Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000090: Facioscapulohumeral Composite Functional Outcome Measure (FSHD-COM)
Letter of Intent

Administrative Structure:

Description of the submitter including, but not limited to, principal investigator(s), working group member(s), institutions, and contact information not contained within the cover letter.

Dr. Jeffrey Statland is an Assistant Professor of Neurology at the University of Kansas Medical Center and co-Director of our Muscular Dystrophy Association clinic. He has specialty training in Experimental Therapeutics of Neurological Disorders, obtained at the University of Rochester Medical Center (T32 program). His mentor during his fellowship training, Rabi Tawil, MD, is also his co-PI on the current NINOS U01 (U01NS101944) grant to validate the Facioscapulohumeral Muscular Dystrophy Functional Composite (FSHD-COM). The current proposal to seek qualification for the FSHD-COM is being run on the FSHD Clinical Trials Research Network (CTRN). Dr.s Statland and Tawil are co-PIs on the network, which is funded by the advocacy group, the FSH Society, and includes 7 sites with considerable experience running clinical trials in neuromuscular diseases across the United States (Figure 1). The FSHD CTRN has an advisory committee made up of representatives from industry, advocacy groups, clinical trialists, and patient representatives. The FSHD CTRN sites all have developed research infrastructure including coordinators, evaluators, and regulatory specialists. The FSHD CTRN has sponsored training for evaluators on the specific items contained in the FSHD-COM.

Dr. Rabi Tawil is a Professor of Neurology at the University of Rochester Medical Center and the Director of the Fields Center for FSHD Research. Dr. Tawil has a long track record in FSHD clinical and translational research. URMC has recruited hundreds of FSHD patient for various clinical research protocols or trials since the early 1990. They have a list of >450 FSHD patients who have agreed to be contacted for future studies. Ors. Tawil and Statland have worked has worked closely on FSHD projects with all of the CTRN sites.

Figure 1. FSHD CTRN includes 7 sites with considerable experience running clinical trials in neuromuscular diseases.

Concept(s) of interest (COI) for meaningful treatment benefit:

A description of the meaningful aspect of patient experience that will represent the intended benefit of treatment (e.g., presence/severity of symptoms, limitations in performance of daily activities)

We based our conceptual framework for the FSHD-COM on expert opinion about FSHD progression, natural history studies, MRI studies, and patient surveys and registries. Open-ended interviews revealed the most commonly quoted functional motor limitations to be problems with mobility and ambulation, arm, and shoulder limitations.(1) In a survey of >300 individuals with FSHD patients were asked to state whether a particular functional category affected their lives, and if so, then how impactful (Figure 2). The 3 most impactful areas of concern included foot/leg weakness, arm/shoulder weakness, and core/abdominal weakness. The most frequently reported functional motor limitations reported over 6 years of follow up in the US National FSHD Registry were difficulty getting up from lying down in bed and difficulty using arms for activities of daily living.(2)

From a practical point of view FSHD is almost entirely a disease of skeletal muscle. The classic clinical model for FSHD suggests a descending muscular progression affecting first the mimetic muscles of the face, the scapular fixators, and humeral muscles, followed by muscles of the abdomen and paraspinal region, and later muscles of the lower extremity in a scapuloperoneal pattern.(3, 4) In actuality, there is considerable variability between individuals, and side to side asymmetry in muscular involvement.(5) Although severe facial weakness, when present, can be socially limiting, for most people with FSHD the weakness in the face tends to be relatively static. The rate of progression in muscle involvement is slow, at about a loss of 3-5% strength per year.(6) Recent MRI studies have challenged some of the clinical preconceptions about the temporal pattern of muscle involvement - revealing early involvement of muscles of the shoulder girdle, as previously described, but also paraspinal, semimembranosus, and rectus femoris.(5, 7, 8)

From a practical standpoint. this means that improving gait and mobility, trunk or arm function would be meaningful to patients. and outcomes that reflect these functional domains are important for FSHD clinical trials. Any instrument documenting the benefit of a drug in FSHD should capture these key functional domains.

