Clinical Study Protocol

FuRST2.0: Cognitive Pre-Testing for a New Functional Rating Scale for Use in Huntington's Disease

PROTOCOL NO.:	C-000316
ORIGINAL PROTOCOL VERSION NO. AND DATE:	Version 1.0 (03 March 2016)
AMENDED PROTOCOL VERSION NO. AND DATE:	Version 2.0 (23 May 2016) (List of documents included in this version: Amendment 1, 23 May 2016)
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PROTOCOL APPROVAL SIGNATURES

This Clinical Study Protocol is approved by:

Signature: ..... Date: May 24, 2016

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Signature: ..... Date: 5/25/16

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Protocol Number:	C-000316
Protocol Title:	FuRST 2.0: Cognitive Pre-Testing Study for a New Functional Rating Scale for Use in Huntington's Disease
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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 am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice, local regulations (as applicable), the Declaration of Helsinki, and the study protocol (See Appendix B for details). 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.

Investigator's Signature	Date
Investigator Name (Print)	

1. Synopsis

Name of the Funding Organization: CHDI Foundation, Inc.	**Protocol No.:** C-000316
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 Study for a New Functional Rating Scale for Use in Huntington's Disease	
Short Study Title: FuRST 2.0 Cognitive Pre-Testing	
Study Sites/Countries: Approximately 4-10 Enroll-HD (Clinicaltrials.gov NCT01574053) centers in English speaking countries	
Number of Participants Planned: Approximately 40 Huntington Disease Gene Expansion Carrier (HDGEC) participants, both Pre-Manifest and Early-Manifest stages 1-2, distributed in a 1:1 ratio. At least five and up to 20 companions (as defined below) of HDGEC Pre-Manifest participants and 20 companions of HDGEC Early-Manifest participants.	
Participants: Individuals of either gender, equal to or greater than 18 years of age. HDGEC Pre-Manifest and Early-Manifest participants (see inclusion criteria) will be recruited from English speaking Enroll-HD sites. **Companions**: Available companions for HDGEC Pre-Manifest participants will be encouraged to participate (at least five Pre-Manifest's companions are required). Companions will be identified for HDGEC Early-Manifest participants and asked to participate. Companion's participation for HDGEC Early-Manifest participant is mandatory as specified in the inclusion criteria. **Companion Definition:** a person who, in his/her opinion, has sufficient interface and knowledge of the HDGEC participant's capabilities and daily activities, and is acceptable to the HDGEC participant and the Investigator or the Investigator's designee.	
Study Period (months/years): Approximately 8 months.	
Objectives: Primary Objective: to use cognitive pre-testing techniques to determine the need for item refinements in order to finalize development of a functional scale that is understandable to the target population. Exploratory Objective: To explore if there are discrepancies between the scoring on questions by companions and HDGEC participants that may impact on the ability of HDGECs to accurately self-report.	

Study Design:

The scale will be tested as a Patient Reported Outcome (PRO) in that the information will come directly from the HDGEC participant and companion through self-report. The purpose is to identify real or potential comprehension or usage problems with questionnaire items or response options. Through a process of structured cognitive de-briefing with HDGEC participants and companions, independently, followed by qualitative analysis, the final phrasing of the individual items and response options for the scale will be generated. Depending on the results of the first round of cognitive pre-testing, additional rounds of cognitive pre-testing may be required.

Main criteria for inclusion:

1. HDGEC participant must be a participant in Enroll-HD
2. At least 18 years of age
3. Must be fluent in English and had his primary education in English
4. Must be willing and able to provide written informed consent

Pre-Manifest HDGECs

Criteria 1-4, and:

a. CAG length greater than or equal to 40
b. Disease Burden Score greater than or equal to 250 (calculated by the equation: [CAGn-35.5] X age)
c. Diagnostic Confidence Level (DCL) $\leq$ 3
d. At least five Pre-Manifest HDGEC participants should have a companion who is willing to participate in this study and complete the scale independently.

