Institutional Review Board
Human Research Protections
Protocol Narrative ~ Expedited/Full Committee
Biomedical/Clinical Research
Version 2015

Upload this completed narrative and any supplemental documentation to the IRB Application.	**IRB USE ONLY –** **HS#: 2016-3022**
Lead Researcher Name: Neal Hermanowicz, MD	
Study Title: A phase IIa, randomized, double-blind, placebo-controlled study of the safety and efficacy of fenofibrate as a treatment for Huntington's disease	

CLINICAL TRIAL MASTER PROTOCOL AND INVESTIGATIONAL BROCHURE INFORMATION *

	Master Protocol	**Investigator Brochure:** <Specify Drug/Device>	**Investigator Brochure:** <Specify Drug/Device>	**Sponsor Consent Form Template(s)**
Version #:				
´				

[X] This study is investigator-authored (investigator developed the study and is conducting the study at UCI and/or with other non-UCI sites).

* Add columns as applicable

NON-TECHNICAL SUMMARY

Provide a brief non-technical summary or synopsis of the study that can be understood by IRB members with varied research backgrounds, including non-scientists and non-affiliated members.

Huntington's disease (HD) is a devastating neurodegenerative disease that typically strikes in the prime of life and for which no disease modifying treatment is currently available. The purpose of this research study is to study the safety and efficacy of fenofibrate, an FDA-approved drug for high cholesterol and/or elevated triglyerides (fats), as a treatment for Huntington's disease (HD). Subjects who meet the entry criteria will be randomized (3:1) to either 145mg of fenofibrate or placebo.

SECTION 1: PURPOSE AND BACKGROUND OF THE RESEARCH

1. Provide the scientific or scholarly rationale for the research. Describe the relevant background information and the specific gaps in current knowledge that this study intends to address.

Huntington's disease is caused by a CAG repeat expansion that translates into an expanded polyglutamine repeat stretch within the Huntingtin protein (Group, 1993). Symptoms include movement abnormalities, psychiatric disability and cognitive dysfunction, with multiple regions of the brain affected (Ross et al., 2014). PGC-1α is a transcriptional co-activator and key regulator of mitochondrial biogenesis. Recent work has highlighted that PGC-1α links mitochondrial dysfunction and transcriptional dysregulation in many neurodegenerative diseases, including HD. In HD, Alzheimer's disease (AD) and other neurodegenerative diseases, PGC-1α activity and downstream gene expression is significantly reduced with disease progression (e.g. (Cui et al., 2006; Weydt et al., 2006)). PGC-1α can partially reverse the toxic effects of mutant Huntingtin (HTT) expression in cultured striatal neurons and neuroprotection elicited by lentiviral-mediated delivery of PGC-1α in the striatum of transgenic HD mice (Tsunemi et al., 2012). Further, PGC-1α null mice show demonstrable striatal neurodegeneration reminiscent of HD pathology (Lin et al., 2004). PGC-1α protein content in AD is negatively correlated with both neuritic plaque pathology and Aß content (Qin et al., 2009). Importantly, reconstitution of PGC-1α expression attenuates hyperglycemic-mediated beta-amyloidogenesis through attenuation of the forkhead-like transcription factor 1 (FoxO3a) expression and promotion of the alpha-secretase processing of APP (Qin et al., 2009). These data strongly promote PGC-1α as a promising target for therapeutic modulation for HD and other neurodegenerative diseases. The therapeutic potential of PGC-1α up-regulation lies in its ability to increase mitochondrial biogenesis and protect against oxidative stress-mediated cell death.

Because supra-physiologic overexpression of PGC-1α may cause clinically adverse effects (Ciron et al., 2012; Clark et al., 2012), PGC-1α levels must be optimized for efficacy. PGC-1α levels need to be normalized when pathologically down-regulated, as in HD. Thus, pharmaceutical PGC-1α gene modulation, which allows small molecule-mediated temporal and dose-dependent regulation, will be an attractive treatment option. After screening several thousand FDA-approved drugs for potential PGC-1α up-regulation, the Federoff group has identified fenofibrate, a well-tolerated, anti-dyslipidemic medication, approved by the FDA since 1993, as a molecule that can robustly induce PGC-1α gene expression in central nervous system (CNS) cells (unpublished results). The neuroprotective effect of fenofibrate has been demonstrated in rodent models of Parkinson's disease (Barbiero et al., 2014; Uppalapati et al., 2014), and schizophrenia (Rolland et al., 2012), among others. Another fibrate derivative, bezafibrate, which has pan-PPAR agonist activity, also showed neuroprotection in HD mice (Chandra et al., 2016), however may have greater side effects than fenofibrate (Dohmen et al., 2013). Overall, fenofibrate-mediated PGC-1α up-regulation is posited to be a safe and effective intervention for neurodegenerative diseases, associated with PGC-1α deficiency and mitochondrial dysfunction.

While there is evidence that fenofibrate is likely to be safe and well tolerated in humans and may be an effective intervention, this has not yet been tested in HD individuals. We propose to examine the disease-modifying potential of the PGC-1α activating agent fenofibrate in a pilot Phase IIa randomized, double-blind, placebo-controlled clinical trial for 6-months in 20 HD subjects.

2. Provide relevant preliminary data (animal and/or human).

As described above in background, fenofibrate was identified by the Federoff group through a screen of several thousand FDA-approved drugs as a molecule that can robustly induce PGC-1α gene expression in central nervous system (CNS) cells. The data suggests that fenofibrate increases PGC-1α in a dose-dependent manner in the MN9D neuronal cell line and the BV2 microglial cell line.

Moreover, fenofibrate robustly protects MN9D cells from induced oxidative injury and prevents lipopolysaccharide (LPS)-induced inflammation in BV2. The group has also shown that the fenofibrate-mediated anti-inflammatory effect in BV2 cells requires PGC-1α. The molecular mechanisms through which fenofibrate regulates PGC-1α in CNS cells has begun to be elucidated and fenofibrate increases the small heterodimer partner (SHP) in liver by activating the adenosine monophosphate-activated protein kinase (AMPK) signaling pathway in a PPARα-independent manner (Chanda et al., 2009). AMPK is an energy sensor and can phosphorylate PGC-1α and fenofibrate is able to elicit phosphorylation of AMPK.

3. Describe the purpose, specific aims or objectives. Specify the hypotheses or research questions to be studied.

We propose to examine the disease-modifying potential of the PGC-1α activating agent fenofibrate in a pilot randomized, double-blind, placebo-controlled, clinical trial for 6-months in 20 HD subjects with mild impairment. Subjects who meet our entry criteria will be randomized (3:1) to either 145mg daily fenofibrate or placebo. The main hypothesis being tested is that fenofibrate increases PGC-1α, which may play a role in the progression of HD.

4. Describe the primary outcome variable(s), secondary outcome variables, and predictors and/or comparison groups as appropriate for the stated study objectives/specific aims.

We are interested in establishing the parameters for a future definitive Phase IIb clinical trial of fenofibrate in HD. Here, we wish to determine critical parameters including length of the trial and effect sizes for adequately powering the future study. Our primary outcome measure for this study will be levels of PGC-1α obtained from leukocyte RNA and protein. Our primary outcome will be change in PGC-1α RNA and protein levels over the 6-month trial. We will measure plasma levels of fenofibrate as a secondary outcome. HD is a complex disease, affecting motor, cognitive, and psychiatric domains. Thus, we will measure these domains primarily through the Unified Huntington Disease Rating Scale (UHDRS) (Group, 1996), the Montreal Cognitive Assessment (MoCA), and the Clinical Global Impression scale (CGI). (Tabrizi et al., 2013). Additional tests may include improvement in behavior as measured by the Problem Behaviors Assessment (Kingma et al., 2008), and function as measured by the Total Functional Capacity (Dorsey et al., 2013).

PGC-1α measurements. Blood samples will be collected in the morning, after an overnight fast and withholding all morning medications. Samples will be obtained at baseline and at the monthly visits throughout the trial. PGC-1α RNA and protein from peripheral blood mononuclear cells (PMBC's) will be measured by qRT-PCR and enzyme-linked immunosorbent assay (ELISA) respectively. RTPCR will be performed by the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). Each 25µl reaction consists of PGC-1α specific primers (Hs01016719_m1), cDNA template and qPCR gene expression Mastermix (Life technologies). Cycle threshold values for each reaction are adjusted automatically, and the fold changes are determined. The fold-changes values are derived relative to control and are represented as means + SEMs of mRNA expression normalized to ß-actin and comparison made using ANOVA PGC-1α protein expression will also be performed using a PGC-1α ELISA kit (USA biological) as per the instructions of the manufacturer.

