be performed in persons aged 50-80 years with genetically confirmed FSHD.

APPENDIX D. GLOSSARY

Accurate (*Accuracy, Accurately*)
The correctness (closeness to true value) and quality of the assessment measures and biomarkers.

Accessibility
This refers to the extent to which individuals, particularly patients and research participants, can easily and equitably participate in and benefit from clinical research studies. Accessibility in clinical trials is a critical aspect of ensuring that research is inclusive, ethical, and representative of diverse populations.

Adverse Event
An adverse event (AE) is any unfavorable, unintended, and/or untoward occurrence, i.e. disease, sign, or symptom (including an abnormal laboratory finding) that is temporarily associated with the use of an intervention, medical therapy, or procedure. An adverse event may or may not be considered related to The intervention medical therapy, or procedure may or may not be considered causal of the adverse event(s). Such events can be related to the therapy, dos, route of administration, patient, or caused by an interaction with behavior, another drug(s), or procedure(s).

Types of Adverse Events:

- **Serious Adverse Events (SAEs):** Critical and potentially life-threatening occurrences that demand immediate attention and intervention. They often result in severe harm, disability, incapacity, hospitalization, or death. SAEs are a significant focus in clinical trials and healthcare, as they require thorough investigation and reporting
- **Anticipated Adverse Events:** Those side effects and/or complications that are expected or known to occur as a result of a specific treatment, medication, or medical procedure. These events are typically outlined in product labeling, **informed consent** documents, or study protocols, and healthcare providers or researchers are prepared to manage them.
- **Unanticipated Adverse Event:** Unexpected and uncommon occurrences that were not foreseen based on available knowledge and prior experience. These events often trigger further investigation to determine their cause, risk factors, and potential implications for patient safety.

Advisory Board
A select group of topical experts and big-picture thought leaders who contribute their wisdom, knowledge and guidance to various aspects of the prize including, but not limited to: (i) assisting with the establishment of qualifications for prospective Judges; (ii) recommending members of the Judging Panel; (iii) assisting with development of testing protocols and judging criteria; (iv) and providing input toward the development of these Competition Guidelines.

Aging
A complex process involving genetic, environmental, and behavioral factors. Aging is associated with physiological and cognitive changes that can lead to biological and functional decline.

Alumni Network
A community of former and current XPRIZE competitors and teams through which XPRIZE and such teams can continue to communicate and collaborate with one another. The objectives of the Alumni Network are to monitor post-prize impact; to support and scale team solutions; to create opportunities for networking among alumni and with XPRIZE's partnership ecosystem; to provide continuing education for competitors; to invite and engage alumni in various conferences and events. Registered teams are automatically enrolled but may opt out at any time.

Animal Care and Use
This refers to the ethical and responsible treatment of animals used in scientific studies, testing, or teaching. It involves ensuring their welfare, minimizing harm, and adhering to strict ethical and regulatory guidelines. Key aspects include:

- The proper housing, feeding, healthcare, and overall management of animals used in research, testing, or education. It involves measures to ensure the animals' well-being and to minimize pain, distress, or suffering.
- Policy and approvals required to minimize use and impact. Approval from institutional animal care and use committees (IACUCs) or similar regulatory bodies is usually mandatory before any animal research can commence. These committees assess research proposals to ensure that the research is scientifically valid and ethically conducted. Researchers must justify the use of animals and demonstrate that alternative methods are insufficient.
- Veterinary care required, including regular health assessments, disease prevention, prompt treatment of illnesses or injuries, surgical procedures, anesthesia, and post-operative care to minimize pain and distress, and humane endpoints.

Assessment Measures
Performance-based and objective outcome measurements on activity that evaluates and tests a specific function(s).

Benefit
A conferred clinical benefit is one that prolongs life, improves function, and/or improves the way a patient feels. Clinical significance is a change in a subject’s clinical condition regarded as important whether or not due to the intervention.

