Competition Guidelines

December 22, 2025

Version 2.2

COMPETITION GUIDELINES

XPRIZE Healthspan will be governed by these Competition Guidelines. The 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 D.

XPRIZE may revise 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.

Changes from previous Competition Guidelines, v.2.1

1. Updates to the Competition Timeline: pages 17-20
    - Several dates pertaining to the Primary Registration, Semi-Finals, and Finals phases of the Competition have been updated for accuracy.
2. Updates to Inclusion Criteria for Finals Trials: pages 5, 14, 16, 17, 27, 34, 36, 77, 81, 84
    - The upper age limit for trial participants was increased from 80 years to 90 years for the tracks of the Competition (Healthspan & FSHD).
3. Alignment of Finals Application materials and judging for Milestone 2 Awards with the posted application guidelines and submission template: pages 32-33
4. Updates to Endpoints and Outcomes for XPRIZE Healthspan Finals Trials, pages 40-45
    - Muscle mass assessments will now serve as a strongly recommended but optional measure that may strengthen the overall interpretation of a Team's results. While muscle mass assessments are not mandatory, teams are encouraged to include muscle measures by urinary D3 Creatine dilution or imaging methods if feasible.
    - Finalist Teams must use CANTAB to assess cognitive function.
    - iAGE and IMM-AGE were named as 2 out of the 3 tests of immune function for Finals. A third biospecimen-based test will be named prior to Finals judging. This measure will use biospecimen collections outlined in Standard Operation Procedures that will be finalized with Finalist teams and Central Laboratory.
5. Updates to Endpoints and Outcomes for FSHD Bonus Prize, pages 45-46
    - Refer to the FSHD Rules and Regulations for more details.

What has not changed:

The eligibility requirements, prize purse, prize structure, and overall scope of the competition have not changed.

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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 brings 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 solutions**, 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 translate their discoveries to clinical trials. Teams may pursue testing of a variety of therapeutic interventions - including but not limited to drugs, biologics, gene therapies, devices, dietary, lifestyle, or behavioral approaches, administered alone or in combination.

Teams will be required to deliver their therapy in 1 year or less in persons aged 50-90 years who are free of major or life-threatening disease and disability. The winning team will demonstrate that their therapeutic solution 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 less than 1 year 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 solutions 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 and further increases are projected for decades to come.[1, 2] Yet the additional years of lifespan are not necessarily coupled with an extended period spent in relatively good health, or ***healthspan***.[3] 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) alone.[4] Globally people are living longer, but for an extended period with chronic disease, disability, and high healthcare costs.[5]

This demographic shift will affect developed and developing countries alike.[6] By 2040, China will be home to nearly half a billion people over 60.[7] By 2050, Brazil's population of adults aged 65 and older is set to triple.[8] 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.[9]

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.[10] For example: in the US, every 1% increase in healthcare spending leads to a 0.083% decrease in GDP growth rate.[11] 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.[12] Globally, healthcare expenditure rose 4 to 10-fold over the last 15-20 years, and in China, healthcare expenditures exceeded the GDP growth rate.[13, 14] 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.[15] 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.[9]

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.[16]

Biological Aging Promise. Over the past few decades, remarkable progress has occurred in the science of aging.**[17]** Studies have implicated genetic and biological pathways that modulate healthy lifespan in species that have diverged greatly over evolutionary time periods, and demonstrated that aging-related pathways **provide logical targets** for intervention[18, 19] 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 rapamycin) 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.[20] Newer gene therapies, senotherapeutics, chemically-induced reprogramming, and vaccine or immunotherapies are now in development and show early promise in model organisms.

Hope for FSHD. Facioscapulohumeral muscular dystrophy (FSHD) is a type of muscular dystrophy in which there is progressive muscle degeneration and muscle weakness; there is currently no treatment or cure.[21] For FSHD, the prevalence, underlying genetics, molecular causes and pathobiology of FSHD have been increasingly understood.[22, 23] Average age of diagnosis is 29-32 years, with age of onset correlated to allele size. Identification of the genetic causes has been established, with two main primary forms – the more common FSHD type 1 and relatively rare FSHD type 2 (FSHD1 and FSHD2 respectively). FSHD1 and FSHD2 genetic forms have a truncated D4Z4 region on Chromosome 4 leading to depression of a silenced transcription factor DUX4 with FSHD2 being further defined by hypomethylation due to mutations in methylation genes (SMCHD1, DNMT3B, and LIRF1). This leads to muscle inflammation, degradation and replacement by fatty and fibrotic tissue and impaired muscle function at ages much earlier than natural aging. Though better understanding of the molecular basis of FSHD has led to multiple potential therapeutic strategies, including some entering clinical trials, the gap to novel therapies remains large.

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%.[2, 24] 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 improve healthspan 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.[25] 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.[5]

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 therapeutics 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 an active intervention 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 solutions 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 therapeutics to an individual's unique biology, recognizing 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 therapeutics to market.

Disparities in Access. Even when effective therapeutics exist, they can be costly and out of reach for many individuals.[26] 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,[27] and modern weight management drugs like the GLP-1 agonist (semaglutide) at US$900 - $1350 per month.[28] Such costs may put undue financial burden on those who most need access. Therefore, **accessibility**, affordability, and practicality of the therapeutic solution 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 or device / protocol administration, clear instructions, easy-to-open product packaging, and temperature stability and shelf-life. We are particularly keen to develop therapeutic solutions that can improve aging equitably so that vulnerable populations may benefit globally.

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 specific regional 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. Moreover, teams must recruit roughly similar numbers of men and women into their trials; nonbinary persons may also be eligible.

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) and opening for Primary Registration (31 July 2024) this Competition has raised funds from private individuals and foundations across the world. The prize purses 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).

NOTE: Teams registered for the Healthspan Prize may also compete in the FSHD Bonus Prize or transfer tracks during the Competition for no additional registration fee (with letter of intent to transfer submitted for Judges review)

(1) HEALTHSPAN

MILESTONE-PRIZE AWARDS:

First $10M Milestone Prize: By mid-2025, up to 40 of the registered teams will be selected by the **Judging Panel** and receive an equal split of the **$10 Million** Milestone Prize purse to support their ongoing work. This award is determined by the judges based upon evidence and materials submitted by teams in their Qualifying Submissions (due 20 December 2024; view the Guidelines for Qualifying Submissions here).

Second $10M Milestone Prize: In mid-2026, up to 10 of the registered teams (as selected by the Judging Panel) will receive an equal split of the **$10 Million** Milestone Prize purse to support their ongoing work. This award is determined by the judges based upon evidence and materials submitted by teams in Semi-Finals testing and the team Finals Application.

Teams not selected to receive milestone prizes by the Judging Panel are also invited to continue in the Competition. Unawarded teams must submit a letter of intent to continue and address recommendations provided by the Judging Panel or the prize operations team.

GRAND-PRIZE AWARDS:

Material Transfer Agreements (MTA) and Data Use Agreements (DUA)

(2) FSHD BONUS PRIZE

FSHD MILESTONE PRIZE AWARD:

First $2M Milestone Prize: After 1 year, up to the top 8 registered teams (as selected by the **FSHD Judging Panel**) will receive an equal split of the **$2 Million** Milestone Prize purse to support their ongoing work. This award is determined by the judges based upon evidence and materials submitted by teams.

The remaining teams not selected by the FSHD Judging Panel are also invited to continue in the Competition. Unawarded teams must submit a letter of intent to continue and address recommendations provided by the FSHD Judging Panel or the prize operations team.

FSHD BONUS PRIZE AWARD:

A bonus purse totaling $8,000,000 will be awarded to the First Place Team in the FSHD Bonus Prize. The best team who conclusively demonstrates, to the satisfaction of the FSHD Judging Panel, evidence of substantial improvement in muscle function based on: 1) fat infiltration in muscle or change in a relevant FSHD biomarker AND 2) corresponding improvement of muscle function, compared with controls, through a therapeutic treatment lasting 1 year (or less) is eligible to win **$8 Million** of the bonus prize purse.

Please see Section 9 for more information on judging criteria for Healthspan and FSHD Bonus Prize tracks.

3. HEALTH AND SAFETY OVERVIEW

Safety is our top priority. Developing and testing therapeutics carries a variety of risks for **human subjects**. 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. **Teams must provide XPRIZE documentation that their interventions have been approved by their local safety review board or regulatory agency**. **Teams must also ensure that informed consent documents include statements that permits XPRIZE to access data for judging.**

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. Further details will be released in the **Rules & Regulations**, which will function as the common clinical protocol for Finalists. 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 safety and minimized risk to human subjects. XPRIZE reserves the right to disqualify teams who are found to be operating in an unsafe or unethical manner.

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. Teams may be required to obtain insurance coverage as required by their institutions or clinical trials centers; the insurance requirement is included in the **Competitor Agreement** (linked here).

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

- Teams will comply with all relevant environmental, health, and safety regulations, including ***obtaining informed consent*** for research participants.
- Teams must ensure compliance with institutional and national regulatory standards for research involving human subjects and obtain 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 as part of the Qualifying Submission or Finals Application and reviewed by the Judging Panels prior to testing.
- Teams must make sure that all risks to participants related to their involvement in studies

are minimized, not just those risks resulting directly from therapeutic interventions (e.g. minimize risk of functional testing, blood-draw, etc.

4. COMPETITION STRUCTURE

Competing teams will innovate across early-stage therapeutic testing — from research and development to clinical trials testing in persons 50-90 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 interim 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 50-90 years.

FSHD Bonus Prize of $10M will focus on Facioscapulohumeral Muscular Dystrophy (FSHD) with one interim milestone prize awarded in recognition of a research and development phase, and will culminate in final adjudication of the Bonus Prize based on testing interventions in clinically approved genetically tested FSHD individuals aged 50-90 years.

Teams may register to compete in one or both tracks. Teams registered in Healthspan track may transfer to FSHD Bonus Prize track with no additional registration fee during the Competition by submitting a letter of intent to transfer tracks to XPRIZE for review by the Judging Panel(s). Refer to Section 2 for details about all **prize purses**. Two Independent Judging Panels for XPRIZE Healthspan and the FSHD Bonus Prize will be assembled to evaluate each stage and adjudicate the winning team(s) based on **Finals Testing** criteria.

COMPETITION STAGES & MILESTONES

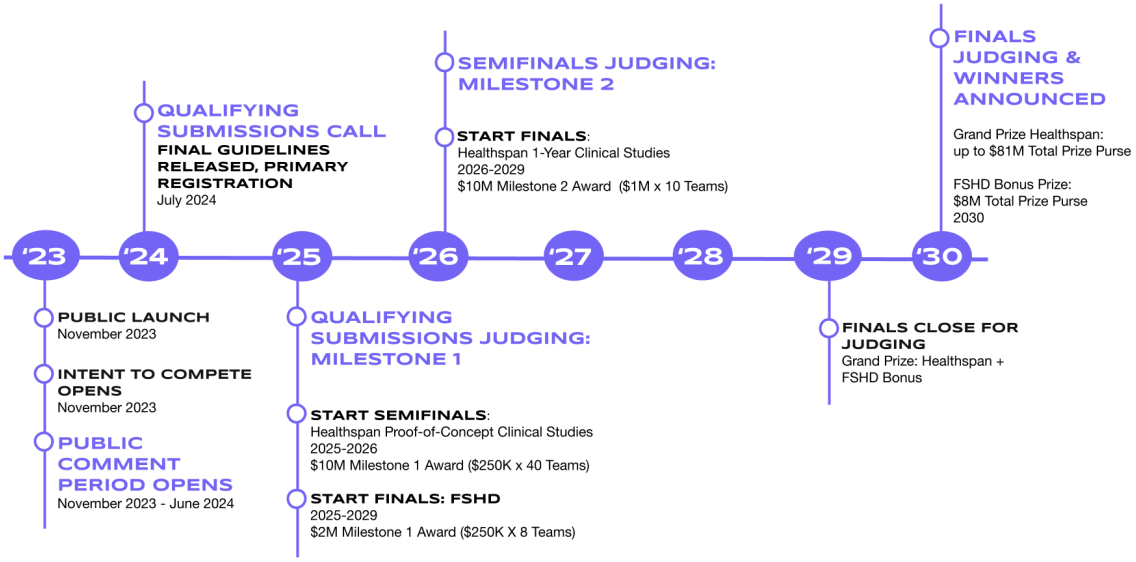
Competition Milestone dates may be subject to change.

XPRIZE Healthspan will take place over 7 years with 2 milestones along the way. Following deliberation and decision by the **Judging Panels**, XPRIZE will directly notify all teams who are selected for an award of each milestone prize. The FSHD Bonus Prize will follow the same general timeline. An additional 12 months post-awarding will be devoted to amplifying the impacts of XPRIZE Healthspan.

