Risperidone for the treatment of Huntington's disease chorea

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PROTOCOL SYNOPSIS

FULL STUDY TITLE	Risperidone for the treatment of Huntington's disease chorea
CLINICAL PHASE	Phase II
INVESTIGATORS/ STUDY GROUP	Ruth Schneider (PI), Fred Marshall (Co-PI), Giovanni Schifitto (Co-I), Jamie Adams (Co-I), Christopher Tarolli (Co-I), Nasir Udin (Co-I)
STUDY OBJECTIVE	1) To determine the preliminary efficacy and safety of risperidone for the treatment of HD chorea. 2) To assess whether frontostriatal structural and functional connectivity is predictive of risperidone clinical response and whether clinical response is associated with increased functional connectivity. 3) To assess the ability of wearable accelerometers to detect chorea severity and the responsiveness of wearable accelerometers to the effect of risperidone treatment.
STUDY RATIONALE	Chorea is present in over 90% of individuals with HD, negatively impacts quality of life, causes functional disability, and is a treatment priority for individuals living with HD. While there are two FDA-approved treatments for HD chorea, tetrabenazine and deutetrabenazine, the majority of HD experts eschew these costly medications in favor of atypical antipsychotics, for which there is little evidence from controlled trials. Clinical trial data is needed to support the safety and efficacy of antipsychotics, such as risperidone, for the treatment of HD chorea. The inclusion of neuroimaging will enable a better understanding of the brain networks that sub-serve chorea and the potential identification of neuroimaging predictors of clinical response. The inclusion of wearable sensors will further the development of a novel outcome measure by assessing their responsiveness to chorea treatment.
STUDY SITES	University of Rochester
STUDY PERIOD	18 months
STUDY POPULATION AND NUMBER OF SUBJECTS	12 to 16 participants with manifest HD and UHDRS TMC ≥ 8
STUDY DESIGN	This is a single-center, blinded-rater, open-label dose response study of risperidone for the treatment of HD chorea.
MAIN INCLUSION/ EXCLUSION CRITERIA	*Inclusion Criteria:* 1. Manifest HD (DCL 4 + CAG repeat ≥ 37 or family history of HD) 2. UHDRS TMC ≥ 8 3. UHDRS Total Functional Capacity ≥ 5

	4. Subject willing and able to provide written informed consent OR legally authorized representative provides written informed consent 5. Between 18 and 65 years of age *Main Exclusion Criteria:* 6. Use of antipsychotic, levodopa, amantadine, dopamine agonist, monoamine oxidase inhibitor, or other disallowed medication in the 30 days prior to the baseline visit 7. Prior non-response to risperidone or intolerability to risperidone (in the investigator's opinion) 8. Allergy or hypersensitivity to risperidone 9. Dysphagia that in the investigator's opinion would preclude participation in the study 10. Active suicidal ideation or psychiatric condition that in the investigator's opinion would preclude participation in the study 11. QTc > 460 msec for women or >450 msec for men on 12-lead EKG 12. History of cardiac arrhythmia or congenital long QT syndrome 13. Significant renal impairment (creatinine clearance < 30 mL/min as estimated by the Cockgroft-Gault formula) or hepatic impairment (AST or ALT > 2.5 times upper limit of normal OR alkaline phosphatase or total bilirubin > 2 times upper limit of normal) 14. Active drug or alcohol abuse or dependence 15. Pregnant or breast-feeding 16. Any contraindication to MRI (e.g. pacemakers, aneurysm clips, metallic prostheses, shrapnel fragments, claustrophobia) 17. History of active (clinically significant) skin disorder that would interfere with sensor adherence 18. History of allergic response to adhesives 19. Pacemaker, AICD, or other implantable stimulator 20. Use of an investigational drug in the 30 days prior to the baseline visit 21. Inability to complete study activities, as determined by the study team 22. Clinically significant parkinsonism as determined by expert investigator assessment
DOSAGE	Participants will initiate risperidone 0.5 mg nightly the day after the baseline visit. Dose assessment will occur at pre-specified intervals during the titration phase (week 2, 3, 4, 6, 7). The investigator will increase the dose by 0.5 mg at the week 2, week 3, week 4, and week 6 visits until either optimal chorea benefit has been obtained, an intolerable adverse event occurs, or the maximum allowable dose (3.0 mg) is reached. The investigator should consult with the participant (and care partner) and use all available study information in determining whether the optimal dose has been reached. To ensure that the participant is on a

	stable dose by week 8, the dose at week 7 may be decreased but should not be increased. The maximum dosage reached should be maintained during the maintenance phase (week 8-week 12). Reductions and discontinuation of study drug will be allowed at any time during the study in the setting of an adverse event. Following the week 12 visit, participants may choose to remain on drug at the discretion of their treating clinician, but otherwise will complete a short taper with follow-up by phone at week 13.
DURATION OF TREATMENT	12 weeks
PRIMARY OUTCOME MEASURE(S)	The primary outcome measure is UHDRS TMC score, as assessed by blinded expert-rater review of video recordings.
SECONDARY OUTCOME MEASURE(S)	Efficacy: 1. UHDRS component and total scores 2. Clinical global impression of change (CGI) (investigator) 3. Patient global impression of change (PGI) 4. Chorea Index as measured by MC10 wearable sensors 5. Quantifiable chorea score as measured by Q-Motor Safety and Tolerability: 1. Adverse events and serious adverse events 2. UHDRS parkinsonism score 3. Epworth Sleepiness Scale 4. QTc on 12-lead EKG 5. Barnes Akathisia Scale 6. Weight and vital signs 7. Lipids, CBC with differential, CMP (with fasting glucose) Cognition and Psychiatric Features 1. Columbia Suicide Severity Rating Scale 2. Problem behaviors assessment short form 3. Hospital anxiety and depression scale 4. Apathy Scale 5. Montreal Cognitive Assessment
NEUROIMAGING	Neuroimaging will include examination of brain grey and white matter atrophy, functional connectivity (via resting state fMRI, rs-fMRI), and structural connectivity (via diffusion MRI, dMRI) at two time points, between screening and baseline (off drug) and between week 8 and week 12 (maintenance phase, on drug). All imaging will be conducted on a research dedicated 3T whole-body Siemens Prisma scanner (Erlangen, Germany), equipped with a 64-channel receive-only head coil and body coil transmission, and high-performance gradients of max strength 80mT/m and slew rate of 200mT/m/s. The MRI protocol includes 3D T1w MPRAGE [TR/TE = 1400/2.34 ms; 1 mm

	isotropic resolution] and T2w SPACE sequence [TR/TE = 3200/444 ms; 1 mm isotropic resolution] anatomical images, single-shell dMRI [64 diffusion-encoded (b=1000 s/mm^2) and 5 reference (b = 0 s/mm^2) images; TR/TE = 4300/69 ms; 1.5 mm isotropic resolution] and rs-fMRI [TR/TE = 993/43 ms, number of volumes = 300, 2 mm isotropic resolution] using EPI sequences.
SENSORS	During the screening and week 8 visits, participants will be fitted with 3 MC-10 BioStamp nPoint wearable sensors (chest, arm, leg), prior to completing in-clinic motor assessments. Following each of these visits, participants will wear the sensors at home for 1 week.
SAFETY CONSIDERATIONS	According to the package insert, in risperidone clinical trials the most common adverse reactions (≥10%) were somnolence, increased appetite, fatigue, rhinitis, upper respiratory tract infection, vomiting, coughing, urinary incontinence, increased saliva, constipation, fever, parkinsonism, dystonia, abdominal pain, anxiety, nausea, dizziness, dry mouth, tremor, rash, akathisia, and dyspepsia. To minimize the risk of side effects, we will follow a slow titration and limit the total daily dose to 3.0 mg. Safety and tolerability will be closely monitored by study investigators. If an intolerability or adverse event occurs, depending on the severity of the event, investigators may decide to decrease the study drug or to discontinue the study drug. Participants will be able to withdraw from the study at any time.
SAMPLE SIZE CONSIDERATIONS	There are no prior clinical trials from which to estimate an effect size for risperidone and this represents a convenience sample. We are relying on data from studies of existing treatments to inform power analysis and the identification of a chorea effect less robust than existing treatments would dampen enthusiasm for risperidone. In a clinical trial of tetrabenazine, over 12 weeks there was a 5.0-unit change (SD 3.7 units) in total maximal chorea score.[11] A sample size of 11 participants will provide > 98% power to detect a 5.0 unit difference or greater, using a one-sample t-test at the 5% significance level. A sample size of 12 participants will account for an estimated 8% drop-out rate.

1. PURPOSE OF STUDY

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease characterized by psychiatric features, cognitive impairment, and motor abnormalities that affects approximately 40,000 individuals living in North America.[1] Chorea is present in over 90% of individuals with HD,[2] negatively impacts quality of life, causes functional disability, and is a treatment priority for individuals living with HD.[3] While there are two FDA-approved treatments for HD chorea, tetrabenazine and deutetrabenazine, the majority of HD experts eschew these costly medications in favor of atypical antipsychotics,[4] for which there is little evidence from controlled trials. Clinical trial data is needed to support the safety and efficacy of antipsychotics, such as risperidone, for the treatment of HD chorea. Moreover, our approach to treatment and assessment of response to treatment would be enhanced by a better understanding of the brain networks that sub-serve chorea and the use of novel outcome measures that enable in-home assessment.