Biomarker
A biomarker in clinical trials is a measurable and quantifiable biological or molecular indicator

used to evaluate various aspects of a participant's health, disease state, or response to a therapeutic intervention. Biomarkers serve as essential tools in clinical research to assess the safety and efficacy of treatments, track disease progression, predict outcomes, and stratify patient populations. They encompass a broad range of parameters, including genetic, genomic, proteomic, biochemical, or imaging characteristics, and are employed to provide objective data and insights that aid in decision-making throughout the trial process. Biomarkers play a crucial role in advancing precision medicine by enabling researchers to tailor treatments to individual patients or specific subgroups based on their unique biological profiles.

Catchment Area

The location selected and/or approved by XPRIZE to conduct testing defined by geographic area and inclusive of the population recruitment in clinical trials testing.

Clinical Trials

In relation to XPRIZE healthspan, clinical trials are research studies on human participants for prospective study of biomedical or behavioral interventions.

Competitor Agreement

A legal and binding document that details the responsibilities of competitors for the prize.

Core Problems

Challenges that currently inhibit clinical translation of therapeutic treatments that XPRIZE Healthspan and XPRIZE FSHD could help solve.

Data Coordinating Center

Centralized repository that collects and monitors information supporting the management of multi-center, multi-location studies. DCC can provide common questionnaires, data collection forms and data management and integration along with statistical analysis, overall study training, protocol development and review, manuals of procedures, coordination and quality assurance, including coordination of activities of the Data and Safety Monitoring Board (DSMB), trial management systems, and coordinating external scientific advisory committees.

Data Management System

Critical phase in clinical research, which leads to generation of high quality, reliable, and statistically sound data from clinical trials. Clinical data management ensures collection, integration and availability of data at appropriate quality and cost. It includes adequate process knowledge that helps maintain the quality standards across clinical trials and is involved in various procedures from case report form designing to annotation, database design, data-entry and validation, discrepancy management, medical coding, data extraction, and database locking for the

assessment of quality at regular intervals during the lifespan of a trial.

Discretionary Late Registration

A limited opportunity to enable select teams to join the competition after the standard registration deadline. Interested teams should contact XPRIZE for more details about entering at healthspan@xprize.org.

Endpoints

Targeted outcomes that are statistically analyzed and relevant allowing for the determination of both the efficacy and safety of a therapeutic and/or intervention being used in a study or trial. This may include multiple clinical outcomes that can be measured.

Endpoints Committee

Board made up of scientists external to the XPRIZE Healthspan and FSHD Bonus Prize competitions. The board is comprised of technical experts, evidence-based advisors, and general advisors The board is comprised of technical experts, evidence-based advisors responsible for guiding the competition guidelines including but not limited to clinical trial design with inclusion group criteria and functional endpoint measures.

Institutional Review Board (IRB)

Group that is formally convened and assigned to review and monitor research and development studies and/or clinical trials involving human subjects. They can make suggestions, and approve or disapprove defined protocols and procedures. Their role considers the rights and well-being of human subjects participating in a study and/or trial.

Feasibility

Process of evaluating the ease and possibility of conducting a particular study or trial. This includes levels of feasibilities that involve (1) program level with considerations on ethical and regulatory concerns (i.e. prevalence of disease or condition), (2) study level (i.e. technical and operational concerns), and site or investigator level (i.e. recruitment , quality, infrastructure).

Finals Testing

The last set of testing events for the prize that will determine the Grand Prize winning teams; prospective 1 year clinical trials in prize-defined populations using a common data management system for judging.

Finalist Verification

This is a mandatory update to ensure teams are prepared to proceed to Finals Testing. This will most likely consist of clinical trials protocols, regulatory approvals, safety and feasibility data and

monitoring plans, evidence and data provided in **Semifinals testing**, and access to appropriate resources to complete the regulatory approved 1 year clinical trials in prize-defined populations.