Early-Manifest (Stage 1&2) HDGECs

Criteria 1-4, and:

a. CAG length greater than or equal to 36
b. DCL=4
c. Total Functional Capacity (TFC) $\geq$7
d. Participants whose companion is willing to participate in this study and complete the scale independently

Main criteria for exclusion:

1. Significant cognitive or any other impairment sufficient to interfere with study associated tasks as judged by the study Investigator or the Investigator's designee
2. Currently participating in a clinical trial involving an investigational medicinal product

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 items that respondents do not understand or understand differently
3) Questions that respondents cannot answer accurately
4) Scaling severity choice difficulties
5) Questions that are strongly influenced by cultural meaning and norms or that make respondents uncomfortable
6) Suggestions for better wording and other changes for modification

Statistical Methods:

Qualitative analytic methods will be used to evaluate the data in order to determine the appropriateness of the instructions and each question included in the questionnaire, based on observations provided by the interviewer and the expressed understanding of the HDGEC participant and companion being de-briefed during the cognitive pre-testing session

To address the exploratory objective, two quantitative analyses (Kolmogorov-Smirnov test and Lin's Concordance Correlation Coefficient (CCC)) will be performed to assess if the two sources (HDGEC participants and companions) have similar distributions of FuRST 2.0 scores.

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2. List of Abbreviations

Abbreviation	Definition
CCC	Concordance Correlation Coefficient
DCL	Diagnostic Confidence Level
EC	Ethics Committee
FA	Functional Assessment
FDA	Food and Drug Administration
FuRST	Functional Rating Scale Taskforce
GCP	Good Clinical Practice
HD	Huntington's Disease
HDGEC	Huntington's Disease Gene Expansion Carriers
HDID	HD Identification Number
HIPAA	Health Insurance Portability Accountability Act of 1996
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ISCED	International Standard Classification of Education
IS	Independence Scale
IRB	Institutional Review Board
PBA-s	Problem Behavior Assessment - Short Form
PRO	Patient Reported Outcome
QC	Quality control
TFC	Total Functional Capacity
UHDRS	Unified Huntington's Disease Rating Scale
UTHSC	University of Texas, Health Science Center

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, however, for patients in the very early stages of disease or those who are pre-symptomatic the scale exhibits a ceiling effect[4]. As a result, when attempting to measure functional performance in people with HD who are Pre-Manifest 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. 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[5,6].

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 Pre-Manifest HD patients. This work resulted in the first iteration of the FuRST rating scale (FuRST 1.0). 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 Pre-Manifest 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 Pre-Manifest and Early-Manifest Huntington Disease Gene Expansion Carrier (HDGEC).

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 to assess functional abilities. In the current study, these draft items will be subjected to cognitive pre-testing using HDGECs, companions and interviewers to assess the ease-of-use of the scale, the ease of comprehension of individual items and rating anchor definitions, applicability of individual 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 participants, companions or interviewers. Once the items are proven adequate through cognitive pre-testing, the penultimate items for inclusion in the final scale will be field-tested is a larger cohort of Pre-Manifest and Early-Manifest HDGEC participants and their companions. This field test will be performed under a separate protocol.

4. Study Objectives

Primary Objective: to use cognitive pre-testing techniques to determine the need for item refinements in order to finalize development of a functional scale that is understandable to the target population.

Exploratory Objective: to explore if there are discrepancies between the scoring on questions by companions and HDGEC participants that may impact on the ability of HDGECs to accurately self-report.

5. Study Design

5.1 Overall Study Design

The scale will be tested as a Patient Reported Outcome (PRO) in that the information will come directly from the HDGEC participant and companion through self-report. The purpose

is to identify real or potential comprehension or usage problems with questionnaire items or response options. Through a process of structured cognitive de-briefing with HDGEC participants and companions, independently, followed by qualitative analysis, the final phrasing of the individual items and response options for the scale will be generated. Depending on the results of the first round of cognitive pre-testing additional rounds of testing may be required.

5.2 Rationale for Study Population

For the purpose of this study, Pre-Manifest HDGEC is defined as HDGEC with a Disease Burden Score ≥ 250 indicating a potential onset of HD motor symptoms within 15 years (+/- 5yrs.)[7]. Early-Manifest HDGEC are defined as having a TFC ≥7 at the time of enrollment in this study.