Adverse Events. We will monitor for known side effects of fenofibrate including, but not limited to,

myalgia, elevated blood pressure, and specifically alterations in hepatic or renal function, and photosensitivity using a questionnaire specifically designed for this purpose, blood pressure readings, and blood tests of renal and hepatic function at every monthly visit. In accordance with the recommendation in the package insert for fenofibrate, serum level of HDL-C will be assesses at Baseline Visit, week 12 and week 24. There are no contraindications for concurrent statin and fenofibrate use, but idiopathic myopathy and myositis are more common among patients treated with both agents. Fenofibrate is the only fibrate that does not appear to produce a substantial pharmacokinetic effect on statin elimination. Subjects can withdraw for any reason at any time.

5. List up to ten relevant references/articles to support the rationale for the research. Do not append an extensive NIH-grant-style bibliography.

REFERENCES

Barbiero, J.K., Santiago, R., Tonin, F.S., Boschen, S., da Silva, L.M., Werner, M.F., da Cunha, C., Lima, M.M., and Vital, M.A. (2014). PPAR-alpha agonist fenofibrate protects against the damaging effects of MPTP in a rat model of Parkinson's disease. Progress in neuro-psychopharmacology & biological psychiatry *53*, 35-44.

Chanda, D., Lee, C.H., Kim, Y.H., Noh, J.R., Kim, D.K., Park, J.H., Hwang, J.H., Lee, M.R., Jeong, K.H., Lee, I.K.*, et al.* (2009). Fenofibrate differentially regulates plasminogen activator inhibitor-1 gene expression via adenosine monophosphate-activated protein kinase-dependent induction of orphan nuclear receptor small heterodimer partner. Hepatology *50*, 880-892.

Chandra, A., Sharma, A., Calingasan, N.Y., White, J.M., Shurubor, Y., Yang, X.W., Beal, M.F., and Johri, A. (2016). Enhanced mitochondrial biogenesis ameliorates disease phenotype in a full-length mouse model of Huntington's disease. Hum Mol Genet.

Ciron, C., Lengacher, S., Dusonchet, J., Aebischer, P., and Schneider, B.L. (2012). Sustained expression of PGC-1alpha in the rat nigrostriatal system selectively impairs dopaminergic function. Hum Mol Genet *21*, 1861-1876.

Clark, J., Silvaggi, J.M., Kiselak, T., Zheng, K., Clore, E.L., Dai, Y., Bass, C.E., and Simon, D.K. (2012). Pgc-1alpha overexpression downregulates Pitx3 and increases susceptibility to MPTP toxicity associated with decreased Bdnf. PloS one *7*, e48925.

Cui, L., Jeong, H., Borovecki, F., Parkhurst, C.N., Tanese, N., and Krainc, D. (2006). Transcriptional repression of PGC-1alpha by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration. Cell *127*, 59-69.

Dohmen, K., Tanaka, H., and Haruno, M. (2013). Effectiveness of fenofibrate in comparison to bezafibrate for patients with asymptomatic primary biliary cirrhosis. Fukuoka igaku zasshi = Hukuoka acta medica *104*, 350-361.

Dorsey, E.R., Beck, C.A., Darwin, K., Nichols, P., Brocht, A.F., Biglan, K.M., and Shoulson, I. (2013). Natural history of Huntington disease. JAMA neurology *70*, 1520-1530.

Group, H.S. (1996). Unified Huntington's Disease Rating Scale: reliability and consistency. . Movement disorders : official journal of the Movement Disorder Society *11*, 136-142.

Group, T.H.s.D.C.R. (1993). A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell *72*, 971-983.

Kingma, E.M., van Duijn, E., Timman, R., van der Mast, R.C., and Roos, R.A. (2008). Behavioural problems in Huntington's disease using the Problem Behaviours Assessment. General hospital psychiatry *30*, 155-161.

Lin, J., Wu, P.H., Tarr, P.T., Lindenberg, K.S., St-Pierre, J., Zhang, C.Y., Mootha, V.K., Jager, S., Vianna, C.R., Reznick, R.M.*, et al.* (2004). Defects in adaptive energy metabolism with CNS-linked hyperactivity in PGC-1alpha null mice. Cell *119*, 121-135.

Qin, W., Haroutunian, V., Katsel, P., Cardozo, C.P., Ho, L., Buxbaum, J.D., and Pasinetti, G.M. (2009). PGC-1alpha expression decreases in the Alzheimer disease brain as a function of dementia. Archives of neurology *66*, 352-361.

Rolland, B., Marche, K., Cottencin, O., and Bordet, R. (2012). The PPARalpha Agonist Fenofibrate Reduces Prepulse Inhibition Disruption in a Neurodevelopmental Model of Schizophrenia. Schizophrenia research and treatment *2012*, 839853.
Ross, C.A., Aylward, E.H., Wild, E.J., Langbehn, D.R., Long, J.D., Warner, J.H., Scahill, R.I., Leavitt, B.R., Stout, J.C., Paulsen, J.S.*, et al.* (2014). Huntington disease: natural history, biomarkers and prospects for therapeutics. Nature reviews Neurology *10*, 204-216.
Tabrizi, S.J., Scahill, R.I., Owen, G., Durr, A., Leavitt, B.R., Roos, R.A., Borowsky, B., Landwehrmeyer, B., Frost, C., Johnson, H.*, et al.* (2013). Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. Lancet Neurol *12*, 637-649.
Tsunemi, T., Ashe, T.D., Morrison, B.E., Soriano, K.R., Au, J., Roque, R.A., Lazarowski, E.R., Damian, V.A., Masliah, E., and La Spada, A.R. (2012). PGC-1alpha rescues Huntington's disease proteotoxicity by preventing oxidative stress and promoting TFEB function. Science translational medicine *4*, 142ra197.
Uppalapati, D., Das, N.R., Gangwal, R.P., Damre, M.V., Sangamwar, A.T., and Sharma, S.S. (2014). Neuroprotective Potential of Peroxisome Proliferator Activated Receptor- alpha Agonist in Cognitive Impairment in Parkinson's Disease: Behavioral, Biochemical, and PBPK Profile. PPAR research *2014*, 753587.
Weydt, P., Pineda, V.V., Torrence, A.E., Libby, R.T., Satterfield, T.F., Lazarowski, E.R., Gilbert, M.L., Morton, G.J., Bammler, T.K., Strand, A.D.*, et al.* (2006). Thermoregulatory and metabolic defects in Huntington's disease transgenic mice implicate PGC-1alpha in Huntington's disease neurodegeneration. Cell metabolism *4*, 349-362.

SECTION 2: ROLES AND EXPERTISE OF THE STUDY TEAM

1. List all research team members who will interact or intervene with human subjects or will have access to identifiable private information about human subjects. *Include additional rows for Co-researchers and Research Personnel, as needed.*
2. For each research team member, indicate all applicable research activities the individual will perform. *Finalizing informed consent is reviewing, answering/asking questions, confirming competency, as necessary, and signing/confirming the informed consent.*
3. If applicable, list the Faculty Sponsor as a Co-Researcher who will have research oversight responsibilities.

Lead Researcher:

Name and Degree: Neal Hermanowicz, MD

Position/Title and Department: Professor, Neurology. Director, Movement Disorders Clinic

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Hermanowicz is board certified in Neurology and has completed a formal fellowship in Movement Disorders, which included extensive experience with patients having Huntington's disease. Dr. Hermanowicz serves as the Director of the UCI Movement Disorders program He has served as a principal investigator or sub-investigator for numerous multicenter, pharmaceutical and investigator initiated trials in Parkinson's and other neurological diseases. For this study he will be responsible for recruitment, consenting all of the subjects, performing all physical and

neurological exams, reviewing medical history, inclusion/exclusion criteria, adverse events and biopsies. He will have access to subject identifiable data.

Co-Researcher:

Name and Degree: Howard Federoff, MD, PhD

Position/Title and Department: Vice Chancellor, Health Affairs, Professor of Neurology

Team Member will: **[ ]** serve as Faculty Sponsor with research oversight responsibilities

[ ] Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[ ]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Federoff is board certified in internal medicine, endocrinology and metabolism. He has expertise in clinical lipidomics and regulators of metabolism and energetics. His group has conducted longitudinal clinical observational studies in seniors at risk for neurodegenerative diseases to define lipid metabolomics changes. He collaboratively secured several INDs; most recently as the founder and leader of the Parkinson's Gene Therapy Study Group. He continues as co-investigator of this ongoing trial at the NINDS. His group will be responsible for all measures relating the pharmacodynamics of fenofibrate responses ascertained from analyses of PMBCs.

Co-Researcher:

Name and Degree: Leslie M. Thompson, PhD

Position/Title and Department: Professor, Psychiatry and Human Behavior; Neurobiology and Behavior

Team Member will: **[X]** Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Thompson is an established and productive HD investigator, having worked in the field for over 25 years beginning as a member of the international consortium that identified the causative gene in 1993 (Group, 1993), with a strong track record of leading and participating in multi-disciplinary and collaborative HD research. Dr. Thompson is also a member of the scientific advisory board for the Huntington Study Group, whose role is to evaluate clinical trial protocols for HD. Dr. Thompson will manage the overall study progress, assist with patient recruitment at the UCI HD clinic and consents, data analyses and will have access to subject identifiable private information.

