Rules and Regulations:
FSHD Bonus Prize Finals

October 15, 2025

Draft Version 1.3

FSHD BONUS PRIZE RULES & REGULATIONS

Launched alongside XPRIZE Healthspan, the $10M FSHD Bonus Prize will be governed by these **Rules and Regulations**. All participating Teams must adhere to these Rules to be qualified for selection as a winner of the FSHD competition track. These Rules supplement the XPRIZE Healthspan Competition Guidelines and are issued for the **Finals** round of the FSHD Bonus Prize competition. Failure to adhere to these Rules may result in consequences as detailed in the Competitor Agreement.

XPRIZE may revise the published Rules and Regulations at any time during the Competition to provide additional information or to improve the quality of the Competition. Updated versions, amendments, technical notes, appendices, or other documents may continue to elaborate on the Competition's operations, including but not limited to exact dates and locations of events, specific technical thresholds for testing, and operational information. Unanticipated issues that arise or new technological advancements may require modifications to the Rules. XPRIZE reserves the right to revise these rules as it, in its sole discretion, deems necessary. All **registered teams** will be notified of the published Rules and Regulations, and of any revisions made to that document in a timely manner. Official updates will be communicated to team leaders by email. Please send any questions or feedback about this document to healthspan@xprize.org.

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1. Competition Overview

Background

Facioscapulohumeral muscular dystrophy (FSHD) is a genetically defined muscular dystrophy in which there is progressive muscle degeneration and muscle weakness; there is currently no treatment or cure[1-3]. The disease generally manifests in early adulthood with heterogenous muscle weakness in the face and upper limbs that progresses more broadly to other muscle groups during the course of a patient's lifetime, severely affecting strength, mobility and quality of life. Two forms of FSHD, with distinct genetic causes have been identified: FSHD1, the most common form, is caused by truncated D4Z4 repeats on Chromosome 4 leading to de-repression of a silenced transcription factor DUX4, whereas FSHD2, affecting ~5% of FSHD patients, is caused by mutations in certain epigenetic regulatory genes (SMCHD1, DNMT3B, and LIRF1). These mutations lead to hypomethylation at the D4Z4 repeats and allow the misexpression of the pathogenic protein DUX4[4]. Hence, both FSHD1 and FSHD2 are caused by the misexpression of DUX4 and can be considered toxic gain-of-function diseases. DUX4 misexpression leads to inflammation, progressive skeletal muscle degradation and replacement by fatty and fibrotic tissue which in turn may contribute to the disease pathophysiology[3-4]. Therapeutic strategies that promote skeletal muscle stabilization/growth, target DUX4 directly and/or any of DUX4's downstream pathological cascade have the potential of ameliorating the impact of the disease trajectory and benefit patient's quality of life.

About the FSHD Bonus Prize

The overall premise of the **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. The Competition challenges Teams to develop and successfully test a therapeutic within one year or less in persons with a genetically confirmed diagnosis of FSHD who are free of other major or life-threatening diseases.

The Competition occurs in two phases: Milestone and Finals. The Milestone prize of $2M was equally distributed to 8 teams (as selected by the FSHD Judging Panel) in May 2025, in recognition of their therapeutic approach, research plan, and preliminary data presented in their qualifying submissions. A Finals prize purse totaling $8M will be awarded to the First Place Team in the FSHD Bonus Prize who conclusively demonstrates, to the satisfaction of the FSHD Judging Panel, evidence of substantial improvement in 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

genetically confirmed FSHD patients aged 50-80 years without additional major life-threatening conditions or disability. For more detailed information, please refer to Appendix E of the Competition Guidelines.

Status of the Competition

The Competition remains open to existing and new teams through December 20, 2027. Existing teams that were not awarded the Milestone prize should notify the Prize Organizers at healthspan@xprize.org of their intent to continue in the competition and may use the feedback provided by the FSHD Judging Panel to address any shortcomings in their study.

New teams who are not currently registered may still register and submit a Letter of Intent (LoI) to healthspan@xprize.org. The prize operations team will review incoming LoIs on a rolling basis and notify the team of their approval to enter the Competition. If approved, the team must complete all other registration requirements and submit their Qualifying Submission in the Prize Operations Platform (POP). For detailed instructions on how to proceed with a new application, please refer to Section 3 of this document.

