



PREDICT-HD

CRF COMPLETION GUIDELINES

Principal Investigator:

**Jane S Paulsen PhD
University of Iowa
Departments of Psychiatry, Neurology,
Psychology and Neurosciences
Iowa City IA, 52242
United States**

Roland Zschiegner
Jeremy Bockholt
Jane Paulsen
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INTRODUCTION

This document provides a historical look at the guidelines provided for Case Report Form (CRF) completion in the PREDICT-HD study. The study is divided into two parts. The first part is considered the 1.0 study or the 1st half of the study (funded by the original and the first renewal of NIH NS040068) and the second part is considered the 2.0 study or the 2nd half of the study (funded by the second renewal of NIH NS040068). The 1.0 study collected data from 2002 through the beginning of 2009. The 2.0 study started collection in 2009 and went through 2014 for the majority of the sites with only The University of Iowa collecting supplemental data for one of 12 funded ancillary studies from 2014 to 2017 as there were three years of ancillary funding programmatically linked to the PREDICT-HD parent study through NIH.

This document is divided into sections that correspond to the conceptual domains collected by CRFs in PREDICT-HD. Other domains that were not driven by case report forms, such as Biomarkers and Imaging, are also included with details on how the sample/image was collected. The domains that are contained in this document are Cognitive, Demographics/Medical History/Genetics, Functional, Motor, Psychiatric, Biomarker, and Imaging. Each section provides a description of each measure (if applicable), citations of measure publication, specific methods implemented in PREDICT, and training instructions. Where applicable, training documentation for both 1.0 and 2.0 study sections is provided, particularly when there was variation in training. Further information can also be found in the protocol document.

2001-2009 1.0 STUDY CRF OVERVIEW

CASE REPORT FORM INSTRUCTIONS

GENERAL DESCRIPTION OF CASE REPORT FORMS (CRFS)

The Schedule of Activities details the activities required at each visit (see Section II for the Schedule of Activities). The first page of the CRF binder (Schedule of CRF Completion) lists the CRFs to be completed at each visit.

The CRFs are printed on 2-part or 3-part (depending on the form), no-carbon-required (NCR) paper. Each page has a form name consistent with its content. The CRF pages are not paginated but have 'level' numbers that correspond to the Schedule of CRF Completion. Designated pages have "sign off" and/or "staff code" sections that must be completed by site staff indicated.

CRF Distribution

Sites will be mailed a sufficient number of CRF binders for each study participant, as well as extra screening/baseline packets. These extra pages should be used as replacements in a binder when a study participant is screened but does not proceed to enrollment. Site staff should monitor CRF supplies and submit a CRF Order Form to order additional quantities as needed. *Please allow one week for delivery.*

Submitting CRFs to the CTCC

The sites are responsible for submitting the top white copy of the CRFs to the Clinical Trials Coordination Center (CTCC) at the University of Rochester by regular mail. The yellow copy of each form is to be retained in the binder. If corrections need to be made after the white copy has been submitted to the CTCC, corrections should be made on the yellow copy and a photocopy of that page will be sent to the CTCC.

It is preferable that all forms from a given visit be submitted at the same time. Please include photocopies of requested logs at each visit even if there are no additions or revisions. **If a participant misses a visit, the Signature Form for that visit still needs to be completed and submitted to the CTCC. Please note: The Project Coordinator must be called if a participant misses a visit.**

After each visit, the 2-part CRF Transmittal Log (See Appendix IV) should be completed. The top white copy should be included in the mailing envelope with the CRF's for that visit, and a copy retained at the site. Only those CRFs actually being submitted with the log should be checked off. If any CRFs from the visit are temporarily held at the site, these should be recorded on the yellow copy of the Transmittal Log when they are submitted later. A photocopy of the yellow copy should be sent to the CTCC with any corrections. The original yellow copy should be retained at the site.

Pages of a given CRF should be arranged in numerical order by "level" number. The CRFs should be placed in the mailing envelope in the order listed on the log. Because the CTCC coordinates multiple trials, it is

essential that all envelopes mailed to the CTCC list the name of the trial. Pre-printed labels for this purpose will be supplied to sites by the CTCC (see Appendix IV).