Companion is defined as a person who, in his/her opinion has sufficient interface and knowledge of the HDGEC participant's capabilities and daily activities, and is acceptable by the HDGEC participant and the Investigator or the Investigator's designee. To ensure an adequate representation of HDGEC and companion dyads who complete the FuRST 2.0 independently, the enrollment distribution will be monitored. We anticipate enrolling 20 Pre-Manifest and 20 Early-Manifest HDGECs. All of the Early-Manifest and at least five Pre-Manifest participants are required to have a companion who will complete the scale, independently. Other available companions for Pre-Manifest participants will be encouraged, but not required to participate and complete the scale independently as well. This study will have 40 HDGEC participants, and a minimum of five and up to 20 companions of HDGEC Pre-Manifest participants and 20 companions of HDGEC Early-Manifest participants. HDGEC participants for this study will be recruited from the Enroll-HD study (Clinicaltrials.gov NCT01574053), a global observational study of HD that expedites selection of participants in studies like this. 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.

5.3 Selection Criteria

5.3.1 Inclusion Criteria

1. HDGEC participant must be a participant in Enroll-HD
2. At least 18 years of age
3. Must be fluent in English and had his primary education in English
4. Must be willing and able to provide written informed consent

Pre-Manifest HDGECs

Criteria 1-4, and:

a. CAG length greater than or equal to 40
b. Disease Burden Score greater than or equal to 250 (calculated by the equation [CAGn-35.5] X age)
c. Diagnostic Confidence Level (DCL) < 3
d. At least five Pre-Manifest HDGEC participants should have a companion who is willing to participate in this study and complete the scale independently.

Early-Manifest (Stage 1&2) HDGECs

Criteria 1-4, and:

a. CAG length greater than or equal to 36
b. DCL=4
c. TFC ≥7
d. Participants whose companion is willing to participate in this study and complete the scale independently

For companion:

Companion is defined as a person, who in his/her opinion, has sufficient interface and knowledge of the HDGEC participant's capabilities and daily activities, and is acceptable by the HDGEC participant and the Investigator or the Investigator's designee.

5.3.2 Exclusion Criteria

1. Significant cognitive or any other impairment sufficient to interfere with study associated tasks as judged by the study Investigator or the Investigator's designee
2. Currently participating in a clinical trial involving an investigational medicinal product

5.4 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
- Investigator decides that, in the interest of the participant, it is not medically acceptable to continue participation in this study

- CHDI Foundation, Inc. terminates this study

5.5 Criteria for Termination of this Study

CHDI Foundation, Inc. may terminate this study prematurely for any reason. The Investigator may cease participating as an investigator for this study for any reason. The Institutional Review Board (IRB)/ Ethics Committee (EC) should be informed promptly.

Conditions that may warrant termination 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 Investigator/Institution should promptly inform the study participants.

5.6 Replacement of Participants

For participants who withdraw from this study prior to completing the scale and cognitive de-brief, the participant or the dyad will be replaced, as applicable.

6. Rater Qualification

Each selected site will have a minimum of two cognitive pre-testing interviewers (henceforth referred to as “raters”). The following rater qualifications will be met through rater training (see 6.1):

- Understanding that the goal of cognitive interviewing is to identify real or potential comprehension or usage problems with questionnaire items or response options and only secondarily to obtain responses to the items.
- Interpersonal skills that can put a respondent at ease including the flexibility needed to adapt the activity to the respondent’s needs. It is important to conduct the interview using easy to understand language while obtaining the needed information via patient verbal reports. The interviewer must also have the ability to observe the HDGEC respondent and the companion respondent 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 respondent to clarify or expand on their verbal report until it is fully explained and understood by the interviewer. The interviewer also has to be patient, unhurried, and comfortable with silence in allowing the respondent time to think through their verbal reports before moving on to the next item.

- Enough exposure to the subject matter of the instrument to enable them to answer a respondent's questions or clarify items the respondent may have difficulties with so that the respondent can select a response and report on encountered difficulties.
- Some basic knowledge of questionnaire design and potential biasing behavior on the part of the interviewer such as asking leading questions about potential difficulties.

6.1 Rater Training

No formal rater training is required to administer the FuRST 2.0 rating scale since it is intended to be self-administered. However, there will be a training for the interviewers who conduct cognitive de-brief sessions. In addition, participating sites will be provided with an interview guide containing detailed instructions for implementing and administering the cognitive pre-testing as well as for recording observational and verbal report data.