Research Personnel:

Name and Degree: Yuna Muyshondt, MPH

Position/Title and Department: Preclinical Development Team Project Manager

Team Member will: **[X]** Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Yuna Muyshondt, MPH is a Preclinical Development Team Project Manager with more than 10 years of experience managing large-scale, multi-site research studies and clinical trials. Yuna has a Masters in Public Health from Columbia University with extensive program management experience and excellent knowledge of clinical research regulatory affairs. She will support, facilitate and coordinate the daily clinical trial activities and play a critical role in the conduct of the study. By performing these duties, she will work with the PI, department, sponsor, and institution to support and provide guidance on the administration of the compliance, financial, personnel and other related aspects of the clinical study. Yuna will assist with patient navigation and screening to link potential subjects to relevant clinical trials and will have access to PHI.

Research Personnel:

Name and Degree: Everlyne Gomez, M.Sc.

Position/Title and Department: Senior Coordinator in Neurology

Team Member will: **[x]** Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

Everlyne Gomez, M.Sc., is a Senior Clinical Research Coordinator in the Department of Neurology. She has a graduate degree in Molecular Neuroscience from the University of Toronto and 11+ years of clinical research experience. Her relevant background includes MRI-based studies of Alzheimer's disease, drug trials for Traumatic Brain Injury, and prenatal programming effects on infant brain development. She is adept at managing and conducting research projects from the beginning (Institutional Review Board submissions, creation of all study documents/CRFs, hiring and training staff, acting as main liaison for ancillary departments, problem solving study logistics) to end (data collection, reporting adverse events, statistical analyses, presentation of results, and manuscript writing). She will assist with study coordination, regulatory matters, study procedures, and data entry and management. She will assist in the consent process but will not finalize consents. She will have access to subject identifiable data.

Research Personnel:

Name and Degree: Breana Chew, BA

Position/Title and Department: Junior Specialist in Neurology

Team Member will: **[ ]** Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

Breana Chew graduated from Cal State Long Beach, and is currently a research coordinator in the Department of Neurology at UCI. She has worked on several movement disorder studies, including those for Huntington's disease and Parkinson's disease. She will serve as study coordinator on this project and will assist with study coordination, regulatory matters, study procedures, and data entry and management. She will have access to subject identifiable data. She will assist in the consent process but will not finalize consents.

Research Personnel:

Name and Degree: Jaclyn Alcazar, BS

Position/Title and Department: Junior Specialist in Neurology

Team member will: : **[ ]** Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

Jaclyn graduated from UCI with a degree in Biology and now works in the Department of Neurology at UCI. As an undergraduate student, she worked with Dr. Hermanowicz and his team on several neurological clinical trials. She will assist with study coordination, regulatory matters, study procedures, and data entry and management. She will have access to subject identifiable data.

Research Personnel:

Name and Degree: David Bisares, BS

Position/Title and Department: Junior Specialist in Neurology

Team member will: : **[ ]** Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

David Bisares graduated from UCI with a degree in Biology and now works in the Department of Neurology at UCI. As an undergraduate student, he worked with Dr. Hermanowicz and his team on several neurological clinical trials. He will assist with study coordination, regulatory matters, study procedures, and data entry and management. He will have access to subject identifiable data.

Research Personnel:

Name and Degree: Dr. Mark Mapstone

Position/Title and Department: Professor, Neurology

Team Member will: **[X]** Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience): Dr. Mapstone is a licensed clinical neuropsychologist with fellowship training in clinical trials in dementia and movement disorders. He will oversee the cognitive assessments as part of this study. He will train the research staff on administration of the cognitive assessments. He will assist with data management and analysis and will have access to subject identifiable private information.

Research Personnel:

Name and Degree: Isabella Sanchez, BS

Position/Title and Department: Graduate Student, Neurobiology and Behavior

Team member will: : **[ ]** Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

Isabella is a graduate student in the Department of Neurobiology and Behavior at UCI. As an undergraduate student, she worked in a psychiatric facility assisting patients. She currently works with Dr. Hermanowicz, who is her clinical faculty mentor, shadowing him in his Movement Disorders Clinic. She will assist with study coordination, study procedures, and data entry and management. She will have access to subject identifiable data.

Research Personnel:

Name and Degree: Adreanne Rivera, BS

Position/Title and Department: Junior Specialist in Neurology

Team member will: : **[ ]** Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities *(describe below)* **[X]** Access subject identifiable data

Adreanne Rivera, B.S., graduated from UC San Diego with a degree in Human Biology and Cognitive Science and is currently a Junior Specialist in the Department of Neurology at UC Irvine. She will assist on this study with regulatory matters, visit preparation, study procedures, and data entry and management. She will have access to subject identifiable data. She will also assist in the consent process, but will not finalize consents.

SECTION 3: SUBJECT POPULATION(S) (INDIVIDUALS/RECORDS/SPECIMENS)

A. Subjects To Be Enrolled on this UCI protocol (Persons/Records/Biospecimens)

1. Complete the table of subject enrollments below. *Include additional rows for subject category/group, as needed.*
2. If the study involves the use of existing records or biological specimens, specify the maximum number to be reviewed/collected and the number needed to address the research question.

Category/Group (e.g., adults, controls, parents, children)	**Age Range** (e.g., 7-12, 13–17, adults)	**Maximum Number to be Consented or Reviewed/Collected** (include withdrawals and screen failures)	**Number Expected to Complete the Study *or Needed to Address the Research Question***
Adults, with a positive gene test with ≥36 CAG repeats within the previous six (6) months	21-85, inclusive	25	20
		Total: 25	

B. Overall Study Sample Size

If this is a multi-site study, provide the total number of subjects to be enrolled from all sites.

[X] Not applicable: This study will only take place at UCI, and does not involve other sites.

Total number of subjects across all sites is 25.

C. Eligibility Criteria

1. Identify the criteria for inclusion and exclusion.

Inclusion criteria:

- Adults of either sex, ages 18 or older.
- Subjects must have clinical findings of Huntington's disease and a confirmatory family history of Huntington's disease, or clinical findings of Huntington's disease and a CAG repeat expansion of $\geq$ 36.
- Subjects must have a score of $\geq$ 7 on the Total Functional Capacity (TFC) scale.
- Proficiency with written and spoken English and corrected vision or hearing to complete the cognitive testing.
- Subjects must be capable of providing informed consent and complying with study procedures.
- Subjects must be able to take oral medication.
- Good overall health status with no known problems anticipated over the course of the trial.
- Women of child bearing potential (i.e., not postmenopausal or surgically sterile) must have a negative pregnancy test, be non-lactating and use adequate contraception methods during the study. Adequate contraception methods include abstinence, oral, implanted or injected contraceptives (e.g., birth control pills, intrauterine device), barrier (e.g., vaginal ring or diaphragm/cervical cap with spermicide), transdermal patch and/or partner vasectomy. Reliable contraception must be in use 30 days prior to Baseline Visit.

Exclusion criteria:

- History of known sensitivity or intolerance to any fibrate medication.
- Exposure to an investigational medication within the 30 days prior to baseline visit.
- Other major neurological disease [e.g., multiple sclerosis, Parkinson's disease, cortical stroke, etc]
- Clinically significant hepatic disease, gallbladder, or severe renal dysfunction, including primary biliary cirrhosis, and unexplained persistent liver function abnormality.
- Baseline Visit creatinine greater than 2.0 mg/dL.
- History of gallstones.
- Use of Coenzyme Q10 at a dose greater than 600 mg daily within 30 days of Baseline Visit.
- Current or history of substance (alcohol or drug) abuse within one year of baseline visit.
- Current or recent (within 3 months of screen visit) use of dopamine blocking agents such as:
    - tetrabenazine
    - antipsychotics
    - metoclopramide
    - prochlorperazine

- HAART

- and any current or recent (within 3 months of screen visit) fibrate medication (fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, or clinofibrate).
- Diagnosis of myopathy/myositis.
- Current use of Warfarin (Coumadin).
- Current use of statins (e.g., Simvastatin, Atorvastatin, etc.)
- Clinical evidence of unstable medical illness according to judgment of the investigator.
- Clinical evidence of unstable psychiatric illness, including psychosis, untreated major depression, or suicidal ideation within 90 days prior to baseline visit.

2. If eligibility is based on age, gender, pregnancy/childbearing potential, social/ethnic group, or language spoken (e.g., English Speakers only), provide a scientific rationale.

[ ] Not applicable: Subject eligibility is not based on these factors.