Timeframe for Submitting CRFs

In order to maintain an accurate and up-to-date database, CRFs (except Cognitive testing) for Screening/Baseline and all subsequent visits must be completed and sent to the CTCC by surface mail within one week of the scheduled visit. PREDICT CRFs for the Cognitive testing only should be sent to the University of Indiana by Fed-Ex ground mail (or equivalent) within one week of the scheduled visit.

Sites should retain any signed consent forms for those participants who do not continue past the screening/baseline visit.

Log of Investigators, Staff, and Study Related Duties

Any person recording data on the case report form MUST enter their staff code, print and sign their name, and list their role in the study on the Staff/Study Related Duties Log (see Appendix IV). A copy of this page needs to be returned to the CTCC at the beginning and end of the study.

Overview of Data Processing at the CTCC

When completed CRFs are received, CTCC staff will date-stamp the forms, log them into the database as received, and send them out for data entry. Automated error checking will be routinely conducted on the database. Site Coordinators will receive a Data Clarifications Worksheet (see Appendix IV) approximately every 4 – 6 weeks to report any possible errors. Coordinators will also receive a Missing Forms Report (see Appendix IV) approximately every 6 weeks to serve as a reminder that outstanding forms need to be submitted.

Data Clarification Process

Data Clarification Worksheets (see Appendix IV) will be routinely prepared by the CTCC and mailed to the coordinator for a prompt response. Directions for addressing clarifications will accompany the reports. If corrections to the CRF are required, they should be made to the yellow copies of the CRF, initialed and dated. After corrections are made, a photocopy of the corrected yellow copy of the CRF should be sent to the CTCC, along with the top copy of the data clarification worksheet. The bottom copy of the Data Clarification Worksheet should be retained at your site in the CRF binder. The signature of the investigator and date is required on the Data Clarification Worksheet to verify that he/she has reviewed and agrees with the corrections.

GENERAL DIRECTIONS FOR COMPLETION OF CRFs

Legibility

For the benefit of data entry, print legibly and use a black pen. Remember that you must press hard when completing the original to make (two) legible copies beneath. Each participant CRF binder contains a card stock sheet that should be inserted between page sets to avoid marking through to the next page set.

Missing Data

All data fields on the form must be completed.

Use "U" anytime a response is unavailable or unknown. For example, if an interruption occurs during the Baseline Visit and the participant's pulse is inadvertently not taken, enter "U" in the box for "pulse". **Whenever "U" is used**, an explanation of the unavailability of the data should be included in the comment section and source documentation. NOTE: This should only be used when indicated on the form.

Use "N" anytime a question is not applicable in the given situation. For example, questions regarding childbearing status would not apply to a male participant. NOTE: This should only be used when indicated on the form.

If the space provided for a response is more than a single box, enter "U" or "N" in the leftmost space and draw a line through any remaining spaces, e.g.,

U		

Right Justifying Data

Numeric fields (numbers) must be right justified, i.e., the last digit of the number must be entered in the rightmost space. Unnecessary spaces to the left should be filled with zeros. For example, the number 98 would be recorded as

Right

0	0	9	8
---	---	---	---

 justified

Dates

Dates should be filled out in the format MM-DD-YEAR (month-day-year).

PLEASE NOTE: All dates should be written with 4 digits in the year, e.g., 06/30/2001.

Days and months that only have one digit should be preceded with zeros. For example, September 1, 2001 should be written as

0	9	0	1	2	0	0	1
---	---	---	---	---	---	---	---

If the day or month is not known, fill the appropriate date fields with "UU", (except for Reportable Events (RE's), which require entry of a complete date) i.e.,

0	9	U	U	2	0	0	1
---	---	---	---	---	---	---	---

Decimal Points

If a decimal point is pre-printed on the form, enter the data around the decimal point, filling any blank spaces with a zero. For example, 9.3 would be entered as

0	9	.	3	0
---	---	---	---	---

Time

All times should be recorded in the 24-hour clock format (e.g., 7 PM = 19:00).