Aim 1: To determine the preliminary efficacy and safety of risperidone for the treatment of HD chorea.
Hypotheses:
1A) There will be a 5.0 unit difference or greater between baseline and week 12 in the primary outcome measure of the Unified Huntington's Disease Rating Scale Total Maximal Chorea (UHDRS TMC) score
1B) Risperidone treatment is tolerable, as defined by ≥9 of 12 participants completing 12 weeks on study drug (any dose).

Aim 2: To assess whether frontostriatal structural and functional connectivity is predictive of risperidone clinical response and whether clinical response is associated with increased functional connectivity.
Hypotheses:
2A) Decreased structural and functional connectivity of the frontostriatal pathways will be associated with chorea severity and thus predict the observed response to risperidone
2B) Clinical response to risperidone will be associated with increased functional connectivity

Aim 3: To assess the ability of wearable accelerometers to detect chorea severity and the responsiveness of wearable accelerometers to the effect of risperidone treatment.
Hypotheses:
3A) Wearable sensors will measure chorea severity as determined by the Chorea Index and correlate with traditional measures (e.g. UDHRS).

3B) Wearable sensors will detect changes in chorea as determined by the Chorea Index in response to risperidone treatment with at least as much sensitivity as traditional assessments (e.g, UHDRS TMS, UHDRS chorea subscores).

2. BACKGROUND AND RATIONALE

While two vesicular monoamine transporter type 2 (VMAT-2) inhibitors, tetrabenazine and deutetrabenazine, have received FDA approval for the symptomatic treatment of chorea in HD following pivotal double-blind, randomized, placebo-controlled studies,[5,6] they are prohibitively expensive. According to the Institute for Clinical and Economic Review, the annual wholesale acquisition cost for deutetrabenazine (36 mg daily dose) is $90,071 and for tetrabenazine (25 mg daily dose) is $19,885-$76,087.[7] This stands in stark contrast to the calculated annual cost of $35 for risperidone (2 mg daily dose).[8] Antipsychotic drugs are routinely used in clinical practice for the treatment of HD chorea and expert-established clinical practice guidelines recommend antipsychotic drugs as first-line treatment for chorea in the setting of depression, psychosis, aggression, and/or non-compliance.[4,9] The majority of HD experts favor antipsychotic drugs as the first-line treatment for HD chorea;[4] our recent poll of 22 Huntington Disease Society of America (HDSA) Centers of Excellence Center Directors revealed that 12 (54.5%) favor atypical antipsychotics (most commonly risperidone) and 9 (41%) favor VMAT-2 inhibitors.[10] Of those who preferred VMAT-2 inhibitors, the most commonly cited reason was the existence of clinical trial data.

There have been few clinical trials of atypical antipsychotic drugs for HD chorea.[11,12,13,14,15,16,17] There have not been any prior prospective clinical trials of risperidone. However, several case reports and case series support the potential benefit of risperidone for the treatment of chorea.[18,19,20,21] Moreover, in a retrospective chart review study, Duff et al compared 17 individuals with HD treated with risperidone against 12 individuals with HD not treated with any antipsychotic medication.[22] The mean (SD) risperidone dose was 2.5 (1.9) mg daily (range 0.75-6.0 mg) and the mean time between pre-treatment evaluation and post-treatment evaluation in the risperidone group was 14.8 (8.2) months (control group 11.0 (3.7) months). While the control group had significant worsening of UHDRS[23] total motor scores, the risperidone group had stable UHDRS total motor scores. Désaméricq et al examined the effects of antipsychotic and tetrabenazine treatment in a large observational, prospective cohort (Huntington French-Speaking Group).[24] 63% of 956 were treated with an antipsychotic (with 13% on risperidone) or tetrabenazine and when comparing long-term outcomes between the different groups, no differences in rate of decline of motor or behavioral function were identified. Differences in cognitive decline were seen, with benzamide antipsychotics (e.g. amisulpride, levosulpiride) associated with the greatest cognitive decline. Schultz et al examined the effects of risperidone, olanzapine, and tetrabenazine treatment in another large, observational, prospective cohort (Enroll-HD).[25] The mean (SD) risperidone dose was 1.76 (1.6) mg daily and olanzapine dose was 6.95 (5.88) mg daily. Changes in UHDRS total motor score were comparable between these groups and the tetrabenazine group suggesting comparable chorea benefit.

Neuroimaging

The pathological hallmark of HD is degeneration of striatal medium spiny neurons, but there is also widespread cortical atrophy, and chorea is thought to reflect dysfunction of the cortico-striatal motor circuit.[26] Neuroimaging studies have shown that motor dysfunction is associated with caudate atrophy,[27] altered motor cortico-striatal circuits,[28] altered cortico-cortical networks,[29] degeneration of the corpus callosum body,[30] and decreased insular functional connectivity.[31] Different neuroimaging metrics correlate with HD genetic burden,[32] motor function,[33] and clinical progression[34] and offer promise as longitudinal disease biomarkers.

Clinical experience demonstrates that there is heterogeneity in response to HD chorea treatment. Some patients have chorea that is refractory to treatment with VMAT-2 and antipsychotic medications; others demonstrate differential improvement with one class compared to the other. Different motor phenotypes have been recognized in HD[35] and it may be that clinical heterogeneity in response to chorea treatment reflects underlying neurobiological differences. Research in schizophrenia suggests that changes in functional connectivity occur with antipsychotic treatment[36] and that differences in cortical thickness[37] and white matter tract integrity[38] may predict response to antipsychotic treatment.

Here, we propose to take advantage of advanced analytical approaches to fully evaluate structural and functional connectivity, identify predictors of clinical response to risperidone treatment and examine neuroimaging changes associated with risperidone treatment.

Wearable Sensors Background (MC10)

HD research and care have also been hampered by the limitations of existing clinical measures and a lack of objective measures of chorea. The UHDRS[29] is commonly used in clinical trials to assess motor function but the scale has several limitations: it is categorical, subjective, must be administered by a trained rater, and some items exhibit poor interrater reliability.[39] New objective disease measures are needed. Objective quantitative-motor (Q-motor) assessment[40] is sensitive to HD clinical progression[41], and has been used in clinical trials[42] but must be performed in a clinic setting. Wearable sensors, which enable unobtrusive monitoring in the home environment, may be an ideal tool for assessing HD motor function. Preliminary work has established the feasibility of wearable sensors in HD,[43,44] which can objectively measure motor features of HD, but further work is needed to establish their sensitivity to detect chorea and responsiveness to treatment.

MC10 has developed the BioStamp nPoint™, a FDA 510(k) cleared medical device. This multimodal, reusable and rechargeable biosensor uses flexible and stretchable electronics to enable unobtrusive wear on the body and monitoring in the home. The sensors have accelerometry, gyroscopy, and ECG/EMG capabilities. A docking station enables wireless recharging and data collection (**Figure 1**).

Figure 1: MC10 wearable sensor system and physical placement of sensors

UR investigators have completed a 12-month study in which individuals with HD, prodromal HD, and healthy controls wore the MC10 sensors in clinic and at home. Analysis of accelerometer data has resulted in the development of a novel metric for quantifying truncal chorea, referred to as the Chorea Index,[45] which correlates with the truncal chorea rating on the UHDRS, both in clinic and at home. Analysis also resulted in quantifying gait metrics and activity patterns (amount of time spent sitting, standing, walking and lying down), which were significantly different between individuals with HD and control participants.[45]

3. ADMINISTRATIVE ORGANIZATION

Participating URMC departments/centers include the Department of Neurology and the Center for Advanced Brain Imaging & Neurophysiology (UR CABIN).

4. STUDY DESIGN

This is a single-site, blinded-rater, open-label dose response study of risperidone for the treatment of HD chorea that incorporates brain MRI with novel methods of structural and functional connectivity data integration and wearable sensors. The study will include a titration phase and a maintenance phase. Risperidone dosage assessment, with consideration to chorea benefit and tolerability, will occur at regular intervals during the titration phase until the optimal dosage has been reached. During the maintenance phase, the participant's optimal dosage will be continued. The primary outcome measure is the UHDRS total maximal chorea (TMC) score, as assessed by expert-rater review of video recordings. All expert-rater assessments of video recordings will be performed at the time of subject study completion, and raters will be blinded to the study visit.

Screening Phase (7-45 days)

All participants determined to be eligible will have the MC10 sensors placed at the conclusion of the screening visit and be instructed to wear the sensors for 1 week following the visit. If they are later found to be ineligible on the basis of screening laboratory results or an inability to discontinue a disallowed medication, they will be

instructed to remove and return the wearable sensors. Participants will also be scheduled for a brain MRI, which will occur prior to the baseline visit.

Titration Phase (8 weeks)
Risperidone will be initiated at 0.5 mg daily the day after the baseline visit with a planned increase to 0.5 mg twice daily after 7 days. The dose will be assessed at pre-specified intervals for the duration of the titration phase (week 2, week 3, week 4, week 6, and week 7). The investigator will increase the dose by 0.5 mg at the week 2, week 3, week 4, and week 6 visits until optimal chorea benefit has been obtained, the participant experiences an intolerable adverse event, or the maximum allowable dosage (3.0 mg daily) is reached. To ensure that the participant is on a stable dose by week 8, the dose at week 7 may be decreased but should not be increased. The MC10 sensors will be placed at the week 8 visit and participants will be instructed to wear the sensors for 1 week following the visit (during the maintenance phase).

