Clinical Study Protocol	
FuRST2.0: Cognitive Pre-testing for a New Functional Rating Scale for Use in Huntington's Disease – Round 2	
PROTOCOL NO.:	C-000918-3
EudraCT/IND NO.:	N/A
INVESTIGATIONAL PHASE:	N/A
CHIEF CLINICAL OFFICER:	Cristina Sampaio, MD, PhD CHDI Management, Inc. 155 Village Boulevard Suite 200 Princeton, NJ 08540 Office Phone: +1-609-945-9600 Fax: +1-609-452-2160 Email: Cristina.Sampaio@chdifoundation.org
FUNDING ORGANIZATION:	CHDI Foundation, Inc. 155 Village Boulevard Suite 200 Princeton, NJ 08540 Office Phone: +1-609-945-9600 Fax: +1-609-452-2160
CLINICAL SCIENCE LEADER	Pua Feigenbaum, PhD CHDI Management, Inc. 155 Village Boulevard Suite 200 Princeton, NJ 08540 Office Phone: +1-609-945-9582 Email: pua.feigenbaum@chdifoundation.org
AMENDED PROTOCOL VERSION AND DATE:	Version 3.0 (10 Jun 2019)
AMENDED PROTOCOL VERSION AND DATE:	Version 2.0 (05 Mar 2019)
ORIGINAL PROTOCOL VERSION AND DATE:	Version 1.0 (10 Sep 2018)

CONTACT SHEET

Site Contact Information

The contact information of all site principal investigators (PIs) is specified in the study manual.

Funding Organization Contact Information

Funding Organization:	CHDI Foundation, Inc. 155 Village Boulevard Suite 200 Princeton, NJ 08540 Phone: 609-945-9600 Fax: 609-452-2160
Monitoring:	CHDI Foundation, Inc. or a qualified designee
Medical Monitor:	N/A

PROTOCOL APPROVAL SIGNATURES

This Clinical Study Protocol is approved by:

Signature: ..... Date: 6/10/2019

Cristina Sampaio, MD, PhD
Chief Clinical Officer
CHDI Management, Inc.

Signature: ..... Date: 6/10/19

Rebecca L. M. Fuller, PhD
Director, Clinical Outcomes
CHDI Management, Inc.

Signature: ..... Date: 6/10/2019

Pua Feigenbaum, PhD
Clinical Research Program Manager
CHDI Management, Inc.

Signature: ..... Date: 6/10/2019

Nancy LaPelle, PhD
Cognitive Pre-testing and Data Analysis Consultant
Consultant to CHDI Management, Inc.

Signature: ..... Date: June 11, 2019

Glenn T. Stebbins, PhD
Professor of Neurological Sciences
Rush University Medical Center

Site Principal Investigator Signature Page

Protocol Number:	C-000918-3
Protocol Title:	FuRST 2.0: Cognitive Pre-testing for a New Functional Rating Scale for Use in Huntington's Disease – Round 2
Amended Protocol Version and Date:	Version 3.0 (10 Jun 2019)
Amended Protocol Version and Date:	Version 2.0 (05 Mar 2019)
Original Protocol Version and Date:	Version 1.0 (10 Sep 2018)
Funding Organization:	CHDI Foundation, Inc. 155 Village Boulevard Suite 200 Princeton, NJ 08540 Office Phone: +1-609-945-9600

By my signature below, I hereby attest that I have read and that I understand and will abide by all the conditions, instructions, and restrictions contained in the attached protocol. I confirm that I am qualified by education, experience and training to serve as an investigator for this clinical study and agree to conduct and supervise the described study.

I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice, local regulations (as applicable), the Declaration of Helsinki, applicable regulatory requirements and the study protocol. I agree to conduct this study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in this study.

Additionally, I will not initiate this study without approval of the appropriate institutional review board (IRB)/ethics committee (EC), and I understand that any changes in the protocol must be approved in writing by the Funding Organization and the IRB/EC before they can be implemented, except where necessary to eliminate hazards to participants.

_____ _____

Site Principal Investigator's Signature Date

_____

Site Principal Investigator Name (Print)

1. Synopsis

Name of the Funding Organization: CHDI Foundation, Inc.	**Protocol No.:** C-000918-3
Name of Investigational Medicinal Product: N/A	**EudraCT No.:** N/A
Phase of Development: N/A	**IND No.:** N/A
Study Title: FuRST 2.0: Cognitive Pre-testing for a New Functional Rating Scale for Use in Huntington's Disease – Round 2.	
Short Study Title: FuRST 2.0 Cognitive Pre-testing – Round 2.	
Study Sites/Countries: Approximately 4-8 study sites in the United States and Canada; all study sites will be active sites in Enroll-HD study (Clinicaltrials.gov NCT01574053).	
Participants: **An HDGEC:** Premanifest and early-manifest Huntington's disease gene expansion carrier (HDGEC) who is also a participant in Enroll-HD and meets the protocol selection criteria for the HDGEC. HDGEC participants will be recruited from English speaking Enroll-HD sites. **A Companion:** A person who, in his/her opinion, has sufficient interaction and knowledge of the HDGEC participant's capabilities and daily activities, is acceptable to the HDGEC participant and the site principal investigator (site PI) or site PI's designee and meets the protocol selection criteria for the companion. The companion's participation is optional in this study.	
Number of Participants Planned: Approximately 40 HDGEC participants, premanifest and early-manifest distributed in approximately a 1:1 ratio, who complete the cognitive interview. Approximately 0-40 companions who complete the cognitive interview together with their corresponding HDGEC participant.	
Study Period (months/years): The study recruitment is expected to last approximately 7 months.	
Study Objective: Primary Objective: Use cognitive pre-testing (CPT) techniques to determine the need for refinements in scale items, response options, instructions and disclaimer statement in order to finalize development of a functional scale that is understandable to the target population.	
Study Endpoint: Primary Endpoint: Recommended modifications to FuRST 2.0 scale items, response options, instructions and disclaimer statement, if warranted by the qualitative analysis results.	

Study Design:

The proposed study is a single, cross-sectional cognitive interview of functional rating scale administered to HDGECs and potentially, their companions. The scale will be tested as a patient reported outcome (PRO) in that the information will come directly from the HDGEC participant or the HDGEC participant together with his/her companion through self-report. The purpose is to identify real or potential comprehension or usage problems with scale items, response options, instructions and disclaimer statement. Through a structured cognitive interview with the HDGEC participants or the HDGEC participants together with their companions, followed by qualitative analysis, the final phrasing of the individual scale items, response options, instructions and disclaimer statement for the scale will be generated. Depending on the results of this round of CPT (CPT-Round 2), an additional round of CPT may be required in a separate study.

Figure 1 outlines the overall study design, procedures and analysis.