1	9	:	0	0
---	---	---	---	---

Visit Number

- Use **01** for Visit Screening/Baseline (Visit 1), **02** for Visit 2, and so on
- Use **UN** for unscheduled visits.

Participant ID Number

Participants who meet **all** of the eligibility criteria and are enrolled in the study will be assigned a participant number at the screening/baseline visit (Visit 1) during the enrollment call to the CTCC. This number is required on all visit forms.

Companion ID Number

Each participant will be required to bring a companion to each visit. The sites will assign that companion a number beginning with the letter “C” followed by 01, 02, 03 etc. For example, the companion at a participant’s visit 1 will be assigned the number C – 01. If the companion is the same person throughout each participant visit, they will keep that number. It is only necessary to change the companion number when the companion changes. For example, if a participant brings a different person to Visit 2, then the companion number would be “C – 02”. Once the number is assigned to a companion, that particular companion will always be referred to by that number. (Companion Joe Smith was at Visit 1 and was assigned “C – 01” and that will be his number only. If another companion comes for Visit 2, he/she will be assigned another number, i.e., “C – 02”, and so on). Therefore, if the companion at Visit 1 is the same as the companion at Visit 3, there is no need for a new assignment number for that companion (you would use the companion’s originally assigned number of “C-01”).

Site-Initiated Correction of Mistakes

If you make a mistake while completing a form, draw one horizontal line through the erroneous entry. **Do not erase or use correction fluid (white-out), and do not write over or obliterate the original response.** Write the correct response directly **above** the original if possible. If there is not room above, put the corrected entry to the side or bottom of the original response. These instructions apply to the participant and companion.

Each correction must be initialed and dated by the staff member making the correction. **Initial and date** the correction in such a way that your initials and the date will not be misinterpreted as being part of the corrected entry. Participants and companions will use a date only – NO INITIALS.

All persons entering data on the CRFs must fill out the Staff/Study Related Duties Log (see Appendix IV). Your site monitor will review this at each visit and provide updated copies to the CTCC. Please be sure to update it as staff changes occur.

2009-2014 2.0 STUDY

DATA ACQUISITION

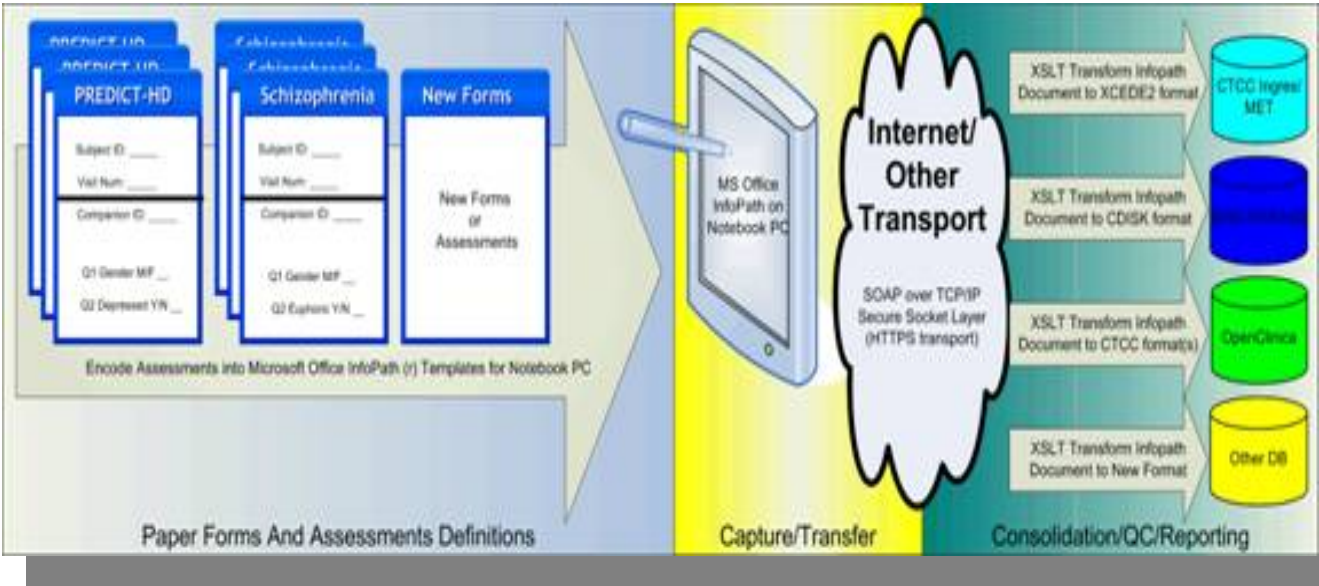
The Electronic Data Capture Services (EDCS) are designed to improve the quality, timeliness, and flexibility of capturing and reporting research information. The software used for the EDCS is a combination of Microsoft Office InfoPath[®], a customized data and communications manager client, and an Apache Tomcat based SOAP server. Some of the advantages of the system include: 1) Forms can be completed on a notebook PC or desktop PC; 2) In the event of a network outage forms are saved locally and can be retransmitted at a later date; 3) Microsoft InfoPath can support multiple languages and produces a standards-based XML form as its' output.