The cognitive interviewer training will include the following topics:

- Purpose of cognitive pre-testing 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 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 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 respondent
- Review of the question-by-question interview guide and how to use it to document in a legible way:
    - interviewer observations
    - respondent questions raised regarding the item
    - cognitive test data from the respondent in response to interviewer probes
    - companion observations
    - 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 respondent's verbal reports)

- Identifying respondent behavioral difficulties such as long silences, contradictory responses, reluctance to respond or other manifestations of discomfort

7. Administration of the FuRST 2.0 Rating Scale

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

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

8. Cognitive Pre-testing

8.1 Purpose of Cognitive Pre-testing

The overall goal is to ensure the rating scale items, the concepts that are being assessed, and response options are communicated in the questionnaire in a way that can be understood by HDGEC participants and their companions in the intended way. The cognitive pre-testing interviews usually consist of probes to ascertain:

1. The respondent's comprehension of the items (what does the respondent think the question is asking?);

2. Difficulties the respondent may encounter with recall needed to answer the question;

3. Difficulties with the time frame of reference the question is based on;

4. Any role that reluctance or social desirability may have in answering items accurately and thoughtfully;

5. Comprehension of the response options and whether the respondent can relate his/her response to the scoring criteria used in the items.

After qualitative data analysis (cf Section 12), the rating scale items may be modified based upon the review of cognitive test findings, and, if necessary, additional rounds of cognitive pre-testing will be required to confirm item performance and respondent understanding. This

would involve further testing with a small number of participants (HDGEC or HDGEC and his/her companion) on slightly re-worded scale items.

8.2 Cognitive Pre-testing Methodology

The cognitive pre-testing methodology involves respondent (HDGEC participant/companion) de-briefing using a think-aloud approach while responding to each item, as well as verbal probes administered by the cognitive interviewer after each item is completed.

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

a. Complexity or length of questions and response options that may inhibit understanding
b. Words and concepts used in the items that respondents do not understand or understand differently
c. Questions that respondents cannot answer accurately
d. Scaling severity choice difficulties
e. Questions that are strongly influenced by cultural meaning and norms or that make respondents uncomfortable
f. Suggestions for better wording and other changes for modification.

There is no general consensus on the sample sizes needed for adequate cognitive pre-testing[8]. While small samples (5-15) have often been used, Blair and Conrad[8], 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. Beatty and Willis[9] 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 cognitive pre-testing to be conducted in iterative rounds of smaller sample sizes where revisions are made between rounds.

Other important considerations for the sample size in a cognitive pre-test are the training and expertise of the cognitive interviewer. Those are important in identifying problems effectively; experienced interviewers uncover problems at higher rates than less experienced interviewers. Less experienced interviewers 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 interviewers who will 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 Pre-Manifest and Early-Manifest stage 1/2 HDGEC participants distributed in a 1:1 ratio, at least five and up to 20 companions of HDGEC Pre-Manifest participants and 20 companions for Early-Manifest participants. Three detailed manuals will be drafted which will be used by cognitive pre-testing administrators to guide their cognitive pre-testing activities for HDGEC participants and companions. These manuals will include sufficient detail to standardize the pre-defined probes used in the cognitive pre-testing process across all sites engaged in testing. However, interviewers will also be encouraged to take the time to generate additional probes as needed to clarify potential problems.

The following manuals will be written:

a. The Interview Guide (HDGEC participant): FuRST 2.0 Cognitive Pre-test Instructions: Manual of instruction for cognitive interviewers on how to administer the questionnaire to HDGEC participant.
b. The Interview Guide (Companion): FuRST 2.0 Cognitive Pre-test Instructions: Manual of instruction for cognitive interviewers on how to administer the questionnaire to the HDGEC participant's companion.
c. FuRST Cognitive Test Data Entry Guide: Manual of instructions on how to complete data entry into the data capture spreadsheet.

A data capture spreadsheet will be developed and formatted using Microsoft Excel. This data capture spreadsheet is intended to be used to export data collected during cognitive pre-testing for analysis.

The overall methodology and materials will be initially used in a pilot at one center to ensure instructions, methods, and use of materials is clear and understandable.

8.2.1 Conducting the Cognitive Pre-test

Participants will be asked by the cognitive interviewer to voice aloud any difficulties they are having while attempting to answer each item. The cognitive interviewer will observe and note observed and/or voiced difficulties and will answer respondent 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 respondents interpreted the questions and selected a response option.