TABLE 1. Competition Summary Table

XPRIZE Healthspan	FSHD Bonus Prize
• Intent to Compete • Team Registration & Qualifying Submission • Semi-Finals: Early-Stage Clinical Studies • Finals: 1-Year Clinical Trial Testing Period • Finals: Judging Period • Scaling & Impact	• Intent to Compete • Team Registration & Qualifying Submission *(no Semi-Finals)* • Finals: 1-Year (or less) Clinical Trial Testing Period • Finals: Judging Period • Scaling & Impact

FIGURE 1. Competition Timeline



Milestone 1. Qualifying Submission

Qualifying Submission is the first formal opportunity for prospective teams to demonstrate their ability to proceed through the Competition, and ultimately succeed and deliver an effective solution. The Qualifying Submission is the means by which teams are initially assessed by XPRIZE Judges for their ability to ultimately compete in the XPRIZE Healthspan and FSHD Bonus Prize. For more information, please refer to the Qualifying Submission Guidelines.

Registered teams are required to submit a proposal for Healthspan and FSHD Judging Panels' consideration of their therapeutic intervention. The Qualifying Submission should include information about the team, the environment or clinical center used for testing, data supporting their therapeutic solution, evidence of progress to date, approach to testing, evidence that regulatory requirements are or will be met, timelines, scalability and accessibility assessment, and readiness for testing. **Submissions are due on December 20, 2024;** Healthspan and FSHD Judging Panels will convene through March 2025.

For XPRIZE Healthspan, up to 40 teams will be chosen as Semi-Finalists and share a Milestone 1 prize purse of $10,000,000, and FSHD Bonus Prize, up to 8 teams will be chosen as Finalists and share a Milestone 1 prize purse of $2,000,000 (e.g., $250,000 awarded to each team, if 8 teams are chosen).

Note: Teams competing in BOTH XPRIZE Healthspan and FSHD Bonus Prize must submit TWO

Qualifying Submissions applications – one submission to each of the prize tracks – as the Competition stages, patient populations, and judging panels differ.

Milestone 2. Semi-Finals Testing

Early stage and Proof-of-Concept (PoC) Studies are typically short (less than 30-60 days), small (5-20 people receive active therapeutic intervention), and relatively inexpensive studies that are used to help design and justify larger clinical trials. For XPRIZE Healthspan, the PoC studies in Semi-Finals are used to indicate the team's readiness for Finals, ability to recruit human subjects and conduct a clinical trial, and feasibility of approach.

We allow our teams the flexibility to define key design features needed to demonstrate feasibility and readiness in Semi-Finals. Teams will propose their own study design, endpoints and assessment measures needed, and criteria used to support go / no-go decisions in their Qualifying Submissions. Teams are encouraged to discuss their approach with XPRIZE operations.

Semi-Finals testing will last approximately **one calendar year**. At the end of Semi-Finals, teams will submit their enrollment reports, analyses, de-identified raw data, and a Finals Application. Up to 10 teams will be chosen as Finalists and share a Milestone 2 award of $10,000,000 ($1M per team). For more information, please refer to the Finals Submission Guidelines.

Note: Semi-Finals will not be conducted for the FSHD Bonus Prize; Qualified FSHD teams will advance directly to Finals: 1-Year Clinical Trials.

Finals Testing - 1-Year Clinical Trials

To be eligible to win the Grand Prize, teams must recruit participants and conduct prospective clinical trials with a 1 year (or less) intervention period in persons aged 50-90 years without major life-threatening conditions or disability. To be eligible to win the Grand Prize, teams must demonstrate their therapeutic solution can restore muscle, cognitive, and immune function (all three) using common clinical protocols to be included in Rules & Regulations document. Prior to the start of Finalists' trials, the assessment measures and specific adjudication criteria for awarding will be made available.

Data for XPRIZE Healthspan must be recorded in a centralized database that will be managed by the **XPRIZE Healthspan Data Coordinating Center at the University of Utah (XPRIZE-Utah DCC)**. The XPRIZE-Utah DCC is an independent entity with a contract to operate with XPRIZE and tasked with providing comprehensive support for the collection, coordination, management, reporting, and storage of data arising from XPRIZE Healthspan Finalists' clinical trials. A pre-specified set of biospecimens will be collected according to standard operating procedures outlined by XPRIZE. Teams can collect additional data provided it does not limit or interfere with

the assessments required for judging. XPRIZE and Utah DCC key personnel and XPRIZE Healthspan Judging Panel members must be able to visit the Teams' laboratories and audit their results.

For awarding, the magnitude of the improvement across all three systems compared with controls will be indexed to a personalized response threshold by the XPRIZE-Utah DCC. The response thresholds used for awarding will be determined by the expected age-related declines over 10 years, 15 years, or 20 years in a referent **population** such as the Baltimore Longitudinal Study of Aging (BLSA).[29, 30, 31] Please see Section 9 and subsection Finals Judging for details.

Finals Testing – FSHD Bonus Prize

To be eligible to win the FSHD Bonus Prize, teams must recruit participants and conduct prospective clinical trials with an intervention period one year or less in genetically confirmed FSHD patients aged 50-90 years and without additional major life-threatening conditions or disability. Teams must demonstrate their therapeutic solution substantially improves FSHD-relevant muscle outcomes muscle function based on: 1) 10% or more reduction in muscle fat infiltration or change in a relevant FSHD biomarker AND 2) a 20% corresponding improvement of muscle function based on at least three FSHD-relevant functional measures, through a therapeutic treatment lasting 1 year (or less) in 4 genetically confirmed FSHD patients aged 50-90(*) years without additional major life-threatening conditions or disability. FSHD Bonus Judging Panel must be able to visit the Teams' laboratories and audit their results as necessary.

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 **$500 Pre-Registration Fee**
November 2023 to June 2024	Public Comment Period	Comments may be sent to healthspan@xprize.org
PRIMARY REGISTRATION & QUALIFYING SUBMISSIONS		

By July 31, 2024	Published Official Competition Guidelines	Published Competition Guidelines and Application for Qualifying Submission released Competitor Agreements available (see Team Registration)
July 31, 2024 - December 20, 2024	**Primary Registration Period**	**Primary Registration Deadline: December 20, 2024, USD $1000.** **Signed Competitor Agreement required with payment (see Team Registration)**
August 26, 2024	Team Summit	In-person at Aging Research and Drug Discovery Meeting in Copenhagen, and/or virtual meetings
December 20, 2024	**Qualifying Submission Deadline**	**Detailed Qualifying Submission Deadline for Judging and Milestone 1 Awards (see Competition Stages)**
February-March 2025	Qualifying Submission Judging (Healthspan and FSHD Milestone 1 Awards)	Judging Panels review submitted qualifying materials for XPRIZE Healthspan and FSHD Bonus
March-April 2025	Healthspan Semi-Finalist and FSHD Bonus Finalist Teams Notified	Up to 40 Healthspan Teams and up to 8 FSHD Teams will share Milestone 1 prize purses (see Prize Purses) Qualified FSHD Teams will advance to FSHD Bonus Prize Finals (to be held concurrently with Semi-Finals for the Healthspan Prize)
May 12-14, 2025	Milestone 1 Award Ceremony Team Summit and Investors Summit	Award Ceremony for XPRIZE Healthspan and FSHD Bonus teams for Milestone 1 prize purses. Concurrent Team Summit and opportunity for teams to meet and pitch to potential Investors or Funders.
HEALTHSPAN SEMI-FINALS START AND FSHD BONUS FINALS START		
June 1, 2025	Semi-Finals Discretionary Late Registration Open	Late Registration Fee, **USD $10,000** See Team Registration for details

November 2025	FSHD Finals Rules & Regulations published	Rules for final round of FSHD Bonus Prize released
By February 2026	XPRIZE Healthspan Rules & Regulations published	Rules for final round of XPRIZE Healthspan released
April 13, 2026	**Data and Finals Application Submission Deadline for Healthspan Semi-Finals Judging**	**Judging Panel reviews submitted materials for XPRIZE Healthspan**
May-June 2026	Semi-Finals Judging (Milestone 2 Award) and Finalist Teams notified	Independent Judging Panel reviews finals applications submitted for XPRIZE Healthspan
August 11-13, 2026	Milestone 2 Award Ceremony and Team Summit	Finalist Teams Announced at Award CeremonyUp to 10 Healthspan Teams will share Milestone 2 prize purse (see Prize Purses) Concurrent Team Summit to review protocol for Finalist Clinical Trials, and initiate team coordination with the DCC
HEALTHSPAN FINALS START		
August 2026	Finals Discretionary Late-Registration Open	Late Registration Fee of **USD $100,000** to support ad hoc Judging Panels review and onboarding
February 2027	Finals Discretionary Late-Registration Closes	Close last Competition entry period for the Healthspan track
December 2027	FSHD Finals Discretionary Late-Registration Closes	Last Competition entry period for the FSHD Bonus track closes
2027 - 2029	Teams Summit & Interim Reporting	In-person and/or virtual meetings to foster collaboration opportunities and align resources and assessment measures
By December 2029	Finalists Study Close-Out	Clinical trials data close-out and Finals judging procedures
By January 2030	**Final Data Submission Deadline for All Finalist Teams**	**Final data and specimen submissions XPRIZE Healthspan teams** **Final report submission from XPRIZE FSHD Bonus Prize teams**

Q3-Q4 2030	Finals Judging	Independent Judging Panels review submitted finals materials XPRIZE Healthspan and FSHD Bonus Prize
By December 2030	**Grand Prize Award Ceremony and Winners of Healthspan and FSHD Bonus 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 business 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.

Eligible Organizations

Public or Private Higher Education Institutions

- Public or Government Controlled Institutions of Higher Education
- Private Institutions of Higher Education

Nonprofits Other Than Institutions of Higher Education

- Nonprofits with 501(c)(3) IRS Status (Other than Institutions of Higher Education)

- Nonprofits without 501(c)(3) IRS Status (Other than Institutions of Higher Education)

For-Profit Organizations
- Sole Proprietors
- Small Businesses
- For-Profit Organizations (Other than Small Businesses)

Eligible Individuals (Team Leader)
Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Team Leader is invited to work to develop a Qualifying Submission.

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. Teams can also transfer from the XPRIZE Healthspan track to the FSHD Bonus Prize track during the Competition by submitting a letter of intent to transfer registration that will be reviewed and approved by the judging panel(s).

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 solution if they define their screening approach *a priori*. This screening must be used to identify a distinct therapeutic solution (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 solution, and 2) each distinct therapeutic solution must be submitted by a

unique contact Team Leader. Please refer to the Competitor Agreement for more details. Duplicate or highly overlapping therapeutic solutions will not be advanced. This means if judges identify two or more meritorious teams with substantial overlap, only one competing team with that unique therapeutic / combination will be allowed to advance. The competing teams with overlapping therapeutics will be asked to convene and determine a course of action, for example, to collaborate and merge as a single team. If a merger or collaboration is not achieved, only one team will be selected to advance.

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, areas of expertise)
- Proposed solution focus areas (e.g., device, biologic, etc.)
- Areas of technical or subject matter expertise a team has or will seek support
- Whether the team is open to collaboration opportunities or investment / funding

Registration Submissions are due by the standard registration deadline of each Competition track but it is recommended to complete the submission sooner. Completing the Registration Submission for a given track will allow access to subsequent activities within that track, especially Registration Fee payment and Competitor Agreement signature activities.

XPRIZE encourages teams to begin designing their therapeutic solutions 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, and convening Healthspan and FSHD Judging Panels. Team Registration must take place by the registration deadlines below.

Registration Dates:

- Intent to Compete: November 29, 2023 - July 30, 2024
    - Fee: $500
- Primary Registration: July 31, 2024 - December 20, 2024
    - Fee: $1000
- Discretionary Late Registration: January 1, 2025 to February 2027
    - Fee: $10,000 and up (see below)
- Discretionary Late Registration for the FSHD Bonus Prize will remain open until December 20, 2027 for both new or existing teams.

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 (healthspan@xprize.org).

Teams competing in XPRIZE Healthspan can also submit their therapeutic under the FSHD bonus track to compete for the FSHD Bonus Prize at no additional registration fee. Qualified Teams competing in the Healthspan Competition can transfer to the FSHD Bonus track at no additional registration fee, but must submit a letter of intent to transfer to XPRIZE for review by the FSHD Judging Panel.

If teams are unable to fund the registration fee, XPRIZE Healthspan will consider requests for discounted or waived fees for nonprofit teams - including academic or research institutions and student-led groups - or other valid reasons of financial hardship. Approvals are determined on a case-by-case basis; please submit inquiries to healthspan@xprize.org.