Participant Selection Criteria

An HDGEC Inclusion Criteria:

An HDGEC will be included in this study if all of the following criteria are met:

1. Identified as an active participant in Enroll-HD (participants who have completed their last onsite Enroll-HD visit within approximately 15 months)
2. At least 18 years of age
3. Fluent in English and had his/her primary education in English
4. Able and willing to provide critical feedback (per site principal investigator (PI) or site PI's designee discretion)
5. Willing and able to provide written informed consent

Premanifest HDGEC

Criteria 1-5, and:

a. Cytosine, Adenine, Guanine (CAG) length ≥ 40
b. Disease burden score (DBS) ≥ 250 (calculated by the equation: [CAGn-35.5] X age)
c. Diagnostic confidence level (DCL) ≤ 3

Early-manifest HDGEC

Criteria 1-5, and:

a. CAG length ≥ 36
b. DCL=4
c. Total Functional Capacity (TFC) ≥ 11

A Companion of an HDGEC Inclusion Criteria

A companion of an HDGEC will be included in this study if all of the following criteria are met:

1. At least 18 years of age
2. Fluent in English and had his/her primary education in English

3. In his/her opinion, has sufficient interaction and knowledge of the HDGEC participant's capabilities and daily activities
4. Is acceptable to the HDGEC participant and the site PI or site PI's designee
5. Willing and able to provide written informed consent

An HDGEC/a companion of HDGEC Exclusion Criterion:

An HDGEC/a companion of an HDGEC will be excluded from this study if the following criterion is met:

1. Significant cognitive or any other impairment sufficient to interfere with study associated tasks as judged by the site PI or the site PI's designee

Criteria for Evaluation:

Analysis of observational and verbal reports will mainly focus on identifying:

1. Complexity or length of questions and response options that may inhibit understanding
2. Words and concepts used in the scale items that participants do not understand or understand differently
3. Questions that participants cannot answer accurately
4. Scaling severity choice difficulties
5. Questions that are strongly influenced by cultural meaning and norms or that make participants uncomfortable
6. Suggestions for better wording and other changes for modification in scale items, response options, instructions and disclaimer statement

Statistical Methods:

Data collected during cognitive interviews will undergo qualitative analysis to determine the clarity and appropriateness of each scale item, its response options, instructions and disclaimer statement included in the scale.

Based on observational data provided by the interviewer and data recorded capturing the expressed issues identified by the HDGEC participant or the HDGEC participant together with his/her companion being interviewed, a report containing the comparative summary tables with findings grouped thematically for each FuRST 2.0 scale item and its response options across participants, will be prepared. This report will also include any identified issues relating to the instructions and the disclaimer statement and issues that cut across FuRST 2.0 scale items and its response options with a summary of solutions suggested by the HDGEC participants or the HDGEC participants together with their companions.

Comments and concerns related to scale items, response options, instructions and disclaimer statement will be reviewed by CHDI Foundation, Inc. and its collaborators and recommendations regarding modifications of specific scale items, response options, instructions and disclaimer statement will be evaluated.

Figure 1: FuRST 2.0 – CPT-Round 2 Study Plan

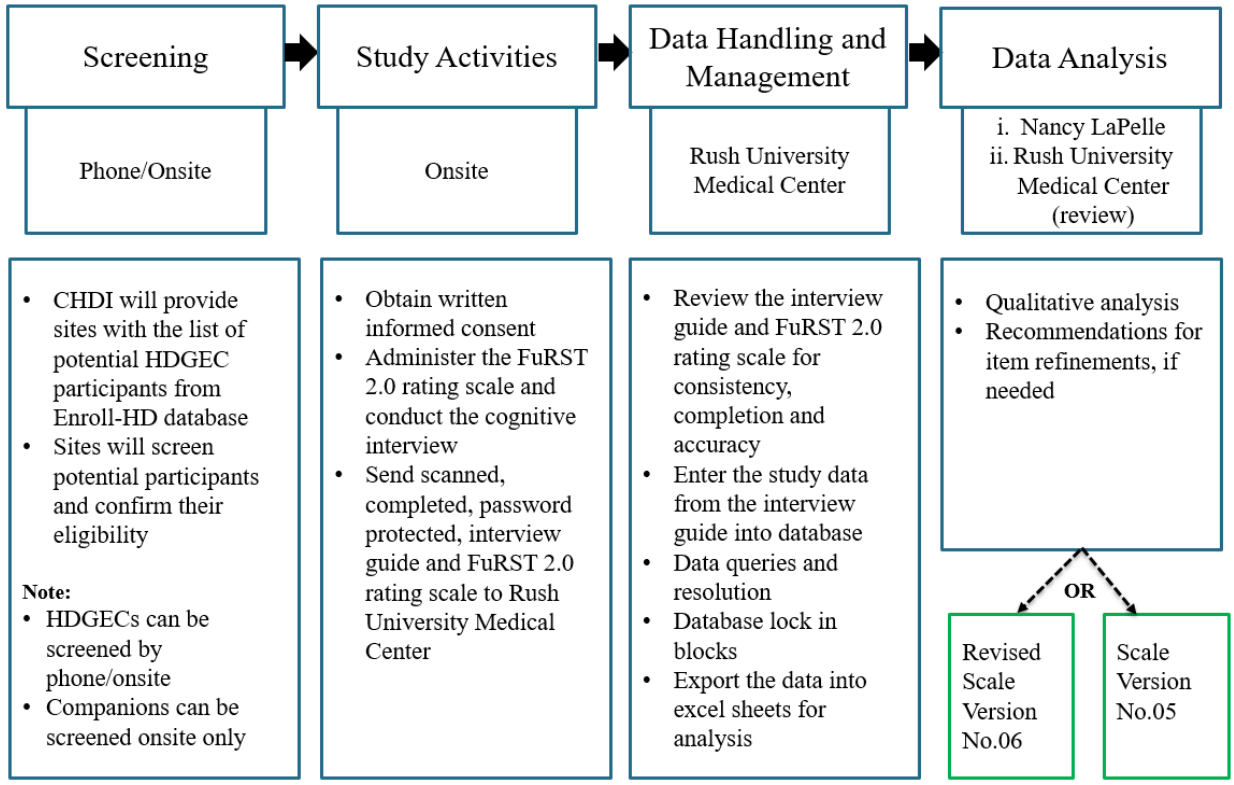


Table of Contents

2. List of Abbreviations

Abbreviation	Definition
CAG	Cytosine, Adenine, Guanine
CPT	Cognitive pre-testing
CPT-Round 1	Cognitive pre-testing study-round 1
CPT-Round 2	Cognitive pre-testing study-round 2
CRF	Case report form
DBS	Disease burden score
DCL	Diagnostic confidence level
DMP	Data management plan
EC	Ethics committee
FISMA	Federal Information Security Management Act
FuRST	Functional Rating Scale Taskforce
GCP	Good Clinical Practice
HD	Huntington’s disease
HDGEC	Huntington's disease gene expansion carrier
HDID	HD Identification Number
HIPAA	Health Insurance Portability Accountability Act of 1996
HTTPS	Hypertext Transfer Protocol secure
ICF	Informed consent form
ICH	International Conference on Harmonization
IRB	Institutional review board
ISF	Investigator site file
PRO	Patient reported outcome
REDCap	Research Electronic Data Capture
TFC	Total Functional Capacity
UHDRS	Unified Huntington’s Disease Rating Scale
UPS	Uninterruptible power supply

3. Introduction

3.1 Background

According to Wang, functional status is a patient-oriented meaningful health outcome which concerns individual daily functioning[1]. It includes an individual's ability to meet basic needs, maintain the ability to fulfill roles in family and society, and ensure maintenance of overall health and well-being[2]. In the context of clinical trials, measures of functioning combined with other endpoints provide data that can connect symptom improvement with impact on everyday life. This type of evidence can provide insight into the actual level of impact that a clinical change has on a person's overall well-being.