8.2.2 Cognitive Pre-testing Data Capture

Data will be captured during the cognitive pre-test (handwritten legibly or entered into a laptop or other electronic device with a keyboard) by the cognitive interviewer in a participant-specific copy of the interview guide. The final copy of the completed interview guide for each cognitive interview will include the site name and number, cognitive interviewer's name, HDGEC participant Research ID (taken from Enroll-HD study), and whether or not a companion was present and participated in this study. Scanned, signed documents of the completed interview guide will be sent to University of Texas (UTHSC) for data analysis. Originals of the signed interview guide will be maintained by the site. If CHDI Foundation will require Originals for archiving, photocopies will be archived onsite.

8.2.3 Cognitive Pre-testing Data Analysis

All data collected through the cognitive pre-testing will be grouped by site. Data will have been coded by FuRST 2.0 item number and cognitive test probe number, exported into a data capture spreadsheet and merged into a single spreadsheet for each site. Once the data from all cognitive pre-testing documents received from sites are merged into a single spreadsheet for analysis, the FuRST 2.0 item numbers and cognitive test probe numbers will be used to enable the sorting of all data related to each specific FuRST item across all cognitive pre-testing participants at that site for analysis.

9. 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.

9.1 Use of Enroll-HD Data

Enroll-HD data will be extracted from Enroll-HD database for exploratory post hoc analyses. The data to be collected are specified in Appendix A of this protocol.

Data captured in Enroll-HD 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 participants and sites as these data do not need to be collected multiple times. The data may also be used by the site or Enroll-HD researchers to pre-qualify participants based on specific requirements set forth in this protocol.

10. Risk/Benefit Analysis

This is a non-interventional, minimal risk study during which participants will complete a rating scale, answer questions, and have their responses recorded. Due to the nature of this study, we do not anticipate having any clinically significant safety events. The only 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. There is no direct benefit for the HDGEC participant, or companion. The results of this study may help to develop a reliable functional scale that might help other people with HD in the future.

11. Monitoring

Due to the nature of this study, non-interventional, with minimal risk, most of the monitoring activities will be done by remote review of data sent by the sites. Onsite monitoring will be done by CHDI or qualified designee and includes (but is not limited to) verification of informed consent.

12. Statistical Methodology

Analysis of cognitive pre-testing data will follow a qualitative analytic plan. Using the sorted spreadsheet for each site, an analysis of the data collected for each item on the FuRST2.0 questionnaire will be performed in order to determine the appropriateness of the instructions and each item/response option included in the questionnaire. Based on observational data provided by the interviewer and data recorded capturing the expressed understanding of the HDGEC participant or companion being de-briefed during the cognitive pre-testing session, a comparative summary of findings across sites will be completed and comments and concerns related to questionnaire items will be reviewed and recommendations regarding modifications of specific items will be evaluated.

To address the exploratory objective, two analyses will be performed to assess if the two sources (HDGEC participants and companions) have similar distributions of FuRST 2.0 scores. The first analysis is a Kolmogorov-Smirnov test to ascertain if the two distributions are drawn from the same population. If the two distributions are similar, a non-significant Kolmogorov-Smirnov is expected. The second analysis will be a Lin's Concordance Correlation Coefficient (CCC). This statistic measures the similarity of two response sets assessing exact matches. If the two sources are providing similar matches, a high Lin's CCC (standardly defined as equal to or greater than 0.90) is expected. Both the Kolmogorov-

Smirnov and Lin's are applicable to smaller datasets; therefore current sample sizes are adequate.

12.1 Data Management

Data from the cognitive pre-testing will be entered into the database system downloaded to excel spreadsheets on a site by site basis in the format used for the qualitative analysis. Before spreadsheets are delivered for analysis, a quality control (QC) check of 100% of the generated spreadsheets will be performed to ensure accurate data generation. Corrections will be made as necessary. Spreadsheets for qualitative analysis will be constructed, following the completion of the QC check.

12.2 Audits and Inspections

CHDI Foundation, Inc., regulatory authority, 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. audit or regulatory inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted according to the protocol, Good Clinical Practice (GCP), International Conference on Harmonization (ICH) guidelines, and any other applicable regulatory requirements. Investigators should contact CHDI Foundation, Inc. immediately if contacted by a regulatory agency about an inspection at their site.

12.3 Amendments

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

12.4 Record Keeping

12.4.1 Drug Accountability

This section is not applicable as no drug is involved.