Maintenance Phase (4 weeks)
The maximum dosage reached should be maintained during the maintenance phase (week 8-week 12), however, reductions/discontinuation will be allowed in the setting of an adverse event. The second brain MRI should occur during the maintenance phase. Following the week 12 visit, participants may choose to remain on drug at the discretion of their treating clinician, but otherwise will complete a short taper with follow-up by phone.

4.1. SUBJECT POPULATION

a) **Number of Participants:** We anticipate screening 16 individuals in order to meet our enrollment goal of 12 subjects. Evaluable subjects who withdraw from the study prior to initiating drug treatment may be replaced to meet the enrollment goal.

b) **Gender and Age of Participants:** There will not be any enrollment restrictions based upon gender. Participants must be between 18 and 65 years of age.

c) **Racial and Ethnic Origin:** There will not be any enrollment restrictions based upon race or ethnic origin.

Huntington's disease is characterized by a triad of motor abnormalities, psychiatric symptoms, and cognitive impairment. As such, we will allow adults with decisional impairments to participate. In the case of absence of consent capacity, we will obtain informed consent from a legally authorized representative. This is described under more detail in Section 7.

4.2. STUDY DRUG

4.2.1 Study Drug

Risperidone is a selective monoamergic antagonist with high affinity for serotonin $5HT_2$, dopamine D_2 receptors, α_1 and α_2 adrenergic receptors, and H_1 histaminergic receptors. In adults, it is FDA-approved for use in bipolar disorder and schizophrenia. While commonly used in clinical practice, it is considered investigational for HD chorea. As per FDA policy (https://www.fda.gov/media/79386/download), this study is exempt from IND requirements because:

- risperidone is lawfully marketed in the U.S
- we do not intend to report the investigation to the FDA in support a new indication or change in labeling of risperidone
- we do not intend to use the investigation to support a change in the advertising for risperidone
- the study does not involve a route of administration, dose, or patient population that significantly increases the risk associated with risperidone

Risperidone does carry a black box warning for increased mortality in elderly patients with dementia-related psychosis. Given this, elderly patients over the age of 65 will be excluded. The study is designed, in part, to assess the tolerability of risperidone in this population. Adverse events will be closely monitored. The risperidone label can be found at https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020272s056,020588s044,021346s033,021444s03lbl.pdf

4.2.2 **Study Drug Packaging, Distribution, and Accountability**

The Investigational Drug Service at the University of Rochester will manage the packaging and distribution of the study drug in conjunction with the study team. 0.5 mg tablets of the study drug will be purchased in bulk. The study drug will be repackaged into labeled bottles. The Investigational Drug Service will dispense bottles. Medication labels will be provided by the Investigational Drug Service and labeling will include the study number, route of administration, quantity, directions for use, storage conditions, and additional space for information to be completed by a study team member (dispensing date, participant number). The drug will be stored at the site in a locked storage area with controlled temperature (59°- 77° F).

At each in-person visit participants will receive an adequate supply of study drug to ensure that participants have a sufficient supply of study drug to last until their next visit. Participants will be asked to return all study bottles.

4.2.3 **Study Drug Dose Adjustment**

The maximum allowable dose and dose levels were selected in accordance with prescribing guidelines and clinical experience. Participants will initiate risperidone 0.5 mg nightly (level 1) the day after the baseline visit with a pre-

planned increase to 0.5 mg twice daily after 7 days. Dose assessment will occur at pre-specified intervals during the titration phase. At the week 2, 3, 4, and 6 visits, the investigator will increase the dose by 0.5 mg (Table 1) until either optimal chorea benefit has been obtained, an intolerable adverse event occurs, or the maximum allowable dose is reached. The investigator should consult with the participant (and care partner) and use all available study information in determining whether the optimal dose has been reached. To ensure that the participant is on a stable dose by week 8, the dose at week 7 may be decreased but should not be increased. The investigator may decrease the dose or discontinue the study drug in the event of an adverse event.

Table 1: Risperidone Dose Levels

Dose Level	Total Daily Dose	Morning Dose	Evening Dose
1*	0.5 mg	None	0.5 mg
2	1.5 mg	0.5 mg	1 mg
3	2 mg	1 mg	1 mg
4	2.5 mg	1 mg	1.5 mg
5	3 mg	1.5 mg	1.5 mg

*With increase to 0.5 mg twice daily after 7 days.

The drug should be taken orally and can be taken with or without food. For twice daily administration, the doses should be spaced approximately 12 hours apart. A drug diary will be used to provide instructions on how to take the medication and to help with adherence.

After the week 12 visit, participants on study drug will begin a short taper off of study drug. Participants with a total daily dose of ≥2.5 mg will be instructed to decrease to 1mg twice daily for 3 days then decrease to 0.5 mg twice daily for 3 days then stop. Participants with a total daily dose of 1.5-2 mg will be instructed to decrease to 0.5 mg twice daily for 3 days then stop. Participants with a total daily dose of 0.5-1 mg will be instructed to stop the drug without a taper.

Participants who discontinue study drug and do not withdraw their consent, will continue to be followed in the study.

4.2.4 **Allowed Medications**

CYP2D6 inhibitors (e.g. fluoxetine, bupropion, and paroxetine), cimetidine, and ranitidine, which may result in increased serum concentrations, will be permitted as titration is being performed slowly and our maximal total daily dose is only 3.0 mg.

CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbital), which may result in decreased serum concentrations of risperidone, will be allowed.

Vesicular monoamine transporter-2 inhibitors will be allowed but stable dosages for 30 days prior to the baseline and for the duration of the study will be required. We recognize that the vesicular monoamine transporter-2 inhibitors have been associated with QT prolongation; the mean increase in QTc interval with tetrabenazine 50 mg is 8 msec (https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021894lbl.pdf) and the mean increase in QTc interval with deutetrabenazine 24 mg is 4.5 msec (https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208082s000lbl.pdf). Given that risperidone treatment may also be associated with QT prolongation, we will obtain baseline and follow up EKGs and will keep the maximum total daily dose to 3 mg. In addition, we are excluding those > 65 years of age and with a history of cardiac arrhythmias or congenital long QT syndrome.

4.2.5 **Disallowed Medications**

The following medications will not be allowed from 30 days prior to the study and for the duration of the study:

- Selective and non-selective monoamine oxidase inhibitors
- Typical or atypical antipsychotics
- Levodopa (any formulation)
- Dopamine agonists
- Valproate
- Furosemide
- QT Prolonging Drugs (Table 2)

Table 2: QT Prolonging Drugs	
Amiodarone	Levomethadyl
Arsenic trioxide	Mesoridazine
Azithromycin	Methadone
Bepridil	Moxifloxacin
Chloroquine	Pentamidine
Chlorpromazine	Probucol
Clarithromycin	Procainamide
Disopyramide	Quinidine
Dofetilide	Sevoflurane
Domperidone	Sotalol
Droperidol	Sparfloxacin
Erythromycin	Thioridazine
Flecainide	Vandetanib
Halofantrine	Vardenafil
Ibutilide	

Escitalopram and citalopram will be allowed with the following dose restrictions. The maximum total daily dose of citalopram will be 20 mg for individuals who are ≥ 60

years of age, are known CYP2C19 poor metabolizers, or are taking certain CYP2C19 inhibitors (cimetidine, omeprazole, esomeprazole, lansoprazole, fluconazole, fluoxetine, fluvoxamine, and ticlopidine). For all others, the maximum total daily dose of citalopram will be 40 mg. The maximum total daily dose of escitalopram will be 10 mg for individuals who are ≥ 60 years of age and 20 mg for all others.

Participants will be permitted to discontinue a disallowed medication in order to enroll in the study. Any discontinuation of disallowed medications for the purpose of enrollment in the study will be done only after the participant has completed the informed consent process, and all reductions and discontinuations will be completed under the guidance of the clinical investigator and/or the patient's treating neurologist. Participants discontinuing a disallowed medication must remain off the disallowed medication for 30 days prior to the Baseline visit and must remain off the disallowed medication for the entirety of the Titration and Maintenance periods in the study.

Concomitant medications will be collected at each visit and verified in the electronic medical record whenever possible. If treatment with a disallowed medication is required, the study drug should be discontinued and the participant should continue in the study off of the study drug. The study drug may be restarted after the disallowed medication is stopped.

4.2.6 Pregnancy and Nursing

Female participants of childbearing potential will be advised to use adequate birth control as there is insufficient data regarding the effects of risperidone on the fetus. Adequate birth control methods include surgical sterilization, a partner who has had a vasectomy, oral contraceptives, condom plus spermicidal cream/jelly, cervical cap plus spermicidal cream/jelly, diaphragm plus spermicidal cream/jelly, intrauterine device (in place for at least 3 months) plus spermicidal cream/jelly, or contraceptive implant or injection. Abstinence is considered an acceptable contraceptive regimen.

If a participant becomes pregnant during the study, it is important that they notify a study team member immediately. In such an event, the study drug must be discontinued immediately. The participant may continue in the study off of study drug. All attempts will be made to follow the participant until delivery.

4.3 **MC10 SENSORS**

MC10 has developed the BioStamp nPoint™, a FDA 510(k) cleared medical device. This multimodal, reusable and rechargeable biosensor uses flexible and

stretchable electronics to enable unobtrusive wear on the body and monitoring in the home. The sensors have accelerometry, gyroscopy, and ECG/EMG capabilities. A docking station enables wireless recharging and data collection

The study team at the University of Rochester will receive the wearable sensor patches from MC10 and store the sensors in a secure office, accessible only to research study team members with access. All records pertaining to supply receipt, distribution, and return will be maintained by the research team.