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 after a team makes their registration fee payment. The Competitor Agreement will be available for teams to review in detail before signing.

6. RESEARCH TYPES

Qualifying Research Types
Secondary research, preclinical studies in animal models, clinical observations in patient populations, and *in silico* research are acceptable supporting evidence for Qualifying Submissions. However, to advance through Semi-Finals and Finals, clinical trials in human subjects, per defined criteria below, are required.

For the purposes of this prize, support of human subjects research is defined as below:
Human subject means a living individual about whom an investigator (whether professional or student) conducting research:

- Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
- Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

Clinical Trials Definitions
Required: Semi-Finals and Finals require interventional clinical studies in human subjects. We define *clinical trials* as a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Your study is considered to meet the XPRIZE definition of a clinical trial even if:

- Your study uses healthy participants
- Your study does not include a comparison group (e.g., placebo or control)
- Your study is only designed to assess biological process, or the pharmacokinetics, safety, and/or maximum tolerated dose of an intervention
- Your study utilizes a behavioral or lifestyle intervention

All competing teams who advance in the Semi-Finals will conduct clinical trials by XPRIZE definition criteria above. Competitors must also abide by the local regulatory agency's rules and policies, and must have appropriate regulatory approvals and safety oversights per their clinical center prior to enrolling human subjects. The teams must also include permissions and informed consent statements to allow XPRIZE to access clinical trial data and biospecimens for judging.

Semi-Finals Research Types
Semi-Finals will include early-stage and proof-of-concept trials. For the purposes of XPRIZE Healthspan, these studies can be used to show feasibility of approach, develop participant

recruitment strategies, demonstrate study methods, evaluate best therapeutic solution dosing / formulation / route of administration / protocol / combination, provide initial estimates of safety, and generate other supportive data useful for planning the 1-year clinical trials required for Finals testing. *Semi-Finals testing is not required for the FSHD Bonus Prize.*

Finals Research Types

Finals will entail 1-year Single-Crossover Randomized Phase II Clinical Trials in persons free of life-threatening illness and disability aged 50-90 years. For the FSHD Bonus prize, similar trial designs are recommended but conducted in persons with genetically confirmed FSHD and the trial duration will be less than 1 year. The response thresholds required for adjudication and prize awarding will be personalized (based on within-person improvements compared to their baseline measurements) and determined by XPRIZE and announced prior to Finals judging. These are prospective trials and Finalist teams will be expected to use a common clinical protocol and the XPRIZE Healthspan will central data collection and management system as outlined in the Rules & Regulations that will be provided to Finalists prior to testing.

7. MILESTONE 1: QUALIFYING SUBMISSION

This section contains a brief overview of the Qualifying Submission Process. Please see the Qualifying Submission Applications for the Healthspan and FSHD Bonus Tracks here. Teams interested in competing in BOTH Healthspan and FSHD Bonus Prize must submit two Qualifying Submission applications, one to each of the two prize tracks as Competition stages, patient populations, and Judging Panels differ.

TABLE 3. Qualifying Submission Dates and Judging Dates

Due Date	**Review Dates**		
Qualifying Submission (Healthspan and FSHD)	**XPRIZE Internal Administrative Review**	**XPRIZE Judges Review & Notifications**	**Milestone 1 Award Ceremony**
December 20, 2024	January 2025	March-April 2025	May 12, 2025

- All Qualifying Submissions are due by 7:00 PM Pacific Standard Time.
- Competitors are encouraged to apply early to allow adequate time to make any corrections to errors found in the Qualifying Submission by the due date.
- No late applications will be accepted for consideration of an award at Milestone 1.

The Qualifying Submission is the first formal opportunity for prospective teams to demonstrate their ability to proceed through the Competition. The Qualifying Submission is the means by which teams are initially assessed by XPRIZE Judges for their ability to ultimately compete in XPRIZE Healthspan and FSHD Bonus Track.

The Qualifying Submission is a written declaration of the skills, experience, clinical and laboratory facilities, and attributes of teams as well as an outline of the proposed therapeutic solution and plans for advancement in the Competition. XPRIZE does not expect that the Qualifying Submission will be a full representation of the final tested therapeutic. XPRIZE expects and anticipates that the Qualifying Submission will provide:

- background and rationale on the therapeutic or combination of therapeutics
- documented proof that the intervention has been regarded as safe by a regulatory body or is under consideration by an appropriate safety and regulatory body
- evidence supporting use of the therapeutic on relevant endpoints or biomarkers
- an assessment of safety and potential risks and benefits to human subjects

- supporting information demonstrating skills and experience of the team
- evidence of the quality of the clinical center that will be engaged for testing
- appropriate regulatory approval or evidence that regulatory approval will be obtained prior to testing
- description of the early stage clinical testing proposed for judging of Semi-Finals stage of Competition
- Statement describing sources and scope of funding and state of intellectual property for their proposed solution

In summary, the Qualifying Submission will describe the teams' therapeutic solution, supporting evidence, strengths of team and clinical center, and proposals for Semi-Finals early stage clinical testing (or Finals testing for FSHD Bonus Track). Qualifying Submissions should take a risk-based approach to answering the questions herein. XPRIZE does not require all clinical studies to be completely described at the time of Qualifying Submission but does expect teams to demonstrate the ability to fully address all criteria in the fullness of time.

Review and Selection Process
Qualifying Submissions will be evaluated for scientific and technical merit by Healthspan and Judging Panels convened by XPRIZE Foundation. Teams must reference the Qualifying Submissions guidance documents for the description of submission components, page-limits, detailed list of judging criteria.

For teams competing in both Healthspan and FSHD, please note that two independent Judges Panels will be convened, one for each prize track. Separate Qualifying Submissions must be completed for each prize track.

Completed Qualifying Submissions undergo a selection process in which only those applications that are fully complete will be reviewed by Judges Panels and assigned an overall score. These judged applications will receive a brief written critique.

Appeals of Judges Review will not be accepted.

The judges will use the questions detailed above to evaluate the teams' solutions based on:

1. Team
2. Environment & Clinical Center(s)
3. Scientific Rationale & Preliminary Data
4. Approach to Semi-Finals Testing *(or Finals for FSHD Bonus)*
    a. Study Design
    b. Ethical Issues
    c. Data Management & Statistical Analyses

    d. Sample Size Justification
5. Study Timeline
6. Scale & Accessibility

Each of the above categories has a possible range of 1 to 9 points, with 1 being the best and 9 being the worst. The Overall Score will also be on a 1-to-9 point scale and will reflect the assessment of the complete Qualifying Submission.

Human subject safety, financial fitness to compete (resourcing plan), safety and handling of potential biohazards that may be encountered in the development, distribution, storage, or handling of their therapeutic solution will also be considered as either acceptable or unacceptable. Biological hazards (biohazards) refer to biological substances that may pose a threat to the health of living organisms, including humans. This can include medical waste or samples of a microorganism, plants, animals or their byproducts, viruses, or toxins from a biological source that can affect human health.

Overall Score

The weighting of categories is a collective decision that the judges will make during the Judging Summit, which is a meeting that takes place before the presentation of the Semi-Finalist teams. The judges will review the questions and discuss their relevance and importance for the Competition. They will also consider the feedback and input from the prize operations team, Scientific Advisory Board, and Co-Title sponsors, who are the stakeholders that define the problem and the requirements for the Competition.

The Overall Score may not be the average of all component scores. Judges will assign different weights to each question to reflect their relative importance, impact on the overall submission, and potential success of the team in the 7-year XPRIZE Healthspan Competitions. This ensures that the judges reward the teams that demonstrate the most effective and feasible solutions for the XPRIZE Healthspan challenge to proceed to Semi-Finals.

The judges will also document the score for each of the 6 judged components and provide the rationale for how these component scores drive the Overall Score.

The judges can revise or adjust the weights during the final presentation if they encounter new information or insights that affect their evaluation of the teams' solutions.

Selection Process

Applications will first be subject to administrative review and screened for completeness. Judges will review screened applications deemed acceptable for review. The Judges will convene to select the Top 40 best performing teams (lowest overall scores) for XPRIZE Healthspan, and up to

the top 8 teams for FSHD Bonus Prize. These selections will be submitted to XPRIZE and the Co-title Sponsors for review and acceptance prior to notification of teams.

Milestone 1 Awarding

The Top 40 best performing teams (lowest total scores) for XPRIZE Healthspan will be announced as Semi-Finalists in acknowledgment of their promising research and to provide initial support for the next stage of testing (Semi-Finals) in the Competition.

Up to the Top 8 best performing teams (lowest total scores) for the FSHD Bonus Prize will be announced as Finalists in acknowledgment of their promising research and to provide initial support for the next stage of testing (Finals) in the Competition. This is the only milestone award for the FSHD Bonus Prize.

Competition Advancement

The teams selected for Milestone 1 awarded will automatically advance through to the Semi-Finals stage of testing.

Additional teams may opt to continue in the Competition if their Qualifying Submission was reviewed but was not awarded. The judges' comments will be provided to teams, and teams who wish to continue are encouraged to address concerns raised by judges during the review process. Non-awarded teams must state their intent to remain in the Competition and are encouraged to meet with the XPRIZE Healthspan operations team to discuss options for remaining in the Competition.

Discretionary Late-Registration

A discretionary late-registration period will continue through Semi-Finals. Teams registering after the deadline must first consult with the XPRIZE Healthspan operations team and provide a letter of intent to compete (up to 2 pages, emailed to healthspan@xprize.org). If the letter of intent to compete is approved, these teams must complete a Qualifying Submission that will be administratively screened and reviewed by an ad hoc judges' panel. Approved late-registrations are not eligible for Milestone 1 awarding and must adhere to all deadlines for submissions of data and reporting by Semi-Finalist teams.

8. MILESTONE 2: SEMI-FINALS TESTING

This section briefly describes the requirements and judging criteria for Semi-Finals testing for Healthspan. There are no Semi-Finals for FSHD Bonus Prize.

Purpose & Objectives

Early stage and Proof-of-Concept (PoC) Studies are typically short (less than 30-60 days), small (5-20 people receive active therapeutic intervention), and relatively inexpensive studies that are used to help design and justify larger clinical trials. For XPRIZE Healthspan Semi-Finals, these trials are used to indicate readiness for Finals and feasibility of approach.

We allow our teams the flexibility to define key design features needed to demonstrate feasibility and readiness in Semi-Finals, but are encouraged to discuss approaches with XPRIZE Healthspan operations. Teams will propose their own study design, endpoints and assessment measures needed, and criteria used to support go / no-go decisions. Qualifying Submissions will be used as the primary application to proceed to Semi-Finals Testing, and are due December 20, 2024.

During Semi-Finals teams are expected to engage the clinical center that will be used in Finals and conduct a small study to demonstrate likelihood of successful completion of a 1-year clinical trial in Finals. Teams will be responsible for submitting regulatory and human subjects safety approvals, engaging a clinical center for testing, acquiring and administering the therapeutic solution, collecting and managing data, and submitting reports to XPRIZE. Semi-Finals trials should also provide evidence that it will be feasible to enroll and retain participants meeting their Inclusion and Exclusion Criteria. It is not necessary that team solutions reach statistical significance criteria $p<0.05$, but data should support planning, logistics, and infrastructure for 1-year clinical trials.

The XPRIZE Healthspan Data Coordinating Center at University of Utah (XPRIZE-Utah DCC) will NOT be engaged for prospective data collection and management, but may assist in auditing data reports and de-identified data. Teams must ensure appropriate permissions are obtained and consent statements to allow XPRIZE access to de-identified data sets for the purpose of results audit and verification as needed.

Data Submission & Finals Application. At the end of Semi-Finals teams will submit:

1. Recruitment / enrollment reports
2. Analyses and data reports
3. De-identified data set
4. Finals application

The data and reports will undergo verification and review and will be formatted for judging. In some cases the de-identified data will be reanalyzed to confirm reported results. The Finals application guide is available here. Information in the publicly available Finals Application details the recommended information teams should include in their application to allow Milestone 2 judging of the:

1. Team
2. Clinical center
3. Scalability & Accessibility of the Therapeutic Solution
4. Scientific Rationale
5. Preliminary Data and Reports from Semi-Finals
6. Finals Testing Approach
7. Timeline
8. Safety, human participant protections, regulatory approvals, and resourcing plans

The Finals Application will be supplemented by data reports from Semi-Finals, including:

1. Regulatory approval notice or ethical assurance for Semi-Finals studies
2. Recruitment and enrollment reports for Semi-Finals
3. Primary analyses from Semi-Finals (if additional space needed)
4. De-identified data set for Semi-Finals
5. References
6. Regulatory Approval Letter(s), Consent, or plan for submission for Finals (if available)

Judging Semi-Finals / Milestone 2

Judges will review team-provided analysis reports, a Finals application, and they may access and reanalyze de-identified raw data files. The judges will use the questions detailed above to evaluate the teams' solutions based on:

1. Team
2. Clinical center
3. Scalability & Accessibility of the Therapeutic Solution
4. Scientific Rationale
5. Preliminary Data and Reports from Semi-Finals
6. Timeline
7. Finals Testing Approach

Each of the above 7 categories has a possible range of 1 to 9 points, with 1 being the best and 9 being the worst. The Overall Score will also be on a 1-to-9 point scale and will reflect the assessment of the complete Finals Application. Human subject safety, financial fitness to compete (resourcing plan), and regulatory approvals will also be considered as either acceptable or unacceptable. Up to 10 teams will be chosen as Finalists for XPRIZE Healthspan and share a Milestone 2 award of $10,000,000 (e.g., $1M each for 10 awarded teams).