Participating sites will be provided two notebook PC's running Microsoft Windows operating system. Coordinators/Users will require approximately 2-3 hours of training on form completion and another 2-3 hours of training on the proper use of a notebook PC*.

Predict HD assessments and forms will be entered directly on a tablet type Personal Computer (PC) using a writing stylus. Primary data transfer will occur via a secure internet connection to Simple Object Access Protocol (SOAP) WEB Services to the Clinical Trials Coordination Center at The University of Rochester in New York for inclusion into the Predict HD data repository. A second data transfer will occur to a secure SOAP web service at the University of Iowa for archival purposes in standard XML formatted documents on a secure file server.

**Details outlining Electronic Data Capture and proper usage of notebook PC can be located on Share Point website.*

DATA ACQUISITION FLOW



SECTION 1: COGNITIVE

OVERVIEW OF CHANGES TO THE PREDICT-HD COGNITIVE BATTERY

This section provides an overview of changes in the cognitive battery over the course of the Predict-HD study - from the start of the project through the end of PREDICT-HD. As this project developed, we maintained the test measures that showed the greatest sensitivity, whilst test measures that showed less sensitivity or were deemed redundant or infeasible were excluded from the battery. In addition, some individual tests were also changed to provide greater sensitivity and/or efficiency. This overview is divided into two sections: Section 1 documents which tasks were added/dropped over this period (either from the battery as a whole, or from selected participant visits) and Section 2 documents changes that have been made to individual tests within the battery.

SECTION 1: CHANGES TO THE COGNITIVE BATTERY

The Predict-HD cognitive battery has had four 'life-stages' across the course of the project, in which tests were added or dropped. Table 1 shows which cognitive tasks were included in the Predict-HD battery in which participant visits (1-7), throughout the course of Predict-HD.

Stage 1: Start of Project to July 2006

All sites administered the same battery of 23 cognitive tasks, 18 of which were administered on the first visit. The 3 UHDRS tests (SDMT, Verbal Fluency and Stroop) were administered on every visit (1-5); other tasks were administered biennially (most on visits 1, 3 and 5; others on 2 and 4). Exceptions were the Dual Verbal Working Memory task (Numbers) which has strictly been administered only on Visit 1, and Categories, which was administered with a counterbalance on condition (implicit v explicit) on Visits 2-5.

Stage 2: August 2006 to March 2008

This stage is identical to Stage 1 with the following exceptions: 1) Shifter was excluded from the battery because of copyright issues (last administration: 7/25/2006), and 2) Visit 6 started up (absent an approved IRB protocol for Visit 6) using only 10 core tasks. Seven were included because they were the most sensitive to disease status/progression. These included SDMT, Stroop, Trails, Smell ID, Tapper, and Emostatic. ANART was retained as the IQ estimate and Verbal Fluency was included not because it was particularly sensitive but because it is part of the UHDRS.