12.4.2 Health Insurance Portability Accountability Act of 1996

The Investigator agrees to comply with all applicable federal, state, and local 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 Investigator 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.

12.4.3 Financial Disclosure

This section is not applicable to this non-interventional, cognitive pre-testing study.

12.4.4 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.

12.4.5 Retention of Study Documents

Study documents should be retained for a period of time specified in the site agreement. The Investigator must not destroy any study-related records without receiving approval from CHDI Foundation, Inc. The Investigator must notify CHDI Foundation, Inc. in the event of accidental loss or destruction of any study records.

12.5 University of Texas, Health Science Center (UTHSC) Database

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant data. By signing the protocol, the institution and Investigator commit to complying with all related applicable international and local laws and regulations as well as any applicable Safe Harbor privacy principles.

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.

The UTHSC uses the OpenClinica system for electronic data capture. In total, OpenClinica operates three database servers with only one functioning as the "active" database server at any given time. The two other slave database servers are synchronized with the primary database, with a maximum lag allowance of up to 10 seconds. One of the slave database servers is in the same data center as the active database server. The other slave database

server is located in the secondary data center. This set-up ensures we do not lose any database changes in the event of catastrophe.

UTHSC maintains all data in a SAS 70 Type II audit certified data center that meets ISO 17799 standards for information security. Access to any instance is limited, via login credentials, to authorized users for the web interface only. Users have no access to the server itself, except through defined application and programmatic interfaces. OpenClinica employees are only granted access to computer and networking areas necessary to perform their duties. Each user's installation is separate, and cannot be accessed from any other user installation. The connection to the hosted instance is encrypted by means of secure socket layer. The UTHSC uses a Sharepoint website as a repository for manuals, study documents, training materials, and user support documents relating to the conduct of all aspects of this study.

13. Administrative Structure of this Study

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

Function	Organization
Data management	University of Texas, Health Science Center, Houston, TX: Dr. Luo Sheng; Dr. Barbara Tilley Consultant: Dr. Nancy LaPelle
Statistical & qualitative analysis	University of Texas, Health Science Center Houston, TX: Dr. Luo Sheng; Dr. Barbara Tilley Consultant: Dr. Nancy LaPelle Rush University, Chicago, IL: Dr. Glenn Stebbins
Quantitative Analyses	University of Texas, Health Science Center Houston, TX: Dr. Luo Sheng; Dr. Barbara Tilley
Reporting	University of Texas, Health Science Center Houston, TX: Dr. Luo Sheng; Dr. Barbara Tilley Rush University, Chicago, IL: Dr. Glenn Stebbins Consultant: Dr. Nancy LaPelle

14. Appendix A – Schedule of Events

Cognitive Pre-testing	-21 to -1 (within 21 days prior to Day 1)	Day 1
Phone screen**	X	
Check inclusion/exclusion		X
Obtain informed consent*		X
Demographic data		X
Cognitive pre-testing data		X
Disease-related data (from Enroll-HD***): UHDRS Motor Functional assessments ((TFC, Independence Scale (IS), Functional Assessment (FA)) Cognitive test scores from the Enroll-HD core battery PBA-s (Problem Behavior Assessment- Short Form)		X
International Standard Classification of Education (ISCED) (from Enroll-HD) - education level***		X
Comorbid Conditions (from Enroll-HD***)		X
Concomitant Medications (from Enroll-HD***)		X

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

** Phone screen to potential HDGEC-participants (who are also participants in Enroll-HD) to assess their interest to participate in this study, availability of companion greater than 18 years old, and to evaluate protocol requirements regarding English fluency and exclusion criteria. The phone screen will be conducted by the Investigator or the Investigator's designee.

*** Collect for HDGEC participants only

15. Appendix B – Ethical Standards

Ethics and Regulatory Considerations

This study will be conducted according to 21 CFR Part 50, (Protection of Human Subjects), 21 CFR Part 56 (IRB), International Conference on Harmonization Guidance for Industry, E6 GCP: Consolidated Guidance, the Nuremberg Code, and the Declaration of Helsinki.