Currently, the Unified Huntington's Disease Rating Scale (UHDRS) is the most commonly-used rating scale in Huntington's disease (HD). The UHDRS has several sub-scales that measure motor, cognitive, behavioral and functional domains. The Total Functional Capacity (TFC) scale is part of the UHDRS and is used as a measure of functioning[3]. It addresses several areas of functioning: occupation, finances, domestic chores, activities of daily living, and care level. Scores range from 0 to13, with higher scores indicating better function. The scale measures a person's capacity to function, rather than their actual performance, as assessed by the rating clinician. The TFC is reported to decline by about one point per year in symptomatic HD patients[4], however, for patients in the very early stages of disease or those who are pre-symptomatic, the scale exhibits a ceiling effect[5-7]. As a result, when attempting to measure functional performance in people with HD who are premanifest or early-manifest the TFC is not useful and a new functional rating scale is needed.

Recent research suggests that early interventions may be required to slow the progression of neurodegeneration in HD[8]. In order to measure changes earlier in HD new functional rating scales that are more sensitive and appropriate for this patient population are needed. Several efforts are underway to address this significant gap with the goal of developing and validating new scales that can be employed in future clinical trials[9, 10]

3.1.1 The Functional Rating Scale Task Force (FuRST) Scale 2.0

The Functional Rating Scale Task Force (FuRST) was formed in 2010 to develop a functional rating scale for premanifest and early-manifest HD patients. This work resulted in the first iteration of the FuRST rating scale: Functional Rating Scale Task Force for pre-Huntington Disease (FuRST -pHD)[10]. After further evaluation by rating scale development experts it was decided not to move forward with validation due to problems with preliminary clinimetric results and the cumbersome nature of the structured interview methodology. FuRST 2.0

builds on previous work to develop a functional rating scale that is clinimetrically robust and easy to administer in the clinical research setting.

3.2 Study Rationale

Advocacy groups and regulatory agencies have highlighted assessment of functional abilities from the patient's perspective in neurological disorders as a desirable data collection method. Assessing the positive impact of a treatment on patient function, in addition to symptom improvement or disease modification, provides a patient-centric justification for an intervention. Currently, there are no acceptable assessments of functional ability for premanifest and early-manifest HD. The overall goal of the FuRST 2.0 program is to use state-of-the-art clinimetric techniques to develop a valid and reliable functional abilities measure for use in premanifest and early-manifest Huntington's disease gene expansion carriers (HDGECs).

A Delphi process involving a panel of HD experts, in conjunction with pre-existing data from patient focus groups, was used in order to identify domains of interest to be included in the scale and to develop draft items to be used in assessment of functional abilities. These draft items comprised the draft FuRST 2.0 rating scale version number 02. In the first round of cognitive pre-testing study (CPT-Round 1; NCT02881931), these draft scale items were subjected to cognitive pre-testing (CPT) using HDGECs, companions and interviewers to assess the ease of use of the scale, the ease of comprehension of the instructions, individual scale items and rating anchor definitions, applicability of individual scale items and rating anchors, level of insight as perceived by the interviewer, as well as the comfort with addressing specific issues that may be sensitive to the HDGEC participants, companions or interviewers.

In accordance with the qualitative analyses results of CPT-Round 1, modifications were incorporated into scale items, response options and instructions to form a modified version of the draft FuRST 2.0 scale. This version will be evaluated in this second round of CPT Study (CPT-Round 2), using similar pre-testing technique as used in CPT-Round 1.

CPT is an iterative process which typically has multiple rounds of cognitive interviews, scale revision, and additional cognitive interviews to test the revised scale. Once the scale items are shown to be adequate through CPT, the penultimate items for inclusion in the final scale will be field-tested in a larger cohort of premanifest and early-manifest HDGECs and their companions. This field test will be performed under a separate protocol.

4. Study Objective

Primary Objective: Use CPT techniques to determine the need for refinements in scale items, response options, instructions and disclaimer statement in order to finalize development of a functional scale that is understandable to the target population.

5. Study Endpoint

Primary Endpoint: Recommended modifications to FuRST 2.0 scale items, response options, instructions and disclaimer statement, if warranted by the qualitative analysis results.

6. Overall Study Design

The proposed study is a single, cross-sectional cognitive interview of functional rating scale administered to HDGECs and potentially, their companions. The scale will be tested as a patient reported outcome (PRO) in that the information will come directly from the HDGEC participant or the HDGEC participant together with his/her companion through self-report. The purpose is to identify real or potential comprehension or usage problems with scale items, response options, instructions and disclaimer statement. Through a structured cognitive interview with the HDGEC participants or the HDGEC participants together with their companions, followed by qualitative analysis, the final phrasing of the individual scale items, response options, instructions and disclaimer statement for the scale will be generated. Depending on the results of CPT-Round 2, an additional round of CPT may be required in a separate study.

Figure 1 outlines the overall study design, procedures and analysis.

7. Study Population

Participants will consist of approximately 40 premanifest and early-manifest HDGECs distributed in approximately a 1:1 ratio and approximately 0-40 companions. The companions will complete the cognitive interview together with their HDGEC participants. The companion's participation is optional in this study. For additional details regarding sample size in this study, please refer to Section 12.1 ("Determination of Sample Size and Statistical Aspects of Study Design"). Participants will be identified and recruited via study sites that participate in Enroll-HD.

7.1 Rationale for Study Population

Difficulties with self-reporting in HD are reported to be associated with reduced insight[11] and the results of the CPT-Round 1 study (NCT02881931) suggested impaired self-reporting due

to reduced insight in early-manifest HDGECs with TFC scores of 7-10. Thus, we are recruiting early-manifest HDGECs with TFC score greater than or equal to 11. The Companion of the HDGEC participant will complete the cognitive interview together with his/her HDGEC participant, when available. However, the companion's participation is optional in this study.

For the purpose of this study, premanifest HDGEC is defined as an HDGEC with a disease burden score (DBS) ≥ 250, indicating a potential onset of HD motor symptoms within 15 years (+/- 5yrs.)[12]. Early-manifest HDGEC is defined as having a TFC greater than or equal to 11 at the time of enrollment in this study.

HDGEC participants for this study will be recruited from the Enroll-HD study (Clinicaltrials.govNCT01574053), a global observational study of HD that acts as a platform to expedite selection of participants in studies recruiting HDGECs[13]. In addition, with the consent of participants, data from the Enroll-HD study will be used in this study, thus decreasing participant burden by not having to repeat assessments.