Therapeutic Treatments Description

The Competition is designed to incentivize the development and testing of novel therapeutics that can improve the functional losses associated with FSHD disease progression. Teams may consider any number of approaches, from addressing the root cause of FSHD (e.g. misexpression of DUX4) to strategies that may slow down downstream effects of the disease pathology, such as oxidative stress, gene mis-regulation, inflammation, fibrosis, fatty infiltration and/or muscle cell replacement, either alone or in combination.

2. FSHD Bonus Prize Competition Timeline

FSHD Bonus Prize Timeline Summary	
• May 2025 - December 20, 2027	Late Registration & Qualifying Submission
• May 2025 - December 2029	Finals: 1-Year (or less) Clinical Trial Testing Period Annual Team Summits
• 2030	Finals: Judging Period and Award Notifications
• 2031	Scaling & Impact

Please note that the FSHD Bonus Prize timelines are distinct from the Healthspan competition and DO NOT include a second milestone award. As of May 2025, competing teams in the FSHD Bonus Prize are in the Final Round of the competition and have the remaining time to design and complete their clinical trials.

Depending on the mode of therapeutic intervention, a sample timeline (for illustrative purposes) is shown below:

2025 – Collect pre-clinical data, including PK/PD in appropriate *in vivo* models

2026 – Conduct Investigational New Drug (IND) enabling studies (Toxicology, CMC) according to International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and/or complete orders/manufacturing of nutritional product or nutraceutical and ensure compliance with appropriate International Standards Organization (ISO) standards and certification and GMP where applicable. For more information on regulatory compliance, please refer to the FSHD Toolkit – Regulatory Resources.

2027 – Complete the clinical trial design, site(s) selection*, any required/appropriate regulatory filing(s), and obtain Institutional Review Board (IRB) approval to initiate recruitment and clinical trials by year's end.

2028 – Conduct clinical trial

2029 – Complete trial & submit all clinical trial data with topline results/analysis by the end of December 2029

2030 – Selection of Prize Winner

*** Patient Recruitment**

Please note that patient recruitment in a rare disease, such as FSHD, can be challenging and competitive given the increasing number of ongoing and planned clinical trials. Many clinical trial centers estimate recruitment at approximately 1 participant per month. To help expedite recruitment, teams are encouraged to reach out to local patient advocacy groups and neuromuscular clinical centers for assistance, as well as engaging multiple clinical trial sites to meet recruitment needs. A list of Patient Advocacy Group has been listed in the Clinical and Patient Advocacy folder of the FSHD Toolkit.

3. Late Registration & Qualifying Submission

TABLE 1. Steps for Registration & Entry into the FSHD Bonus Prize
• Interested Teams to submit a Letter of Intent (LoI) • XPRIZE notifies teams of their eligibility to enter the competition • Approved teams register on Prize Operations Platform (POP) • Upload Qualifying Submissions • Sign Competitor Agreement • Pay the Late Registration Fee (if applicable)

New Team Entries

New teams interested in entering the FSHD Bonus Prize Competition must first submit a 1-page Letter of Intent to: healthspan@xprize.org. Please provide:

- Brief overview of the team
- Description of the proposed therapeutic
- Rationale for its use in XPRIZE FSHD Bonus Prize
- Any available supportive data
- Disclosure of affiliation with a University, Non-Profit, or other academic/public research institution which may qualify for waived fees

Please note that teams may register to compete in one or both prize tracks: FSHD Bonus Prize and XPRIZE Healthspan competition, but should make certain that their LoI addresses the distinct requirements for each prize. It is recommended for teams to submit separate LoIs to more easily separate their different objectives for each competition.

All submitted Letters of Intent will be reviewed by the XPRIZE Healthspan and FSHD Bonus Prize Operations team for approval to formally enter into the Competition. If approved, the team will be permitted to complete all other registration requirements and submit their Qualifying Submission in the XPRIZE Prize Operations Platform (POP).

Please refer to the "Discretionary Late Registration" section within www.xprize.org/prizes/healthspan/resources for more detailed guidance on Late Registration.

For information on how to register a team in the Prize Operations Portal (POP), please refer to the following How to Guide.

Existing Healthspan Teams

Existing Qualified/Semi-Finalists in the Healthspan Competition who have not previously submitted a Qualifying Submission for the FSHD Bonus Prize track, may opt to do so at any time prior to the Dec 20, 2027 deadline. This is encouraged and teams can do so via a cross-over application process. For more information, please message healthspan@xprize.org with a LoI to discuss the FSHD Bonus Prize requirements and any adjustments that may be needed to be competitive in this track.

