Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000129: Advanced Gait Analysis
Letter of Intent

Administrative Structure:

This proposal is being submitted by MC10, Inc. Contacts for this COA proposal:

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Concept(s) of Interest (COI) for Meaningful Treatment Benefit:

Huntington's Disease (HD) is an autosomal dominant neurodegenerative disease affecting approximately 3 per 100,000 people worldwide. Patients experience a multitude of motor symptoms including chorea, dystonia, imbalance, falls, as well as progressive cognitive and behavioral decline. Typical onset is after age 35, with documented cases of early onset and juvenile HD noted in the literature. Age at onset, progression speed and other features of the disease are related to specific mutation, the production of mutant *huntingtin* protein, and the number of CAG nucleotide repeats in the mutant gene. This symptom complex is currently inexorable with death being the inevitable outcome. See, for example, previous work by Bates [9] and Dorsey [10].

A major component of the motor dysfunction is the development of a progressive gait abnormality that has been well documented beginning in the prodromal period and severe and disabling in manifest HD patients. While gait disturbances are common in many neurodegenerative diseases, the specific nature of the gait disturbance in HD not only differs from normal, but also from the disturbances that characterize other diseases such as Parkinson's Disease or Multiple Sclerosis.

The natural history of HD has been well characterized, but essentially only when the classical signs and symptoms are overtly manifest. During the pre-symptomatic and prodromal periods there are limited data describing the subtle, slow deterioration presaging the manifest disease recognizable as HD. Moreover, little information is available for parsing the contributions of chorea, dystonia and gait abnormalities to the increased risk of falls.

Adams [4] and Dinesh [5] have described that symptomatic HD subjects spend more than 50% of their time laying down. This is presumably to mitigate the exhausting nature of chorea, and to reduce fall risk. The same group from the University of Rochester has published preliminary work demonstrating the grossly disordered actigraphic gait signature of HD subjects and the temporary effects of tetrabenazine restoring that pattern towards normal.

HD patients are most commonly assessed through the Unified Huntington's Disease Rating Scale (UHDRS). The FDA's CDER's Clinical Outcome Assessment (COA) Compendium (August 2019 version) has two references to the UHDRS associated with two approved therapeutics with HD related claims: 1) as a qualified COA measurement for Chorea to measure Huntington's chorea, and 2) as a COA for measuring Chorea generally for Huntington's disease.

These COAs are important to HD research but are also limited by their nature. Under any conditions the UHDRS is subjective, integer-based and assessed intermittently and infrequently. Moreover, while the UHDRS may indicate the severity a subject's gait disturbance, it does nothing to describe the disturbance objectively nor does it quantify the degree of deviation from normal.

Because of the monogenetic nature of HD, the disease is a target for disease modifying therapy. Some of these therapies are directed at replacing or silencing the defective gene, modifying the production of the defective [huntintin] protein, or blocking its effects. In spite of optimistic therapeutic options there are no objective functional assessments that could document arrest of the progression, nor quantify reversal/improvement of the functional impairment. Moreover, empirically it would be likely that earlier intervention would be preferred, yet even the UHDRS does not usefully assess the pre-symptomatic or prodromal HD patient due to ceiling effects present in this specific HD population. Thus, criteria for early intervention would currently have no functional basis and could only rely on brain imaging and CAG repeat analysis. For gene therapy specifically, there are no objective metrics for early detection of disease onset to guide the timing of intervention. Such objective signs of onset are simply not measurable with current technology and PRO/COA.

MC10 proposes to develop an outcome measure focused on the specific gait abnormality in HD populations. We propose to look at the spatiotemporal parameters of gait and identifying the metrics that are most sensitive to disease progression over the entire course of HD. Initiating the assessments prior to UHDRS applicability may be particularly useful for early detection and assessment of the disease in consideration of disease modifying treatment or actual gene therapy.

Context of Use for COA Qualification:

a. Targeted study population: Ambulatory adults with pathogenic genetic mutation and CAG expansion indicative of Huntington's Disease with or without motor manifestations.

b. Targeted study design and statistical analysis plan: to understand the smallest measurable, repeatable, clinically significant change in gait metrics from an initial baseline period to a defined follow-up period presumed to be at least 4 weeks later. We will apply either a

control-treatment or cross-over design, or a natural history study studying the progression of the disease.

c. Applicable study settings for future clinical trials: Future clinical trials evaluating drugs intended to minimize disease progression or treat the motor symptoms of HD patients will benefit from the proposed advanced gait analysis. Additionally, benefits may accrue when smaller patient sample sizes and shorter follow-up periods are enabled due to the potential for measurement of smaller changes in gait as a result of the expected higher signal-to-noise ratio of digital technology over physician rated integer scales such as the UHDRS.

   Initial study settings will be in the United States where the BioStamp nPoint is cleared for use. Expanded use will occur in accordance with specific international regulatory approvals.

COA Type: Digital Health Technology

References:

1. Moon Y, McGinnis RS, Seagers K, Motl RW, Sheth N, Wright JA, Jr., et. al. (2017) Monitoring gait in multiple sclerosis with novel wearable motion sensors. PLoS ONE 12(2): e0171346. doi: 10.1371/journal.pone.0171346.

2. Carlozzi, N.E. et. al., Understanding the outcomes measure used in Huntington disease pharmacological trials: A systematic review. J Huntington's Dis. 2014: 3(3): 233-252.

3. Mestre, T. A. MD, MSC, Maria Joao Forjaz, PhD, et. al. Rating Scales for Motor Symptoms and Signs in Huntington's Disease: Critique and Recommendations. Mov Disord Clin Pract. 2018 Mar-Apr; 5(2): 111-117.

4. Adams JL, Dinesh K, Xiong M, et al. Multiple Wearable Sensors in Parkinson and Huntington Disease Individuals: A Pilot Study in Clinic and at Home. Digital Biomarkers 2017;1:52-63. 10.1159/000479018.

5. Dinesh K, Xiong M, Adams JL, Dorsey RE, Sharma G. Signal analysis for detecting motor symptoms in Parkinson's and Huntington's disease using multiple body-affixed sensors: A pilot study. 2016 IEEE Western New York Image and Signal Processing Workshop (WNYISPW); 2016 18-18 Nov. 2016. P. 1-5. 10.1109/WNYIPW.2016.7904834.