7.2 Selection Criteria

7.2.1 Inclusion Criteria

An HDGEC will be included in this study if all of the following criteria are met:

1. Identified as an active participant in Enroll-HD (participants who have completed their last onsite Enroll-HD visit within approximately 15 months)
2. At least 18 years of age
3. Fluent in English and had his/her primary education in English
4. Able and willing to provide critical feedback (per the site principal investigator (PI) or site PI's designee discretion)
5. Willing and able to provide written informed consent

Premanifest HDGEC

Criteria 1-5, and:

a. Cytosine, Adenine, Guanine (CAG) length ≥ 40
b. DBS ≥ 250 (calculated by the equation [CAGn-35.5] X age)
c. Diagnostic confidence level (DCL) ≤ 3

Early-manifest HDGEC

Criteria 1-5, and:

a. CAG length ≥36

b. DCL=4
c. TFC ≥11

A companion of an HDGEC will be included in this study if all of the following criteria are met:

1. At least 18 years of age
2. Fluent in English and had his/her primary education in English
3. In his/her opinion, has sufficient knowledge of the HDGEC participant's capabilities and daily activities
4. Is acceptable to the HDGEC participant and the site PI or site PI's designee
5. Willing and able to provide written informed consent

7.2.2 Exclusion Criterion

An HDGEC/a companion of an HDGEC will be excluded from this study if the following criterion is met:

1. Significant cognitive or any other impairment sufficient to interfere with study associated tasks as judged by the site PI or the site PI's designee

7.3 Recruitment

Study sites will contact potential HDGEC participants for screening by phone or in person. Potential HDGEC participants who meet the protocol selection criteria for the HDGEC and agree to participate in this study will provide written informed consent. Screening of companions will be conducted in person. Companions who meet the protocol selection criteria for the companion and agree to participate in this study will provide written informed consent.

7.4 Criteria for Study Withdrawal

Participants may be discontinued from participation in this study for the following medical or administrative reasons:

- Withdrawal of consent by the participant
- Noncompliance, including refusal to complete the scale or answer interviewer's questions and/or failure to adhere to the study requirements as outlined in the study protocol
- Decision of the site PI that, in the interest of the participant, it is not medically acceptable to continue participation in this study
- Termination of this study by CHDI Foundation, Inc.

7.5 Criteria for Termination of this Study

CHDI Foundation, Inc. may terminate this study prematurely for any reason. The site PI may cease participating as a site PI in this study for any reason. The institutional review board (IRB)/ethics committee (EC) should be informed promptly by the site PI/institution.

Conditions that may warrant termination by CHDI Foundation, Inc. include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the participants enrolled in this study, or potential study participants
- A decision on the part of CHDI Foundation, Inc. to suspend or discontinue this study

If this study is prematurely terminated or suspended for any reason, the site PI/institution should promptly inform the participants.

7.6 Replacement of Participants

HDGEC participants who withdraw from this study prior to completing the cognitive interview will be replaced so that the final number of completed interview guides (defined in Section 11: “Data Collection and Handling”), will be in accordance with the description in Section 7 (“Study Population”).

8. Cognitive Pre-testing

8.1 Purpose of Cognitive Pre-testing

The overall goal of CPT is to ensure the instructions, rating scale items, the concepts that are being assessed and response options are communicated such that they are understood by the participants in the intended way. The cognitive testing interviews usually consist of probes to ascertain:

1. The participant’s comprehension of the scale items (what does the participant think the question is asking?);
2. Difficulties the participant may encounter with the recall needed to answer the question;
3. Difficulties with the time frame of reference for the question;
4. Any role that reluctance or social desirability may have in answering questions accurately and thoughtfully;
5. Comprehension of the response options and whether the participant can relate his/her response to the scoring criteria used in the scale items.

After qualitative data analysis (please refer to Section 12.2: “Data Analysis”), the scale items may be modified based upon the review of cognitive interview findings, and, if necessary, an additional round of CPT will be implemented in a separate study to confirm scale item performance and respondent understanding.

8.2 Cognitive Pre-testing Methodology

The CPT methodology involves participant debriefing using a think-aloud approach while responding to each scale item, as well as verbal probes administered by the cognitive interviewer (henceforth referred to as “rater”) after each scale item is completed.

Analysis of observational and verbal reports will mainly focus on identifying:

1. Complexity or length of scale items and response options that may inhibit understanding
2. Words and concepts used in the scale items that participants do not understand or understand differently
3. Questions that participants cannot answer accurately
4. Scaling severity choice difficulties
5. Questions that are strongly influenced by cultural meaning and norms or that make participants uncomfortable
6. Suggestions for better wording and other changes for modification

9. Rater Qualification

Each selected site will have a minimum of one rater. The following rater qualifications will be met through rater training (please refer to Section 9.1: “Rater Training”)

- Understanding that the goal of cognitive interviewing is to identify real or potential comprehension or usage problems with scale items or response options and only secondarily to obtain responses to the scale items.
- Interpersonal skills that can put the participant at ease including the flexibility needed to adapt the activity to the participant’s needs. It is important to conduct the interview using easy to understand language, while obtaining the needed information via the participant’s verbal reports. The rater must also be able to observe the participant and note any discomfort, confusion, or inability to recall information needed to select a response option.
- Experience performing qualitative interviews where probing (sometimes unscripted) is often needed to get a participant to clarify or expand on their verbal report until it is fully explained and understood by the interviewer. The rater also has to be patient,

unhurried, and comfortable with silence in allowing the participant time to think through their verbal reports before moving on to the next scale item.
- Enough exposure to the subject matter of the instrument to enable them to answer the participant's questions or clarify scale items the participant may have difficulties with, so that the participant can select a response and report on encountered difficulties.
- Some basic knowledge of questionnaire design and potential biasing behavior on the part of the rater such as asking leading questions about potential difficulties.

9.1 Rater Training

Adequate training for the raters who conduct cognitive interview sessions shall be provided. In addition, participating sites will be provided with an interview guide containing detailed instructions for implementing and conducting the cognitive interview as well as for recording observational and verbal report data.

The rater training will include the following topics:

- Overview of the FuRST 2.0 scale, its target population, and intent of each question and response options
- Purpose of CPT and why it is necessary
- Types of questionnaire problems to look out for and probe for, such as confusing instructions, question length or complexity, wording, difficult technical terms, vagueness in the scale item or response options, unhelpful reference periods, difficulty with recalls, difficulty with requested computations, incomplete knowledge, insensitive content, lack of appropriate or complete response options
- Understanding of the intent of the questions being tested and the cognitive testing probes
- In-depth qualitative cognitive interview techniques and how these differ from quantitative interviewing techniques (e.g., administer questions slowly and allow time for thoughtful responses)
- Introducing the cognitive interview process to the participant
- Review of the question-by-question interview guide and how to use it
- Document in a legible way:
    - Rater observations
    - Participant questions raised regarding the scale item
    - Cognitive test data from the participant in response to rater probes
    - Any suggestions for changes to the rating scale items or self-administration instructions

- Knowledge of the types of probes to be used in cognitive interviewing that may supplement those in the interview guide (i.e., probes that would be composed/improvised in response to participant's verbal reports)
- Identifying participant's behavioral difficulties such as long silences, contradictory responses, reluctance to respond or other manifestations of discomfort

10. Study Procedures

Following IRB/EC approval, CHDI will provide study sites with a list of potentially eligible HDGEC participants from the Enroll-HD study. The site PI or site PI's designee will screen potential HDGEC participants, by phone or in person to assess their interest in participating in this study and to confirm eligibility based on HDGEC selection criteria. The site PI or site PI's designee will screen potential companions in person to assess their interest in participating in this study and to confirm eligibility based on the companion selection criteria. Once participants have confirmed their interest in participating in this study, they must provide written consent and sign the informed consent form (ICF). Signed ICFs will be filed by the site PI or site PI's designee in the investigator site file (ISF).