Qualifying Submissions

Following the review and acceptance of the submitted LoIs, the XPRIZE Operations team will notify the team leaders of their eligibility to formally enter the competition. The teams will then be able to register in the POP (if they have not already done so), submit their Qualifying Submission application, sign the Competitor Agreement, and pay any registration fees.

New Qualifying Submissions

For information on Qualifying Submissions requirements, please refer to the FSHD Bonus Prize Qualifying Submission Guidelines. A complete submission will include the following sections:

1. Team
2. Environment & Clinical Center(s)
3. Scientific Rationale & Preliminary Data
4. Approach to Finals Testing
    a. Study Design
    b. Ethical Issues
    c. Data Management & Statistical Analyses
    d. Sample Size Justification
5. Study Timeline
6. Scale & Accessibility
    a. Human Subjects Safety
    b. Resourcing Plan

c. Biohazards

Cross-Over Qualifying Submissions

Existing Healthspan teams electing to cross-over into the FSHD Bonus Prize are encouraged to adapt their existing Healthspan qualified submission to match the requirements of the FSHD Bonus Prize competition. These adjustments may include the different timelines between the two tracks, as well as the clinical endpoints and patient population/recruitment strategies.

Competitor Agreement

For more information on the Competitor Agreement, please refer to the Team Competitor Agreement.

New Team Registration Fees

The FSHD Bonus Prize retains the $1,000 registration fee for commercial teams. The entry fee for academic and non-profit teams are waived. Existing Healthspan competitors with an approved qualifying submission are exempt from additional registration fees.

Next Steps

Upon submission, the XPRIZE Operations Team and FSHD Judging Panel will review the Qualifying Submission for completeness and notify teams of their successful submission. Teams with incomplete entries and/or scientific concerns will be notified of these deficits and provided an opportunity to either address these in a revised submission or withdraw from the competition. The Judging Panel is to remain neutral throughout the competition and will not be providing feedback to applicants on ways to improve their scientific strategies and clinical protocols. Their role will be limited to identifying potential issues and safety concerns to the participating patients. Please note that due to time constraints, it is advisable for new teams to submit their study plan as early as possible to allow the judging panel ample time to review each application.

4. Outcomes Assessments

FSHD Bonus Prize Finals Study Design:

To be eligible to receive the Grand-Prize Award, 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).

Biomarkers:

Fat fraction, fibrosis, muscle mass and related measures may be assessed in a variety of ways, including DEXA scans and Magnetic Resonance Imaging (MRI). In lieu of MRI, teams may explore alternative imaging approaches, such as ultrasound and/or other potentially emerging novel imaging-analysis software, as well as biochemical/molecular analyses from muscle biopsies (e.g. DUX4 or DUX4-regulated gene panel), and circulating blood and/or urinary biomarkers[5-11]. For more information on biomarkers, please refer to the Biomarker folder in the FSHD Toolkit.

Centralized Blood Collection for an FSHD Biorepository:

With the constant development of molecular biomarkers, teams are strongly encouraged to collect plasma and serum blood samples at baseline and during/following treatment for downstream exploratory analyses and biobanking. Examples of protocols can be found in APPENDIX A. Interested teams should review and incorporate the sample IRB language into their applications and follow the recommended blood collection and storage protocols for consistency (Sample informed consent language can be found in APPENDIX D). The FSHD Bonus Prize sponsors have established a relationship with a preferred biorepository (Coriell Institute for Medical Research) for the collection and banking of biological samples. As new FSHD-relevant biomarkers become available, the Prize Sponsor may provide centralized testing of banked samples to participating teams to support their therapeutic approach.

For more information on biobanking at Coriell, please contact:

Brittany Kerr
Manager, Business Development
Coriell Institute for Medical Research
403 Haddon Avenue, Camden, NJ 08103
(856) 580-6251 | bkerr@coriell.org
businessdevelopment@coriell.org

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:

1. 6-minute walk test (6 MWT)[12]
2. Gait speed (GS)[13,14]
3. Grip test (GT) using handgrip dynamometer[15]
4. Knee extensor maximum voluntary contraction (MVC)[16]
5. Knee extensor power (or 1-Repetition Maximum)[16]
6. Timed up and go (TUG)[17]
7. Revised Upper Limb Module (RULM)[18,19]
8. FSHD-COM (complete test or selected components)[20]#
9. Reachable Workspace (RWS)[21,22]##
10. Novel, validated functional endpoint relevant to FSHD

Links to standard protocols for muscle functional outcomes will be uploaded on the FSHD TOOLKIT portal. If teams opt to use novel readouts and/or alternative protocols, detailed instructions/guidelines of the study protocols will need to be provided in the study design of the qualifying submission, progress report and/or final report.