FSHD

Facioscapulohumeral muscular dystrophy is a genetically defined neuromuscular disease associated with two distinct genetic mechanisms. FSHD1 is associated with a reduction in D4Z4 repeat units on the distal end of chromosome 4q (4q35 locus) and FSHD2 due to mutations on genes involved in chromosomal methylation including SMCHD1, DNMTB3 and LRIF1. Both genetic causes lead to derepression of genes in the D4Z4, of which the transcription factor DUX4 is thought to play a pivotal role based on its cytotoxic effects when overexpressed in somatic cells including muscle and in myoblasts obtained from FSHD patients.

Generalizability

A measure of how useful the results of a study or clinical trial are for a broader group of people or situations including representativeness of local recruitment and/or catchment area which consider racial, ethnical, socioeconomic, cultural, gender inclusion. If the results of a study are broadly applicable to many different types of people or situations, the study is said to have good generalizability.

Geroscience

An interdisciplinary approach to the enhancement of healthspan and lifespan by identifying the drivers of the aging process, a major risk factor for common chronic conditions and diseases. It is the intersection of basic aging biology, molecular and cellular mechanisms, chronic disease, and health. A goal of geroscience is to develop targeted therapeutic treatments for these drivers of aging, as a way to prevent common chronic diseases, rather than targeting the diseases themselves after they develop.

Human Subjects

Refers to individuals who participate in the clinical trial as research participants. These individuals are often patients or healthy volunteers who voluntarily agree to be part of the study to evaluate the safety and efficacy of a new medical intervention, such as a drug, medical device, or treatment. Competing teams in the clinical trials competition should demonstrate a strong understanding of the ethical and regulatory guidelines governing human subjects' participation in clinical trials. This includes knowledge of Good Clinical Practice (GCP) and relevant regulations like the Declaration of Helsinki and the International Conference on Harmonisation (ICH) guidelines.

Informed Consent

All Human subjects that are participating in teams' clinical trials must provide informed and voluntary consent before participating in the clinical trial(s). They should receive clear and

comprehensive information about the study's purpose, procedures, potential risks, and benefits. Informed consent ensures that participants understand what they are getting involved in and can make an educated decision about their participation.

Judging Panel

The subject matter and technical experts who serve as an impartial and independent evaluation team for all aspects of this prize. Judges score the team submissions and make the final award determinations in both the Semifinals and the Finals Competitions.

PICOT

This refers to clinical trials parameters used for judging Finalists: Population (P), Intervention (I), Control (C), Outcomes (O), Timeline (T).

Population

The subset of enrolled patients who received any amount of a study therapeutic or drug. This is the set of patients in the assigned treatment group.

Public Comment Period

Feedback about the Competition Guidelines may be submitted by any readers, general public, regulatory agencies, advocacy groups, funding agencies, key stakeholders, and prospective competitors from November 29, 2023 - June 30, 2024. XPRIZE will review the comments and take any potential revisions to the guidelines into consideration.

Prize Operations Platform (POP)

The standard internal XPRIZE portal for teams to complete required activities in this competition.

Prize Purse

This refers to money offered, won, or received as a prize. It also refers to the overall amount of funds allocated to all prizes in this competition.

Proof of Concept Trials (Semifinals)

For the competition this will consist of trials of up to 60-days to show feasibility of therapeutic treatments in terms of approach, safety, and early estimates of effect in two of the primary target areas (muscle, cognitive, immune function) that suggest next stage phase II trials are warranted. Teams will be responsible for submitting regulatory and human subjects safety approvals, data and safety monitoring reports, evidence of target engagement or pharmacodynamic / pharmacokinetic response (if necessary for novel drugs), or to submit drug labeling for repurposed agents, or comprehensive instructions provided to human subjects for dietary / lifestyle / behavioral interventions. Teams must provide evidence that it will be feasible to enroll and retain participants

meeting their Inclusion and Exclusion Criteria in proposed trials.