The sensors will be applied at the screening and week 8 visits, as described in Section 8.2. After completing all sensor activities, the sensors should then be removed and, with the docking station, mailed back in pre-paid packaging or returned in-person.

Sensor data will be used to calculate a Chorea Index score, or average amount of chorea over a given period of time, using algorithms from our previous work. We will also analyze activity patterns and gait.

4.4 NEUROIMAGING

All imaging will be conducted on a research dedicated 3T whole-body Siemens Prisma scanner (Erlangen, Germany), equipped with a 64-channel receive-only head coil and body coil transmission, and high-performance gradients of max strength 80mT/m and slew rate of 200mT/m/s. The MRI protocol includes 3D T1w MPRAGE [TR/TE = 1400/2.34 ms; 1 mm isotropic resolution] and T2w SPACE sequence [TR/TE = 3200/444 ms; 1 mm isotropic resolution] anatomical images, single-shell dMRI [64 diffusion-encoded (b=1000 s/mm^2) and 5 reference (b = 0 s/mm^2) images; TR/TE = 4300/69 ms; 1.5 mm isotropic resolution] and rs-fMRI [TR/TE = 993/43 ms, number of volumes = 300, 2 mm isotropic resolution] using EPI sequences.

Neuroimaging will occur at two time points, between screening and baseline (off drug) and between week 8 and week 12 (maintenance phase).

5. INCLUSION AND EXCLUSION CRITERIA

5.1 INCLUSION CRITERIA

- Manifest HD (Diagnostic Confidence Level 4 + CAG repeat ≥ 37 or family history of HD)
- UHDRS Total Maximal Chorea (TMC) ≥ 8
- UHDRS Total Functional Capacity ≥ 5
- Subject willing and able to provide written informed consent OR legally authorized representative provides written informed consent*
- Between 18 and 65 years of age

*A care partner will be required to attend all visits for all subjects with a TFC 5-7 at screening OR when consent was provided by a legally authorized representative.

5.1 EXCLUSION CRITERIA

- Use of antipsychotic, levodopa, dopamine agonist, monoamine oxidase inhibitor or other disallowed medication in the 30 days prior to the baseline visit (see Section 4.2.5)*
- Prior non-response to risperidone or intolerability to risperidone (in the investigator's opinion)
- Allergy or hypersensitivity to risperidone
- Dysphagia that in the investigator's opinion would preclude participation in the study
- Active suicidal ideation or psychiatric condition that in the investigator's opinion would preclude study participation
- QTc > 460 msec for women and QTc > 450 msec for men on 12-lead EKG
- History of cardiac arrhythmia or congenital long QT syndrome
- Significant renal impairment (creatinine clearance < 30 mL/min as estimated by the Cockgroft-Gault formula) or hepatic impairment (AST or ALT > 2.5 times upper limit of normal OR alkaline phosphatase or total bilirubin > 2 times upper limit of normal)
- Active drug or alcohol abuse or dependence
- Pregnant or breast-feeding
- Any contraindication to MRI (e.g. pacemakers, aneurysm clips, metallic prostheses, shrapnel fragments, claustrophobia)
- History of active (clinically significant) skin disorder that would interfere with sensor adherence
- History of allergic response to adhesives
- Pacemaker, AICD, or other implantable stimulator
- Use of an investigational drug in the 30 days prior to the baseline visit
- Inability to complete study activities, as determined by the study team
- Clinically significant parkinsonism as determined by expert investigator assessment

*Participants currently taking a disallowed medication will be allowed to reduce and discontinue the disallowed medication in order to qualify for study participation. Disallowed medications must be discontinued at least 30 days prior to the baseline visit.

6. RECRUITMENT METHODS

We anticipate that the majority of participants will be identified within the clinical practices of faculty in the UR Department of Neurology. To minimize undue influence, discussion of research participation should occur after all clinical care related activities have been completed. Potential participants may also be asked to

spread the word about the study and share our contact information with any other individuals who may wish to enroll in the study. We will use multiple methods to identify potential participants; beyond recruiting from clinical practices, other sources will include support groups, interest registries, and affinity organizations. Recruitment avenues include:

(1) We may use the eRecord "My Reports" function to regularly generate lists of patients seen in the UR neurology department with a diagnosis of Huntington's disease. The research team will give each neurology provider a list of their identified patients and the date of their next upcoming clinic visit so that he or she may consider whether their patient may be appropriate for participation.

(2) The study will be posted on appropriate clinical research registries including, but not limited to, HD Trial Finder, Research Match, and the UR Health Research website.

(3) We will reach out to individuals who expressed interest in participating in future research studies through avenues including the UR Department of Neurology Study Interest Registry (STUDY00000537), and the CTSI Volunteer Registry (STUDY00001978).

(4) We will reach out to local patient advocacy groups and other health-related community organizations to increase awareness and engage potential participants. We will promote the study at regional symposiums and other events. Additional efforts may be made to promote the study in the local news media and social media outlets.

(65 We may use i2b2, TriNetX, or another appropriate informatics tool to identify Huntington's disease patients seen at the UR movement disorders clinic and then send an RSRB-approved recruitment letter and research brochure to the identified patients.

The study team will track recruitment metrics such as how potential participants learned about the trial, referral source, number who are found to be ineligible, reasons for ineligibility, number who decline, reasons for nonparticipation of potentially eligible participants (when available), and number who enroll. This information will be reviewed monthly to identify any problems and develop strategies to enhance recruitment.

7. CONSENT PROCESS

Interested potential participants will be contacted by a study coordinator who will provide a brief overview of the study, assess their interest, and schedule them for a screening visit, at which time eligibility will be confirmed and written informed consent will be obtained. Written informed consent and HIPAA authorization will be obtained using an IRB-approved consent form. The study coordinator obtaining consent will be trained in human subject's protection according to University of

Rochester IRB procedures.

Capacity to consent to the study will be determined by the study coordinator during the consent process. As delineated in the consent form, capacity will be determined based on the potential participant's understanding of why the study is being done, what will happen during the study, possible risks and benefits, alternatives to participation in the study, how personal information will be protected, and what to do if there is a problem or question.

Investigators and study team members will ensure that prospective participants have sufficient knowledge and understanding of the details of the study to allow them to make an informed decision whether or not to participate. Prospective participants will be provided with an opportunity to ask questions. Every effort will be made to provide potential participants with a copy of the consent form prior to the screening visit.

Prospective participants will also be asked to consent to future contact to update their contact information and inform them about future studies (STUDY00000537). Participants may decline to consent to this aspect and still participate in the study.

Documentation of consent will be stored in a secure filing cabinet at the UR and will only be accessible to members of the UR study team. A copy of the consent form will be provided to the participant upon obtainment of consent. Consent acknowledgment will be electronically recorded in REDCap. If an individual is unable or unwilling to consent, the individual will be excluded from the study but their routine clinical care will not be affected.

Consent Process for Adults with Decisional Impairment:
If an individual is not capable of giving consent to participate, we will obtain informed consent from a legally authorized representative.

8. STUDY PROCEDURES

8.1 SCHEDULE OF ACTIVITIES

	Screening (-7-60 days)	Baseline (Week 0)	Week 2 (±-3 days)	Week 3 (±3 days)	Week 4 (±3 days)	Week 6 (±-3 days)	Week 7 (±3 days)	Week 8 (±-3 days)	Week 12 (±-3 days)	Week 13 (±-3 days)	PW Visit
			TITRATION					MAINTENANCE			
	Clinic	Clinic	TC	Clinic	TC	Clinic	TC	Clinic	Clinic	TC	Clinic
Informed Consent	X										
Eligibility	X										
Confirm HD Diagnosis	X										
Demographics	X										
Health History	X										
Concomitant Medications	X	X	X	X	X	X	X	X	X		X
Vital Signs + Physical Measurements	X	X		X		X		X	X		X
Physical Exam	X										
12-lead EKG	X					X			X		
Chemistry/Hematology	X					X			X		
Pregnancy Test	S	U						U			
C-SSRS		X		X		X		X	X		X
UHDRS-Motor (VR)	X	X		X		X		X	X		X
UHDRS-Cognition		X		X		X		X	X		X
UHDRS-Behavior		X		X		X		X	X		X
UHDRS-Functional Assessment		X							X		X
UHDRS-Independence		X							X		X
UHDRS-TFC	X	X							X		X
PBA-Short form		X		X		X		X	X		X
HADS		X		X		X		X	X		X
Epworth Sleepiness Scale		X		X		X		X	X		X
Barnes Akathisia Scale		X		X		X		X	X		X
Apathy Scale		X		X		X		X	X		X
MoCA		X						X	X		
Q-Motor		X						X			

Assess Adverse Events		X	X	X	X	X	X	X	X		X
Assess Dose			X	X	X	X	X	X			X
Assess Drug Adherence				X		X		X	X	X	X
CGI		X		X		X		X	X		X
PGI		X		X		X		X	X		X
Neuroimaging	X[1]							X[2]			
MC10 WEARABLE SENSORS											
Apply Sensors	X							X			
Lying Position Activity	X							X			
10 Meter Walk test (VR)	X							X			
Wear sensors x 1 week	X							X			
Daily journal x 1 week	X							X			

S Serum pregnancy test for women of childbearing potential
U Urine pregnancy test for women of childbearing potential
[1]Should occur prior to baseline visit.
[2]Should occur prior to week 12 visit.