9. GRAND PRIZE: FINALS TESTING

FINALS TESTING SUMMARY

This preliminary Finals Testing Framework was informed by a panel of Scientific and Technical Advisors (Appendix D). Further details and clinical protocols will be found in Rules & Regulations. Trial design is subject to change; teams will be notified of changes made to the key trial criteria.

Teams will conduct 1-year single-crossover controlled phase 2 trials with personalized response thresholds to conclusively demonstrate that their therapeutic solution - administered alone or in combination - can improve tests of muscle, cognition, and immune function. Members of the Judging Panels, the DCC, and key prize operations personnel must be given access to Teams' laboratories, clinical research centers, and access to data for judging and audit of results.

Phase: Phase 2

Number of Clinical Centers: Teams can engage a single or multiple Clinical Centers, but must provide information on the centers and environment to XPRIZE for review and judging.

Population. Primary eligibility criteria for XPRIZE Healthspan are persons aged 50-90 years, free of major life-threatening disease and disability; or with genetically confirmed FSHD for the FSHD Bonus Prize. Teams may recruit persons with evidence of functional decline, presence of a subclinical or managed condition or disease, or other *a priori* defined indicator of elevated risk of healthspan decline. Teams will define key criteria for inclusion / exclusion (with input from judges).

Intervention(s). In the context of XPRIZE Healthspan, "therapeutic treatments" (or "therapeutics", "therapeutic solutions", or "therapeutic interventions") refers to active drugs, biologics, devices, gene therapies, nutritional supplements, dietary interventions, lifestyle interventions or other approaches - alone or in combination. This list is not exhaustive.

Control. Teams must include defined time controls, standard of care, or other alternative as appropriate for the proposed approach to minimize confounding and bias. When possible, assignments should be randomized and masked.

Healthspan Outcomes. The following outcomes will be assessed using standard protocols by individuals who are masked to group assignment. See section on Endpoints for both preferred and acceptable measures:

> **Muscle Function Outcomes:** Improvement from baseline that exceeds personalized response thresholds in endurance capacity (6MWT *mandatory*, peak VO_2 *optional*) and lower body power.
>
> **Cognitive Function Outcomes:** Improvement from baseline that exceeds personalized response thresholds as measured by the CANTAB computerized cognitive assessment that

include measures of memory, executive function / attention, processing speed. Functional assessment batteries will be supported by circulating biomarkers measured by XPRIZE Central Laboratories.

Immune Function Outcomes: Improvement from baseline that exceeds personalized response thresholds in 2 out of 3 biospecimen-based biomarker categories as measured by XPRIZE Central Laboratories. Specifically, iAge and IMM-AGE scores comprise 2 of the assessments, with a 3rd biospecimen-based measure to be named prior to the end of Finals (e.g., may include *ex vivo* naïve immune response to a new stimulus).

Tertiary Endpoints: Several suggested measures are provided to aid judging considerations of safety or broaden scientific impact, but not included in primary Grand Prize judging criteria. These will be detailed in Rules & Regulations, and may include changes in outcomes that are not domain specific, patient reported outcomes, self-reported health events, adherence, novel biomarkers, and clinical risk factors.

Healthspan Grand Prize Judging Criteria. Awarding is based on personalized response thresholds based on epidemiological and population data (See **Figure 4**). Each participant's change from baseline (the average of 3 baseline measurements) to the achieved XPRIZE-defined personalized response values based on the average of 2-3 post-intervention measurements will determine a 'positive response' outcome for each assessment.

FSHD Outcome. The following outcomes will be assessed using standard protocols by individuals who are masked to group assignment. Also see section on FSHD Outcomes & Endpoints. Improvement from baseline that exceeds (1) a 10% reduction in muscle fat fraction using any appropriate imaging method OR an acceptable muscle-derived or circulating biomarker AND (2) a 20% improvement in at least 3 functional tests from relevant clinical outcomes assessment, such as, but not limited to, the following list:

1. 6 minute walk test (6 MWT)
2. Gait speed (GS)
3. Grip test (GT) using handgrip dynamometer
4. Knee extensor maximum voluntary contraction (MVC)
5. Knee extensor power (or 1-Repetition Maximum)
6. Timed up and go (TUG)
7. Revised Upper Limb Module (RULM)
8. FSHD-COM (complete test or select components)
9. Reachable Workspace (RWS)
10. Novel, validated functional endpoint relevant toFSHD

Time. XPRIZE Healthspan finalist trials will be conducted over 4 years (2026 - 2029). Trials schedule of assessments should include three consecutive baseline assessments followed by a 1-year therapeutic intervention period with repeat interim and post-intervention follow-up

assessments. Enrolled XPRIZE Healthspan participants are anticipated to participate for a minimum of 14 months, with a median duration of 16 months expected. The FSHD Bonus prize intervention period will be one year or less, with recommended intervention duration provided in FSHD Bonus Rules & Regulations.

FINALS PARTICIPANT ENROLLMENT AND RETENTION

Overview of Participant Enrollment

Participants in the finalists' trials must be 50-90 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 intervention time frame. Suggested 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 50 years of age 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. An estimate of the number of participants enrolled and randomized will be provided by teams. The Judging Panels 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 approximately 100 total participants will be required to achieve the large effects required to win the Grand Prize for XPRIZE Healthspan (recommended minimum 40, maximum 200 total participants are allowable). Given the rarity of FSHD, the anticipated sample size for the FSHD Bonus prize is at least 40 total participants required for Finals testing though teams must still provide power calculations and sample size justification.

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 ethnic and racial composition reflective of the geographic region from which recruitment will occur. Teams should proactively incorporate best practices to build diverse and inclusive research participant recruitment strategies, and XPRIZE 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-Utah DCC** 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 therapeutics. In the context of XPRIZE Healthspan, therapeutic solution 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, therapeutic interventions can be proposed for use alone or in combination. The Healthspan and FSHD Judging Panels will review therapeutic interventions from teams' Qualifying Submissions for safety, feasibility, and appropriateness for testing within the Competition. In each case the teams must demonstrate adequate preclinical evidence, 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.

Interventions cannot include measures used for endpoint assessment. For example, training 1-repetition maximum using similar equipment to that used to test muscle power is disallowed, as is training on the same (or very similar) computerized measures of cognitive function.

When exercise is included as a component of a team's therapeutic solution, our judges will review to ensure it does not substantially overlap with proposed endpoint assessments and may provide

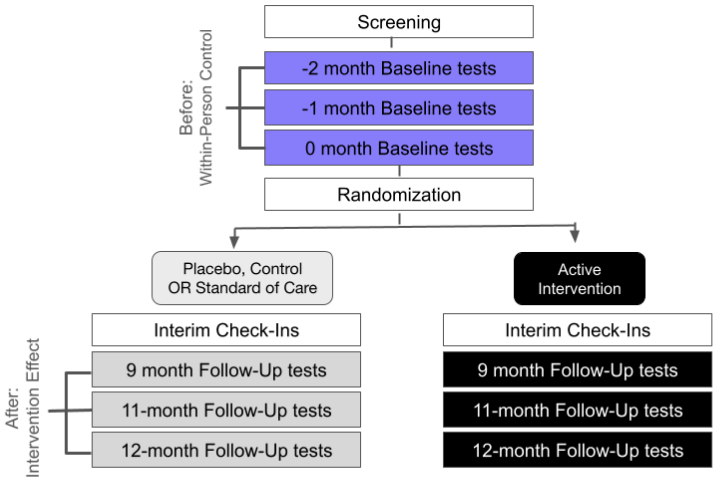
additional guidance. For example, activity levels may be monitored for all teams, and we strongly suggest teams provide information on World Health Organization recommended guidelines on activity levels to all participants (therapeutically treated and control groups) as a standard of care.

FINALS TESTING STUDY DESIGN

Finals Study Design. To be eligible to receive the Grand-Prize Award, teams must conclusively demonstrate that their therapeutic solution improves tests of muscle, cognition, and immune function in 1-year single-crossover controlled phase 2 trials with personalized response thresholds. This design permits determination of the effect of a therapeutic solution within a study participant and is robust to high heterogeneity of effect, non-ideal conditions, and differing participant characteristics that will be encountered in the prize. Team data must be collected prospectively. XPRIZE Healthspan Finalists must report data to the **XPRIZE-Utah DCC** who will provide comprehensive support for the collection, coordination, management, reporting, analysis and storage of data arising from trials needed for Judging.

This is a before / after intervention experimental clinical study design with a single cross-over that consists of a 3 month baseline period and 1-year intervention window (**Figure 2**); Note that FSHD Bonus Prize may be less than 1 year intervention window. Key features are 3 x repeat baseline testing and up to 3 x repeat follow-up testing. This is intended to establish a baseline control condition (purple bars) to evaluate the magnitude of within-person change following randomization to intervention (gray-scale bars). Baseline and Follow-Up tests include the Healthspan or FSHD Outcomes and Endpoints summarized above and described below in Finals Testing Outcomes and Endpoints. XPRIZE and the Utah DCC will provide clinical protocols, **standardized operating procedures (SOPs)** for specialized data and biospecimen collections, and training to Finalist teams. The trial design may be two arms (active intervention vs control), or include alternatives that may be compared to each other or to control condition - e.g. subcomponents of active interventions for factorial designs.

FIGURE 2. Finals Study Design Schematic: 1-year single-crossover controlled phase II trial



Finals Study Assessment Schedule. All Finalist teams will use a common-assessment schedule but be allowed to add more measurements if they wish. The therapeutic will be evaluated in a 1 year intervention window (e.g. judged Follow-Up testing through 12 months after Baseline testing). FSHD Bonus may be evaluated in less than a 1-year window; the suggested schedule will be outlined in the FSHD Rules & Regulations. Interim data collection (e.g., 6 months) for outcome measure assessment 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. Frequency and duration of intervention or therapeutic combinations during the 1 year period is at teams' discretion per their therapeutic intervention. For the FSHD Bonus Prize, a similar approach should be implemented.

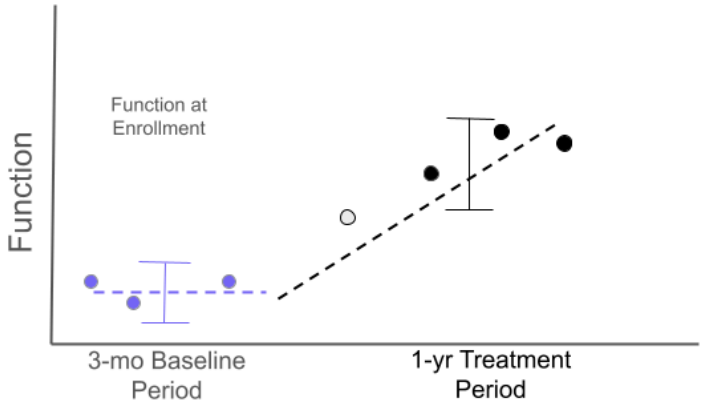
TABLE 4. Example Finalist Study Assessment Schedule

Assessment	Screen	Base V1	Base V2	Base V3	Random	FU V1	FU V2	FU V3	FU V4
	-1mo	0mo	1mo	2mo		6mo	9mo	11mo	12mo
Screening	X								
Muscle		X	X	X		X	X	X	X
Cognitive		X	X	X		X	X	X	X
Immune		X	X	X		X	X	X	X
Biospecimen		X	X	X		X	X	X	X
Safety / Clinical		X	X	X		X	X	X	X

Evaluating Within-Person Improvements in XPRIZE Healthspan. Figure 3 below depicts how XPRIZE will determine the targeted or required change in function using longitudinal assessment in a single participant. Three assessments from Baseline Visits (Figure 3, purple) and three

Follow-Up Visits (Figure 3, black) will be obtained at the Team's clinical center and used for outcome determination. Interim assessments are used to support judging (Figure 3, gray). The proportion of positive responders (those who exceed personalized response thresholds) in the treated relative to control will be used for prize adjudication. **The age- and sex-specific personalized response thresholds will be determined by XPRIZE**, and will indicate the targeted or required change necessary to exceed 10 year, 15 years, and 20 years declines based on a referent population (see Healthspan Finals Judging Criteria for details).