Protocol

This refers to a detailed and systematic plan or set of procedures that outlines all aspects of a clinical study. It serves as a comprehensive document that provides specific instructions and guidelines for conducting the study in a standardized and scientifically rigorous manner. Here are key elements typically included in a clinical trial protocol:

- **Study Objectives:** The protocol defines the primary and secondary objectives of the clinical trial. These objectives outline what the study aims to achieve, such as evaluating the safety and efficacy of a new treatment or assessing a particular health outcome.
- **Study Design:** It describes the overall design of the study, including the type of study (e.g., randomized controlled trial), the number of study arms, the duration of the study, and the schedule of assessments and interventions.
- **Inclusion and Exclusion Criteria:** The protocol specifies the criteria that potential participants must meet to be eligible for the study (inclusion criteria) and those factors that disqualify them from participation (exclusion criteria).
- **Interventions:** Details about the experimental interventions (e.g., drugs, treatments, procedures) and their administration are outlined, including dosages, schedules, and methods of administration.
- **Endpoints and Outcome Measures**: The protocol defines the specific measurements and assessments that will be used to evaluate the study's outcomes. These may include clinical endpoints, laboratory tests, patient-reported outcomes, and safety assessments.
- **Randomization and Blinding:** If applicable, the protocol explains the randomization process (how participants are assigned to different study groups) and the blinding (or masking) procedures to minimize bias in the study.
- **Data Collection and Analysis:** It outlines the data collection methods, including data sources, data collection forms, and data management procedures. The protocol also describes the statistical methods that will be used to analyze the collected data.
- **Safety Monitoring:** Procedures for monitoring and reporting adverse events or safety concerns are specified to ensure participant safety throughout the study.
- **Ethical Considerations**: The protocol includes information on obtaining informed consent from study participants, as well as ethical considerations and safeguards to protect the rights and well-being of participants.
- **Study Timeline and Milestones:** A timeline for the study, including key milestones and dates for recruitment, data collection, and completion, is typically included.
- **References:** Relevant references to prior research, scientific literature, and regulatory documents that support the study design and rationale are cited.

Qualifying Submission

This submission consists of a series of questions to be answered that outline the expertise, capabilities and plans for testing the therapeutic treatments that each team will create. It will also require an Executive Summary of up to six pages of text, and any supporting images, diagrams, or charts, as well as regulatory approvals, clinical protocols, human subjects safety plans or animal care and use descriptions, safety monitoring and risk minimization, and detailed description of pharmacodynamic / pharmacokinetic response to therapeutic, product labeling, or detailed description of dietary and lifestyle intervention protocols.

Rules & Regulations

A document detailing the testing protocols, specific rules, dates/times, and other details that will govern the competition and will be binding on teams. The Rules & Regulations for Semifinals and Finals testing will supersede the Competition Guidelines; all teams will be notified of the Rules & Regulations and any modifications to the Rules & Regulations in a timely manner.

Regulatory Approvals

This process can and may differ for each location or country based on specific requirements for each region. In general, regulatory approvals follow a process by government agencies to review and evaluate an intervention, treatment, therapeutic, or drug's effect to determine if the benefits outweigh known and potential risk for the intended population.

Semifinals Testing

The set of testing events for the prize that will help determine which teams progress to Finals Testing.

Safety

Safety involves a commitment to ethical and responsible practices, rigorous monitoring, and adherence to relevant laws and regulations to protect the well-being of humans, animals, or the environment, depending on the specific domain.

- **Safety for Human Subjects.** In the context of clinical trials and research involving human subjects, "safety" refers to the protection of the physical, emotional, and psychological well-being of individuals participating in the study. It encompasses measures to minimize risks, ensure informed consent, and monitor and report adverse events. Safety for human subjects is a fundamental ethical principle, and it involves adherence to ethical guidelines and regulations to prevent harm or discomfort to participants.
- **Animal Care and Use Safety.** "Safety" in the context of animal care and use pertains to the ethical treatment and welfare of animals used in research, testing, or teaching. It involves providing appropriate housing, nutrition, veterinary care, and enrichment for animals to ensure their well-being. Safety measures also include procedures to minimize pain and

distress and to follow ethical guidelines and regulations governing the humane treatment of animals in research settings.