8.2 STUDY VISITS

8.2.1 **Screening Visit**

Prior to completing any study activities, written informed consent will be obtained. The study coordinator and investigator will assess potential participants for study eligibility. Participants will be assigned a unique participant identification number. If a participant is being withdrawn from a medication to qualify for the study (detailed in Section 4.2.5), the consent form must be signed prior to the initiation of the withdrawal.

Evaluations:

- Informed Consent
- Eligibility Criteria Review
- Confirm HD Diagnosis
- Demographics
- Health History
- Concomitant Medications
- Vital Signs + Physical measurements
- Physical Examination
- 12-lead EKG
- Chemistry/hematology
- Pregnancy test (serum, for women of childbearing potential)
- UHDRS-Motor (VR)
- UHDRS-TFC

MC10 Activities:

- Application of MC10 wearable sensors
- Lying position activity
- 10 meter walk test (VR)
- Wear sensors x 1 week

- Daily journal x 1 week

Three sensors will be applied using double-sided adhesives to the chest, arm and leg. The arm and leg sensor will be applied to the most affected side as determined by the investigator. In the case of symmetric symptoms, the arm and leg sensors will be placed on the dominant side. The sensors will be applied before the performance of standard clinical motor assessments (UHDRS-Motor), which will be video-recorded and logged into the BioStamp NPoint Investigator Application. Videos will be stored in Box. For the lying position activity, participants will be asked to lay in each of four positions (supine, prone, and on both sides) for approximately 30 seconds.

After the visit, participants will wear the sensors and complete a daily journal for one week. For 6 days, participants will wear the sensors during waking hours and recharge them nightly. Beginning on Day 7, participants will wear the sensors continuously for 24 hours. This will permit the capture of sleep data. On Day 8, after 24 hours of continued use, participants will remove the sensors and return them with the docking station either by pre-paid packaging or in-person. In the journal, participants will record the predominant activity that they engage in (sitting, standing, walking, lying down) for every hour of the day during the recording period and any falls.

Neuroimaging will be scheduled to occur at least 1 week following the screening visit (following completion of the wearable sensory portion of the Screening phase), but prior to the baseline visit.

Screen Fails: All screening tests/procedures are for research purposes only. Data gathered during the screening process will be retained.

8.2.2 **Baseline Visit**

The baseline visit will occur within 7-45 days of the screening visit. Prior to the baseline visit, laboratory study results obtained at the screening visit must be reviewed and eligibility confirmed, neuroimaging must be obtained, the first wearable sensor period must be completed, and all disallowed medications must have been discontinued for ≥30 days. Participants will be supplied with study drug and the first dose of study drug should be taken the following morning.

Evaluations:

- Concomitant Medications Update
- Vital Signs + Physical measurements
- Pregnancy test (urine, for women of childbearing potential)
- C-SSRS
- UHDRS-Motor (VR)
- UHDRS-Cognition

- UHDRS-Behavior
- UHDRS-Functional Assessment
- UHDRS-Independence
- PBA-Short form
- Hospital Anxiety and Depression Scale
- Epworth Sleepiness Scale
- Barnes Akathisia Scale
- Apathy Scale
- MoCA
- Q-Motor
- CGI
- PGI
- Assess Adverse Events

8.2.3 **Week 3 Visit**

The Week 3 visit should occur within 21 ± 3 days of the baseline visit. Previously dispensed study drug bottles will be collected and new study drug bottles dispensed.

Evaluations:

- Concomitant Medications Update
- Vital Signs + Physical measurements
- C-SSRS
- UHDRS-Motor (VR)
- UHDRS-Cognition
- UHDRS-Behavior
- PBA-Short form
- Hospital Anxiety and Depression Scale
- Epworth Sleepiness Scale
- Barnes Akathisia Scale
- Apathy Scale
- Assess Adverse Events
- Assess Dose (Section 8.3.24)
- Assess Drug Adherence
- CGI
- PGI

8.2.4 **Week 6 Visit**

The Week 6 visit should occur within 42 ± 3 days of the baseline visit. Previously dispensed study drug bottles will be collected and new study drug bottles dispensed.

Evaluations:

- Concomitant Medications Update
- Vital Signs + Physical measurements
- 12-lead EKG
- Chemistry/hematology, (at investigator's discretion) approximately two tablespoons
- C-SSRS
- UHDRS-Motor (VR)
- UHDRS-Cognition
- UHDRS-Behavior
- PBA-Short form
- Hospital Anxiety and Depression Scale
- Epworth Sleepiness Scale
- Barnes Akathisia Scale
- Apathy Scale
- Assess Adverse Events
- Assess Dose
- Assess Drug Adherence
- CGI
- PGI

8.2.5 **Week 8 Visit**

The Week 8 visit should occur within 56 ± 3 days of the baseline visit. Previously dispensed study drug bottles will be collected and new study drug bottles dispensed.

Evaluations:

- Concomitant Medications Update
- Vital Signs + Physical measurements
- Pregnancy test (urine, for women of childbearing potential)
- C-SSRS
- UHDRS-Motor (VR)
- UHDRS-Cognition
- UHDRS-Behavior
- PBA-Short form
- Hospital Anxiety and Depression Scale
- Epworth Sleepiness Scale
- Barnes Akathisia Scale
- Apathy Scale
- MoCA
- Q-Motor
- Assess Adverse Events
- Assess Dose
- Assess Drug Adherence

- CGI
- PGI

MC10 Activities:

- Application of MC10 wearable sensors
- Lying position activity
- 10 meter walk test (VR)
- Wear sensors x 1 week
- Daily journal x 1 week

Three sensors will be applied using double-sided adhesives to the chest, arm and leg. The arm and leg sensor will be applied to the most affected side as determined by the investigator. In the case of symmetric symptoms, the arm and leg sensors will be placed on the dominant side. The sensors will be applied before the performance of standard clinical motor assessments (UHDRS-Motor), which will be video-recorded and logged into the BioStamp NPoint Investigator Application. For the lying position activity, participants will be asked to lay in each of four positions (supine, prone, and on both sides) for approximately 30 seconds.

After the visit, participants will wear the sensors and complete a daily journal for one week. For 6 days, participants will wear the sensors during waking hours and recharge them nightly. Beginning on Day 7, participants will wear the sensors continuously for 24 hours. This will permit the capture of sleep data. On Day 8, after 24 hours of continued use, participants will remove the sensors and return them with the docking station either by pre-paid packaging or in-person. In the journal, participants will record the predominant activity that they engage in (sitting, standing, walking, lying down) for every hour of the day and any falls.

Neuroimaging should occur between the week 8 and week 12 visit. A urine pregnancy test should be obtained prior to neuroimaging for all women of childbearing potential.

8.2.6 **Week 12 Visit**

The Week 12 visit should occur within 84 ± 3 days of the baseline visit. Previously dispensed study drug bottles will be collected. Participants will be instructed how to taper off of study drug.

Evaluations:

- Concomitant Medications Update
- Vital Signs + Physical measurements
- 12-lead EKG
- Chemistry/hematology (approximately two tablespoons)
- C-SSRS

- UHDRS-Motor (VR)
- UHDRS-Cognition
- UHDRS-Behavior
- UHDRS-Functional Assessment
- UHDRS-Independence
- UHDRS-TFC
- PBA-Short form
- Hospital Anxiety and Depression Scale
- Epworth Sleepiness Scale
- Barnes Akathisia Scale
- Apathy Scale
- MOCA
- Assess Adverse Events
- Assess Drug Adherence
- CGI
- PGI

8.2.7 **Telephone Visits (Week 2, Week 4, Week 7, Week 13)**

The Week 2 visit should occur within 14 ± 3 days of the baseline visit. The Week 4 visit should occur within 28 ± 3 days of the baseline visit. The week 7 visit should occur within 49 ± 3 days of the baseline visit. If scheduling requires two separate phone calls for each telephone visit, one with the study coordinator and one with the investigator, this will be allowed.

Evaluations:

- Concomitant Medications Update
- Assess Adverse Events
- Assess Dose

The Week 13 visit should occur within 91 ± 3 days of the baseline visit. At this visit, the coordinator will assess drug adherence and verify that the participant has completed their study drug taper. This visit does not need to occur for any participants who did not require a study drug taper. Coordinators may also use this visit to follow up on any unresolved adverse events.

8.2.8 **Unscheduled Visits**

An unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by an investigator. The date and reason for the unscheduled visit will be recorded. The following evaluations may be performed, as deemed necessary by the investigator.

Evaluations:

- Concomitant Medications Update

- Vital Signs + Physical measurements
- Physical Examination
- 12-lead EKG
- Chemistry/hematology (approximately two tablespoons)
- Pregnancy Test
- C-SSRS
- UHDRS-Motor
- UHDRS-Cognition
- UHDRS-Behavior
- Assess Adverse Events
- Assess Dose
- Assess Drug Adherence

8.2.9 **Premature Withdrawal Visit**

Subjects may withdraw from the study at any time. In the event of a premature study withdrawal (either participant or investigator initiated), a premature withdrawal visit should occur. Reasons for premature withdrawal will be documented. At the time of the visit, participants will be instructed to discontinue their study drug, if they have not done so already. If the participant is unwilling or unable to come in for a premature withdrawal visit, a telephone visit (evaluations described in Section 8.2.6) should be performed whenever possible.