10.1 Administration of the FuRST 2.0 Rating Scale

The FuRST 2.0 scale is a participant self-report instrument using paper and pencil. The scale should be administered in a quiet place without external distractions. Participants should be given as much time as they need to complete each item of the scale.

The rater will observe the scale item completion process by the participant, and note any observed difficulties or questions raised while attempting to complete the scale item. Following the completion of each scale item, the rater will use a series of probes to obtain a verbal report from the HDGEC participant or the HDGEC participant together with his/her companion, concerning any difficulties they experienced while trying to understand and complete the scale item.

10.2 Conducting the Cognitive Interview

The rater will conduct the cognitive interview with the HDGEC participant or the HDGEC participant together with his/her companion, in person. The participant(s) will be asked by the rater to voice aloud any difficulties they are having while attempting to answer each scale item. The rater will observe the participant(s) and record observed and/or voiced difficulties and will answer participant(s) questions as needed. Follow-up cognitive test-probes will be used after the participant completes each item of the scale to gain a better understanding of how the participant(s) interpreted the questions and selected a response. Study procedures

related to capturing the data in the interview guide (defined in Section 11 “Data Collection and Handling”), sending the completed scale and interview guide to Rush University Medical Center, data entry into Research Electronic Data Capture (REDCap) and exporting the data for data analysis are indicated in Section 11: “Data collection and Handling”.

11. Data Collection and Handling

The following detailed manual will be drafted and used by raters to guide their cognitive interview for the participants.

1. FuRST 2.0 interview guide - cognitive testing instructions (interview guide): Manual of instructions for raters on how to administer the questionnaire to the participant(s) and to record qualitative data. This interview guide is also considered the case report form (CRF).

This interview guide will include sufficient detail to standardize the pre-defined probes used in the cognitive interview process across all sites engaged in testing. However, raters will also be encouraged to take the time to generate additional probes as needed to clarify potential problems or encourage the participant to think critically and identify potential difficulties.

11.1 Data Collection

Data will be handwritten legibly during the cognitive interview by the rater in a participant-specific copy of the interview guide. Scanned documents of the completed scale and completed signed interview guide will be sent to Rush University Medical Center for data entry into REDCap database. Originals of the signed interview guide will be maintained by the site. If CHDI Foundation, Inc. requires original documents for archiving, photocopies will be archived onsite.

Detailed information of data collection on site and on the transfer of these data to Rush University Medical Center is available in the study data management plan (DMP).

11.2 HD Identification Number

All HDGEC participants in this study will also be participants in the Enroll-HD study (ClinicalTrials.gov identifier NCT01574053) and have an Enroll-HD Huntington’s Disease Identification Number (HDID); it is not necessary to generate a new HDID. The HDID is a unique 9-digit number used to protect the identity of HDGEC participants and link their clinical information to other HD studies in which they may participate.

In this study, HDGEC Research ID, taken from Enroll-HD study, will be included in applicable study documents such as the interview guide.

11.3 Data Management

The following manuals will be written and used for data entry/export:

1. FuRST 2.0 Cognitive Test Data Entry/Export Guide: Manual of instructions on how to complete data entry into the FuRST 2.0 Data Export Template.
2. FuRST 2.0 Data Export Template: Data export spreadsheet into which the data collected during the cognitive interview and entered into REDCap, are exported for qualitative analysis. This spreadsheet will be developed and formatted using Microsoft Excel.

Data from the completed interview guides will be reviewed and entered into the REDCap database system. Data will be extracted in the format of FuRST 2.0 Data Export Template excel spreadsheets used for the qualitative analysis.

Detailed information on handling the data obtained in this study is presented in the study DMP.

11.4 Rush University Medical Center Database

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant data. By signing the protocol, the institution and the researcher commit to complying with all applicable federal, state, local and international laws and regulations relating to data protection and the privacy of patient health information.

All accounts are password-protected. Permissions are carefully maintained to allow only the required level of access to study data. The operating environment requires username/password authentication and implements its own permissions structure at the file system level based on user ID and group ID. Files and directories are carefully set with only the required level of access. User ID's are required to change password on a regular basis.

Rush University Medical Center is a designated REDCap partner. The REDCap system provides a 21 CFR Part 11, Federal Information Security Management Act (FISMA), and Health Insurance Portability Accountability Act of 1996 (HIPAA)-compliant environment for data capture and management. At Rush University Medical Center, REDCap servers are maintained and secured at two parallel data centers in Chicago. All servers are located in a locked data center with access limited to authorized personnel via a biometrics access system. Each data center has a Sinorix™ 227 and Ecaro-25™ Clean Agent Chemical Fire Suppression Systems; redundant backup diesel generator and uninterruptible power supply (UPS) systems, as well as redundant chillers for cooling.

The Rush University Medical Center data network uses Virtual Machines servers (OS: Red Hat 6) and is segmented and protected from the internet by a Palo Alto Networks® firewall. Backups are restored on a daily basis from cloning the database servers from the day before. Access to the network from the internet requires multi-factor authentication with secure socket layer connection using the Hypertext Transfer Protocol secure (HTTPS) protocol. All network users are required to have a unique login and password.

11.5 Use of Enroll-HD Data

Enroll-HD data will be extracted from Enroll-HD database, as needed. Data captured in Enroll-HD database will be used for HDGEC participants who have agreed to share their data and participate in other studies using their Enroll-HD data. This will decrease the burden on HDGEC participants and sites as these data do not need to be collected multiple times. This data will also be used by the site to pre-qualify HDGEC participants based on specific requirements set forth in this protocol. The data collected from Enroll-HD that will be utilized in this study include, but are not limited to CAG length and TFC score recorded closest to the cognitive interview date.

12. Statistical Methodology

12.1 Determination of Sample Size and Statistical Aspects of Study Design

There is no general consensus on the sample sizes needed for adequate CPT[14]. Prior studies have documented that major improvements in questions and quality of response data can be obtained with relatively few CPT interviews[15, 16].While small samples (5-15) have often been used, Blair and Conrad[14] in a study aimed at identifying an optimal sample size for effective cognitive pre-testing, found that a sample of 50 was necessary to identify 80% of the known problems in a questionnaire developed for the trial, and that as many as 90 interviews were needed to identify all known problems (as determined by experts). They concluded that carrying out more cognitive interviews than are normally done is probably a good resource investment as the probability of detecting more issues will increase. Beatty and Willis[17] argue that the sample can be selected to cover more effectively as much of the conceptual terrain of the questionnaire as possible and should represent demographic as well as geographic variety. Beatty and Willis further suggest that, rather than conducting one round of cognitive pre-testing with a very large sample, general guidance calls for CPT to be conducted in iterative rounds of smaller sample sizes where revisions are made between rounds.