Genetic testing of subjects under the age of 18 is highly discouraged for genetic counseling purposes due to the inability to treat the disease in any way, and to allow individuals to perform informed consent when they reach adulthood. Because of the complex considerations of predictive genetic testing for HD, minors are excluded from this study.

Most of the families seen in the clinic speak English, even if as a second language. The cognitive testing tools employed in this study have not all been validated in languages other than English. Subjects will therefore be required to be proficient in spoken and written English.

SECTION 4: RECRUITMENT METHODS

Check any of the following methods that will be used to recruit subjects for this study:

[ ] This study involves no direct contact with subjects (i.e., use of existing records, charts, specimens).

Specify database or IRB-approved protocol number (HS#), if applicable: <Type here>

[X] Advertisements, flyers, brochures, email, Facebook, and/or other media.

Specify where recruitment materials will be posted: Gottschalk Medical Plaza, UCI HD Clinic

If subjects will be recruited by mail, e-mail, or phone, specify how their contact information will be obtained: <Type here>

Submit recruitment materials for IRB approval.

[X] The study will be listed on Clinicaltrials.gov. *All clinical research must be registered.*

[X] The study will be listed on the UC Irvine Health Clinical Trials web page.

Submit the UCIMC Standard Research Recruitment Advertisement for IRB approval.

[ ] The UCI Social Sciences Human Subjects Lab/Sona Systems will be used.

Submit the Social Science Human Subject Pool Recruitment Advertisement for IRB approval.

[ ] Referral from colleagues

- Study team will provide colleagues with UCI IRB-approved recruitment materials for distribution to potential subjects (e.g., recruitment flyer, introductory letter);
- An IRB-approved recruitment letter will be sent by the treating physician. The letter will be signed by the treating physician and sent to his/her patients to inform them about how to contact study team members; and/or
- Colleagues obtain permission from interested patient to release contact information to researchers.
- Study team does not have access to patient names and addresses for mailing.
- If colleagues will screen their patients' medical records to determine subject eligibility and approach patients directly about study participation: *Complete Appendix T to request a partial waiver of HIPAA Authorization.*

Submit recruitment materials for IRB approval.

[ ] Study team will contact potential subjects who *have given prior permission to be contacted* for research studies.

Specify when and how these individuals granted permission for future contact: <Type here>

Specify database or IRB-approved protocol number (HS#): <Type here>

[X] Study team members will approach their own patients, students, employees for participation in the study.

[X] Study team will screen UCIMC medical records to which they have access to determine subject eligibility. The patients' physicians will approach patients directly about study participation.

Complete Appendix T to request a partial waiver of HIPAA Authorization.

[X] Other Recruitment Methods: The study and opportunity for participation will be verbally presented to the Orange County Huntington's disease support group by Dr. Hermanowicz. Contact information for Dr. Hermanowicz will be verbally provided. No written materials will be provided.

SECTION 5: INFORMED CONSENT PROCESS

A. Methods of Informed Consent

1. Indicate <u>all</u> applicable informed consent methods for this study. *Submit the consent/assent document(s) with your e-IRB Application (e.g., Study Information Sheet, Recruitment script, Consent Form, etc.). Only IRB approved consent forms (containing the IRB approval footer) may be used to consent human subjects at UCI.*

[X] Written (signed) informed consent will be obtained from subjects. Signed informed consent, parental permission, and/or child assent will be obtained from subjects, as applicable.

[ ] Requesting a waiver of written (signed) informed consent. Signed consent will not be obtained; consent will be obtained verbally or via the web. Informed consent, parental permission and/or child assent will be obtained from subjects, as applicable.

Complete Appendix P.

[ ] Requesting to seek surrogate consent from a legally authorized individual. Surrogate consent may be considered <u>only</u> in research studies relating to the cognitive impairment, lack of capacity or serious or life-threatening disease and conditions of the research subjects.

Complete Appendix E.

[ ] Requesting a waiver of informed consent. (i.e., consent will not be obtained). *Skip to Section 5.B.*

Complete Appendix O.

2. Indicate where the consent process will take place.

[X] In a private room
[ ] In a waiting room
[ ] In an open unit
[ ] In a group setting
[ ] The internet
[ ] In public setting
[ ] Over the phone
[ ] Other (specify): <Type here>

3. Specify how the research team will assure that subjects have sufficient time to consider whether to participate in the research.

[X] Subjects will be allowed to take home the unsigned consent form for review prior to signing it.

[ ] Subjects will be allowed <Type here> hours to consider whether to consent.

[ ] Other (specify): <Type here>

4. If children are enrolled in this study, describe the parental permission process and the child assent process.

[X] Not applicable: Children are not enrolled in this study.

<Type here>

5. Some subjects may be vulnerable to coercion or undue influence, such as those who are economically or educationally disadvantaged, mentally disabled, or students (undergraduate, graduate, and medical students) and employees of UCI (administrative, clerical, nursing, lab technicians, post-doctoral fellows and house staff, etc.), describe the procedures to ensure the voluntary participation of these individuals.

[ ] Not applicable: Subjects are not vulnerable to coercion or undue influence.

[X] Other (specify): Subjects will be informed that no matter what they decide regarding their participation, their care received from their physician will not be affected.

B. Health Insurance Portability and Accountability Act (HIPAA) Authorization

Indicate all applicable HIPAA authorization methods for this study.

[ ] Not applicable: Study does not involve the creation, use, or disclosure of Protected or Personal Health Information (PHI).

[ ] Requesting a Total waiver of HIPAA Authorization. HIPAA authorization will not be obtained at all for the study.

Complete Appendix T.

[X] Requesting a Partial waiver of HIPAA Authorization. HIPAA authorization will not be obtained for screening/recruitment purposes. However, written (signed) HIPAA research authorization is obtained for further access to personal health information.

Complete Appendix T.

[X] Written (signed) HIPAA Research Authorization will be obtained from subjects. Signed authorization, parental authorization, and/or child assent will be obtained from subjects, as applicable.

Complete the HIPAA Research Authorization form.

C. Methods of Informed Consent for non-English Speakers

1. Indicate the applicable informed consent method for non-English speakers.

[X] Not applicable: Only individuals who can read and speak English are eligible for this study. *Scientific justification must be provided in Section 3.C.2.*

[ ] The English version of the consent form will be translated into appropriate languages for non-English speaking subjects once IRB approval is granted. *The translated consent form must be submitted to the IRB for review prior to use with human subjects. Only IRB approved consent forms (containing the IRB approval stamp) may be used to consent human subjects at UCI.*

[ ] Requesting a short form consent process.

Complete Appendix Q.

The short form process will be used for the following occasional and unexpected languages:

[ ] All non-English languages

[ ] All non-English languages except Spanish

[ ] Other languages (specify): <Type here>

2. Explain how non-English speaking subjects will be consented in their language and who will be responsible for interpreting and facilitating the informed consent discussion for the non-English speaking subjects.

[ ] At least one member of the study team is fluent in the language that will be used for communication, and that study team member(s) will be available during emergencies.

For all members of the study team responsible for obtaining informed consent from non-English speaking subjects, provide their qualifications to serve in this capacity (i.e. language fluency) in Section 2.

[ ] The study team has 24-hour access to a translation service with sufficient medical expertise to discuss the research in this study.

[ ] Other (explain): <Type here>

SECTION 6: RESEARCH METHODOLOGY/STUDY PROCEDURES

A. Study Location

Specify where the research procedures will take place (e.g. UCI Douglas Hospital – Cardiac Care Unit, UCI Main Campus Hewitt Hall, UCI Health – Pavilion II, UCI Family Health Center, Anaheim, Irvine High School).

If research activities will also be conducted at non-UCI locations (e.g., educational institutions, businesses, organizations, etc.), Complete Appendix A. Letters of Permission or other documentation may be required (e.g. Off-site Research Agreements or IRB Authorization Agreements).

The study procedures will take place at Gottschalk Medical Plaza or the Institute for Clinical and Translational Sciences (ICTS) in Hewitt Hall.

B. Study Design

1. Include an explanation of the study design (e.g., randomized placebo-controlled, cross-over, cross-sectional, longitudinal, etc.) and, if appropriate, describe stratification/ randomization/blinding scheme.

Overall Strategy: We propose to examine the disease-modifying potential of the PGC-1α activating agent fenofibrate in a pilot randomized, double-blind, placebo-controlled clinical trial for 6-months in 20 newly diagnosed gene positive HD subjects. Subjects who meet our entry criteria will be randomized (3:1) to either 145mg daily fenofibrate or placebo. The main hypothesis being tested is that fenofibrate increases PGC-1α and slows the progression of HD. Our primary outcome will be change in PGC-1α RNA and protein levels over the 6-month trial. In secondary analyses, we will examine drug effects on cognitive, psychiatric, and functional outcomes. This pilot clinical study will be conducted by Neal Hermanowicz, MD.