General Instructions

This non-interventional study is subject to GCP regulations and guidance issued by the Food and Drug Administration (FDA) and are included in, but not limited to, the following parts of the CFR and guideline document:

- 21 CFR Part 11 – Electronic Records
- 21 CFR Part 50 – Protection of Human Subjects
- 21 CFR Part 56 – Institutional Review Boards
- FDA Information Sheets – Guidance for Institutional Review Boards and Clinical Investigators, 1998 Update
- ICH E6 – Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance

The purpose of these regulations and legal obligations is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

- human subjects are provided with an adequate understanding of the possible risks of their participation in this study, and that they have a free choice to participate or not;
- this study is conducted with diligence and in conformance with the protocol in such a way as to ensure the integrity of the findings;
- the potential benefits of the research justify the risks.

16. Appendix C – Investigator Obligations

Per Title 21 of the US Government Code of Federal Regulations (21 CFR) Parts 50 and 56, the study protocol and the final version of the subject ICF will be approved by the IRB before enrollment of any subjects. The opinion of the IRB/EC will be dated and given in writing. A copy of the letter of approval from the IRB/EC and a copy of the approved ICF will be received by CHDI Foundation prior to shipment of study supplies to the Investigator.

The Investigator 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 subjects. The Investigator will also ensure that no changes will be made to the protocol without IRB/EC approval.

As a part of the IRB/EC requirement for continuing review of approved research, the Investigator will be responsible for submitting periodic progress reports to the IRB/EC as applicable.

Written informed consent must be given freely and obtained from every participant prior to study participation. The rights, safety, and well-being of the trial participants are the most important considerations and should prevail over interests of science and society.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s). Study personnel will not include individuals against whom sanctions have been invoked after scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

Protection of Human Subjects (21 CFR Part 50) and Informed Consent

Written informed consent must be obtained from every participant before entry into this study. It must be given freely and not under duress. This consent must be documented by use of an IRB/EC-approved ICF 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. The original copy must be kept in the Investigator's files and made available to CHDI Foundation, Inc. or FDA 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. The ICF must have been reviewed and approved by CHDI Foundation, Inc. and by the Investigator's IRB/EC prior to the initiation of this study. The FDA may reject otherwise scientifically valid studies if proper informed consent has not been obtained from all participants.

Study Documentation

IRB/EC Review/Approval

The protocol and informed consent for this study, including advertisements used to recruit participants, if applicable, must be reviewed and approved by an appropriate IRB/EC prior to enrollment of participants in this study. It is the responsibility of the Investigator to assure 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. A letter documenting the IRB/EC approval which specifically identifies the study/protocol must be received by CHDI Foundation, Inc. prior to initiation of this study. Amendments to the protocol will be subject to the same requirements as the original protocol.

A progress report with a request for re-evaluation and re-approval will be submitted by the Investigator to the IRB/EC at intervals required by the IRB/EC, and not less than annually. A copy of the report will be sent to CHDI Foundation, Inc.

After completion or termination of this study, the Investigator will submit a final report to the IRB/EC and to CHDI Foundation, Inc., if required. This report should include: deviations from the protocol, the number and types of participants evaluated, the number of participants who discontinued (with reasons), results of this study, and should comply with IRB/EC requirements.

Study Files

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

Due to the nature of this pre-testing, non-interventional, minimal risk study only specific essential documents will be filed, including but not limited to: IRB/EC submissions and approval letter, IRB/EC approved documents: protocol, ICF, scale and interview guides (and queries, if applicable); IRB composition, Protocol Signature Page, training log, enrollment log (indicating study participants), delegation log, CV & medical license (if applicable) of the Investigator, co-investigators, raters and other study personnel, as appropriate, correspondence regarding this study and signed ICFs.

Patient Confidentiality

The anonymity of participating participants must be maintained. Participants will be identified by the HDGEC participant Research ID number and the letter P (for HDGEC participant) or C (for companion) on study documents submitted to the University of Texas,

Health Science Center and clinical monitor, as required. Documents that will be submitted to the clinical monitor and that identify the participant (e.g., the signed informed consent document) must be maintained in strict confidence by the Investigator, except to the extent necessary to allow auditing by the FDA, the clinical monitor, or CHDI Foundation, Inc. personnel, representatives and agents.

All information regarding the nature of the proposed investigation provided by CHDI Foundation, Inc. to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the participant, or the FDA) must be kept in confidence by the Investigator.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant data. By signing the protocol, the institution and Investigator commit to complying with all related applicable international and local laws and regulations as well as any applicable Safe Harbor privacy principles.