Evaluations:

- Concomitant Medications Update
- Vital Signs + Physical measurements
- C-SSRS
- UHDRS-Motor (VR)
- UHDRS-Cognition
- UHDRS-Behavior
- UHDRS-Functional Assessment
- UHDRS-Independence
- UHDRS-TFC
- PBA-Short form
- Hospital Anxiety and Depression Scale
- Epworth Sleepiness Scale
- Barnes Akathisia Scale
- Apathy Scale
- Assess Adverse Events
- Assess Drug Adherence
- CGI
- PGI

8.3 **STUDY ASSESSMENTS**

8.3.1 Study Duration

The individual's participation in the study will last for approximately 14-20weeks. The overall anticipated duration of the study is 18 months.

8.3.1 Participant Information

Demographics, health history, and concomitant medications will be obtained at screening. Concomitant medications will be updated at each study visit.

Medical and Safety Assessments

8.3.2 Physical Examination

A brief physical examination will be performed by the investigator at the screening visit. This will include examination for parkinsonism.

8.3.3 Physical Measurements and Vital Signs

Participant height, weight, respiratory rate, blood pressure, heart rate, and temperature will be collected by a study coordinator at the screening visit. Weight, respiratory rate, blood pressure, heart rate, and temperature will be collected at subsequent in-person visits.

Sitting blood pressure and heart rate will be measured after 3 minutes of rest. Readings will be repeated every 3 minutes until two consecutive readings are similar to ensure that baseline has been reached. Standing blood pressure and heart rate will be measured after 3 minutes of standing by a study coordinator.

8.3.4 Electrocardiogram

A 12-lead electrocardiogram will be obtained by a trained study coordinator. ECG readings will be provided by a cardiologist.

8.3.5 Chemistry and Hematology

A fasting comprehensive metabolic panel, fasting lipid panel, and complete blood count with differential will be obtained at screening and week 12. At the investigator's discretion (e.g. in the event of leukopenia identified on baseline CBC or a reported history of drug-induced leukopenia), labs may also be repeated at week 6. All blood tests will be obtained on-site and sent to URMC Labs for processing. Screening labs may be repeated one time if abnormal to confirm eligibility. Each blood draw will be approximately two tablespoons in size.

8.3.6 Pregnancy Screening

A serum pregnancy test will be obtained at screening for all women of child-bearing potential. All blood tests will be obtained on-site and sent to URMC Labs for processing. A urine pregnancy test will be obtained at baseline (prior to drug initiation) and week 8 (prior to neuroimaging) for all women of child-bearing potential.

8.3.7 Adverse Events

Soliciting of adverse events will be non-specific. Participants will be asked the question, "Do you feel different in any way since your last research study visit?" All adverse events occurring after the screening visit will be reported. All subsequent adverse events will be reported regardless of suspected relationship to the study device. Adverse events not previously documented in the study will be recorded in the adverse event section in the case report form. The nature of each individual event, date and time of onset, duration, severity, and relationship to treatment will be established by the investigator. Likely alternative etiologies should be recorded for events considered unrelated to study device.

Adverse events already documented in the CRF, at a previous visit, and designated as 'continuing' should be reviewed at each visit. If an adverse event is resolved, then the documentation in the CRF must be completed to that effect. If an adverse event changes in frequency or severity during a study period, then a NEW record of that event will be initiated. A record of all adverse events will be reviewed periodically by the study investigators. The documentation and classification of adverse events is further reviewed in Section 16.

8.3.10 Epworth Sleepiness Scale (ESS)

The ESS is a validated, self-administered scale for the assessment of excessive daytime sleepiness.[46] The study coordinator will instruct the participant on how to complete this questionnaire and will subsequently review the questionnaire for completion.

8.3.11 Barnes Akathisia Scale

The Barnes Akathisia Scale, which has been used in clinical trials of tetrabenazine for HD chorea, includes objective observation and subjective questions to assess for the presence and severity of drug-induced akathisia.[47]

Huntington's Disease Motor Assessments

8.3.12 Confirmation of Diagnosis of Manifest Huntington's Disease

Manifest HD, defined as UHDRS Diagnostic Confidence Level (DCL) 4 + CAG repeat ≥ 37 or family history of HD will be confirmed by an investigator. No genetic testing will be done as a part of this study.

8.3.13 Unified Huntington's Disease Rating Scale (UHDRS)

The UHDRS is a validated assessment of HD.[48] The complete UHDRS includes the following assessments: motor, cognitive, behavioral, functional, independence, and total functional capacity. The cognitive assessment includes the verbal fluency test, symbol digit modalities test, and stroop interference test (color naming, word reading, interference). Ideally, the same rater should complete a given section at each visit. The UHDRS Motor will be video-recorded. Videos will be independently rated by raters blinded to the study visit.

8.3.14 Clinical Global Impression (CGI) and Patient Global Impression (PGI) Scales

The CGI is an observer-rated scale that measures impression of severity (CGI-S) and change (CGI-C). The CGI-C is rated on a 7-point scale from 1 (very much improved) to 7 (very much worse). The CGI-S and CGI-C will be completed by an investigator. Similarly, the PGI is a patient-rated scale that measures impression of change (PGI-C). The PGI-C will be completed by the participant and reviewed by a study coordinator.

8.3.15 Quantitative Motor (Q-Motor) Assessments

Q-Motor assessments are performed using force transducers and a grip device that includes a position sensor. The following tasks will be performed separately on each side: digitomotography (speeded finger tapping), dysdiadochomotography (pronation-supination), manumotography and choreomotography (grip force and chorea analysis), and pedomotography (speeded foot tapping). The Q-Motor takes approximately 15-3- minutes to administer. Data transfer will be performed using a secure web based platform.

8.3.16 10 Meter Walk Test

The 10 meter walk test is a validated measure of walking function. The test asks individuals to walk a total of 10 meters with the time taken to walk over the middle 6 meters recorded to allow for acceleration and deceleration. The test is performed at normal walking speed and participants are allowed to use assistive devices if they typically walk with them. Administration of the 10-meter walk will be video-recorded.

8.3.17 Wearable Sensor Daily Journal

Participants will maintain a daily journal in which they record the predominant activity that they engage in (sitting, standing, walking, lying down) for every hour of the day during the recording period, as well as any falls. Participants will complete this journal for 1 week following the screening visit and the week 8 visit (during the time when they are wearing the sensors).

Huntington's Disease Psychiatric and Cognitive Assessments

8.3.18 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a validated tool that will be used to screen for suicidal ideation and behavior and assess the level of risk.[49] It will be administered by a trained rater.

8.3.19 Problem Behavioral Assessment – short (PBA-s)

The PBA-s is a validated, semi-structured interview with 11 items that is designed to assess the severity and frequency of common behavioral problems in HD.[50] It will be administered by a trained rater.

8.3.20 Montreal Cognitive Assessment (MoCA)

The MoCA assesses visual-spatial and executive function, language, short-term memory, attention, abstraction, and orientation. It will be administered by a trained coordinator.

8.3.21 Hospital Anxiety and Depression Scale (HADS)

The HADS is a self-rated measure with anxiety and depression subscales that is recommended for screening in HD.[51] The study coordinator will instruct the participant on how to complete this questionnaire and will subsequently review the questionnaire for completion.

8.3.22 Apathy Scale (AS)

The AS is a clinician-rated scale, that has been used in other HD studies and is recommended for screening for apathy in HD.[51] The AS assesses the presence and severity of apathy.[52]

Study Drug Assessment

8.3.23 Drug Adherence Assessment

Participants will be asked to use a dosing diary to track study drug adherence. Participants will also be verbally asked whether they have missed any doses since their last visit and will be instructed to bring previously dispensed study drug bottles to each in-person visit. Pill counts will be performed by the study coordinator and the results recorded on a standard data form to monitor participant adherence. At the end of the study, all returned study medication will be counted and compared to the data form. Any discrepancies will be resolved and the data form will be updated as necessary.

8.3.24 Dose Assessment

During the titration phase, the investigator will assess the dose at week 2, week 3, week 4, and week 6 and increase the dose by 0.5 mg until either optimal chorea

benefit has been obtained, an intolerable adverse event occurs, or the maximum allowable dose is reached. The investigator should consult with the participant (and care partner) and use all available study information in making this decision (see Section 4.2.3).

During the maintenance phase, the maximal dose reached should be continued unless an adverse event occurs that warrants dose reduction or discontinuation.

8.4 Electronic Medical Record

When relevant, the participant's electronic medical record may be reviewed to obtain/verify participant information. Information concerning participation in this study will be included in the participant's electronic medical record. Lab test results may also be included in the participant's electronic medical record.

8.5 Return of Research Results

Most research results will not be provided to the participant. There will be two exceptions. 1) Results of laboratory studies and EKGs may be provided at the discretion of an investigator. Incidental findings that might have health consequences for the participant will be communicated to the participant and his/her primary care provider and/or primary neurologist.

2) Conditions can be diagnosed from having access to research quality brain MRI. Our scans are not read by a neuro-radiologist and the subjects are explicitly told that the experiment will not provide information as to their health status. However, if the researcher suspects something abnormal, they will seek advice from a qualified neuroradiologist. Interested individuals who sign a release form may receive an electronic format image of their brain.

9. RISKS TO SUBJECTS

9.1 General

1) Participants may find it uncomfortable to respond to some of the questions contained in the evaluations. Participants will not be required to answer any questions that make them uncomfortable. All study personnel will be appropriately trained in the administration of study assessments.

2) Blood draws may cause pain, redness, bruising, or infection at the site of the needle stick. The study team member conducting the blood draw will be appropriately trained.