FSHD-COM is composite test developed and licensed by the University of Rochester Medical Center. For licensing enquiries, please contact:

Brett L. Kinsler, DC
Research Assistant Professor of Neurology
Center for Health + Technology (CHeT)
CHeT Health Division Director
UR Ventures Senior Licensing and Development Director

University of Rochester Medical Center
Brett.Kinsler@chet.rochester.edu

The use of Reachable Workspace (RWS) requires specialized equipment. For more information, please contact Dr. Jay J. Han or Bioniks.
https://www.sciencedirect.com/science/article/abs/pii/S0960896625000069

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[23, 24]

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[20]. Teams may opt to carry out the full battery of FSHD-COM assessments for a more comprehensive evaluation.

Additional Assessment Measures and Judged Criteria

Safety, Tolerability, Scalability: Teams will need to report 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). 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 and biomarkers relevant to FSHD disease pathology. Biospecimens or circulating/excreted drug levels may also be used to evaluate adherence if needed and depending on the therapeutic.

Tertiary Endpoints: Teams may also consider additional validated tertiary endpoints not listed in the list of Biomarker or Functional Outcomes. These may include:

- Patient Reported Outcomes and Quality of Life surveys,
- Computerized assessments for depression symptoms, mood, or emotional bias test (e.g. NIH Toolbox[25])

5. Finals Trial Design

Trial Design:

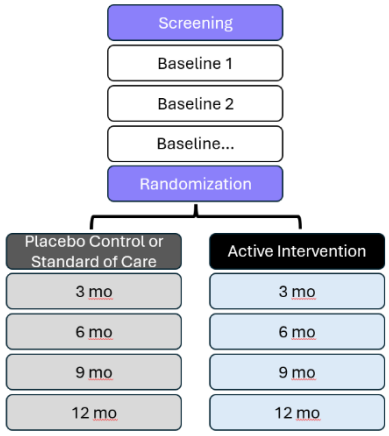
Teams are encouraged to conduct a randomized, double-blind, placebo controlled(*) phase 2 clinical trials to demonstrate that their therapeutic solution - administered alone or in combination - substantially improves FSHD-relevant muscle outcomes and muscle function. Alternative statistically robust designs will also be considered. Trial design may include two or more arms (active intervention vs. control and/or alternative active comparators). A sample of alternative study designs can be found in APPENDIX E.

> *(*) If the prescribed interventions are not amenable to placebo control, Teams must provide scientific justification and describe use of appropriate natural-history comparators.*

The intervention period should be 1 year or less, with pre-specified assessments and CDEs collected at regular intervals. Schedule of assessments should include at least two consecutive baseline assessments to establish test-retest reliability and minimize learning/training effects that may bias study results. Quarterly functional assessments are strongly encouraged during the interventional phase (See Figure 1).

Figure 1: Double-blind placebo-controlled design

While teams can incorporate any relevant clinical outcome assessments, they must include the listed common data elements. The effect of the therapeutic intervention will be evaluated in a 1 year or less, with a minimal of quarterly assessments. Safety monitoring, adverse event tracking, patient-reported outcomes, and adherence measures will also be assessed during the intervention based on a schedule determined in the study design per their therapeutic intervention.



Run-In Period: A run-in period may be used to stabilize baseline measures, identify safety issues, and detect poor adherence. IRB-approved justification and protocols must be provided to the Judging Panel prior to trial start. A minimum of two baseline measurements within one month is highly recommended.

Monitoring Retention: Adherence to treatment and scheduled clinic visits (including allowable windows) must be systematically monitored by Teams and summarized in regular interim reports for review.

Frequency of Data Collection: While the clinical study design is left to the discretion of the competing teams, it is recommended that teams strive to obtain a minimum of two baseline measurements to establish test-retest reliability and minimize any potential learning effect that may bias the study. In addition, quarterly assessments of functional outcomes, as well as minimally invasive biomarker sample collection (e.g. blood), are encouraged.

Clinical Centers: Teams can engage single or multiple clinical trial sites; site qualifications and environment must be provided for review by the FSHD Judging Panel before trial initiation.