N=388	Very much	Moderately	Slightly	Not at all
Foot/leg weakness	58%	22%	14%	7%
Arm/shoulder weakness	53%	35%	11%	1%
Core/abdominal weakness	51%	30%	13%	6%
Fatigue	35%	39%	21%	4%
Pain	19%	34%	33%	15%
People's lack of understanding	19%	25%	33%	24%
Having to keep my FSHD secret	10%	8%	16%	67%
Loss of facial expression	9%	20%	35%	38%
Breathing issues	6%	16%	28%	50%
Hearing loss	5%	11%	25%	59%
Speech impairment	2%	6%	28%	64%

Figure 2. Patient-reported areas of clinical concern.

Targeted labeling or promotional claim(s) based on the clinical outcome assessment to be developed:

A drug which affected the rate of progression or improved the FSHD-COM could be expected to improve function in key FSHD domains; these include activities like walking, bending over, and lifting the arms.

COU for COA qualification:

Targeted study population including a definition of the disease and selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, comorbidities, language/culture groups)

Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common muscular dystrophies. Since 1991, studies have shown the worldwide prevalence of FSHD ranging between 2.03 to 6.8 per 100,000 individuals, and the prevalence in the United States is commonly quoted as 1 in 15,000, or approximately 21,000 individuals affected in the United States.(9) FSHD can be diagnosed over the full course of a lifespan, from the very young to very old. No clear racial or ethnic differences are evident in FSHD. Extramuscular manifestations of FSHD include retinal vascular changes, hearing loss, and cognitive difficulties, but in their clinically symptomatic forms are quite rare, affecting only 1-5% of the population, and almost entirely confined to individuals with the most severe form of the disease, with 1-3 residual D4Z4 repeat units remaining.(10) While cardiac conduction abnormalities have been described these are almost entirely atrial, and almost never symptomatic.(11) About 10% of patients will have restrictive respiratory involvement, which most commonly follows skeletal muscular weakness, is more frequent once a patient is wheelchair bound, and about 1-3% will require the use of non-invasive ventilation.(12)

Two genetically distinct but clinically indistinguishable forms of FSHD occur. More than 95% of patients have FSHD type 1 (FSHD1), which is characterized by deletion of large repeated elements on the long arm of chromosome 4q (the D4Z4 region).(13) Normal individuals have more than 10 repeats, and patients with FSHD1 have between one and 10 repeats. A minority of patients have FSHD type 2 (FSHD2), which is caused by a deletion-independent mechanism.(14) Both FSHD1 and FSHD2 have a common downstream mechanism, with loss of methylation in the D4Z4 region and epigenetic depression of a normally silenced gene, DUX4, which is believed to cause disease through a toxic gain-of-function mechanism.(15) The vast majority of patients meeting clinical criteria for FSHD will have FSHD1 (approximately 95%).

Inclusion/Exclusion: The vast majority of patients will have FSHD 1, be clinically effected, but still ambulatory- this is the most likely target for early clinical trials. However clinically and molecularly patients with FSHD2 would be expected to be similar to FSHD1. While there is a more severe phenotype largely affecting children, this represents less than 10% of patients, so would likely not be the target of early clinical trials.

Targeted study design and statistical analysis plan:

The primary goal of this proposal is to hasten drug development in FSHD by validating the FSHD-COM. To achieve this goal, we will conduct a prospective 18- month study of 150 patients at 7 sites. The 7 participating sites are part of the established FSHD Clinical Trial Research Network. The FSHD-COM data will be used to establish multi-site intra-rater reliability, validity, and sensitivity to disease progression of the COA compared to standard FSHD outcomes and to determine the Minimal Clinically Important Change (MCIC).

All formal statistical tests will be performed using a 5% level of significance (two-tailed). Likewise, associations will be described using regression coefficients and correlation coefficients, along with associated 95% confidence intervals. The assumptions underlying all statistical models will be thoroughly checked using appropriate graphical and numerical methods. In the face of nonlinearity or non-normality, appropriate remedial measures (e.g., variable transformation) will be attempted.

Reliability and Validity. Test-retest reliability of the FSHD-COM measurements (components and composite scores), for each site and overall, will be quantified using intraclass correlation coefficients computed using one-way random effects models. Ninety-five percent lower confidence bounds will be computed for these quantities. The cross-sectional data obtained in 150 FSHD patients at baseline will be used to describe the sample and examine the relationships between the FSHD-COM and clinical severity scores, different measures of patient-reported function, strength, lean body mass, and D4Z4 deletion size. These bivariate associations will be examined using standard correlation and regression analyses. A factor analysis will be performed to examine the structure of the FSHD-COM and determine whether the different components group together in a logical manner; Cronbach's a will be used to assess the internal consistency of the scale.