3) Breach of confidentiality is a potential risk. To minimize the risks of breach of confidentiality, all study data will be maintained in secure systems. Additionally, any paper documents with identifiable information will be stored in a secure location and all information sharing will occur in a secure and HIPAA-compliant

manner. If a breach of confidentiality occurs, the participant(s) and investigators will be immediately notified and appropriate steps will be taken to minimize the risk of a future breach of confidentiality occurring.

9.2 **Study Drug**

According to the FDA label:

"The most common adverse reactions in clinical trials (≧10%) were somnolence, appetite increased, fatigue, rhinitis, upper respiratory tract infection, vomiting, coughing, urinary incontinence, saliva increased, constipation, fever, parkinsonism, dystonia, abdominal pain, anxiety, nausea, dizziness, dry mouth, tremor, rash, akathisia, and dyspepsia. The most common adverse reactions that were associated with discontinuation from clinical trials (causing discontinuation in >1% of adults and/or >2% of pediatrics) were somnolence, nausea, abdominal pain, dizziness, vomiting, agitation, and akathisia."

Additional recognized risks include:

- Orthostatic hypotension
- Hypersensitivity reactions
- Neuroleptic malignant syndrome
- Tardive dyskinesia
- Hyperglycemia
- Hyperprolactinemia
- Leukopenia/neutropenia
- Prolonged QT syndrome
- Cognitive impairment
- Dysphagia
- Priapism

Risperidone is routinely used in clinical practice for the management of chorea in Huntington's disease. To minimize the risk of side effects, we will follow a slow titration and limit the total daily dose to 3.0 mg. Safety and tolerability will be closely monitored by study investigators. Safety evaluation, described in detail in Section 8.3, will include vital signs, orthostatic vital signs, Barnes Akathisia Scale, multiple cognitive assessments, Epworth Sleepiness Scale, electrocardiogram, and chemistry/hematology. If an intolerability or adverse event occurs, depending on the severity of the event, investigators may decide to decrease the study drug or to discontinue the study drug. Participants will be able to withdraw from the study at any time.

9.3 **MC10**

1) When placing any adhesive onto skin, irritation or redness may occur. If skin irritation develops after the visit while wearing the sensors, participants will be instructed to remove the sensors and contact the study team. Individuals with an

active (clinically significant) skin disorder or an allergic response to adhesives will not be eligible to participate in the MC10 component.

2) Video recordings will be transmitted in encrypted form and stored in Box, a secure, HIPAA compliant database at the University of Rochester. Participants may be identified from these videos, as they include views of the face and full body; however, the study team will be instructed to minimize the use of the participant's name during the recording portion of the visit. Although data will be stored in secure servers in a HIPAA compliant manner at the University of Rochester, there is still the potential of a breach in confidentiality of study data. Study data will be maintained after the end of participation in the study; however, all study-related videos will be deleted within 5 years of study completion.

9.4 **NEUROIMAGING**

There is no immediate risk from exposure to magnetic fields of 3 Tesla. Possible anxiety may result from claustrophobia or dizziness experienced by the subjects when placed in the magnet. During the imaging portion of the experiment, subjects must remain in the bore of the magnet, which is approximately 3 feet in diameter. Also, the scanning coil closely encloses the subject's anatomy being imaged. These two factors may increase the likelihood of claustrophobia. Should the subject feel discomfort, the experiment will be terminated upon their request.

In rare cases, contact with the MRI transmitting and receiving coil or conductive materials such as wires, or skin-to-skin contact that forms conductive loops, may result in excessive heating and burns during the experiment. The operators of the MRI scanner will take steps, such as using foam pads when necessary, to minimize these risks. The subjects will be informed of the risk and instructed to immediately report any heating sensations. In the rare event that this would occur the experiment will be terminated and if necessary we will have the subject seek medical treatment.

Subjects will be screened for magnetic material before each study. Subjects with pacemakers, aneurysm clips (metal clips on the wall of large artery), metallic prostheses (including heart valves and cochlear implants) or shrapnel fragments are at risk in an MR environment. Welders and metal workers are also at risk for injury because of possible small metal fragments in their eyes. Those at risk will be excluded from the study.

The effect of exposure to MRI scanning on an unborn child is unknown. Exposure to MRI scanning might be harmful to a pregnant female or an unborn child. There are no established risks at this time, but the subjects will be informed that there is a possibility of a yet undiscovered pregnancy related risk.

MRI scanning produces a loud tone that can cause damage to the inner ear if appropriate protection is not used. Adequate protections in the form of earplugs or close fitting silicon-padded headphones will be provided.

10. POTENTIAL BENEFITS TO SUBJECTS

Participants may experience an improvement in chorea as a result of participation in this study, however, risperidone is readily available and may be prescribed in the context of routine clinical care.

11. COSTS FOR PARTICIPATION

Neither the participant nor the participant's insurance will incur any cost as a result of participation in this study.

12. PAYMENT FOR PARTICIPATION

Participants will receive $100 for each week that they wear the sensors and complete the accompanying daily journal (for up to $200). Participants will be compensated after return of the sensors and charging station. Participants will receive $50 for completion of each neuroimaging session (for up to $100). Participants will be compensated via checks.

13. SUBJECT WITHDRAWALS

Participants will be advised in the written informed consent forms that they have the right to withdraw from the study at any time without prejudice. Participants may be withdrawn by the investigator/sponsor for any reason they see fitting or appropriate, e.g.:

(1) Non-compliance with study drug or procedures
(2) Receipt of disallowed medications that cannot be discontinued
(3) An adverse event which in the investigator's judgment puts the participant at risk
(4) Illness that prevents continued trial participation
(5) Termination of study funding

Premature withdrawal will be defined as withdrawal from the study prior to completion of the week 12 visit. If a participant who has started the study withdraws or is withdrawn from the study prematurely, every effort should be made to complete the premature withdrawal visit. Reasonable effort should be made to contact any participant lost to follow-up during the course of the study in order to complete study related assessments and retrieve any outstanding data. Those withdrawn may be replaced. All reasons for subject withdrawals from the study will be recorded in the source documentation. If a participant withdraws from the study, data and information that was collected prior to withdrawal may still be used and shared with others.

14. PRIVACY AND CONFIDENTIALITY OF SUBJECTS AND RESEARCH DATA

Data management and storage for patient-reported outcome measures and traditional in-clinic measures will be performed using REDCap, which is designed specifically for use in research and restricts access to study data. REDCap was developed in a manner consistent with HIPAA security requirements and is recommended to University of Rochester researchers by the URMC Research Privacy Officer and Office for Human Subject Protection. REDCap servers are housed in a local data center at the University of Rochester and all web-based information transmission is encrypted.

All participant data will be identified solely by a unique subject ID to allow participant data to be linked and analyzed by the broader research community. Subject names or personal identifiers will not appear on any research materials. Participant confidentiality will be assured through a multi-layered approach, entirely compliant with HIPAA regulations. All study documents will be labeled using the participant's unique subject ID number. All records pertaining to the study will be kept in a secure location with limited access and destroyed according to institutional guidelines.

Participants may be re-contacted, but only if they consent to future contact.

14.1 MC10

All data transmitted from the devices to investigators will have participant identifiers to minimize association with personal information. Data on the sensors are raw, tri-axial acceleration and ECG data with no identifying information. The data collected by each wearable sensor is stored locally on non-volatile memory. It will be transmitted to a custom-built mobile application requiring an authorized user login via Bluetooth technology, then encrypted using the high-grade, industry-standard Advanced Encryption Standard (AES) algorithm and stored on the local SQLite mobile database. Upon connection to either a WiFi or cellular network, data will be uploaded to MC10's secure cloud, where it may be accessed by the University of Rochester. Patient identities and health information will not be transmitted to MC10.

Data management and storage for the raw data collected from the wearable sensors will occur via MC10's secure, collaborative web-based study portal, which enables 24/7 data access, staff-specific encrypted login credentials, and cloud-based storage and backup. Participants will only be identified by participant identifier in the MC10 database. Qualified researchers at the University of Rochester and MC10 will have access to de-identified raw sensor data.

Since assessments will be video-recorded in clinic, images of study participants will be seen by the research team at the University of Rochester. The videos will be stored on secure servers in the University of Rochester's Box account in a folder only shared

with the UR research team members. All UR research team members will undergo Human Subjects Research training.

15. DATA / SAMPLE STORAGE FOR FUTURE USE

Data obtained during this study (device data, patient-reported outcomes, and clinician-derived outcomes) will be banked for future research use. All patient-reported and clinician-derived outcomes will be stored in a secure database (REDCap) only accessible by research team members. The data will only be shared with researchers that are a part of this study using a HIPAA compliant, secure, encrypted mechanism, through REDCap or a cloud-like service like Box.com or other secure data transfer procedure.

16. DATA AND SAFETY MONITORING PLAN

Safety and tolerability will be closely monitored by study investigators. If an intolerability or adverse event occurs, depending on the severity of the event, investigators will decide whether to decrease study drug or to discontinue the study drug. If during the administration of the C-SSRS or PBA-S, suicidal ideation or suicidal behavior is identified, the investigator will determine the most appropriate next step. The most appropriate next step may include recommendation to contact their primary care provider and/or mental health provider, referral to the national suicide prevention hotline, or referral to the Comprehensive Psychiatry Emergency Program, among other options. Participants will be able to withdraw from the study at any time.

16.1 Adverse Event Definition

An adverse event is any symptom, sign, illness, or event which develops or worsens during the course of the study, whether or not the event is considered related to study drug.