Open Label Extension (Optional): When recruiting volunteers in a degenerative indication, such as FSHD, patients may be hesitant to participate if there is a likelihood of being assigned to the placebo arm of the study without the opportunity of receiving the therapeutic intervention. While cross-over clinical trials would allow all participants to receive the treatment during the study, the length of the clinical trial may need to be extended to show a therapeutic benefit. Alternatively, Open Label Extensions (OLE) can mitigate this hesitancy during recruitment by providing the therapy in question to both controls and patients in the interventional arm(s) after the completion of the study. Provided that the therapeutic intervention was deemed safe, competing teams may opt to provide all participants the interventional treatment after the completion of the trial until the approach is either approved by the regulatory agencies or shown to be ineffective. While not all therapeutic interventions are amenable for OLE (e.g. gene therapy), competing teams interested in this approach should also be aware of the financial burden providing an OLE for extended periods might impose on their organization.

Participant Recruitment and Sample Size: Enrollment of participants in Finalists' trials will be performed by a team's clinical trial site(s). An estimate of the number of participants enrolled with appropriate power calculations will be provided by teams. The Judging Panels will review sample size calculations and power analyses and evaluate the feasibility of achieving the specified outcome. The sample size required will be for teams to determine based on estimated therapeutic effects. 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), with 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.

Study Participants: Primary eligibility criteria are persons aged 50-80 years, free of major life-threatening disease and disability with genetically confirmed FSHD[26]. 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 and/or D4Z4 region methylation level) without other comorbidities.

FSHD Patients should have a clinical diagnosis of FSHD in their medical records (ICD-10 code: G71.02 (US); ICD-11 code 8C70.3 (ex-US)). Prior genetic testing results obtained from a CLIA-certified lab would be acceptable to establish eligibility for genetic testing[26]. For more information on FSHD genetic testing, please refer to the Genetic Testing Center folder in the FSHD Toolkit.

Please note that at this time, DNA methylation testing based on saliva sample collections alone do not qualify as genetic confirmation of FSHD[26].

Inclusion/Exclusion Criteria: Each team should strive to develop their own inclusion/exclusion criteria to ensure the safety of the participants. While no specific prescription is made, Teams are encouraged to include a wide range of disease severity in the enrolled cohort to reflect the real-world entire disease spectrum. For example, patients with a FSHD Clinical Score[27] range 2 to 8, excluding patients with only facial weakness and patients with a severe limitation in their ambulatory activity could be considered and/or amended according to the specific protocol, trial design, putative mechanism of action and assessments planned. Suggested eligibility criteria can be found in Appendix B, as are example recruitment and monitoring guidelines (Appendix C).

Controls: Teams must include appropriate controls to minimize confounding and bias. Randomized and masked assignments are preferred. If placebo control (e.g. AAV-gene therapy) is not feasible, teams may use rigorously matched historical controls. All participants must receive standard of care.

Group Size/Data Analysis:

FSHD is characterized by asymmetric and slowly progressive muscle weakness with fat infiltration and ultimately fibrosis, leading to associated with loss of strength and muscle mass[28-30]. Due to the heterogeneous manifestation and slow progression of the disease, standard between-group comparisons, even while using composite measures, may require large number of participants to show effectiveness. Therefore, teams must consult qualified biostatisticians during the design phase of their studies to ensure adequate power.

An alternative to standard group comparisons between treated and controls is to evaluate the within-person change in assessments relative to the participant's baseline (N-of-1 Study). This trial design can include multiple cross-overs or be based on historical baselines, as typically used in gene therapy studies. Due to the heterogeneity of the disease, teams may select personalized assessments most relevant to each patient (e.g. leg weakness vs shoulder/arm weakness). While each participant is effectively serving in an N-of-1 study, multiple participants being assessed across the same personalized assessment can be grouped to provide an average readout for the effectiveness of the therapeutic and compared to controls, who are also mapped against the same personalized assessments.

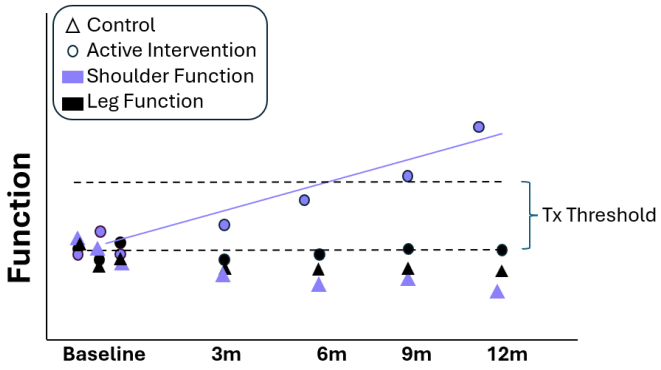
Other options for consideration can include a Personalized Response Threshold (PRT) design. Here, a predetermined therapeutic threshold is established for each participant using a dedicated/unique outcome assessment most relevant for that individual. For example, a mildly affected patient may benefit from a 25% improvement in leg strength, while a more advanced patient may require 60% improvement. Similar to aggregated N-of-1, PRT results can be aggregated to assess the proportion of individuals who reach a predetermined threshold of change between the intervention and control groups.