Other important considerations for the sample size in CPT are the training and expertise of the rater. Those are important in identifying problems effectively; experienced raters uncover problems at higher rates than less-experienced raters. Less-experienced raters may cost less and be easier to recruit, but their lack of expertise may create a need for a larger sample size to identify as many problems. Consequently, we plan to use raters who have some knowledge and experience with the subject matter of the rating scale and then provide them with training in cognitive interviewing skills to ensure they will perform sufficient probing and recording of observations and verbal reports.

All considerations taken together, this study will recruit approximately 40 premanifest and early-manifest HDGEC participants distributed in approximately a 1:1 ratio and approximately 0-40 companions who complete the cognitive interview together with their HDGEC participants. The companion's participation is optional in this study.

12.2 Data Analysis

Data collected during cognitive interviews will undergo qualitative analysis to determine the clarity and appropriateness of each scale item, its response options, instructions and disclaimer statement included in the scale.

The FuRST 2.0 scale item numbers and cognitive test probe numbers will be used to enable the grouping together of all data related to each specific FuRST 2.0 scale item across all participants for analysis. These data items will be identified by source (premanifest or early-manifest participants).

Main steps in the data analysis are outlined below:

1. For each participant, extract those lines from the exported spreadsheet that contain significant data (i.e., the participant has voiced some critical feedback in response to a cognitive interview question regarding the FuRST 2.0 scale item)
2. Merge these extracted lines into a separate spreadsheet for analysis. This spreadsheet will contain cognitive interview data from all participants for that FuRST 2.0 scale item
3. When all significant cognitive interview data from all participants have been merged for each FuRST 2.0 scale item, create a comparative summary table for each FuRST 2.0 scale item containing for each data item:
    a. Site number
    b. Participant ID
    c. Indication of premanifest or early-manifest participant
    d. Text of the data item itself (which may include rater observations as well as comments from the participant)

4. Review these summary tables and thematically group the data items within them related to the nature of the participant's issues with the FuRST 2.0 scale item or its response options

Based on observational data provided by the interviewer and data recorded capturing the expressed issues identified by the participant being interviewed, a report containing the comparative summary tables with findings grouped thematically for each FuRST 2.0 scale item across participants, will be prepared. This report will also include any identified issues relating to the instructions and the disclaimer statement and issues that cut across FuRST 2.0 scale items, with a summary of solutions suggested by the participants.

Comments and concerns related to scale items, response options, instructions and disclaimer statement will be reviewed by CHDI Foundation, Inc. and its collaborators and recommendations regarding modifications of specific scale items, instructions and disclaimer statement will be evaluated.

13. Risk/Benefit Analysis

This is a non-interventional, minimal risk study during which participants will complete a rating scale, be interviewed by a rater and answer questions, and have their responses recorded. Due to the nature of this study, we do not anticipate having any clinically significant safety events. Potential risks to the participant include possible feelings of emotional discomfort or fatigue during the interview process. To minimize risks, the participant is allowed to withdraw from this study at any time.

As with the collection of any personal (private) information, there is also a slight risk of accidental disclosure of information or breach of computer security. There is no direct benefit for the participant. The results of this study may help to develop a reliable functional scale that might help other HDGECs in the future.

14. Monitoring

Due to the nature of this study, (i.e., non-interventional, with minimal risk) monitoring activities will be performed by remote review of data sent by the sites to Rush University Medical Center. Onsite monitoring will be performed by CHDI Foundation, Inc. or a qualified designee and will include (but is not limited to) verification of ICFs, completed scales, interview guides and other study documents as indicated in the monitoring plan.

15. Ethical and Regulatory Considerations

The rights, safety, and well-being of the participants are the most important considerations and should prevail over interests of science and society.

This study is intended to be conducted in accordance with the principles stated in the Declaration of Helsinki and subsequent revisions, in adherence to International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements[i].

15.1 Informed Consent

Informed consent must be given freely, not under duress, and obtained from every participant before entry into this study. The ICF must have been reviewed and approved by CHDI Foundation, Inc. and by an IRB/EC prior to the initiation of this study. A copy of the letter of approval from the IRB/EC and a copy of the approved ICF will be received by CHDI Foundation, Inc. prior to shipment of study documents to the site PI.

Consent must be documented by use of an ICF approved by CHDI Foundation, Inc. and an IRB/EC and signed by the participant. Additionally, the participant must be allowed adequate time to consider the potential risks and benefits associated with his/her participation in this study. A copy of the signed ICF must be given to the participant signing it and the original copy must be filed in the ISF and made available to CHDI Foundation, Inc., monitors, auditors and regulatory authorities' representatives upon request. If, for any reason, participant risk is increased as this study progresses, a revised, IRB-approved ICF must be signed by the participant and the person obtaining consent.

15.2 Ethics Committee Approvals

The protocol, the final version of ICF for this study, advertisements used to recruit participants, if applicable, and any other participant facing documents and/or materials must be reviewed and approved by an appropriate IRB/EC prior to enrollment of participants in this study. It is the responsibility of the site PI to ensure that all aspects of the ethical review are conducted in accordance with the current Declaration of Helsinki, ICH, GCP, and/or local laws, whichever provide the greatest level of protection. Amendments to the protocol will be subject to the same requirements as the original protocol. The site PI will also ensure that no changes will be made to the protocol without CHDI Foundation, Inc. and IRB/EC approval.

Note: [i] The EDC of Enroll-HD, which will provide accessory data, is not fully GCP-compliant because it does not allow an electronic audit trail.

The site PI will ensure that the IRB/EC will be promptly informed of all changes in the research activity and of all unanticipated problems including risk to participants.

A progress report with a request for re-evaluation and re-approval will be submitted by the site PI to the IRB/EC at intervals required by the IRB/EC. A copy of the report will be sent to CHDI Foundation, Inc.

After completion or termination of this study, the site PI will submit a final report to the IRB/EC and to CHDI Foundation, Inc., if required. This report should comply with IRB/EC requirements.

15.3 Study Documentation

The site PI is required to maintain complete and accurate study documentation in compliance with current GCP standards and all applicable federal, state, local and international laws, rules, and regulations relating to the conduct of a clinical study.

The site PI must maintain source documents for each participant enrolled in this study. Source documents may include, but are not limited to: medical record information, original signed ICF, completed signed interview guides and completed scale.

15.4 Participant Confidentiality

To help ensure that the anonymity of participants is maintained, participants will be identified by one or more identification code numbers on study documents submitted by the sites to Rush University Medical Center. These study documents will not contain names, initials, addresses, etc. Only coded data will be given to researchers and other users outside of this study. Data that is stored for future use may be re-coded.

Documents that will be submitted to the clinical monitor and that identify the participant (e.g., the signed ICFs) must be maintained in strict confidence by the site PI, except to the extent necessary to allow auditing by a regulatory authority, the clinical monitor, or CHDI Foundation, Inc. personnel, representatives and agents.

All information regarding the nature of this study provided by CHDI Foundation, Inc. to the site PI (with the exception of information required by law or regulations to be disclosed to the IRB, the participant, or a regulatory authority) must be kept in confidence by the site PI.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant data. By signing the protocol, the institution and site PI commit to complying with all applicable federal, state, local and international laws and regulations relating to the privacy of patient health information, including, but not limited to,

the Standards for Individually Identifiable Health Information, 45 CFR Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 (HIPAA) Privacy Regulation).