Potential participants will be recruited from the UCI HD clinic where the study will be described to potential subjects. If the candidate is interested in participating, informed consent and Health Insurance Portability and Accountability Act of 1996 (HIPPA) authorization will be obtained. After consent, potential participants will be scheduled for the Screening Visit.

Table 1.Study Schema

	Screening Visit	Baseline Visit	1-month visit	2-month visit	3-month visit	4-month visit	5-month visit	6-month visit
Consenting	X							
Review Inclusion/Exclusion Criteria	X	X						
Demographics and family and medical history	X							
Vital signs	X	X	X	X	X	X	X	X
Renal and hepatic blood tests	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X
PGC1-α levels	X	X	X	X	X	X	X	X
Fenofibrate levels		X	X	X	X	X	X	X
Motor, Cognitive, Psychiatric, Functional measures	X	X			X			X

Clinical neurological and physical examination	X	X			X			X
Study drug reconciliation and dispensing		X	X	X	X	X	X	X
Adverse events questionnaire			X	X	X	X	X	X

Procedures: The trial will last 6-months and will require eight study visits: A Screening Visit and Baseline Visit prior to drug and a monthly visit for the 6-month trial (**Table 1. Study Schema below**). All visits will include: a fasting blood draw for leukocyte PGC-1α protein and transcript levels, and plasma fenofibrate levels; medication and medical history update; adverse events questionnaire; study drug accounting and distribution. The Baseline 3-month, and final 6-month study visit will include administration of the UHDRS, MoCA, and CGI (**Table 2. Study Outcomes**). Participants will be provided food and drink following the blood draw and before any clinical examinations and cognitive testing.

Screening Visit.

The following procedures will be performed at the Screening Visit (Visit SC):

- Obtain written informed consent (if not already obtained)
- Subject Number assigned
- Inclusion/exclusion criteria review
- Demographics
- Medical history
- Review concomitant and prior drug usage
- Obtain vital sign measurements
- Conduct general physical exam
- Conduct general neurological exam
- UHDRS Total Functional Capacity (TFC)
- Blood specimen collection for safety laboratory tests, including BUN, creatinine, ALT, AST, hematology, and serum pregnancy test for women of childbearing potential.
- For women of childbearing potential, review of acceptable birth control methods that must be used during the study

All potential participants who meet the eligibility criteria after this screening will be scheduled for the Baseline visit within 14 days.

Baseline Visit.

The following baseline visit procedures will be performed within 14 days from the screening visit:

- Conduct final review of eligibility (prior to first dose). Subjects must continue to meet all inclusion and exclusion criteria at the Baseline Visit.
- Obtain vital sign measurements
- Complete all sections of the UHDRS (Motor, Cognitive, Behavioral, Functional, Independence, and TFC).
- Assess predominant HD symptoms (must be completed by the site investigator)
- Complete Neuropsychological Tests (Hopkins Verbal Learning Test-Revised, Symbol Digit Modalities Test, UHDRS Cognitive, Stroop Word and Benton Judgment of Line Orientation)
- Review concomitant drug usage
- Assess adverse events
- Instruct subject about correct administration of study drug
- Provide instructions to subject and caregiver (if applicable) on study drug consumption, compliance, and reporting of adverse experiences

This visit should take about 2-3 hours.

Following phlebotomy subjects will receive calories and fluids (e.g., energy bar and juice) and then undergo clinical evaluations, including UHDRS, cognitive tests, and CGI-S. Upon conclusion of clinical evaluations the study procedures will be reviewed with the subject and the one month supply of study medication will be provided.

Monthly Visits. The 6, monthly visits will involve a fasting blood draw, a brief clinical examination and completion of an adverse events questionnaire. A pill count will be done to monitor study drug compliance. Monthly visits are expected to last 30 minutes to one hour. The 3- and 6-month visits will include administration of the UHDRS, MoCA, Neuropsychological exams and the CGI.

Randomization. The first 20 participants eligible for the trial after screening will be randomly assigned to either the active drug or placebo group at a 3:1 ratio. Enrollment ID Numbers will be developed by the study statistician and will correspond to specific study drug vials. Study drug will be labeled with a four-digit Enrollment ID Number assigned to that subject.

We will allow patients using statins to enroll in the study because recent guidelines from the American College of Cardiology and the American Heart Association now recommend the use of these drugs in adults as primary preventative therapy for heart disease.

Blinding. The randomization assignment for each participant will be blinded to all clinical investigators and known only to the study statistician who will perform the randomization and maintain the randomization key. Group assignment will be un-blinded after the clinical trial is complete, or if there is a medical emergency for the participant which requires this.

Study Drug. All subjects will receive a one month supply of study medication from the Study Coordinator at the baseline visit and at subsequent monthly visits for a total of 6 months of drug. All study medications (active drug and placebo) will be prepared in identical appearing capsules. The approved dosing of fenofibrate is in 48mg, 96mg, and 145mg capsules with a maximum dose of 145mg per day. Participants assigned to the active drug group will take a single 145mg capsule of fenofibrate daily during the study and participants assigned to the placebo group will take a single, identical appearing inert capsule daily during the study. We will utilize the maximum tolerated dose for each subject beginning at 145mg per day and reduce the dose if significant side effects are encountered (see Adverse Events).

2. Provide precise definitions of the study endpoints and criteria for evaluation; if the primary outcomes are derived from several measurements (i.e., composite variables) or if endpoints are based composite variables, then describe precisely how the composite variables are derived.

Table 2. Study Outcomes

Outcome	Type	Measure
Primary Outcome	PGC-1α activity	Leukocyte PGC-1α RNA and protein concentrations
Secondary Outcome	Fenofibrate	Plasma fenofibrate levels
Secondary Outcome	Motor	Unified Huntington Disease Rating Scale (UHDRS) Motor
Secondary Outcome	Cognition	Montreal Cognitive Assessment (MoCA)
Secondary Outcome	Psychiatric	Unified Huntington Disease Rating Scale (UHDRS) Behavioral
Secondary Outcome	Functional	Clinical Global Impression (CGI-I)

Outcome Measures: We are interested in establishing the parameters for a future definitive Phase IIb clinical trial of fenofibrate in HD. Here, we wish to determine critical parameters including length of the trial and effect sizes for adequately powering the future study. Our primary outcome measure for this study will be levels of PGC-1α obtained from leukocyte RNA and protein. We will measure plasma levels of fenofibrate as a secondary outcome. HD is a complex disease, affecting motor, cognitive, and psychiatric domains. Thus, we will measure these domains primarily through the Unified Huntington Disease Rating Scale (UHDRS), the Montreal Cognitive Assessment (MoCA), and the Clinical Global Impression scale (CGI).

PGC-1α measurements. Blood samples will be collected in the morning, after an overnight fast and withholding all morning medications. PGC-1α RNA and protein from peripheral blood mononuclear cells (PMBC's) will be measured by qRT-PCR and enzyme-linked immunosorbent assay (ELISA) respectively. RTPCR will be performed by the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). Each 25µl reaction consists of PGC-1α specific primers (Hs01016719_m1), cDNA template and qPCR gene expression Mastermix (Life technologies). Cycle threshold values for each reaction are adjusted automatically, and the fold changes are determined. The fold-changes values are derived relative to control and are represented as means + SEMs of mRNA expression normalized to ß-actin and comparison made using ANOVA PGC-1α protein

expression will also be performed using a PGC-1α ELISA kit (USA biological) as per the instructions of the manufacturer.

Statistics. Biostatistics will be performed together with the Biostatistics, Epidemiology, and Research Design (BERD) Unit of the Institute for Clinical and Translational Science.

C. Research Procedures

1. Provide a detailed chronological description of all research procedures.

Table 1.Study Schema

	Screening Visit	Baseline Visit	1-month Visit	2-month Visit	3-month Visit	4-month Visit	5-month Visit	6-mont Visit
Informational session, Consent	X							
Family history, medical history	X							
Renal and hepatic blood tests	X	X	X	X	X	X	X	X
Medication review and medical update	X	X	X	X	X	X	X	X
PGC-1α levels		X	X	X	X	X	X	X
Fenofibrate levels		X	X	X	X	X	X	X
Motor, Cognitive, Psychiatric, Functional measures (UHDRS, MoCA, CGI)		X			X			X
Clinical examination		X			X			X
Study drug reconciliation and distribution		X	X	X	X	X	X	X
Adverse events questionnaire			X	X	X	X	X	X

Procedures: The trial will last 6-months and will require eight study visits: A Screening Visit and Baseline Visit prior to drug and a monthly visit for the 6-month trial (**Table 1. Study Schema**). All visits will include: a fasting blood draw for leukocyte PGC-1α protein and transcript levels, and plasma fenofibrate levels; medication and medical history update; adverse events questionnaire; study drug accounting and distribution. The Baseline 3-month, and final 6-month study visit will include administration of the UHDRS, MoCA, Neurosychological exams and CGI (**Table 2. Study Outcomes**). Participants will be provided a meal following the blood draw and before any cognitive testing.