While teams can select any number of assessments in their trial, specific required assessments are to be included to provide the FSHD Judging Panel the battery of standardized assessments, **Common Data Element (CDE)**, for unbiased comparisons between teams.

Figure 2 depicts a hypothetical heterogeneous decline and response for shoulder and leg functions. For a personalized response threshold, teams must analyze and report whether the individual's average change in measurement values from Baseline to Follow-Up visits meets or exceeds the predetermined response threshold.

FIGURE 2. Example of Within-Person Improvement/Stabilization

Participants in both control and active intervention groups are assessed across multiple endpoints both at baseline and throughout the course of the trial. While the functional performance of participants in the control groups are expected to diminish over time (triangles), the rate for each functional test might vary. Similarly, participants receiving the active intervention (circles) may stabilize or improve across different functional tests.



6. Safety Monitoring and Reporting

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 permit XPRIZE to access data for judging.**

To minimize harm and ensure safety of participants and communities, 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 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, biopsies, scan).

XPRIZE acknowledges the possibility that experimental therapeutics may carry risks of adverse events. Teams may be required to obtain insurance coverage as required by their institutions or clinical trials centers. XPRIZE recommends for teams to secure and maintain, at their own expense, throughout the duration of the competition, insurance that is deemed appropriate and sufficient to cover the risks associated with the party's obligations and performance.

Safety stands as the most critical aspect of all testing rounds of this Competition. Competitors should see Appendix A of the Competition Guidelines for guidance on minimum human subjects safety measures. 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 minimize risk to human subjects. XPRIZE reserves the right to disqualify teams who are found to be operating in an unsafe or unethical manner.

7. Annual Progress Report

Starting in 2026, teams must upload annual updates onto the Prize Operation Platform (POP) by June of each year summarizing progress relative to Section 2's timelines, plus any of the following, as applicable:

Annual Report (core):

1. Summary of Progress to date and planned milestones/goals for the following year (Maximum of 3 pages)
2. Relevant regulatory submissions for clinical trials (IND, CTA, CDT), as applicable and mandated by the team's country of submission. These may include:
    - Pre-clinical pharmacology and toxicology reports
    - Chemistry, Manufacturing and Control (CMC)
    - Clinical protocols and amendments
    - Statistical and analytical plans(#)
    - Investigational brochure
3. Regulatory Compliance report (as applicable):
    - GLP Quality Audit Report
    - GMP Quality Audit Report
    - GCP Quality Audit Report (in lieu of site visits)
    - Development Safety Update Report (DSUR) or equivalent
4. Subject Enrollment Table (once study is ongoing)
5. Statistical Analytical Plan (SAP)
6. Institutional Review Board (IRB) Approval(*)(**)

(#) XPRIZE will not create plans for teams. Teams should consult with qualified statisticians during the design of their clinical trial protocol and include this as part of their annual report.

(*) Include IRB language permitting distribution of de-identified study results to third parties for post-hoc analysis.

(**) See Appendix D language for biomarker-related blood collection and third party testing.

Although the FSHD Judging panel is not required to provide feedback, it may request additional information if potential issues/adverse effects are suspected or identified.

Reports will be kept confidential and will assist XPRIZE in addressing unforeseen issues and scheduling site visits and audits.

8. Final Reporting

Finals Submission: The Finals Submission must include the annual-report elements in Section 7 above plus:

- Clinical Study Report
- SAS (or compatible) data files

To be eligible for the FSHD Bonus Prize, members of the FSHD Judging Panel and key prize operations personnel must be given access to Teams' laboratories, clinical research centers, and access to de-identified data for judging and audit of results. Competing Teams must allow their key data, methodology, breakthroughs and limitations regarding their research to be provided to representatives of Solve FSHD Holdings Ltd. A non-exhaustive list of such additional elements may include the following:

- Trial registration and versioning: Registry IDs (e.g., ClinicalTrials.gov/WHO), protocol/IB version history and amendment log with impact assessments.
- DSMB/DMC: charter, membership, scheduled meetings, and high-level minutes summaries (no unblinded data).
- Monitoring/Audit & CAPA: monitoring visit reports (CRO/internal), major findings, Corrective and Preventive Actions status.
- Outcomes/Imaging/Lab QA: SOP versions, phantom QA, assay validation updates, inter-/intra-rater reliability checks, device calibration logs (dynamometers, inclinometers).
- Training & certification: site initiation, rater training completion logs, GCP/ethics certificates, data privacy (HIPAA/GDPR) and cybersecurity posture for digital endpoints.
- Data integrity: eSource↔eCRF reconciliation metrics, query rates/resolution times, missing-data profile and pre-specified handling plan.
- Diversity & accessibility: recruitment dashboard vs plan (sex balance, race/ethnicity, age, geography) and corrective actions if off-track; accessibility accommodations provided.
- Central imaging standardization (multi-echo Dixon PDFF), phantom QA, and blinded central read.
- Safety detail: line listings for SAEs/AESIs, exposure-adjusted incidence rates, relatedness, protocol deviations impacting safety/privacy, and trend commentary.
- Analytics readiness: finalized Statistical Analytical Plan (SAP) (estimands, intercurrent events, multiplicity, sensitivity), blinding integrity checks and any unblinding incidents.
- Biorepository: chain-of-custody and sample tracking (collection→processing→shipment→storage), assay plan and data-return timelines.
- Digital/novel endpoints: device compliance (wear-time, data completeness), firmware/app versions, validation against gold standards.

- Risk & insurance: certificates/coverage confirmation (limits/riders), risk register with mitigations.
- Transparency & dissemination: publication plan, data-sharing plan (format/metadata, timing), and any IP/FDI constraints.

Safety Analyses:

Adverse events will be coded using a standardized medical dictionary (e.g., Medical Dictionary for Regulatory Activities (MedDRA) to be specified prior to Finals. Safety data will be regularly monitored by 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 pre-specified adverse events of interest will receive special focus as safety requirements for the FSHD Bonus Prize. 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

Individual data will be de-identified to protect the identity of the participants.

9. Site Visits & Audits

The XPRIZE FSHD Bonus Prize sponsor (Solve FSHD and/or their representatives) may request independent audits and/or site visits of the facilities prior to and/or during the clinical trial phase of the competition. The auditors may include officials from the sponsor, members of the judging panel, the Healthspan operations team and/or independent advisors or affiliates to the sponsor. The Healthspan operational team will contact team leaders with ample advanced notification to coordinate any such audits and/or visits. Details on the nature and scope of these will be posted in future updates to the Rules and Regulations document, FSHD Bonus Prize Frequently Asked Questions (FAQ), as well as directly communicated to teams prior to any audits and/or visits.

10. Winners Announcements

Following Finals Testing the FSHD Judging Panel will convene to review and discuss the results and determine the winners of the FSHD Bonus Prize. The winning team(s) will be announced in a Final Award Ceremony in 2030.

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.

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APPENDIX A: SAMPLE BLOOD COLLECTION PROTOCOLS

Protocols for Common Data Elements

Please visit the *FSHD TOOLKIT* for updates as protocols become available.

Protocols for Serum and Plasma collection

Tuck et al. J Proteome Res Standard Operating Procedures for Serum and Plasma Collection: Early Detection Research Network Consensus Statement *Standard Operating Procedure Integration Working Group*

APPENDIX B. SAMPLE INCLUSION / EXCLUSION CRITERIA

Criteria	Description
Inclusion Criteria	
Age	Must be between 50 and 80 years old
FSHD	Must have a clinical diagnosis of FSHD Type 1 or Type 2 along with a clinically approved genetic confirmation of the disease
Consent	Must be able to provide written informed consent to participate in the study
Clinical Severity	Patients should exhibit a FSHD clinical score between X and Y (TBD by each team based on their therapeutic approach and study design).
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	Severe difficulty or inability to perform activities of daily living independently or inability to perform study measures required to test muscle function
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 support study monitoring, impact reporting, and to aid the 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 an adequate number of participants to demonstrate the efficacy of their therapeutic approach. 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, Competing Teams should contact patient advocacy groups and/or the FSHD Clinical Trial Center for assistance. Contact information for these can be found in FSHS TOOLKIT – Clinical & Patient Advocacy Resources.