- **Biologics Safety**. "Safety" for biologics refers to the assessment and management of potential risks associated with biological products, such as vaccines, blood products, and cellular therapies. Biologics safety involves rigorous testing, quality control, and monitoring to ensure that these products are safe for use in humans or animals. Safety also encompasses the detection and reporting of adverse reactions or side effects related to the use of biologics.
- **Environmental Safety.** "Safety" in the environmental context pertains to the protection of the natural environment, ecosystems, and public health from harm or pollution. Environmental safety measures aim to prevent or mitigate adverse effects on air, water, soil, wildlife, and human populations. This includes adherence to environmental regulations, sustainable practices, pollution control, and conservation efforts to maintain a healthy and balanced environment.

Team Definitions

- **Interested Team**: A team or individual that is interested in participating in the competition and has created a profile in the XPRIZE POP system.
- **Registration in Progress**: A team that has completed registration but has not yet paid the fee and signed the Competitor Agreement.
- **Registered Team:** A team that has paid the required registration fee, signed the Competitor Agreement, and is eligible to submit a Qualifying Submission for the Judging Panel's review.
- **Qualified Team:** A team that has been selected by the Judging Panel from the pool of Registered Teams based on the strength of their Qualifying Submission.
- **Semifinalist Team:** A team that has successfully completed the necessary technical submission and is approved by the Judging Panel to advance in the competition.
- **Finalist Team:** A team that has successfully completed Semifinals Testing and is approved by the Judging Panel to attend Finals Testing.

Technical Validation Submission

The process by which Qualified Teams demonstrate they are prepared to proceed to Finals testing. This submission will consist of protocol submissions, regulatory approvals, and resources required to conduct a 1 year clinical trial in a prize-defined population using XPRIZE Data Management System which the Judging Panel will review to verify each team's ability to participate in testing.

Therapeutic Treatment

This refers to any of a myriad of interventions that may be developed or repurposed and tested by the competing teams to address the goal of improving muscle, cognitive and immune function as defined by the criteria listed in Section 6. Therapeutic treatments can include medicinal drugs,

gene therapies, dietary and lifestyle interventions, biologics, devices, electroceuticals, nutriceuticals, and others; can be used alone or in combination; and must meet established safety parameters.

APPENDIX E. EXPERTS LIST

We express immense gratitude to all experts engaged in the competition design process. Thank you for inspiring us, stress-testing assumptions, and challenging conventions. The individuals denoted with an * below formed an **Endpoints Committee** that was active Sept-Nov 2023 and assisted in the selection and evidence base supporting the primary endpoint for the prize.

Additional Technical Consultants and Advisors will be sought for guidance on cognitive / brain aging, international regulatory affairs, bioethics, and specific therapeutics on an as needed basis.

Disclaimer: Statements made by individuals in interviews are representative of their own knowledge and opinion as experts in their fields and not necessarily of their affiliated company or organization. All interviews are conducted under the Chatham House rule, and no information can be attributed to a listed expert without their explicit consent.

NAME	LAST NAME	HON	TITLE	AFFILIATION
Scientific and Technical Advisors				
Patrick	Maxwell*	MD	Regius Professor of Physic Head of the School of Clinical Medicine	University of Cambridge
Steven	Austad*	PhD	Endowed Chair in Healthy Aging Distinguished Professor of Biology	University of Alabama Birmingham
Luigi	Ferrucci*	MD, PhD	Scientific Director	National Institute on Aging, NIH
Thomas	Rando*	MD, PhD	Director, UCLA Broad Stem Cell Research Center	University of California LA
Nir	Barzilai	MD	Director, Institute for Aging Research Ingeborg and Ira Leon Rennert Chair in Aging Research	Albert Einstein College of Medicine
Daniel	Belsky	PhD	Associate Professor of Epidemiology	Columbia University
Peggy	Cawthon	PhD, MPH	Scientific Director	California Pacific Medical Center Research Institute
Eva	Chin	PhD	Executive Director	Solve FSHD
Steve	Cummings	MD	Director of San Francisco Coordinating Center	University of California San Francisco
Aubrey	de Grey	PhD	President and Chief Scientific Officer	Longevity Escape Velocity Foundation
Bill	Evans	MD	Adjunct Professor	Duke University and University of California, Berkeley
George	Kuchel	MD	Director of Uconn Center on Aging	University of Connecticut