Screening Visit. Potential participants will be recruited from the UCI HD clinic where the study will be described and if interested, informed consent and Health Insurance Portability and Accountability Act of 1996 (HIPPA) authorization will be obtained. After consent, potential participants will be scheduled for the first study visit where they will provide medical history, family history, and current medication information. All potential participants will arrive to this morning visit fasting and having withheld all medications from the previous evening. Total Function Capacity (TFC) score will be obtained. General and neurological exams will be conducted. Subjects with a TFC score blow 7 will be excluded. We will collect a blood sample for CBC w/diff, ALT, AST, BUN, creatinine and HDL-C. From the blood work, we will exclude potential participants with evidence of significant hepatic (transaminases >2 × upper limit of normal) renal dysfunction (serum creatinine > 2.0 mg/dl), or HDL-C below normal range (42). Any other

significant abnormality in the blood work that in the judgment of the Study Medical Director would affect participation in the clinical trial would also be considered. All potential participants who meet the eligibility criteria after this screening will be considered eligible for the clinical trial.

Baseline Visit. The baseline visit will be completed within 14 days of the Screening Visit and prior to the administration of any study medication. We will collect a fasting blood sample for baseline leukocyte PGC-1α protein and transcript levels. We will administer the full UHDRS and neuropsychological tests. In addition, the study procedures will be reviewed and a 1-month supply of study medication will be distributed.

Monthly Visits. The 6, monthly visits will involve a fasting blood draw, and query regarding adverse events by the investigators. A pill count will be done to monitor study drug compliance. Monthly visits are expected to last 30 minutes to one hour. The 3- and 6-month visits will include administration of the UHDRS, MoCA, Neuropsychological exams and the CGI.

Randomization. The first 20 participants eligible for the trial after screening will be randomly assigned to either the active drug or placebo group at a 3:1 ratio. We will allow patients using statins to enroll in the study because recent guidelines from the American College of Cardiology and the American Heart Association now recommend the use of these drugs in adults as primary preventative therapy for heart disease.

Blinding. The randomization assignment for each participant will be blinded to all clinical investigators and known only to the study statistician who will perform the randomization and maintain the randomization key. Group assignment will be un-blinded after the clinical trial is complete, or if there is a medical emergency for the participant which requires this.

2. Describe the duration of a subject's participation in the study. If there are sub-studies, include duration of participation in each sub-study.

Subject's participation will include a Screening and Baseline Visit as well as six (6) monthly follow-up visits. Total time for participant's participation is approximately 10 hours over a 7 month period.

3. List data collection instruments (e.g., measures, questionnaires, interview questions, observational tool, etc.).

Investigator-authored, non-standardized, or un-validated measures must be submitted for review.

-Demographics
-Medical History
-Unified Huntington Disease Rating Scale (UHDRS) Motor
-Unified Huntington Disease Rating Scale (UHDRS) Behavioral
-Montreal Cognitive Assessment (MoCA)
-Clinical Global Impression (CGI)
-Neurological examination
-Physical examination

D. UCIMC Supplementary Clinical Services

If a UCIMC clinical unit/department (e.g., phlebotomy for blood draws, pharmacy for dispensing study drug(s), radiation services for X-rays, MRIs, CT scans, and Neurology for lumbar punctures) will perform research-related procedures:

1. List the research procedure (e.g. lumbar puncture, MRI, CT Scan), and
2. Identify the unit/department that will perform the procedure.

[ ] Not applicable: This study does not involve the services of a UCIMC clinical unit/department.

Phlebotomy for blood draws will be performed by Dr. Hermanowicz or registered nurses at the Gottshalk Medical Plaza or the Institute for Clinical and Translational Sciences (ICTS) in Hewitt Hall.

E. Privacy

Privacy is about the subject's ability to control how much others see, touch, or collect information about the subject. Indicate <u>all</u> of the following methods that will be used to assure subject privacy. *Violations of privacy include accessing a subject's private information without consent, asking personal sensitive information in a public setting, being audio recorded or photographed without consent.*

[X] Research procedures (including recruitment) are conducted in a private room.

[ ] Use of drapes or other barriers for subjects who are required to disrobe.

[ ] Only sensitive information directly related to the research is collected about subjects.

[ ] When information is collected from internet sources, the internet site's privacy statement will be reviewed and followed.

Provide a copy of the Data Use Policy to the IRB.

[ ] Other (specify): <Type here>

F. Use of Existing Biological Specimens and/or Existing Information/Data

1. For studies that involve use of existing (i.e. on the shelf; currently available) specimens:
   a. Indicate the source of the specimens and whether the specimens were originally collected for research purposes.
   b. Explain how the existing specimens will be obtained.

[X] Not applicable: This study does not involve use of existing biological specimens.

Source: Indicate <u>all</u> that apply:
[ ] UCI/UCIMC
Originally collected for research purposes: **[ ]** YES; UCI IRB number (i.e. HS#): <Type here>
[ ] NO; explain: <Type here>

[ ] UCIMC Pathology Biorepository will provide specimens.

[ ] Non-UCI Entity; specify: <Type here>
Originally collected for research purposes: **[ ]** YES

Submit a copy of the IRB Approval Notice and Consent Form for the original collection.

[ ] NO; explain: <Type here>

[ ] Other; explain: <Type here>

2. For studies that involve use of existing (i.e. on the shelf; currently available) clinical data:
   a. Specify the source of the clinical data.
   b. Explain how the study team will access the clinical data. *Access to UCI Medical Center medical records for research purposes outside the capacity of the Honest Broker Services, such as access to physician notes, must be obtained from the Health Information Management Services*.

For investigator initiated/authored studies <u>only</u>, submit a data abstraction sheet that includes a complete list of data elements/information that will be collected from (existing) records or submit the case report form (CRF; eCRF).

[ ] Not applicable: This study does not involve use of existing clinical data. *Skip to Section 6.G.*

Source: Indicate <u>all</u> that apply:
[X] UCI/UCIMC.
[ ] non-UCI Entity; specify: <Type here>

How Obtained: Indicate <u>all</u> that apply:
[X] The study team will request specific patient information/data from UCIMC Health Information Management Services.

[X] The study team will review their patients' records and abstract data directly from those records.

[ ] The study team will request specific patient information/data from UCI Health Honest Broker Services. Describe the following:

Cohort selection criteria (e.g., use the available Clinical Terms from the Cohort Discovery Tool such as Demographics: Gender, Diagnoses: Asthma, Procedures: Operations on digestive system): <Type here>

Expected cohort size/patient count: <Type here>

Cohort attributes or data elements (e.g., lab test values, medication, etc.): <Type here>

[ ] Other; explain: <Type here>

3. For studies that involve use of existing (i.e. on the shelf; currently available) clinical data, specify the time frame of the clinical data to be accessed (e.g. records from January 2002 to initial IRB approval).

During the study

G. Collection of Photographs, or Audio/Video Recording

1. Describe all procedures involving the use and/or collection of photographs, or audio/video recording.

[X] Not applicable: This study does not involve photographs or audio/video recording. *Skip to Section 6.H.*

<Type here>

2. Specify if photographs or audio/video recording will include subject identifiable information (e.g., name, facial image). If so, indicate which identifiers will be collected.

<Type here>

3. Explain whether the photographs or audio/video recording will be included in subsequent presentations and/or publications and, if so, whether subject identifiers will be included.

<Type here>

H. Sharing Results with Subjects

1. Describe whether individual results (results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subject or others (e.g., the subject's primary care physician). *Only tests ordered by a physician and conducted in a CLIA certified lab may be shared.*
2. Explain what information will be shared and how the results will be shared.

[ ] Not applicable: Individual results will not be shared with subjects.

Results from blood tests (CBC with differential, AST, ALT, BUN, creatinine and HDL-C) that are abnormal and in the judgment of Dr. Hermanowicz warrant further attention will be shared with the subject, and with the subject's permission, their primary care physician. No other results of research tests will be shared.

3. Describe whether overall study results will be shared with subjects.
4. Explain how results will be shared.

[X] Not applicable: Final study results will not be shared with subjects.

<Type here>

I. Statistical Considerations *(This section is required for Investigator-Authored Research)*

1. Statistical Analysis Plan: Describe the statistical method(s) for the stated specific aims and hypotheses. *Your analysis plans should match the stated study specific aims and hypotheses in Section 1.*

[ ] Not applicable: A statistical analysis plan is not appropriate for this qualitative study design. Plan for assessing study results: <Type here>
Skip to Section 7.