Participant Retention, Withdrawal, or Termination

Monitoring Retention

Adherence to scheduled clinic visits and the corresponding windows surrounding these visits should be contained in the annual reports for interim review and the FSHD 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 must 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.

Premature Termination or Suspension of Study

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

APPENDIX D: SAMPLE INFORMED CONSENT LANGUAGE

Teams are strongly encouraged to collect plasma and serum for blood-based biomarker studies currently in development. While these tests may help support a team's therapeutic approach, proper informed consents will need to be established to allow the distribution of samples to 3rd parties for as-of-yet undetermined assays. In addition, the XPRIZE Healthspan FSHD Bonus Prize competition provides an unprecedented opportunity for the biobanking of blood derived serum, plasma and circulating blood/immortalized cells (e.g. lymphoblasts, iPSCs) from carefully characterized FSHD patients for future studies. To that end, a list of publications and sample informed consents have been collated as guidance for drafting informed consents allowing the dissemination of biomaterials and corresponding unidentified clinical data.

Beskow et al. PloS One Developing a Simplified Consent Form for Biobanking 2010 Oct 8;5(10):e13302. doi: 10.1371/journal.pone.001330

Informed Consent for Secondary Research with Data and Biospecimen – NIH May 2022

Lowenthal et al. Stem Cell Translational Medicine Specimen Collection for Induced Pluripotent Stem Cell Research: Harmonizing the Approach to Informed Consent 2012 May 8;1(5):409–421. doi: 10.5966/sctm.2012-0029

Sample Consent Forms (NIH)

FSHD TOOLKIT – Sample Informed Consent Forms & Material Transfer Agreements

APPENDIX E: ALTERNATIVE STUDY DESIGNS

Teams should consult with an experienced statistician when designing their clinical trial and analytical method. Examples of alternative clinical trial designs for consideration:

- Single cross-over placebo-controlled double-blind[1]
    - This design involves each participant receiving both the investigational treatment and a placebo in a sequential order, with a "washout" period in between to prevent carryover effects. The order in which a participant receives the treatment and placebo is randomized. Double-blind means that neither the participants nor the investigators know which treatment is being administered at any given time. This design is efficient because each participant acts as their own control, reducing variability.
- Adaptive parallel-group (group -sequential looks, blinded variance re-estimation)[2]
    - An adaptive design allows for pre-planned modifications to the trial based on accumulating data, without undermining the trial's validity. A parallel-group design means each group receives a different treatment concurrently. Group-sequential looks refer to interim analyses conducted at specific points during the trial, which can lead to early stopping for efficacy or futility. Blinded sample size re-estimation is a specific adaptation where the sample size is recalculated mid-trial using the observed variance, without unblinding who received which treatment, to ensure the study remains adequately powered.
- Delayed-start/randomized placebo-phase[3]
    - In a delayed-start design, participants are initially randomized to either receive the active treatment immediately (early start group) or a placebo for a fixed period before being switched to the active treatment (delayed start group). The primary goal is to distinguish between symptomatic effects (which would diminish after the placebo group switches) and disease-modifying effects (where the early-start group maintains a persistent advantage over the delayed-start group).
- Randomized withdrawal[4] (treat-all open label, then continue vs. withdraw)
    - This design is often used for therapies that treat chronic conditions. It begins with an open-label phase where all participants receive the active treatment. Those who show a positive response are then randomized to either continue with the treatment or be switched to a placebo. The primary endpoint is typically the time it takes for the disease to relapse or worsen. It's an effective way to demonstrate the continued efficacy of a drug for maintenance therapy.
- Multi-arm, multi-stage (MAMS) with shared control[5]
    - The MAMS design is a highly efficient approach for testing multiple new treatments against a single, shared control arm simultaneously. The "multi-stage" aspect involves interim analyses where poorly performing experimental arms can be dropped for futility.

This allows researchers to focus resources on the most promising treatments without the need for separate, conventionally powered Phase II and Phase III trials.

- External/historical controls with Bayesian dynamic borrowing[6] (pre-specify discounting when exchangeability is low)
    - This modern design incorporates data from sources outside the current trial (e.g., from previous studies, real-world data). Bayesian statistics provide a natural framework for this by using the external data to form a "prior" belief about a parameter, which is then updated by the data from the current trial. Dynamic borrowing is an advanced method where the amount of "borrowing" from the external data is determined by how consistent the external data is with the data being collected in the current trial. Pre-specifying discounting means that rules are set in advance to down-weight the influence of the external data if it appears to be in conflict with the internal data (i.e., when exchangeability is low).

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