FIGURE 3. Within-Person Improvement Example



FINALS TESTING OUTCOMES AND ENDPOINTS

XPRIZE Healthspan Outcomes and Endpoints

The main outcome for Grand Prize adjudication is operationalized as the within-person change in assessments of muscle, cognitive, and immune function relative to baseline. The proportion of individuals who reach a predetermined threshold of change will be compared between intervention and control groups. Each functional domain will be evaluated based on a set of appropriately validated assessment measures. Specific assessments required for teams to include in their Finals trials are given below and a definitive set of **SOPs** will be provided to teams in the **Rules & Regulations** for Finals testing. For the purposes of this prize, muscle function represents a functional domain that is inclusive of measurements such as exercise capacity and leg muscle power; muscle mass is strongly recommended but optional. Similarly, cognitive function will be assessed based on a specific set of computerized neuropsychological assessments, and immune function based on immune cell counts or phenotyping, circulating cytokines, or a proxy for cellular response to immune challenge or exposure.

The specific assessment measures were determined following a public comment period (see Competition Stages and Milestones for timeline) in consultation with scientific and technical

advisors (Appendix D), independent investigators, teams, and regulatory officials. Assessors, data collectors, and similar team staff and investigators should be masked to group assignment conditions during evaluations to whatever extent is possible.

The measures chosen are supported by critical evaluation of test-retest reliability, feasibility of use, and quality of existing data. The measures are meaningful to the general population and predictive of future risk of clinical outcomes relevant to healthspan, like hospitalization, incident disease, disability, or mortality. All teams will be required to use the specific assessment measures detailed in the *to be developed* **Rules & Regulations** clinical protocols for Finals Judging.

Measures that are listed as supportive or recommended but optional may be influential for judge consideration reflecting on collective measurement characteristics in the case of a tie or team data at the cusp of a 10-, 15-, or 20-year thresholds for a given domain.

Finals Endpoint Assessment Measures

MUSCLE FUNCTION

Muscle function will be assessed by Endurance Capacity (6MWT) and Lower Body Power by all teams. Measures of muscle mass are strongly recommended to include for judge consideration but optional for team inclusion in Finals trial protocols.

Strongly recommended but optional measures may be influential for judge consideration reflecting on collective measurement characteristics in the case of a tie or team data at the cusp of a 10-, 15-, or 20-year thresholds for a given domain.

TABLE 5a. MUSCLE ENDPOINT ASSESSMENTS & JUDGING

Subdomain	Assessment Measure	Measured by:
Endurance Capacity*	Primary: 6-minute Walk Test (6MWT)[32] *For Judge Consideration (optional):* *Cardiopulmonary Exercise Test (peak VO_2)*[33]	Team
Lower Body Power*	Primary: Knee Extensor Power or Leg Press Power[34]	Team
Muscle Mass (Supportive)	*For Judge Consideration (optional):* *Urinary D3 Creatine Dilution*[35, 38] *CT muscle volume*[37, 38] *MRI muscle volume*[37]	Team
Muscle Score – exceed threshold for % improvement in Endurance Capacity AND Lower Body Power assessments. All teams must perform 6MTW and lower body power (by either knee extensor or leg press equipment). The strongly recommended but optional measures are used as supportive evidence for judge consideration during grand prize determination. If teams include muscle mass assessment for judge consideration, then they must also show		

measurable improvement in endurance and lower body power.

Procedures detailed in Rules & Regulations; brief descriptions below:

Endurance Capacity (Required) will be measured by 6 minute walk test (6MWT) in all research participants by all teams, but teams may opt to also include the more sensitive Cardiopulmonary Exercise Testing (CPET) derived measures of peak VO2 for judging.

> *6 min walk test, 6MWT (Required)*: Distance achieved over brisk 6-min walk on 30-meter flat course. Protocol includes participant-paced walking performed as quickly as possible without running, using standardized instructions with encouragement. Outcome Measures: Total distance walked (primary), lap times, stops (number/duration), symptoms, assistance required.
>
> *Cardiopulmonary Exercise Test (CPET) - Peak VO2 (Optional)*: Gold standard for endurance/aerobic fitness using incremental exercise test with mask (exhaled gas analysis), heart rate monitor. Teams encouraged to adopt; may be more sensitive than 6MWT. Treadmill or cycle ergometer (consistent per participant). Protocols will include low-intensity warm-up and gradually increasing intensity to near-maximal fatigue. XPRIZE recommends modified Balke protocol, RER >1.05. Outcome Measures: Peak VO2 normalized to body mass (primary), VO_2 and VCO_2, maximum heart rate, ventilatory thresholds, RPE.

Lower Body Power (Required) will be measured by either knee extensor or leg press equipment, but teams have discretion to choose which exercise testing equipment they will use, so long as it is used consistently across and within participants in their trial.

> *Knee Extensor or Leg Press Power (Choose 1)*: Standardized protocols adapted to equipment. Consistent equipment per participant. Protocol: lower-body warm-up, maximal effort contractions "as hard and fast as possible," multiple efforts with 1-minute rest, body mass measured. Outcome Measures: Raw dynamometer data (torque, velocity, time), power (watts) calculated or recorded, normalized to body mass (primary).

Muscle Mass (Optional) is no longer required for measurement by all teams; judges prioritize performance over mass.However, muscle mass remains a supportive measure and teams are encouraged to adopt available methods when possible for judge consideration. Recommended but optional measures:

> *D3 Creatine (D3Cr) Dilution*: 30mg isotope labeled D3-Creatine tablet administered orally and teams obtain a fasting morning urine prior to D3-Cr and 72-144 hours later, with assays by recommended laboratory at UC Berkeley.
> *Imaging*: Computed Tomography (CT) or magnetic resonance imaging (MRI) to determine

muscle volume (thigh or total body), with specific protocols and recorded measures negotiated with XPRIZE and Utah DCC prior to collections.
Exploratory: DEXA or bioelectrical impedance are less rigorous but can be negotiated with XPRIZE and Utah DCC if D3Cr, CT or MRI are not available.

TABLE 5b. COGNITIVE FUNCTION

Subdomain	**Assessment Measure**	**Measured by:**
Memory	CANTAB Paired Associates Learning (PAL) Spatial Working Memory (SWM)	Team
Executive Function & Attention	CANTAB Stop-Signal Task (SST) Digit Symbol Substitution Test	Team
Processing Speed	CANTAB Choice Reaction Time (CRT)	Team
Circulating Biomarkers (Supportive)	*For Judge Consideration:* *e.g. Glial Fibrillary Acidic Protein (GFAP), Neurofilament Light Chain (NfL), phosphorylated tau (p-tau)*	Central Lab
Cognitive Summary Score – exceed threshold in >50% of selected cognitive function tests **NOTE:** Specific CANTAB test battery to be named prior to Finals testing in consultation with teams. Ideally cognitive assessments will require approximately 30 minutes to evaluate. **NOTE: Additional tests could be named.** Blood-based biofluid based biomarkers of brain aging will be measured by central or regional laboratories and used as supportive evidence for judge consideration.		

Detailed procedures will be provided in the Rules & Regulations manual.

CANTAB - Cambridge Neuropsychological Test Automated Battery

All teams must use the CANTAB digital cognitive assessment tool computer-based tests for memory, attention, executive function, reaction time, and processing speed.[39] Tests will be administered on touchscreens/computers in clinics (preferred) or remotely using standardized protocols. Data will be automatically logged and analyzed by XPRIZE-Utah DCC against normative data.

Memory - *Paired Associates Learning (PAL)*: 8 minutes, assesses visual memory and new learning. Outcome measures: errors, trials required, memory scores, stages completed.

Executive Function/Memory - *Spatial Working Memory (SWM)*: 4-6 minutes, assesses visuospatial information retention and manipulation. Self-ordered test measuring strategy and working memory. Outcome measures: errors (selecting empty boxes, revisiting boxes), strategy.

Executive Function/Attention - *Stop Signal Task (SST)*: 14 minutes, measures response

inhibition (impulse control). Outcome measures: direction errors, successful stops proportion, Go trial reaction time, stop signal reaction time (SSRT).

Executive Function - *Digit Symbol Substitution Test (DSST*): 2 minutes, global cognitive ability measure. Outcome measures: total correct, errors, latency (movement/response).

Processing Speed - *Reaction Time (RTI):* 3 minutes, assesses motor/mental response speeds. Outcome measures: reaction time and movement time (simple and five-choice variants).

Biomarker Assessments (Optional)

Not required but supportive of functional tests. Changes in brain aging/cognition biomarkers considered collectively with assessment data; influential in ties or near-threshold cases. Central Laboratory assays supported by XPRIZE budget; data returned to teams.

TABLE 5c. IMMUNE BIOMARKERS

Subdomain	Assessment Measure	Measured by:
Immune Cell Response to Challenge	Dynamic cell response to pathogen or stimulation – or a proxy measure using banked biospecimen (to be determined, measured centrally)	Central Lab
Immune cell composition	Immune Age (IMM-AGE Score)[40]	Central Lab
Inflammatory status	Inflammatory Age (iAge) Score[41]	Central Lab
Other Circulating Biomarkers (Supportive)	*For Judge Consideration:* *Multi-omic analyses and select assays may be used by judges in support of the above, pending development*[42,43,44]	Central Lab
Immune Summary Score – exceed threshold for % improvement in 2 out of 3 measures. **NOTE:** Assays will be performed centrally by XPRIZE Healthspan contracted laboratories. Teams will complete standardized collection and handling of peripheral blood mononuclear cells, plasma, serum, and whole blood. All biomarker data generated centrally for primary judging or judge considerations will be returned to the competing Finalist team. **NOTE: Additional tests could be named.** Blood-based biofluid based biomarkers of immune aging will be measured by central laboratories supported by XPRIZE operations and may be used as supportive evidence for judge consideration.		

A manual for procedures will be provided in the Rules & Regulations. In brief, all teams must collect peripheral blood mononuclear cells (PBMCs), plasma, serum, and whole blood per standardized operation procedures (SOPs) and ship biospecimens to a Central Laboratory for assays. Central Laboratory assay costs will be assumed by XPRIZE Operations. Data from these assays will be automatically logged with the XPRIZE-Utah DCC and analyzed against normative data for judging; raw data from central lab assays will be returned to teams. The following assays will be run centrally:

Immune Cell Response to Challenge (pending) is a measure of immune resilience or response kinetics based on pathogenic exposure or stimulus. A proxy measure of dynamic immune response using banked samples that reflects immune fitness and resilience to exposure will be identified, developed, and validated; prior to implementation using team provided biospecimen, Finalist teams will be consulted.

Immune Cell Composition - IMM-AGE requires collection of whole blood processed by standard procedures into PBMCs and serum. The samples will be processed by central laboratories in a standardized manner with multiple deep phenotyping modalities profiled.

Inflammatory Status - Inflammation Age (iAge) requires collection of whole blood for gene expression and plasma or serum separated for cytokine and chemokine determination by a central laboratory.

Other Supportive Measures (pending). Novel unified metrics of immune aging may be developed or validated during the course of competition and will be considered as supportive of the above primary immune biomarkers listed above. Teams will be consulted prior to any additional testing or consideration of novel biomarkers that may influence evaluations. All raw data generated by central laboratories will be returned to teams.

FSHD Bonus Prize Outcomes and Endpoints

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[45]. Current treatments in FSHD are focused on showing:

1. evidence of reduced fat infiltration in muscle using best practices in medical imaging OR acceptable muscle-derived or circulating biomarker,
   AND
2. corresponding improvements in muscle function.

Many functional endpoints have been tested in FSHD clinical trials[46], with the most common listed below:

Functional Outcomes:

A > 20% improvement from baseline in at least three functional tests from relevant clinical outcomes assessment, such as, but not limited to the following:

- 6 minute walk test (6 MWT)[33]
- Gait speed (GS)[47,48]

- Grip test (GT) using handgrip dynamometer[49]
- Knee extensor maximum voluntary contraction (MVC)[50]
- Knee extensor power (or 1-Repetition Maximum)[50]
- Timed up and go (TUG)[51]
- Revised Upper Limb Module (RULM)[52]
- FSHD-COM (complete test or selected components)[53]
- Reachable Workspace (RWS)[54]
- Novel, validated functional endpoint relevant to FSHD

Common Data Elements (CDEs):

Participating teams must collect CDEs at baseline and preferably at quarterly intervals during the clinical testing phase of the trial. These common data elements are outlined below, while detailed protocols will be uploaded on the FSHD TOOLKIT folder and should be adhered to as much as possible.