16.2 Serious Adverse Event

A serious adverse event is defined as any adverse medical event that results in any of the following outcomes:

- death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- requires medical or surgical intervention to prevent permanent impairment or damage.

In addition, any event which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious adverse event

16.3 **Recording Adverse Events**

At each participant visit the site study staff will assess adverse events by recording all voluntary complaints of the participant and by assessment of clinical features. At each study visit, the participant should be questioned directly regarding the occurrence of any adverse events since his/her last visit. Soliciting of adverse events should be non-specific and participants should be asked the question, "Do you feel different in any way since starting the new treatment?"

All adverse events, whether observed by an investigator, elicited from or volunteered by the participant, should be documented on an Adverse Event CRF. Each adverse event will include a brief description of the experience, the date of onset, the date of resolution, the duration and type of experience, the severity, the relationship to investigational product (i.e., drug or device), contributing factors, and any action taken with respect to the study drug/device. This should also include the investigator's opinion of the possible relationship between the adverse event and the study drug or participation in the study. Likely alternative etiologies should be recorded for events considered unrelated to study drug.

Adverse events already documented at a previous visit and designated as 'continuing' should be reviewed at each visit. The investigator is obliged to follow participants with adverse events until the event has resolved, the condition is considered medically stable, or the participant is no longer available for follow up. Participants who discontinue the study drug due to adverse events will be treated and followed according to established acceptable medical practice. A follow up telephone call will be made to all participants who have unresolved adverse events 30 days from the date of the final study visit. If an adverse event is resolved, the documentation in the CRF must be completed to that effect. If an adverse event changes in frequency or severity during a study period, a NEW record of that event will be initiated. A record of all adverse events will be reviewed periodically by the study investigators.

The recording of adverse events will begin to occur once the participant signs informed consent and continue until the participant completes the study or withdraws from participation.

16.4 **Responsibilities for Reporting Serious Adverse Events**

The investigator should record all serious adverse events that occur during the study period on an Adverse Event CRF. Details included will be the same as those documented for adverse events (as detailed above). The investigator or

their designee will fill out the MedWatch FDA 3500 form for serious adverse events. This will include: an identification that serious event criteria have been met; a detailed description of the event and other relevant information; the current status of the event; if the subject has died, the date of death and autopsy report, if available; and the investigator's current opinion of the relationship between the event and the study drug/participation in the study.

The recording of adverse events will begin to occur once the participant signs informed consent and continue until the participant completes the study or withdraws from participation.

The investigator will comply with regulations and RSRB policy regarding the reporting of adverse events.

16.5 **Assessment of Severity**

Clinical adverse events will be graded on a three-point scale (mild, moderate, severe) and reported on the CRF and in the log. The definitions are as follows:

MILD	no limitation of usual activities
MODERATE	some limitation of usual activities
SEVERE	inability to carry out usual activities

16.6 **Assessment of Relationship**

For each adverse event, the relationship to the study drug will be coded as follows:

DEFINITE Causal relationship is certain (i.e., the temporal relationship between drug exposure and the adverse event onset/course is reasonable, there is a clinically compatible response to de-challenge, other causes have been eliminated and the event must be definitive pharmacologically or phenomenologically using a satisfactory re-challenge procedure, if necessary).

PROBABLE High degree of certainty for causal relationship (i.e., the temporal relationship between drug exposure and the adverse event onset/course is reasonable, there is a clinically compatible response to de-challenge [re-challenge is not required] and other causes have been eliminated or are unlikely).

POSSIBLE Causal relationship is uncertain (i.e., the temporal relationship between drug exposure and the adverse event onset/course is reasonable or unknown, de-challenge/re-challenge information is either unknown or equivocal and while other potential causes may or may not exist, a causal relationship to the study drug does not appear probable).

UNLIKELY Not reasonably related, although a causal relationship cannot be ruled out (i.e., while the temporal relationship between drug exposure

and the adverse event onset/course does not preclude causality, there is a clear alternate cause that is more likely to have caused the adverse event than the study drug).

UNRELATED No possible relationship (i.e., the temporal relationship between drug exposure and the adverse event onset/course is unreasonable or incompatible, or a causal relationship to study drug is implausible).

16.7 Monitoring Plan

The principal investigators will be responsible for the overall conduct of this small, single-center study. A neurologist, who is not involved in the conduct of the study, will be appointed to independently monitor the safety of study participants. If a serious adverse event occurs, a detailed report will be sent to the independent monitor. The independent monitor will periodically review adverse events. Following study initiation, adverse events will be reviewed following enrollment of the first 3 participants and then every three months or more frequently if deemed necessary by the independent monitor. The independent monitor will document the results of each review and the RSRB will be notified of all monitoring activity outcomes. As this is a small, single-center study no interim statistical analyses will be conducted.

17. DATA ANALYSIS PLAN

17.1 Sample Size

There are no prior clinical trials from which to estimate an effect size for risperidone and this represents a convenience sample. We are relying on data from studies of existing treatments to inform power analysis. In a clinical trial of tetrabenazine, over 12 weeks there was a 5.0-unit change in total maximal chorea score with a standard deviation of 3.7 units.[11] A sample size of 11 participants will provide > 98% power to detect a 5.0 unit difference or greater, using a one-sample t-test at the 5% significance level. A sample size of 12 participants will account for an estimated 8% drop-out rate. Below, we account for other potential scenarios:

Treatment effect	SD	Power	Alpha	Drop-out	N
4.0	3.7	0.80	0.05	10%	10
4.0	3.7	0.90	0.05	8%	12
3.4	3.7	0.80	0.05	8%	12
3.0	3.7	0.69	0.05	8%	12

17.2 Statistical Analysis Plan

The primary analysis will use a mixed model repeated measures (MMRM) approach, which will be applied to all post-baseline measures collected up to and including the week 12 visit. The primary outcome measure will be the

change from baseline in UHDRS TMC score at each visit (i.e. 4, 8, and 12 weeks) with the week 12 change as the time point of primary interest. The model will include the baseline value of the outcome variable, week (as a categorical factor), and the interaction between the baseline value and week. An unstructured covariance matrix will be assumed to model the within-subject variability. The Least Squares Means with 95% confidence intervals will be obtained for each week. Missing values will be accounted for by utilizing a maximum likelihood-based approach as part of the MMRM missing at random assumption. Secondary outcome measures (and safety measures) will be analyzed in a similar fashion. Responders will be defined as those "much improved" or "very much improved" on the CGI or PGI. Safety analyses will include tabulating adverse events with corresponding 95% two-sided confidence interval. Serious adverse events (if any) attributable to risperidone treatment will be described in detail. The primary measure of tolerability will be the proportion of participants who complete 12 weeks on study drug; we hypothesize that ≥75% (≥9 of 12 participants) will complete the study.

We will characterize the frontostriatal structural connectivity via probabilistic tractography[53,54] using the striatum as the seed and the frontal cortex as the target, as shown in Fig. 1. The probabilistic tractography will be reconstructed from dMRI and T1w data using the previously reported algorithm.[55,56,57] A similar ROI-based approach will be used for functional connectivity from rs-fMRI data using FEAT and FIX tools in FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). In addition, we will investigate the whole brain structural and functional connectome across subjects.[58,59,60] Additional exploratory analyses will assess cortical thickness and volumetric assessment of basal ganglia. Briefly, cortical thickness will be measured using FreeSurfer (https://surfer.nmr.mgh.harvard.edu/); using the 3D T1w images whole brain volume, whole GM, cortical GM and whole WM volumes will be obtained using FSL SIENAX while separate volumes of the basal ganglia structures will be obtained using FSL FIRST. All the volumes will then be normalized relative to whole head volume for each subject. Note both dMRI and rs-fMRI images will be preprocessed using FSL-based custom pipelines and spatially normalized to MNI template prior to the first and second level analyses. A general linear model will be used to compare regional neuroimaging patterns between risperidone responders and non-responders. Education level, age, sex, and cognitive performance will be included as covariates. To examine associations between neuroimaging metrics and 1) continuous clinical outcomes (such as the UHDRS TMC) we will use Pearson and Spearman correlation coefficients as appropriate and 2) dichotomous clinical outcomes we will use t-tests or chi-square tests as appropriate. Corrections for multiple comparisons will be made using a post-hoc family-wise error (Bonferroni) correction.

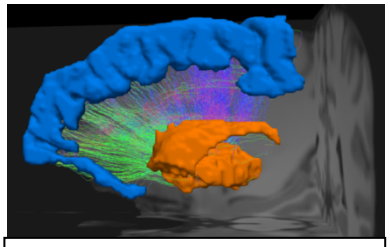

Figure 1: Structural connectivity with tractography: Tracts (green) connecting striatum (orange) and frontal cortex (blue).

The Chorea Index will be generated through analysis of wearable sensor accelerometer data and will be compared to the clinician-rated UHDRS truncal chorea score using correlation analysis. The mean change in the Chorea Index from baseline to week 8 along with the corresponding 95% confidence interval will be determined. The association between the Chorea Index and the UHDRS TMS score will be assessed using correlation analysis for the individual scores as well as the week 8 change.

Exploratory analyses: The association between the Chorea Index and Q-Motor score will be assessed using correlation analysis for the individual scores as well as the week 8 change. [Wearable sensors will detect changes in activity pattern and gait metrics in response to risperidone treatment.] Using MC 10 and University of Rochester developed algorithms, we will compare the amount of time participants spend sitting, standing, lying down and walking before and after treatment with risperidone. We will also compare gait metrics (gait speed, step length, step duration, steps per day) before and after treatment.

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