Relationships between the new COA and other variables such as age, gender, age at symptom onset, years since symptom onset, and years since diagnosis will be similarly examined, but these analyses will be more exploratory in nature since these associations are not necessarily expected to be strong. Similar analyses will be performed to determine the associations between changes in the new COA and changes in the other outcomes (clinical severity scores, measures of patient-reported function, composite strength scores, lean body mass). Associations will be examined using the changes from baseline to 12 and 18 months.

Responsiveness to change over time and MCIC. Paired t-tests will be used to test the null hypothesis of zero mean change at both 12 and 18 months for each measure. The standardized response mean is defined as the mean change divided by the standard deviation of the changes from baseline. For within-group (paired) comparisons, as is the case here, the standardized response mean is equivalent to the paired t-test (the two differ only by a factor of the square root of the sample size). The bootstrap resampling technique will be used to perform formal statistical comparisons among the different outcome measures in terms of these two measures of responsiveness. The mean of this approximate sampling distribution (bootstrap distribution) and a 95% confidence interval (obtained using the 2.5th and 97.5th percentiles of the bootstrap distribution) summarizes the results. If the confidence interval does not contain the value of zero, the conclusion is that there is a significant difference in average effect size between the FSHD-COM and the other outcome. Anchor-based and distribution-based methods will be used to determine the minimal clinically important changes (MCICs) on the FSHD-COM.(113) Mean responses on the FSHD-COM will be described for each of the categories of the domain delta questionnaire (e.g., unchanged, a little better, a lot better, etc.). Receiver operating characteristic (ROC) curve methods will be used to select a cut-off for the 12-month change in the FSHD-COM that is best at minimizing misclassification error, i.e., best distinguishes those who indicate that they are at least "a little better" on the domain-delta questionnaire and those who indicate otherwise. The 12- month changes in the FSHD-COM that correspond to effect sizes ranging from 0.30 to 0.50 standard deviation units will also be described and compared to the MCIC identified by ROC curve methods. These analyses will be repeated for 18-month changes and for other outcome measures.

Applicable study settings for future clinical trials:
The FSHD-COM is applicable across geographic locations and should not be limited by language or culture. The FSHD-COM is to be implemented in an outpatient setting.

COA type: Performance Outcome (PerfO)