FUNCTIONAL DOMAIN	ASSESSMENT
Leg-Function	Go 30' or 10 meter walk-run (10 MWR)
Arm/Shoulder Function	Shoulder Abduction (Left/Right) AND Shoulder Forward Flexion (Left/Right)
Trunk Function	Sit up with feet held
Balance	Timed up and Go (TUG)
Fatigue	6 Minute Walk Test (6MWT)
Muscle Biomarker	Blood Creatine Kinase measures
Patient-Reported Outcomes	FSHD-RODS

The selected CDEs measure different functional capacities across four major domains impacted by FSHD. The majority of these measures are a subset of FSHD-COM, a composite of 15 different assessments currently being evaluated as part of a long-term natural history study. Teams may opt to carry out the full battery of FSHD-COM assessments for a more comprehensive evaluation. See the FSHD Rules and Regulations for more information.

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-Utah DCC 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.

Additionally, while measurements of muscle mass or CPET testing are optional, teams are encouraged to include them if feasible. Additionally, biomarker analyses may be expanded using central laboratory services to strengthen the evidence judges may consider to determine a winner of XPRIZE Healthspan. Muscle mass will serve as a supportive measure that may strengthen the overall interpretation of a team's results.

To support judging considerations above, the following Tertiary Endpoint Assessments may be included. These will be detailed in clinical protocols for Rules & Regulations and finalized with feedback from SAB, regulators, prize partners, and teams. These may include changes in outcomes that are not domain specific, patient reported outcomes, self-reported health events, adherence, novel biomarkers, and clinical risk factors. Examples are listed below, but these are not final. Final tertiary and safety measures will be announced in 2026.

Examples of Tertiary or Safety Assessment Measures:
Changes in outcomes that are not domain specific could include but are not limited to:

- Intrinsic capacity[55]
- Frailty defined as the accumulation of age-related health deficits[56,57]
- Activity levels
- Self-reported health and symptoms
- Overall quality of life
- Computerized assessments for depression symptoms, mood, or emotional bias test (e.g. NIH Toolbox)

Self-reported rates of health events, including but not limited to:

- Falls
- Fractures
- Pneumonia or severe respiratory illness

- Hospitalizations
- Other major health events

Changes in biomarkers of aging and clinical risk factors

- Molecular and cellular biomarker measures consistent with biological age deceleration,may include but is not limited to: proteomic, metabolomic, and DNA-methylation based biomarkers
- Blood pressure
- Body weight and / or body composition
- Hematologic measures (complete blood count)
- Metabolic biomarkers (e.g. glucose, insulin, HbA1c)
- Kidney biomarkers (e.g. cystatin C, eGFR)
- Lipid panel (e.g. total-, low density lipoprotein-, and high density lipoprotein-cholesterol)
- Bone biomarkers (e.g. bone mineral density[58] or plasma bone turnover markers)
- Alzheimer's disease and dementia biomarkers (e.g. neurofilament light chain, glial fibrillary acidic protein, plasma p-tau immunochemical assays)[59]

FINALS JUDGING CRITERIA

XPRIZE Healthspan: Judging Criteria for Grand Prize

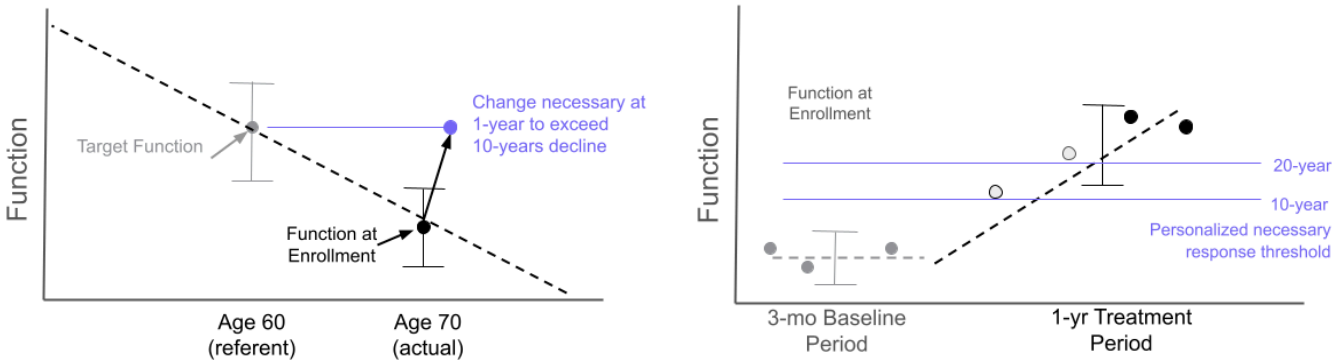
In order to win XPRIZE Healthspan, teams will measure percent within person changes in muscle, cognitive and immune function, with personalized response thresholds to be determined by XPRIZE. Awards will be indexed against the expected 10 year, 15 year, and 20 year declines in established referent populations for each domain.

Personalized Response Thresholds. Hypothetical examples in **Figure 3** above, and **Figure 4** below depicts how XPRIZE will determine the personalized (based on age, sex, and function at baseline testing) response threshold an individual must exceed to demonstrate percent change in function equivalent to expected change over 10 years in a referent cohort. The **XPRIZE-Utah DCC** will analyze and report the change in function with intervention by determining whether the individual's average change in measurement values from Baseline (e.g. months 0, 1, 2) to Follow-Up visits (e.g. months 9, 11, and 12) exceeded the predetermined response threshold. **The personalized response thresholds will be determined by XPRIZE, and will indicate the change necessary to exceed 10 year, 15 year, and 20 years declines based on a referent population. The thresholds for awarding will be released in 2026.**

At least two endpoint assessments per domain (e.g. Endurance Capacity + Muscle Power) or designated composite (e.g. Cognitive Summary Score) must be exceeded to be judged as a positive responder at a given level, and the proportion of positive responders will be used for prize adjudication.

To be eligible for the Grand Prize, the proportion of individuals who met their personalized response thresholds must be greater pre-defined criteria in the active intervention group compared to controls in all three domains (not corrected for multiple comparisons; see Power and Statistical Considerations). For example, if defining criteria are that 30% of participants must exceed personalized response thresholds, then if 37% of participants in the active intervention arm exceed 10-year threshold for muscle measures versus 5% of participants in the control condition for muscle measures, then the >30% criteria would be met and the team would be considered a 'win' for muscle. The proportion of the population required to exceed thresholds will be defined prior to Finals in consultation with advisors, sponsors, teams, and judges.

FIGURE 4. Defining Personalized Response Thresholds



FSHD Bonus Prize: Judging Criteria

FSHD Bonus Prize Criteria. To be eligible to receive the Grand-Prize Award for the FSHD Bonus Prize, teams must conclusively demonstrate that their therapeutic solution improves selected FSHD Outcomes and Endpoints within one year or less in a double-blind placebo-controlled trial or another statistically robust clinical trial design in genetically confirmed FSHD patients. The therapeutic intervention should strive to show:

- > 10% reduction in muscle fat fraction, fibrosis or increase in muscle mass using best-practice biomedical imaging OR a clinically relevant muscle-derived or circulating biomarker
- AND > 20% improvement from baseline in at least three functional tests appropriate to the therapeutic intervention.
    - One functional endpoint may be a novel, validated clinical outcome measure (including AI-enabled measures and/or other novel approaches).

See Appendix E for FSHD Bonus Prize criteria. To be eligible for the FSHD Bonus Prize,

Competing Teams must allow their key data, methodology, breakthroughs and limitations regarding their research to be provided to representatives of Solve FSHD Holdings Ltd.

POWER & STATISTICAL CONSIDERATIONS

Statistical and Analytical Plans

Teams are required to submit their own detailed statistical and data analysis plans based on the single cross-over design with pre-defined personalized response thresholds described in Finals Testing Study Design. The statistical and analysis plans should be prepared as a separate document early during the Competition, which will be reviewed and approved by the XPRIZE **Scientific 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.

The FSHD Bonus Prize will allow for investigator institutionally approved protocols. Please visit the FSHD TOOLKIT for updates as protocols become available.

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. 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, with potential attrition and loss to follow-up addressed. Research questions, hypotheses, and interim monitoring rules should be pre-specified. **We do not require adjustments for multiple comparisons for Grand Prize judging criteria above.**

Statistical Hypotheses

The primary null hypothesis of each of the trials performed in consideration for the Finals Testing in XPRIZE Healthspan is that the proportion of individuals meeting a predetermined personalized (age- and sex-specific) threshold of change in muscle, cognitive, or immune function is the same between active intervention and controls. Spontaneous improvements in control groups used by all the competing teams, collectively, may be evaluated to determine rates of spontaneous improvements across teams.

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). Personalized response thresholds will be calculated by XPRIZE staff and advisors as expected sex-stratified percent changes in function by age (e.g. per decade: 50-59 years, 60-69 years, 70-80, 80-90 years when referent data with per-decade resolution is available) and based on available epidemiological and population data.

These effect sizes (response thresholds) will be provided to teams and described in the **Rules and Regulations** for Finalists.

Rates of all adverse events will be reported for active intervention 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-Utah DCC**. Finalist teams will be trained on how to enter their trials data. Several datasets will be prepared by the XPRIZE-Utah DCC 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 Healthspan and FSHD Judging Panels 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 the Grand Prize 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.

10. 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 Panels' review.
- **Qualified Team:** A team that has been selected by the Judging Panels 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 Panels to advance in the Competition.
- **Finalist Team:** A team that has successfully completed Semifinals Testing and is approved by the Judging Panels to participate in Finals Testing and compete for the Grand Prize. This requires conducting prospective clinical trials using a common XPRIZE Healthspan **Data Coordinating Center** 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.

SCIENTIFIC ADVISORY BOARD

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

SAB will remain in place throughout the Competition to advise XPRIZE regarding scientific and other elements of the Competition. See Appendix D for a list of scientific and technical advisors.

B. **INDEPENDENT ADVISORY BOARD.** The SAB 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, and/or any team or team member. All members of the SAB 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 SCIENTIFIC ADVISORY BOARD.** The duties and responsibilities of the SAB may include, but not be limited to: (i) assisting with the establishment of qualifications for prospective Judges; (ii) recommending members of the Healthspan and FSHD Judging Panels; (iii) assisting with development of testing protocols and judging criteria; and (iv) approving and finalizing the development of these Competition Guidelines.

JUDGING PANELS

A. **SELECTION OF JUDGES FOR HEALTHSPAN AND FSHD BONUS PRIZE.** XPRIZE will propose Judging Panel candidates to the SAB for its review and consideration. The SAB will recommend the candidates it believes are best suited to serve on the Judging Panels. XPRIZE will secure the Judging Panels based on the SAB recommendations. Solve FSHD Holdings Ltd. will nominate judges to the FSHD Bonus Judging Panel. The Judging Panel and FSHD Bonus Judging Panel will each select a Healthspan Chair and FSHD Chair, respectively, from among their members.

B. **INDEPENDENT JUDGING PANEL.** The Judging Panels will be independent of XPRIZE, XPRIZE Sponsors, the current Scientific Advisory Board, Competing Teams and their employers, laboratories, and testing sites (or similar) used by Competing Teams and all affiliates of such entities. 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 Panels 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. Potential conflicts will be managed and disclosed publicly when necessary.

C. **ROLE OF JUDGING PANEL.** The duties and responsibilities of the Judging Panels 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; (ii) the awarding of points and selection of teams that will proceed to each subsequent round of the Competition; and (iii) the selection of the ultimate winners of the Competitions.

D. **GROUNDS FOR JUDGING PANEL DECISIONS.** Official decisions made by the Judging Panels 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 Healthspan or FSHD 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 Healthspan or FSHD Judging Panel shall have the sole and absolute discretion to settle the tie.

E. **DECISIONS OF JUDGING PANEL ARE FINAL.** The Healthspan or FSHD Judging Panel shall have sole and absolute discretion: (i) to allocate duties among the Judges; (ii) after consultation with the Sponsors 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) after consultation with the Sponsors 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 grant Judges full access to review and audit their Entry data, conduct site visits to laboratory facilities or clinical research centers, and will promptly assist with any such information requests from Judges. 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.

11. INTELLECTUAL PROPERTY & DATA OWNERSHIP

Each Team must own, or hold appropriate license rights to, all technologies, methods, resources, and Intellectual Property at the time of signing the Competitor Agreement for entry in the competition (please reference Section 10.1.5 of the Competitor Agreement for more information about license rights). All details relating to team technology, innovations, or methods submitted to XPRIZE will remain strictly confidential unless clearly and specifically noted (please reference Section 9.1.1.1 of the Competitor Agreement for more information about confidentiality).