17. Appendix D – FuRST2.0 Draft Scale:

Draft FuRST 2.0

ver. 02June2015

June 2, 2015

Instructions:

This questionnaire will ask you about your daily activities.

There are questions about many different activities you may do. Most people can do things better at some times than others. We are interested in how you usually do. Please consider your usual day-to-day activities over the past two weeks, including today. Choose the answer that best describes you most of the time. For example, if you do not have problems doing an activity, simply mark 0 - None: Normal. No problems.

Please read each question carefully and consider all of the answers before deciding which answer is best for you.

You may have other medical problems that can impact your day-to-day activities. Do not worry about separating the effects of these problems. Just answer the question with your best response that describes your ability to do each activity.

Use only 0, 1, 2, 3, 4 for answers, nothing else. Do not leave any answers blank.

This questionnaire is for you to complete, either alone or with your caregiver.

Thank you for taking time to complete this questionnaire.

Who is filling out this questionnaire (check the best answer):

____Patient ____Caregiver _____Patient and Caregiver together

1. Over the past two weeks, how well are you communicating with other people? (For example, joining in conversations or staying in touch by telephone, texting or email)

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from doing these activities**.

2. Over the past two weeks, how well are you able to work around the house or at your job? (For example, not making mistakes or finishing everything you wanted to get done)

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from doing these activities**.

3. Over the past two weeks how well are you managing your finances? (For example, being careful using your money or keeping track of how much money you have or paying your bills)

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from doing these activities**.

4. Over the past two weeks how well are you handling your cash or credit cards? (For example, remembering pin numbers, finding your credit cards or taking money out of your pocket, wallet or handbag easily)

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from doing these activities**.

5. Over the past two weeks how well can you get started doing the activities you usually do?

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from starting these activities**.

6. Over the past two weeks, how well can you plan your day-to-day activities?

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from planning activities**.

7. Over the past two weeks how well are you getting around? (For example, getting around in a car, bus or train, or knowing how to get somewhere)

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from doing these activities**.

8. Over the past two weeks how well are you walking? (For example, feeling steady on your feet, going up or down stairs or walking smoothly)

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from doing these activities**.

9. Over the past two weeks how well are you doing your hobbies or other activities you enjoy?

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from doing these activities**.

10. Over the past two weeks how well are you using your hands? (For example typing, writing, turning pages, using a knife, picking things up, carrying a full cup, or turning a key)

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from doing these activities**.

11. Over the past two weeks how well are you talking? (For example, saying what you mean to say or having others understand what you are saying)

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from doing these activities**.

12. Over the past two weeks how well are you able to stay clean and neat? (For example, bathing, combing your hair, doing makeup, shaving, brushing teeth, or cutting your nails)

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from doing these activities**.

13. Over the past two weeks how well are you able to change your clothes or get dressed? (For example, standing on one foot to put on underclothes or pants, do up buttons and zippers, put on jewelry or tie your shoe laces)

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from doing these activities**.

14. Over the past two weeks how well are you keeping to your daily routine? (For example, getting up, going to bed or eating meals at your usual times)

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from doing these activities**.

15. Over the past two weeks how well are you getting to work or appointments on time?

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from doing these activities**.

16. Over the past two weeks how well are you keeping your home, garden or car clean?

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from doing these activities**.

17. Over the past two weeks how well are you able to do exercises you want to do? (For example, walking, jogging, swimming, or playing a sport)

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from doing these activities**.

18. Over the past two weeks how well are you able to keep interested in what's going on? (For example, listening to news, reading a paper or searching the Internet for updates in world affairs, sports, weather)

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from staying interested in these activities**.

19. Over the past two weeks how well are you able to control your temper? (For example, not getting into more arguments than usual or not getting more irritated)

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from controlling my temper**.

20. Over the past two weeks have you had trouble with your sexual interests or function?

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from doing these activities**.

21. Over the past two weeks how well are you able to drive a car?

(For example, controlling your speed or steering)

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from doing these activities**.

22. Over the past two weeks how well are you able to sleep normally? (For example, sleeping through the night or staying awake during the day)

0 Normal. No problems.

1 Slight: I notice some problems, but they cause **no real difficulty**.

2 Mild: These problems cause only **a few difficulties.**

3 Moderate: These problems cause **more than a few difficulties.**

4 Severe: These problems cause **a lot of difficulty** or **prevent me from sleeping normally**.

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