References

1. Johnson NE, Quinn C, Eastwood E, Tawil R, Heatwole CR. Patient-identified disease burden in facioscapulohumeral muscular dystrophy. Muscle Nerve. 2012;46(6):951-3. Epub 2012/12/12. doi: 10.1002/mus.23529. PubMed PMID: 23225386.
2. Statland JM, Tawil R. Risk of functional impairment in Facioscapulohumeral muscular dystrophy. Muscle Nerve. 2014;49(4):520-7. doi: 10.1002/mus.23949. PubMed PMID: 23873337.
3. Padberg GW. Facioscapulohumeral disease. Thesis. Leiden, the Netherlands: University of Leiden. 1982.
4. Ricci E, Galluzzi G, Deidda G, Cacurri S, Colantoni L, Merica B, Piazza N, Servidei S, Vigneti E, Pasceri V, Silvestri G, Mirabella M, Mangiola F, Tona Ii P, Felicetti L. Progress in the molecular diagnosis of facioscapulohumeral muscular dystrophy and correlation between the number of KpnI repeats at the 4q35 locus and clinical phenotype. Ann Neural. 1999;45(6):751-7. Epub 1999/06/09. PubMed PMID: 10360767.
5. Dahlqvist JR, Vissing CR, Thomsen C, Vissing J. Severe paraspinal muscle involvement in facioscapulohumeral muscular dystrophy. Neurology. 2014;83(13):1178-83. doi: 10.1212/WNL.0000000000000828. PubMed PMID: 25142899.
6. Statland JM, McDermott MP, Heatwole C, Martens WB, Pandya S, van der Kooi EL, Kissel JT, Wagner KR, Tawil R. Reevaluating measures of disease progression in facioscapulohumeral muscular dystrophy. Neuromuscular Disorders. 2013;23(4):306-12.
7. Tasca G, Monforte M, Iannaccone E, Laschena F, Ottaviani P, Leoncini E, Boccia S, Galluzzi G, Pelliccioni M, Masciullo M, Frusciante R, Mercuri E, Ricci E. Upper girdle imaging in facioscapulohumeral muscular dystrophy. PLoS One. 2014;9(6):e100292. doi: 10.1371/journal.pone.0100292. PubMed PMID: 24932477; PubMed Central PMCID: PMCPMC4059711.
8. Tasca G, Monforte M, Ottaviani P, Pelliccioni M, Frusciante R, Laschena F, Ricci E. Magnetic Resonance Imaging in a large cohort of facioscapulohumeral muscular dystrophy patients: pattern refinement and implications for clinical trials. Ann Neural. 2016. doi: 10.1002/ana.24640. PubMed PMID: 26994363.
9. Deenen JC, Horlings CG, Verschuuren JJ, Verbeek AL, van Engelen BG. The Epidemiology of Neuromuscular Disorders: A Comprehensive Overview of the Literature. J Neuromuscul Dis. 2015;2(1):73-85. PubMed PMID: 28198707. 10. Statland JM, Tawil R. Facioscapulohumeral Muscular Dystrophy. Continuum. 2016;22(6, Muscle and Neuromuscular Junction Disorders):1916-31. doi:10.1212/CON.0000000000000399. PubMed PMID: 27922500.
11. Laforet P, de Toma C, Eymard B, Becane HM, Jeanpierre M, Fardeau M, Duboc D. Cardiac involvement in genetically confirmed facioscapulohumeral muscular dystrophy. Neurology. 1998;51(5):1454-6. Epub 1998/11/18. PubMed PMID: 9818880.
12. Tawil R, Kissel JT, Heatwole C, Pandya S, Gronseth G, Benatar M, Guideline Development D, Implementation Subcommittee ofthe American Academy of N, Practice Issues Review Panel of the American Association of N, Electrodiagnostic M. Evidence-based guideline summary: Evaluation, diagnosis, and management of facioscapulohumeral muscular dystrophy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic

Medicine. Neurology. 2015;85(4):357-64. doi: 10.1212/WNL.0000000000001783. PubMed PMID: 26215877; PubMed Central PMCID: PMC4520817.

13 Wijmenga C, Hewitt JE, Sandkuijl LA, Clark LN, Wright TJ, Dauwerse HG, Gruter AM, Hofker MH, Moerer P, Williamson R, et al. Chromosome 4q DNA rearrangements associated with facioscapulohumeral muscular dystrophy. Nat Genet. 1992;2(1):26-30. Epub 1992/09/01. doi: 10.1038/ng0992-26. PubMed PMID: 1363881.

14 Lemmers RJ, Tawil R, Petek LM, Balog J, Block GJ, Santen GW, Amell AM, van der Vliet PJ, Almomani R, Straasheijm KR, Krom YD, Klooster R, Sun Y, den Dunnen JT, Helmer Q, Donlin-Smith CM, Padberg GW, van Engelen BG, de Greef JC, Aartsma-Rus AM, Frants RR, de Visser M, Desnuelle C, Sacconi S, Filippova GN, Bakker B, Bamshad MJ, Tapscott SJ, Miller DG, van der Maarel SM. Digenic inheritance of an SMCHD1 mutation and an FSHD-permissive D4Z4 allele causes facioscapulohumeral muscular dystrophy type 2. Nat Genet. 2012;44(12):1370-4. Epub 2012/11/13. doi: 10.1038/ng.2454. PubMed PMID: 23143600.

15 Lemmers RJ, van der Vliet PJ, Klooster R, Sacconi S, Camano P, Dauwerse JG, Snider L, Straasheijm KR, van Ommen GJ, Padberg GW, Miller DG, Tapscott SJ, Tawil R, Frants RR, van der Maarel SM. A unifying genetic model for facioscapulohumeral muscular dystrophy. Science. 2010;329(5999):1650-3. Epub 2010/08/21. doi: science.1189044 [pii] 10.1126/science.1189044. PubMed PMID: 20724583.