Teams will retain ownership of Intellectual Property on any technology or data integration techniques and processes they bring to the Competition, as well as Data developed as part of their Competition entry. Please refer to the Competitor Agreement (Section 8.2) for more details.

For clarity, **Teams solely own their Team Data**. But Teams must grant rights to access and use data by XPRIZE and key XPRIZE partners like the Data Coordinating Center (DCC) for the purpose of judging the prize, evaluating safety or study monitoring, and reporting results of the prize to key stakeholders. XPRIZE and key partners through the DCC may also use de-identified data for public good and to advance science (teams may opt out of future use beyond judging and reporting the prize). XPRIZE will adhere to national or international regulations and medical privacy laws regarding access and use of the data and insights produced as part of the Competition. Teams must include statements in informed consent or participation waivers to allow data access, use, and material transfers to XPRIZE as needed for judging and future analyses. Teams are allowed to use data from their trials for publications, patent filings related to their therapeutic, and commercialization, but must adhere to XPRIZE marketing and communications best practices as detailed in the Team Communications Toolkit. For more details on Intellectual Property, please see the Competitor Agreement and please contact healthspan@xprize.org for questions or concerns.

12. SPONSOR RIGHT OF PARTICIPATION

Eligible Sponsors of XPRIZE Healthspan have the right (but not the obligation), at the eligible Sponsor's sole discretion, to participate for up to 5% in any equity raise by any Team that receives awards from one or more prizes for equity raises by such Team during the Competition and for an additional twelve months after the end of the Competition. For more details on Sponsor Right of Participation, please see the Competitor Agreement (Section 8.3) and contact healthspan@xprize.org for questions or concerns.

13. PAY IT FORWARD

XPRIZE Foundation is able to do its work based upon the funding it receives by entrepreneurial and philanthropic thinkers. To further the long-term sustainability of XPRIZE Foundation and its mission for the benefit of humanity, XPRIZE requests that teams entering its competitions consider participating in its voluntary "Pay it Forward" program. The Pay It Forward program describes how Teams have the option to contribute to the Foundation with a small minority percentage of the financial benefits created by the Team as a result of participating in this competition.

For more details on Pay It Forward, please see Section 7.9 of the Competitor Agreement and please contact healthspan@xprize.org for questions or concerns.

Please note: Team's participation in the Pay It Forward program is voluntary and will not affect or improve Team's chances of winning the Competition. All submissions will be evaluated solely based on their merit, following these Competition Guidelines established for the Competition.

14. APPENDICES

GLOSSARY

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.

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

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 and 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, active intervention, 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.

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

NOTE: XPRIZE Healthspan and FSHD Bonus Prize will be conducted exclusively in Human Subjects. *However, in team Qualifying Submissions they may provide preliminary data collected in animal models. In such cases, we expect that Teams adhered to the ethical and responsible treatment of animals used in their preliminary research, scientific studies, testing, or teaching.* Generally speaking, animal care and use 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 interventions, 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 interventions 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 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. XPRIZE Healthspan will provide a Clinical Protocol for Finalist teams. Here are key elements typically included in a clinical trial protocol:

- **Study Design:** It describes the overall design of the study, including the type of study (randomized? controlled? double-blind?), the number of study arms, the duration of the study, 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, therapeutics, procedures) and their administration are outlined, including dosages, schedules, methods of administration, therapeutic protocols, devices used, recommendations given, etc.
- **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.

Clinical Trial
A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Your study is considered to meet the XPRIZE definition of a clinical trial even if:

- Your study uses healthy participants
- Your study does not include a comparison group (e.g., placebo or control)
- Your study is only designed to assess biological process, or the pharmacokinetics, safety, and/or maximum tolerated dose of an intervention
- Your study utilizes a behavioral or lifestyle intervention

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

Conflict of Interest
Circumstances where the external parties involved may have interests that are not fully aligned with those of XPRIZE or the objectives of the Competition.

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

Data Coordinating Center (XPRIZE-Utah DCC)
Centralized repository that collects and monitors information supporting the management of multi-center, multi-location studies. A 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 was 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 made up of scientists, physicians and potentially patient advocates that is formally convened and assigned to review and monitor research and development studies and/or clinical trials involving human subjects. The IRB can make suggestions, and approve or disapprove defined protocols and procedures. Their role is to protect the rights and well-being of people 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 **Semi-Finals 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 region, 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.

FSHD Bonus Judging Panel

The subject matter and technical experts who serve as an impartial and independent evaluation team for all aspects of the FSHD Bonus Prize. Judges score the team submissions and make the final award determinations in the Finals Competition for FSHD Bonus Prize.

FSHD Bonus Rules and 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 competing in the FSHD Bonus Prize. The Rules & Regulations for Finals testing in FSHD Bonus Prize will supersede the Competition Guidelines; all teams will be notified of the FSHD Bonus Rules & Regulations and any modifications to the FSHD Bonus Rules & Regulations in a timely manner.

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 solutions 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, therapeutic, 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. Moreover, all teams must include a clause in their informed consent documents that permits XPRIZE Healthspan and it's affiliates (e.g. data coordinating center, central laboratory services, biobanks, etc) access to data and biospecimen collected in conduct of trials as necessary for judging and operation of prize.

Judging Panels

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. Judging Panels (plural) refers to both the Healthspan Judging Panel and the FSHD Judging Panel; the two Judging Panels are independent of each other and responsible for judging either the Healthspan Milestones and Grand Prize or FSHD Bonus Prize Milestone and Finals, respectively.

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 active intervention group.

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 (Semi-Finals)
For the Competition this will consist of trials of up to 60-days to show feasibility of therapeutic interventions 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.

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.

Qualifying Submission
Qualifying Submission will describe the teams' therapeutic solution, supporting evidence, strengths of team and clinical center, and proposals for Semi-Finals early stage clinical testing. Qualifying Submissions should take a risk-based approach to answering the questions herein.

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.

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 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.

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.
- **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.

Scientific 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 Panels; (iii) assisting with development of testing protocols and judging criteria; (iv) and providing input toward the development of these Competition Guidelines.

Semi-Finals Testing

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

Standard Operating Procedures (SOPs)

Uniformly written procedures, with detailed instructions to record routine operations, processes and practices followed within XPRIZE Healthspan Competition. In XPRIZE Healthspan and FSHD Bonus, the SOPs and Clinical Protocols will be outlined in the Rules & Regulations. The SOPs help define the expectations XPRIZE has for a team's standard practices and daily processes conducted to assure execution of research tasks in accordance with guidances to improve validity of Grand Prize judging. Should local / state / federal regulations conflict with XPRIZE defined SOPs, XPRIZE operations should be notified to resolve potential discrepancies.

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 Panels' review.
- **Qualified Team:** A team that has been selected by the Judging Panels 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 Panels to advance in the Competition.
- **Finalist Team:** A team that has successfully completed Semi-Finals Testing and approved by the Judging Panels to attend Finals Testing (Healthspan); or is Qualified and approved by the FSHD Judging Panels to attend Finals Testing for FSHD Bonus Prize.

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 Clinical Protocols and a common data collection and management system through the XPRIZE Healthspan Data Coordinating Center which the Healthspan Judging Panel will review to verify each team's ability to participate in testing. The FSHD Bonus Prize will not use a Data Coordinating Center, but data will be submitted to a common data management system and results collated and audited prior to review by FSHD Judging Panel to review and verify each teams' data and results.

Technology

All know-how, information, ideas, solutions, inventions, modifications, prototypes, tools, other tangible embodiments, and works of authorship, including, without limitation, specifications, software, databases, compilations, schematics, documentation, and presentations. Technology includes any therapeutic - including drug, biologic, biosimilars, protocols, devices, etc.

Therapeutics: Therapeutic Treatment / Intervention / Solution

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 9. Therapeutics can include medicinal drugs, gene therapies, dietary and lifestyle interventions, biologics, devices, electroceuticals, nutraceuticals, and others; can be used alone or in combination; and must meet established safety parameters.

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 trial medical officer or designated clinic staff who will review all health assessments, vital signs, medical history, medication / therapeutic intervention 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 Centers 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 / EXCLUSION CRITERIA

Given the scope of the prize (demonstrate improvement in muscle, cognitive and immune function in 1-year), teams are strongly recommended to identify research participants who may be currently experiencing lower function or may be at risk for declining functional ability. Examples may include but are not limited to: older age-range (70-90 years), change in Intrinsic Capacity Score and/or 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 and/or age-acceleration based on epigenetic or other biomarkers, etc.

In addition to suggested Inclusion / Exclusion criteria below, Teams competing in the FSHD Bonus Prize must recruit patients with genetically confirmed FSHD at time of enrollment.

TABLE Appx B. Example Inclusion/Exclusion Criteria for Human Subjects Enrolling in 1 Year Finals

Criteria	Description
Inclusion Criteria	
Age	Must be between 50 and 90 years old
Health Status	Should be in a state of general health that is not severely compromised (i.e. no life threatening illness or disability)
Consent	Must be able to provide written informed consent to participate in the study
Life Expectancy	Should have an estimated life expectancy of at least 5 years, as assessed by the principal investigator based on medical history and current health status
Compliance	Must be willing and able to comply with all study procedures and scheduled visits
Medications	If taking medications, participants must have been on a stable dose for at least 3 months prior to enrollment and should not anticipate changes to their medication regimen
Exclusion Criteria	
Severe Chronic Illness	Severe and poorly managed chronic disease, such as advanced cardiovascular disease, kidney failure awaiting transplant or dialysis, uncontrolled diabetes, severe chronic obstructive pulmonary disease (COPD), or untreatable, terminal cancer
Physical Disability	Dependent on walker or wheelchair; severe difficulty or inability to perform activities of daily living independently or inability to perform study measures required to test muscle function (amputee ok as long as able to walk without walker or wheelchair)
Cognitive Impairment	Significant cognitive impairment or diagnosed dementia that would interfere with the ability to provide informed consent or comply with study procedures
Acute Illness	Acute illness or infection within 3 months prior to enrollment
Unstable Medical Conditions	Unstable or uncontrolled medical conditions, such as unstable angina, recent myocardial infarction (within 6 months), or uncontrolled hypertension
Major Surgery	Major surgery within the past 6 months or scheduled during the study period, including

	severe orthopedic disease awaiting joint replacement surgery.
Severe Psychiatric Conditions	Severe psychiatric conditions, such as major depression, schizophrenia, or bipolar disorder, unless well controlled on a stable medication regimen
Substance Abuse	History of substance abuse or dependence within the past 6 months
Participation in Other Trials	Enrollment in another clinical trial or participation in a clinical trial within the previous 6 months
Allergy to Interventions	Known allergies or adverse reactions to the interventions being tested in the study
Pregnancy	Female participants who are pregnant, planning to become pregnant, or breastfeeding during the study period (peri-menopause or menopause transition acceptable)

APPENDIX C. RECRUITMENT, RETENTION, AND WITHDRAWAL

Below are general guidelines for recruitment and retention for Finals 1 Year Clinical Trials. Teams are encouraged to use their own recruitment and retention methods, but must submit data necessary to construct a CONSORT checklist to the XPRIZE Healthspan Data Coordinating Center to support XPRIZE Healthspan study monitoring, impact reporting, and to aid the Healthspan and FSHD Judging Panels 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 F) 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 Healthspan 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 Panels. 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 50-90 years with genetically confirmed FSHD.

APPENDIX D. LIST OF SCIENTIFIC, TECHNICAL, AND LEGAL ADVISORS

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 between September - November 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.