NAME	LAST NAME	HON	TITLE	AFFILIATION
			Professor of Medicine and Travelers Chair in Geriatrics and Gerontology	
Morgan	Levine	PhD	Principal Investigator	Altos Labs San Diego Institute of Science
Thomas	Osborn	MD	Director of National Center for Collaborative Healthcare Innovation	Veterans Affairs
Graham	Pawalec	PhD	Professor	University of Tuebingen
Nicholas	Schork	PhD	Deputy Director and Distinguished Professor of Quantitative Medicine	Translational Genomics Research Institute
William	Smith	MD	Assistant Professor	Uniformed Services University of the Health Sciences
Risa	Starr	MBA, MPH	Executive Director	Longevity Biotech Association
Erwin	Tan	MD	Director of Thought Leadership	AARP
Roland	Thorpe	PhD	Professor and Co-Director DRPH Concentration in Health, Equity, and Social Justice	Johns Hopkins University Bloomberg School of Public Health
Alex	Zhavoronkov	PhD	CEO	Insilico Medicine
Legacy Advisors (prior to prize launch, Nov 2023)				
Steve	Aoki		Founder	Aoki Foundation
Joe	Betts-laCroix	PhD	CEO	Retro Biosciences
George	Church	PhD	Professor	Harvard Medical School and Massachusetts Institute of Technology
Adam	Marblestone	PhD	CEO	Convergent Research
David	Sinclair	PhD	Professor	Harvard Medical School
Balaji	Srinivasan	PhD	Investor	Formerly CTO of Coinbase and General Partner at a16z
Doris	Taylor	PhD, FACC, FAHA	CEO	Organamet Bio Inc; and RegenMedix Consulting LLC
Eric	Verdin	MD	CEO	Buck Institute for Research on Aging

APPENDIX F. FSHD BONUS PRIZE JUDGING CRITERIA

XPRIZE FSHD Bonus Prize Criteria Determination

Background: With aging there is a ~20% loss of muscle strength over 20 years (i.e. from 40 to 60 yrs of age) (Hunter et al 2000, J Gerontol A Biol Sci Med Sci. 55(6):B264-73). To show age restoration, the XPRIZE recipients would need to show a 25% gain in muscle strength to show reversal from the function of a 60 yr old to that of a 40 yr old (i.e. from 120 back to 150 Nm = 25% relative increase in strength.

In FSHD, there is an asymmetric and progressive muscle weakness and a disease pathology characterized by fat infiltration and ultimately fibrosis associated with the loss of muscle mass (Janssen et al. 2014, PLoS One 9(1): e85416). Current treatments in FSHD are focused on showing reduced fat infiltration in muscle and corresponding improvements in muscle function. Many functional endpoints have been tested in FSHD clinical trials but the most common are:

- 6 minute walk test (6 MWT)
- Gait speed (GS)
- Grip test (GT)
- Knee extensor maximum voluntary contraction (MVC)
- Timed up and go (TUG)
- Revised Upper Limb Module (RULM)

FSHD Bonus Prize Criteria: Based on current available information, an FSHD Bonus Prize team should show:

- a 10% reduction in muscle fat fraction
- AND a 25% improvement in at least 3 of the functional tests (6 MWT, GS, GT, MVC, TUG or RULM)
    - One of the functional endpoints can be a novel, validated clinical outcome measure that has been designed using AI or other novel approaches.

APPENDIX G. XPRIZE HEALTHSPAN ORGANIZATIONAL CHART

The following diagram shows the XPRIZE Healthspan organization and committee structure that define prize roles and responsibilities.