The primary analysis will assess the impact of fenofibrate on leukocyte PGC-1α protein and transcript levels. The effect of fenofibrate on PGC-1 will be analyzed using a repeated measures model. We will use a generalized linear model to examine possible correlations of PGC-1 level with UHDRS Motor change. The UHDRS Motor Scale score change after 6 months of treatment will be examined using an intent to treat principle. We will use a likelihood based mixed effects model, which has greater statistical power and is valid when data is missing at random. Non-random missing data will be examined and analyzed using a pattern mixture model. All analyses will be done by study statisticians using SAS.

2. Describe the primary statistical method(s) that will be used to analyze the primary outcome(s) or endpoints.

PGC-1 measurements. Blood samples will be collected in the morning, after an overnight fast and withholding all morning medications. PGC-1 RNA and protein from peripheral blood mononuclear cells (PMBC's) will be measured by qRT-PCR and enzyme-linked immunosorbent assay (ELISA) respectively. RTPCR will be performed by the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). Each 25µl reaction consists of PGC-1 specific primers (Hs01016719_m1), cDNA template and qPCR gene expression Mastermix (Life technologies). Cycle threshold values for each reaction are adjusted automatically, and the fold changes are determined. The fold-changes values are derived relative to control and are represented as means + SEMs of mRNA expression normalized to ß-actin and comparison made using ANOVA PGC-1 protein expression will also be performed using a PGC-1 ELISA kit (USA biological) as per the instructions

of the manufacturer.

3. Describe the secondary statistical method(s) that will be used to analyze the secondary outcome(s) or endpoints.

UHDRS Motor Scale score change after 6 months of treatment using an intent to treat principle. We will use a likelihood based mixed effects model, which has greater statistical power and is valid when data is missing at random. Non-random missing data will be examined and analyzed using a pattern mixture model. The effect of fenofibrate on PGC-1 will be analyzed using a repeated measures model. We will use a generalized linear model to examine possible correlations of PGC-1 level with UHDRS Motor change.

4. If appropriate describe secondary or post hoc analyses of primary outcome(s) or other exploratory analysis.

<Type here>

5. Sample Size Determination**:** Explain how the overall target sample size was determined (e.g., power analysis; precision estimation), providing justification of the effect size for the primary outcome based on preliminary data, current knowledge/literature and/or cost consideration; if appropriate, provide sample size justification for secondary outcomes. Power analysis should (at least) match the primary outcome/endpoint.

Based on a 50% effect size from our preclinical work on MN9D cells, a sample of 15 subjects will provide 80% power at an alpha level of 0.05. HD is a relatively rare genetic disease.

SECTION 7: RISK ASSESSMENT AND POSSIBLE BENEFITS

A. Risk Assessment

1. Indicate the appropriate level of review of this study, based upon your risk assessment.

[X] This study involves greater than minimal risk to subjects and requires Full Committee review. *Skip to Section 7.B.*

[ ] This study involves no more than minimal risk and qualifies as **Expedited research**.

2. If this study involves no more than minimal risk, provide justification for the level of review and for all applicable Expedited Categories you have chosen.

<Type here>

B. Risks and Discomforts

1. Describe and assess any reasonably foreseeable risks and discomforts — physical, psychological, social, legal or other. Include an assessment of their expected frequency (e.g., common – 65%, less common – 40%, unlikely – 5%, rare - <1%) and the seriousness (mild, moderate, severe). *A bullet point list is recommended. If this study will involve the collection of identifiable private information, even temporarily, for which the disclosure of the data outside of the research could reasonably place the subjects at risk, include the risk of a potential breach of confidentiality.*

Risks and side effects related to fenofibrate may include:

Common risks (frequency is 1% to 10%)

- Abdominal pain
- Back pain
- Asthenia (weakness)
- Flu syndrome
- Diarrhea
- Nausea
- Respiratory Disorder
- Rhinitis (nasal allergy)

Less common risks (frequency is 0.1% to 1%)

- Headache
- Abnormal liver function tests
- Constipation
- Hypertension (high blood pressure)
- Alterations in kidney function

Rare (frequency is 0.01% to 0.1%)

- Accidental injury
- Allergic reaction
- Chest pain
- Cyst
- Fever
- Hernia (an organ or fatty tissue that squeezes through a weak spot in a surrounding muscle or connective tissue)
- Infection
- Pain
- Angina pectoris (chest pain, pressure or squeezing in the chest)
- Arrhythmia (an unusal rate or rhythm of the heart)
- Atrial fibrillation (irregular and often rapid heart rate)
- Cardiovascular disorder
- Coronary artery disorder
- Abnormal electrocardiogram (unusal test of the electrical activity of the brain)
- Extrasystoles (a premature contraction of the heart)
- Hypotension (low blood pressure)
- Migraine

- Myocardial infarct (heart attack)
- Palpitation (perceived abnormal heart rate)
- Peripheral vascular disorder
- Phlebitis (inflammation of a vein)
- Tachycardia (rapid heart rate)
- Varicose vein
- Vascular disorder (vein disorder)
- Vasodilatation (dilation of the blood vessels)

- Venous thromboembolic events (deep vein thrombosis, pulmonary embolus) (a serious blood clot)
- Chronic indigestion
- Dark urine
- Muscle cramps, pain, stiffness, swelling or weakness
- Trouble breathing
- Unusual bleeding or bruising
- Unusual tiredness
- Yellow eyes or skin

Randomization: Subjects will be assigned to a study group by chance (like a coin flip) rather than by a medical decision made by the researchers. The treatment subjects receive may prove to be less effective or to have more side effects than the other study group(s), or than standard treatments available for subjects' condition.

Placebo: During this study there is a 25% chance that subjects will receive a placebo. This could lengthen the amount of time before subjects receive a treatment that may be effective. During this time, subjects may experience worsening of their condition, including increased HD symptoms. The researchers will carefully monitor subjects' condition. Subjects may of course withdraw from the study at any time.

Blood draw: Removing blood by a needle may cause temporary pain, bruising, bleeding, swelling, dizziness, and on rare instances fainting or infection.

Psychological discomforts: Some of the procedures may cause embarrassment or anxiety, or the questions the researchers ask subjects may be upsetting or make subjects uncomfortable. If subjects do not wish to answer a question, they can skip it and go to the next question. If subjects do not wish to participate you can stop.

Unknown risks: There may be risks related to the research that we don't know about yet. However, subjects will be informed of any additional risks to which they may be exposed, and any changes that are made to the study, as a result of any newly-identified risks.

Reproductive Risks: Subejcts should not get pregnant while in this study. The drug used in this study could harm an unborn baby. Check with the researchers about what types of birth control, or pregnancy prevention, to use while in this study. Contraception should be started 30 days prior to the baseline visit.

Subjects should also not breastfeed a baby while in this study, as the drug used in this study could harm a newborn baby.

If subjects are a male, they should not father a baby while on this study.

If the subject or their partner does become pregnant during the study, subjects should contact the researchers immediately.

2. Discuss what steps have been taken and/or will be taken to prevent and minimize any risks/ potential discomforts to subjects. *Examples include: designing the study to make use of procedures involving less risk when appropriate; minimizing study procedures by taking advantage of clinical procedures conducted on the subjects; mitigating risks by planning special monitoring or conducting supportive inventions for the study; implement security provisions to protect confidential information.*

To minimize the risks of a breach in confidentiality, samples and subjects' research records will be given a unique study identifier.

C. Potential Benefits

1. Describe the potential benefits subjects may expect to receive from participation in this study. *Compensation is not a benefit; do not include it in this section.*

[ ] There is no direct benefit anticipated for the subjects.

Subjects who are randomized to the fenofibrate group have the potential of disease-modifying effects on their Huntington's disease course.

2. Specify the expected potential societal/scientific benefit(s) of this study.

This is the first human study to examine the impact of fenfibrate on PGC-1 which may be a path toward modification of disease progression. The results of this study will be used to consider a larger trial to more specifically examine the impact of fenofibrate on the progression of Huntington's disease. The role of PGC-1αis also of interest in other neurodegenerative disease, including Parkinson's disease. Early intervention in the course of neurodegenerative disease with a disease modifying treatment represents a central goal in neuroscience research and enormous potential to alleviate suffering caused by these illnesses.

SECTION 8: ALTERNATIVES TO PARTICIPATION

Describe the alternatives to participation in the study available to prospective subjects. Include routine (standard of care) options as well as other experimental options, as applicable.

[ ] No alternatives exist. The only alternative to study participation is not to participate in the study.

[X] There are routine standard of care alternatives available; specify: Although presently no disease modifying treatment for Huntington's disease exists, there are methods to address symptoms, including medications, such as tetrabenazine for the treatment of chorea.

[ ] There are other alternatives to study participation; specify: <Type here>

SECTION 9: SUBJECT COSTS

1. Indicate below if subjects or their insurers will be charged for study procedures. Identify and describe those costs**.**

[ ] Not applicable: This study involves no interaction/intervention with research subjects. *Skip to Section 10.*

[X] This study involves interaction/intervention with research subjects; however there are no costs to subjects/insurers.