The site PI shall ensure that study participants authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to CHDI Foundation, Inc.

15.5 Amendments

Any amendments to the protocol will be written and approved by CHDI Foundation, Inc. All amendments to the protocol must be submitted to the IRB/EC for approval prior to implementing the changes. In some instances, an amendment to the protocol may require changes to the ICF, which also must be approved by CHDI Foundation, Inc. and submitted for IRB/EC approval prior to administration to participants.

15.6 Audits and Inspections

CHDI Foundation, Inc. and its representatives, regulatory authorities, or IRB/EC may visit the study site at any time during this study or after completion of this study to perform audits or inspections. The purpose of CHDI Foundation, Inc. audits or regulatory inspections is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted according to the protocol, ICH GCP guidelines, and any other applicable regulatory requirements. Site PIs should contact CHDI Foundation, Inc. immediately if contacted by a regulatory agency about an inspection at their site.

15.7 Financial Disclosure

This section is not applicable to this study.

15.8 Record Keeping

15.8.1 Access to Original Records

It is an expectation of regulatory authorities that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation to ensure data integrity. “Original” in this context is defined as the first documentation of an observation and does not differentiate between hard copy and electronic records.

15.8.2 Retention of Study Documents

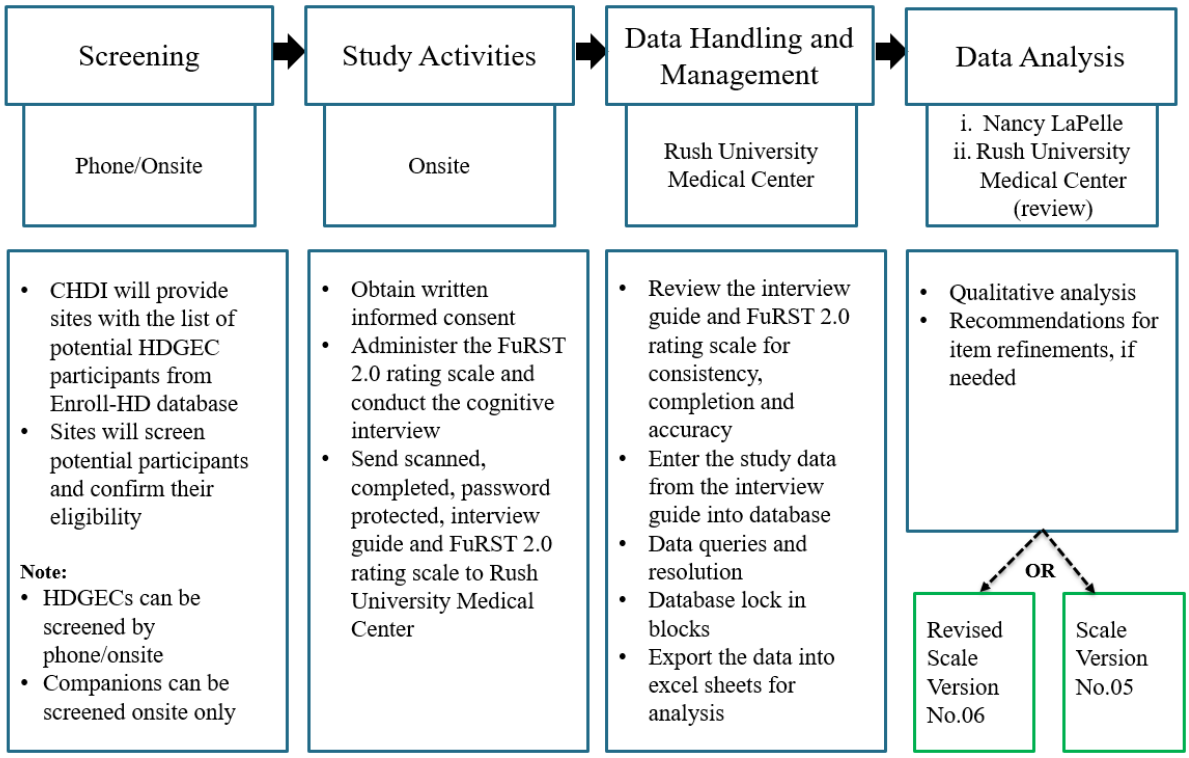
All study documents and records should be retained for a period of time specified in the site agreement. The site PI must notify CHDI Foundation, Inc. in the event of accidental loss or destruction of any study documents and records.

16. Administrative Structure of this Study

This study will be overseen by personnel of CHDI Management, Inc., Rush University Medical Center, and an external consultant. Functions for this study will be performed by the following organizations:

Function	Organization
Data management	Rush University Medical Center, Chicago, IL: Dr. Glenn Stebbins Consultant: Dr. Nancy LaPelle
Statistical & qualitative analysis	Consultant: Dr. Nancy LaPelle Rush University Medical Center, Chicago, IL: Dr. Glenn Stebbins
Reporting	Rush University Medical Center, Chicago, IL: Dr. Glenn Stebbins Consultant: Dr. Nancy LaPelle

17. Appendix A - Figure 1: FuRST 2.0 – CPT-Round 2 Study Plan



18. Appendix B – Schedule of Events

Cognitive Pre-testing Activities	-60 to -1 (within approximately 60 days prior to Day 1)	Day 1
Screening*	X	
Check inclusion/exclusion		X
Obtain informed consent**		X
Demographic data		X
Cognitive interview and data collection***		X

*Screening of potential HDGEC participants (who are also participants in Enroll-HD) to assess their interest to participate in this study and to evaluate protocol selection criteria for HDGEC. Screening will be conducted by phone or in person and can be done on the same day as the cognitive interview.

*Screening of potential companions to assess their interest to participate in this study and to evaluate protocol selection criteria for the companion. Screening will be conducted in person and can be done on the same day as the cognitive interview.

** **Informed consent must be obtained from every participant before entry into a clinical study**.

*** Cognitive interview and data collection will be conducted preferably on the same day ICF is signed.

19. Appendix C – FuRST 2.0 Draft Scale

Draft FuRST 2.0

Version No. 05

June 3, 2019

Instructions

This questionnaire asks you about difficulties you may have doing your day-to-day activities. People may have several medical issues that impact these activities. Do not worry about separating the effects of different medical issues.

This questionnaire is for you to complete alone. Please read each question carefully and consider all the answers before deciding which answer is best for you. Do not leave any answers blank.

Please follow these guidelines when you are answering the questions:

- If you had no difficulty doing an activity or you have **never** done the activity, please choose option a: No.
- If you had any difficulty doing an activity, please choose options b, c, or d indicating the level of difficulty you had: Mild, Moderate or Severe.
- If you used to do an activity but stopped because of your illness, please choose option d: Severe.

For each question below, please circle the letter (a, b, c or d) that best describes how much difficulty you had doing that activity, **on average**, over the **past two weeks.**

Thank you for completing this questionnaire.