TABLE Appx D. List of Scientific and Technical Advisors

FIRST NAME	LAST NAME	HON	TITLE	AFFILIATION
Scientific and Technical Advisors				
Alberto	Aparicio	PhD	Assistant Professor	School of Public and Population Health
Steven	Austad*	PhD	Endowed Chair in Healthy Aging Distinguished Professor of Biology	University of Alabama Birmingham
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
Luigi	Ferrucci*	MD, PhD	Scientific Director	National Institute on Aging, NIH
George	Kuchel	MD	Director of UConn Center on Aging Professor of Medicine and Travelers Chair in Geriatrics and Gerontology	University of Connecticut
Michael	Kyba	PhD	Carrie Ramey / Children's Cancer Research Fund Endowed Professor	University of Minnesota
Morgan	Levine	PhD	Principal Investigator	Altos Labs San Diego Institute of Science
Patrick	Maxwell*	MD	Regius Professor of Physic Head of the School of Clinical Medicine	University of Cambridge
Thomas	Osborn	MD	Director of National Center for Collaborative Healthcare Innovation	Veterans Affairs
Graham	Pawelec	PhD	Professor	University of Tübingen
Thomas	Rando*	MD, PhD	Director, UCLA Broad Stem Cell Research Center	University of California LA
Perminder	Sachdev	MD,PhD	Co-director, Centre for Healthy Brain Ageing	New South Wales Sydney, Australia
Nicholas	Schork	PhD	Deputy Director and Distinguished Professor of Quantitative Medicine	Translational Genomics Research Institute
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

+Indicates former SAB member: Bill Evans (2023-2025)

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
Peter	Bergethon	MD	President and Chief Scientist	Invariant Research Limited
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 E. FSHD BONUS PRIZE - EXCERPTS AND JUDGING CRITERIA

FSHD BONUS PRIZE BACKGROUND

Hope for FSHD. Facioscapulohumeral muscular dystrophy (FSHD) is a type of muscular dystrophy in which there is progressive muscle degeneration and muscle weakness; there is currently no treatment or cure.[21] For FSHD, the prevalence, underlying genetics, molecular causes and pathobiology of FSHD have been increasingly understood.[22, 23] Average age of diagnosis is 29-32 years, with age of onset correlated to allele size. Identification of the genetic causes has been established, with two main primary forms – the more common FSHD type 1 and relatively rare FSHD type 2 (FSHD1 and FSHD2 respectively). FSHD1 and FSHD2 genetic forms have a truncated D4Z4 region on Chromosome 4 leading to depression of a silenced transcription factor DUX4 with FSHD2 being further defined by hypomethylation due to mutations in methylation genes (SMCHD1, DNMT3B, and LIRF1). This leads to muscle inflammation, degradation and replacement by fatty and fibrotic tissue and impaired muscle function at ages much earlier than natural aging. Though better understanding of the molecular basis of FSHD has led to multiple potential therapeutic strategies, including some entering clinical trials, the gap to novel therapies remains large.

FSHD: From Laboratory to Humans. Despite this promise, trials to demonstrate clinical efficacy in older individuals or those diagnosed with FSHD is a slow and arduous process. Moreover, FSHD is arguably one of the most challenging genetic diseases to understand and treat given the complex nature of the gene locus and the fact that FSHD is a toxic, gain-of-function disease.

FSHD BONUS PRIZE TRACK OVERVIEW & TIMELINES

Competing teams will innovate across early-stage therapeutic testing — from research and development to clinical trials testing.

FSHD Bonus Prize of $10M will focus on Facioscapulohumeral Muscular Dystrophy (FSHD) with one milestone prize awarded in recognition of a research and development phase, and will culminate in final adjudication of the final bonus prize based on testing interventions in clinically approved genetically tested FSHD individuals aged 50-90 years.

Teams may register to compete in one or both prize tracks: FSHD Bonus Prize and XPRIZE Healthspan.Teams competing in XPRIZE Healthspan can also submit their therapeutic under the FSHD bonus track to compete for the FSHD Bonus Prize at no additional registration fee. Qualified

Teams competing in the Healthspan Competition can transfer to the FSHD Bonus track at no additional registration fee, but must submit a letter of intent to transfer to XPRIZE for review by the FSHD Judging Panel. Two Independent Judging Panels for XPRIZE Healthspan and the FSHD Bonus Prize will be assembled to review teams and adjudicate the winning team(s) based on **Milestone 1** and **Finals Testing** criteria.

TABLE Appx E. FSHD Timeline Summary	
FSHD Bonus Prize	
• November 2023 - July 2024	Intent to Compete
• July 31 2024 - December 20, 2024	Team Registration & Qualifying Submission
• January 2025 - April 2025	Milestone Judging & Finalist Award Notifications
• May 2025 - December 2029	FSHD Finals: 1-Year (or less) Clinical Trial Testing Period Annual Team Summits
• 2030	Finals: Judging Period and Award Notifications
• 2031	Scaling & Impact

FSHD Qualifying Submission & Milestone Award

The **FSHD Bonus Qualifying Submission** is the means by which teams are initially assessed by the FSHD Judging Panel for their ability to successfully compete in the FSHD Bonus Prize by delivering an effective solution for FSHD. For more information, please refer to the FSHD Qualifying Submission Guidelines.

Registered teams are required to submit a proposal for the FSHD Judging Panel's consideration of their therapeutic intervention. The Qualifying Submission should include information on team, environment or clinical center used for testing, data supporting their therapeutic solution, evidence of progress to date, approach to testing, evidence that regulatory requirements are or will be met, timelines, scalability and accessibility assessment, and readiness for testing. **Submissions reviewed for FSHD Milestone Award eligibility were due on December 20, 2024.** However, the Competition's Finals remains open to both existing and new teams through December 20, 2027.

For FSHD Bonus Prize, up to 8 teams will be chosen as Finalists and share a Milestone prize purse of $2,000,000 (e.g., $250K awarded to each team, if 8 teams are chosen). The FSHD Milestone Award was publicly announced and awarded to 8 teams in May 2025.

Note: Teams competing in BOTH XPRIZE Healthspan and FSHD Bonus Prize must submit TWO Qualifying Submissions applications – one submission to each of the prize tracks – as the Competition stages, patient populations, and judging panels differ.

The **Qualifying Submission** is a written declaration of the skills, experience, clinical and laboratory facilities, and attributes of teams as well as an outline of the proposed therapeutic solution and plans for advancement in the Competition. XPRIZE does not expect that the Qualifying Submission will be a full representation of the final tested therapeutic. XPRIZE expects and anticipates that the Qualifying Submission will provide:

- background and rationale on the therapeutic or combination of therapeutics
- documented proof that the intervention has been regarded as safe by a regulatory body or is under consideration by an appropriate safety and regulatory body
- evidence supporting use of the therapeutic on FSHD relevant endpoints or biomarkers
- an assessment of safety and potential risks and benefits to human subjects, especially those with FSHD
- supporting information demonstrating skills and experience of the team
- evidence of the quality of the clinical center that will be engaged for testing and familiarity with recruiting and conducting trials in persons with FSHD
- appropriate regulatory approval or evidence that regulatory approval will be obtained prior to testing
- Statement describing sources and scope of funding and state of intellectual property for their proposed solution.

In summary, the Qualifying Submission will describe the teams' therapeutic solution, supporting evidence, strengths of team and clinical center, and proposals for Finals testing for FSHD Bonus Track. Qualifying Submissions should take a risk-based approach to answering the questions herein. XPRIZE does not require all clinical studies to be completely described at the time of Qualifying Submission but does expect teams to demonstrate the ability to fully address all criteria in the fullness of time.

Finals Testing – FSHD Bonus Prize Summary

This preliminary Finals Testing Framework was informed by a panel of Scientific and Technical Advisors (Appendix D). Further details and clinical protocols are found in FSHD Rules & Regulations. Trial design is subject to change; teams will be notified of changes made to the key trial criteria.

Teams will conduct single-crossover controlled phase 2 trials to demonstrate that their therapeutic solution - administered alone or in combination - substantially improves FSHD-relevant muscle outcomes muscle function based on: 1) fat infiltration in muscle via any imaging modality or change in a relevant FSHD biomarker AND 2) corresponding improvement muscle function, compared with controls. Members of the FSHD Judging Panel and key prize operations personnel must be given access to Teams' laboratories, clinical research centers, and access to data for judging and audit of results.

Phase: Phase 2

Number of Clinical Centers: Teams can engage a single or multiple Clinical Centers, but must provide information on the centers and environment for review by the FSHD Judging Panel.

Population. Primary eligibility criteria are persons aged 50-90 years, free of major life-threatening disease and disability with genetically confirmed FSHD. Based on the known natural history of FSHD, enrollment for **FSHD Bonus Prize** is suggested to begin at 50 years of age in participants with genetically confirmed FSHD (via D4Z4 Repeat Units or D4Z4 region methylation level) without other comorbidities.

Intervention(s). In the context of the Competition, “therapeutic treatments” (or “therapeutics”, “therapeutic solutions”, or “therapeutic interventions”) refers to active drugs, biologics, devices, gene therapies, nutritional supplements, dietary interventions, lifestyle interventions or other approaches - alone or in combination. This list is not exhaustive.

Control. Teams must include defined time controls, standard of care, or other alternative as appropriate for the proposed approach to minimize confounding and bias. When possible, assignments should be randomized and masked.

FSHD Outcome. The following outcomes will be assessed using standard protocols by individuals who are masked to group assignment. Also see section on FSHD Outcomes & Endpoints. Improvement from baseline that exceeds (1) a 10% reduction in muscle fat fraction using any appropriate imaging method OR an acceptable muscle-derived or circulating biomarker AND (2) a 20% improvement in at least 3 functional tests from relevant clinical outcomes assessment, such as, but not limited to, the following list:

1. 6 minute walk test (6 MWT)
2. Gait speed (GS)
3. Grip test (GT) using handgrip dynamometer
4. Knee extensor maximum voluntary contraction (MVC)
5. Knee extensor power (or 1-Repetition Maximum)
6. Timed up and go (TUG)
7. Revised Upper Limb Module (RULM)
8. FSHD-COM (complete test or select components)
9. Reachable Workspace (RWS)
10. Novel, validated functional endpoint relevant to FSHD

Time. FSHD Bonus Prize finalist trials can be conducted over 2025- 2029. Trials schedule of assessments should include consecutive baseline assessments followed by a therapeutic

intervention period with repeat follow-up assessments. The FSHD Bonus prize intervention period will be less than 1 year, with recommended intervention duration provided in FSHD Bonus Rules & Regulations.

XPRIZE FSHD Bonus Prize Criteria Determination

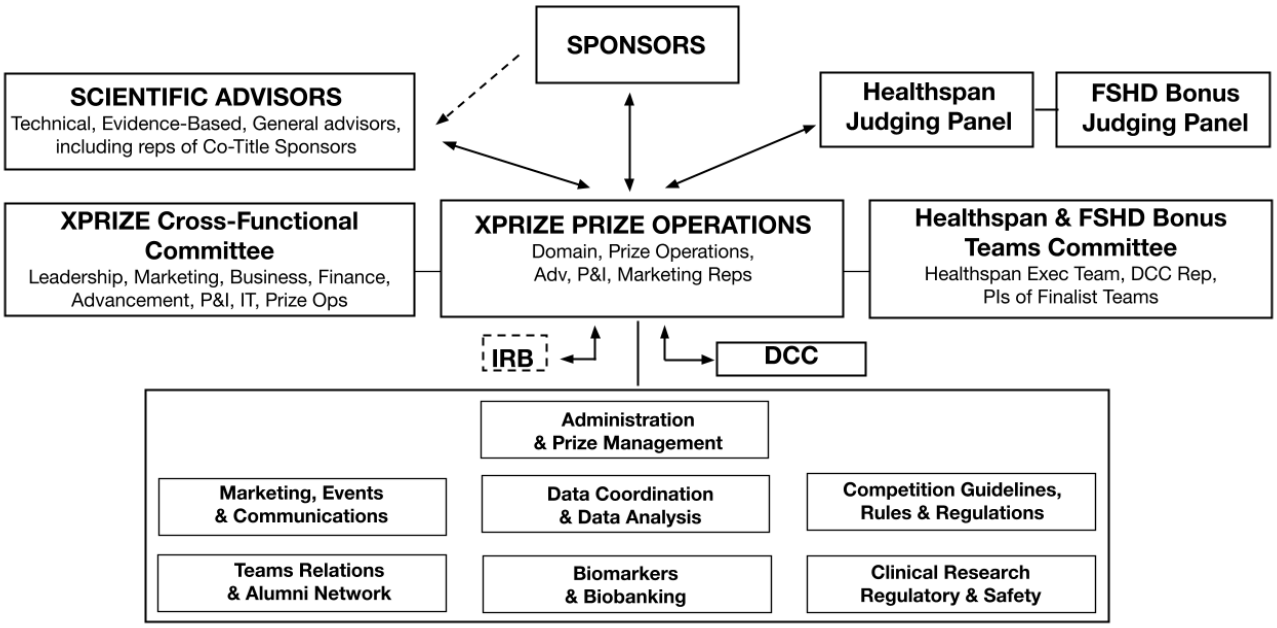
FSHD Bonus Prize Criteria: Based on current available information, a FSHD Bonus Prize team should strive to show:

- a ≥10% reduction in muscle fat fraction, fibrosis or increased muscle mass using best practices in biomedical imaging OR an acceptable muscle-derived or circulating biomarker
- AND ≥20% improvement in at least 3 of the functional tests, as deemed appropriate for the therapeutic intervention.
    - One of the functional endpoints can be a novel, validated clinical outcome measure (including AI-enabled measures and/or other novel approaches).

APPENDIX F. XPRIZE HEALTHSPAN ORGANIZATIONAL CHART

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

Figure Appx F. XPRIZE Healthspan Organizational Chart



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