[ ] This study involves interaction/intervention with research subjects, and there are costs to subjects/insurers: <Type here>

2. If subjects or their insurers will be responsible for study-related costs, explain why it is appropriate to charge those costs to the subjects or their insurers. Provide supporting documentation as applicable (e.g., study procedures include routine (standard of care) procedures; FDA IDE/HDE/IND letter that supports billing to subjects).

[X] Not applicable: The study involves no costs to subjects for study participation.

[ ] Study related costs will be billed to subjects or their insurers for the following reasons: <Type here>

SECTION 10: SUBJECT COMPENSATION AND REIMBURSEMENT

1. If subjects will be compensated for their participation, explain the method/terms of payment (e.g., money; check; extra credit; gift certificate).

[ ] Not applicable: This study involves no interaction/intervention with research subjects. *Skip to Section 11.*

[ ] No compensation will be provided to subjects.

[ ] Compensation will be provided to subjects in the form of cash/gift certificate.

[ ] Compensation will be provided to subjects in the form of a check issued to the subjects through the UCI Accounting Office. The subject's name, address, and social security number, will be released to the UCI Accounting Office for the purpose of payment and for tax reporting to the Internal Revenue Service (IRS).

[X] Other: Parking for study visits will be provided through designated patient parking stalls at each study visit in addition to breakfast following every 12-hour fast for the morning blood draws.

2. Specify the schedule and amounts of compensation (e.g., at end of study; after each session/visit) including the total amount subjects can receive for completing the study. *Compensation should be offered on a prorated basis when the research involves multiple visits.*

   For compensation ≥ $600, subject names and social security numbers must be collected. This information must be reported to UCI Accounting for tax-reporting purposes.

[X] Not applicable: This study involves no compensation to subjects.

Subjects will be compensated with the following schedule and amounts: <Type here>

3. Specify whether subjects will be reimbursed for out-of pocket expenses. If so, describe any requirements for reimbursement (e.g., receipt).

[X] Not applicable: This study involves no reimbursement to subjects.

Subjects will be reimbursed; specify:.

SECTION 11: CONFIDENTIALITY OF RESEARCH BIOSPECIMENS/DATA

A. Biospecimens/Data Storage

1. Indicate all subject identifiers that may be included with the biospecimens or collected for the research study. *If any study-related data will be derived from a medical record, added to a medical record, created or collected as part of health care, or used to make health care decisions the HIPAA policy applies. The subject's HIPAA Research Authorization is required or a waiver of HIPAA Research Authorization must be requested by completing Appendix T.*

[ ] This study does not involve the collection of subject identifiers.

Check all the following subject identifiers will be used, created, collected, disclosed as part of the research:

[X] Names	**[ ]** Social Security Numbers	**[ ]** Device identifiers/Serial numbers
[X] Dates*	**[X]** Medical record numbers	**[ ]** Web URLs
[X] Postal address	**[ ]** Health plan numbers	**[ ]** IP address numbers
[X] Phone numbers	**[ ]** Account numbers	**[ ]** Biometric identifiers
[ ] Fax numbers	**[ ]** License/Certificate numbers	**[ ]** Facial Photos/Images
[X] Email address	**[ ]** Vehicle id numbers	**[ ]** Any other unique identifier

[ ] Other (Specify all): <Type here>

* *birth date, treatment/hospitalization dates*

Indicate how data will be stored and secured, including electronic data as well as hardcopy data paper records, electronic files, audio/video tapes, biospecimens, etc. *If the research data includes subject identifiable data and/or Protected Health Information, the storage devices or the electronic research files must be encrypted. [For guidance on the use of cloud services, please review the UCI OIT policy.]*

Electronic Data/Files (check all that apply):

[ ] Anonymous data will be maintained; no subject identifiers

[ ] Coded data; code key is kept separate from data in secure location.

[X] Data includes subject identifiable information. Provide rationale for maintaining subject identifiable info)**:** This study entails serial collection of data referable to each subject. Data entry will de-identify subjects by using a numerical code.

[X] Data will be stored on secure network server.

[ ] Data will be stored on standalone desktop computer (not connected to network/internet)

[ ] Other (specify here): <Type here>

Hardcopy Data (Records, Recordings, Photographs) and Biospecimens (check all that apply):

[ ] Anonymous biospecimens/data will be maintained; no subject identifiers

[X] Coded data; code key is kept separate from biospecimens/data in secure location.

[ ] Biospecimens/Data includes subject identifiable information (Provide rationale for maintaining subject identifiable info)**:** <Type here>

[ ] Data will be stored in locked file cabinet or locked room.

[ ] Biospecimens will be stored in locked lab/refrigerator/freezer.

[ ] Other (specify here): <Type here>

2. List the location(s) where the data and/or biological specimens will be stored**.**

Stem Cell Research Center, Gottschalk Medical Plaza, and 200 Manchester, Orange, CA, Department of Neurology

3. If subject identifiable data will be transported or maintained on portable devices, explain why it is necessary use these devices. *Only the "minimum data necessary" should be stored on portable devices as these devices are particularly susceptible to loss or theft. If there is a necessity to use a portable device for the initial collection of identifiable private information, the research files must be encrypted, and subject identifiers transferred to a secure system as soon as possible.*

[X] Not applicable: Research data will not be transported or maintained on portable devices.

Research data will need to be maintained on the following portable device(s) for the following reason(s): <Type here>

B. Data and/or Biological Specimens Access

Specify who will have access to subject identifiable data and/or biological specimens as part of this study.

[ ] Not applicable: No subject identifiers will be collected.

[X] Authorized UCI personnel such as the research team and appropriate institutional officials, the study sponsor or the sponsor's agents (if applicable), and regulatory entities such as the Food and Drug Administration (FDA), the Office of Human Research Protections (OHRP), and the National Institutes of Health (NIH).

[ ] Other: <Type here>

C. Data and/or Biological Specimens Retention

Indicate how long subject identifiable data and/or biological specimens, including the subject code key will be retained. *If more than one of the options below is applicable (e.g., the study involves children), records must be kept for the longer period.*

[ ] Not applicable: No subject identifiable research data will be retained.

[ ] Separate code key will be destroyed or subject identifiable information will be removed from the biospecimens and/or data at the earliest convenience, consistent with the conduct of this research. Specify timeframe: <Type here>

[ ] Destroyed once research data is analyzed.

[ ] Destroyed after publication/presentation.

[ ] Will be maintained; specify time frame and provide the rationale: <Type here>

[ ] Will be stored and maintained in a repository for future research purposes.

Complete Appendix M

[X] Will be retained for six years as this research involves Protected Health Information (PHI) (e.g., IRB documentation, consent/assent forms – NOT the actual PHI). *Investigators must destroy PHI at the earliest opportunity, consistent with the conduct of this study, unless there is an appropriate justification for retaining the identifiers or as required by law.*

[ ] Will be retained for seven years after all children enrolled in the study reach the age of majority [age 18 in California] as this study includes children.

[ ] Will be retained 25 years after study closure as this study involves in vitro fertilization studies or research involving pregnant women.

[ ] Will be retained for two years after an approved marketing application, as this is a FDA regulated study. If approval is not received, the research records will be kept for 2 years after the investigation is discontinued and the FDA is notified.

[ ] Other: <Type here>

D. Photographs, Audio/Video Recordings Retention

1. If subject identifiable audio or video recordings will be collected, specify the timeframe for the transcription and describe retention/destruction plans.

[X] Not applicable: Subject identifiable audio/video recordings will not be collected.

[ ] Audio or video recordings transcribed; specify time frame: <Type here>

[ ] Audio or video recordings will be maintained; specify time frame: <Type here>

[ ] Audio or video recordings maintained indefinitely; provide the rationale: <Type here>

[ ] Audio or video recordings destroyed; specify time frame: <Type here>

2. If subject identifiable photographs will be collected, describe retention/destruction plans**.**

[ ] Not applicable: Subject identifiable photographs will not be collected.

[ ] Photographs will be maintained; specify time frame: <Type here>

[ ] Photographs maintained indefinitely; provide the rationale: <Type here>

[ ] Photographs destroyed; specify time frame: <Type here>

E. Certificate of Confidentiality

1. Indicate whether a Certificate of Confidentiality (COC) has been or will be requested.

[X] Not applicable: No COC has been requested for this study.

[ ] A COC will be or has been requested for this study. *The COC application must be submitted to the IRB staff for review after IRB approval.*

[ ] A COC has been obtained for this study. The expiration date of this COC is: <Type here>

Provide a copy of the COC Approval Letter.

2. Explain in what situations the UCI study team will disclose identifiable private information protected by a COC.

<Type here>