1. Over the past two weeks, did you have difficulty interacting with other people in person or over the phone?

a. No: I had no difficulty doing this.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

2. Over the past two weeks, did you have difficulty communicating with other people using electronic devices? Some examples are difficulty texting or using email.

a. No: I had no difficulty doing this **or** I have never done it.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

3. Over the past two weeks, did you have difficulty doing chores around the house?

a. No: I had no difficulty doing this.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

4. Over the past two weeks, did you have difficulty working at your job? Some examples are making mistakes or not finishing everything.

a. No: I had no difficulty doing this **or** I have never done it.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

5. Over the past two weeks did you have difficulty using cash or credit cards? Some examples are difficulty remembering PIN numbers, finding your credit cards or taking money out of your pocket, wallet or handbag.

a. No: I had no difficulty doing this.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

6. Over the past two weeks did you have difficulty managing your finances? Some examples are difficulty keeping track of your bank accounts or paying your bills.

a. No: I had no difficulty doing this **or** I have never done it.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

7. Over the past two weeks, did you have difficulty **planning** your day-to-day activities?

a. No: I had no difficulty doing this.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

8. Over the past two weeks did you have difficulty **getting started** with your day-to-day activities?

a. No: I had no difficulty doing this.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

9. Over the past two weeks did you have difficulty getting to where you needed to go without assistance? Some examples are difficulty getting in or out of a car, bus or train, or difficulty knowing how to get somewhere.

a. No: I had no difficulty doing this.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

10. Over the past two weeks did you have difficulty walking? Some examples are difficulty feeling steady on your feet, going up or down stairs, or walking smoothly.

a. No: I had no difficulty doing this.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

11. Over the past two weeks did you have difficulty doing activities you enjoy?

a. No: I had no difficulty doing this.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

12. Over the past two weeks did you have difficulty using your hands? Some examples are difficulty picking things up, carrying a full cup, or turning a key.

a. No: I had no difficulty doing this.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

13. Over the past two weeks did you have difficulty with your speech? Some examples are difficulty saying what you meant to say or having others understand what you said.

a. No: I had no difficulty doing this.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

14. Over the past two weeks did you have difficulty grooming yourself? Some examples are difficulty bathing, combing your hair, or brushing your teeth.

a. No: I had no difficulty doing this.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

15. Over the past two weeks did you have difficulty dressing yourself? Some examples are difficulty using buttons and zippers, putting on jewelry or tying your shoe laces.

a. No: I had no difficulty doing this.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

16. Over the past two weeks did you have difficulty keeping to your day-to-day routine without assistance? Some examples are difficulty getting up, going to bed or eating meals at your usual times.

a. No: I had no difficulty doing this.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

17. Over the past two weeks did you have difficulty getting to events on time without assistance? Some examples are difficulty getting to movies, family gatherings or other appointments on time.

a. No: I had no difficulty doing this.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

18. Over the past two weeks did you have difficulty keeping your surroundings clean without assistance? Some examples are difficulty cleaning your bedroom, the kitchen, or your car.

a. No: I had no difficulty doing this.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

19. Over the past two weeks did you have difficulty exercising? Some examples are difficulty walking for exercise, jogging, swimming, or playing a sport.

a. No: I had no difficulty doing this **or** I have never done it.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

20. Over the past two weeks did you have difficulty staying involved in what is going on around you? Some examples are difficulty staying up-to-date with important news or events.

a. No: I had no difficulty doing this.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

21. Over the past two weeks did you have difficulty controlling your temper? Some examples are getting irritated or into arguments.

a. No: I had no difficulty doing this.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

22. Over the past two weeks did you have difficulty with your sexual activities?

a. No: I had no difficulty with this.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

23. Over the past two weeks did you have difficulty driving a car?

    a. No: I had no difficulty doing this **or** I have never done it.

    b. Mild: I had difficulty doing this but could still do it well.

    c. Moderate: I had difficultly doing this well.

    d. Severe: I could barely do this **or** I could not do it at all.

24. Over the past two weeks did you have difficulty sleeping? Some examples are difficulty falling asleep, difficulty sleeping through the night, or waking too early.

a. No: I had no difficulty doing this.

b. Mild: I had difficulty doing this but could still do it well.

c. Moderate: I had difficultly doing this well.

d. Severe: I could barely do this **or** I could not do it at all.

Disclaimer: We asked about many problems people with Huntington's disease may have. Some of these questions may apply to you and others may not, but to be complete we are asking all the questions to every person. Thank you for taking the time to complete this questionnaire.

20. References

1. Wang T-J. Concept analysis of functional status. International journal of nursing studies 2004;41:457-462.

2. Leidy NK. Functional status and the forward progress of merry-go-rounds: toward a coherent analytical framework. Nursing research 1994;43:196-202.

3. Huntington Study Group. The Unified Huntington's Disease Rating Scale. Mov Disord 1996;11:136-142.

4. Shoulson I, Kurlan R, Rubin AJ, et al. Assessment of functional capacity in neurodegenerative movement disorders: Huntington's disease as a prototype. Quantification of neurologic deficit Boston: Butterworths 1989:271-283.

5. Marder K, Zhao H, Myers RH, et al. Rate of functional decline in Huntington's disease. Huntington Study Group. Neurology 2000;54:452-458.

6. Mestre TA, Busse M, Davis AM, et al. Rating Scales and Performance-based Measures for Assessment of Functional Ability in Huntington's Disease: Critique and Recommendations. Movement Disorders Clinical Practice 2018;5:361-372.

7. Paulsen JS, Wang C, Duff K, et al. Challenges assessing clinical endpoints in early Huntington disease. Movement Disorders 2010;25:2595-2603.

8. Sampaio C, Borowsky B, Reilmann R. Clinical trials in Huntington's disease: interventions in early clinical development and newer methodological approaches. Movement Disorders 2014;29:1419-1428.

9. Carlozzi NE, Victorson D, Sung V, et al. HD-PRO-TRIAD™ Validation: A Patient-reported Instrument for the Symptom Triad of Huntington's Disease. Tremor and Other Hyperkinetic Movements 2014;4.

10. Vaccarino AL, Sills T, Anderson KE, et al. Assessment of day-to-day functioning in prodromal and early Huntington disease. PLoS currents 2011;3.

11. McCusker E, Loy CT. The many facets of unawareness in Huntington disease. Tremor and Other Hyperkinetic Movements 2014;4.

12. Tabrizi SJ, Langbehn DR, Leavitt BR, et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. The Lancet Neurology 2009;8:791-801.

13. Landwehrmeyer GB, Fitzer-Attas CJ, Giuliano JD, et al. Data analytics from Enroll-HD, a global clinical research platform for Huntington's disease. Movement Disorders Clinical Practice 2017;4:212-224.

14. Blair J, Conrad FG. Sample size for cognitive interview pretesting. Public opinion quarterly 2011;75:636-658.

15. Forsyth B, Rothgeb JM, Willis GB. Does pretesting make a difference? An experimental test. Methods for testing and evaluating survey questionnaires 2004:525-546.

16. Tilley BC, LaPelle NR, Goetz CG, Stebbins GT. Using Cognitive Pretesting in Scale Development for Parkinson's Disease: The Movement Disorder Society Unified Parkinson's

Disease Rating Scale (MDS-UPDRS) Example. Journal of Parkinson's disease 2014;4:395-404.

17. Beatty PC, Willis GB. Research synthesis: The practice of cognitive interviewing. Public opinion quarterly 2007;71:287-311.