Stage 3: March 2008 to Predict 2.0 approval

In March 2008, a number of changes were made to the battery as hardware was transitioned from the large desktop computer to a tablet. Additionally, baseline data had been analyzed on every measure to help make decisions about which tasks would be maintained in a shortened battery being designed for eventual application to clinical trials. To assure smooth transition of hardware and software updates, all changes were first conducted at Iowa only. Amendment 5 was only approved at the Iowa site. For the Iowa site, the Amendment 5 shortened battery was administered on every visit. The tasks in the Amendment 5 shortened battery were the 10 tasks administered at

Visit 6 prior to March 2008 plus HVLT was administered only at Visit 1 (because it had nice cross sectional but limited longitudinal sensitivity to disease status/progression.) Other Amendment 5 changes at Iowa included administering Buttons Blocks 1 and 3 only, counterbalanced for block order, and administering Tapper non-dominant speeded tapping and alternating thumbs paced tapping only (i.e., Blocks 2 and 5.) These tapping tasks were chosen after analyses comparing the task conditions for their sensitivity to HD onset and progression.

Studywide information sessions were conducted to inform sites of the planned assessment changes in the third renewal of the grant. Secondary to staff burden and IRB turn-around times, some sites chose to submit changes in a stair-stepped approach as modifications were rolled out to the sites and other sites chose to wait until all changes were finalized before making IRB modification. The data reflects this variation among sites with differences in data obtained throughout the transition. Absent Amendment 5 being routed at any site other than Iowa, about half of the sites received informal IRB approval to cut, but not add, cognitive measures from an IRB approved protocol (i.e., Visits 1-5). Other sites did not receive permission to cut tasks absent an approved IRB amendment, and continued with the Stage 2 Battery. The sites informally approved by their IRBs to shorten the battery also shortened their Visit 1, 3, and 5 batteries. However, these sites could not add tasks to IRB approved Visits 2 and 4 and so they simply cut to those tasks approved for Visit 2 and 4 that were also in the Amendment 5 battery (i.e., the UHDRS cog tasks = SDMT, Stroop, and Verbal Fluency.) Moreover, these sites did not have the upgraded (approved) software versions. A consequence of this transition to updated hardware and software was some variation in battery completion across sites. Some sites used the Visit 5 menu in the software package, some used the Visit 3 menu, and others used some tasks from one menu and other tasks from others. It is worth noting that none of these sites would have been able to run the counter balancing of Buttons; most did not skip Block 2 of Buttons or Blocks 1 and 3 of Tapper; and they could not run the fast condition of Paced Tapping.

Stage 4: Protocol 2.0 (from June 2009)

The Protocol 2.0 cognitive battery began rolling out at sites 15 June 2009. Sites converted to the 2.0 battery as soon as possible using their tower computers until they received tablet computers and tablet computer training. Sites that did not yet have IRB approval for Protocol 2.0 missed or delayed some visits as the old tower computers were retired on 1 October 2009.

The tasks included in the Protocol 2.0 battery are identical to those included in the shortened Stage 3 battery with some exceptions: Verbal Fluency was excluded and the ANART was administered only at Visit 1 to obtain an estimate of premorbid intelligence. As in Stage 3, HVLT was administered only at Visit 1. After rollout, it was quickly determined that computer programming of the revised Buttons and Chooser tasks were inconsistent due to using the touchscreen (see Note below) as a method of data input. A decision was made at that time to eliminate these tasks from the Protocol 2.0 battery.

Note: The Tasks Buttons and Chooser had an issue of non-responsiveness in the problem. Sites were instructed not to administer Buttons and Chooser tasks to reduce frustration in participants and to record 'computer problems' in the comments for these 2 tasks. Buttons and Chooser were administered on the tablet at a small number of sites from 15 June 2009 to 20 August 2009; however, given the erratic non-responsivity issues, this data was deemed unusable, and the tasks were discontinued.

Dr. Stout chose to step down from the study. Cognitive oversight of the PREDICT-HD study was transferred to Holly Westerveld (Brown University) for all cognitive training as well as quality control/quality assurance of all cognitive data. Under Dr. Westerveld's leadership, all PREDICT-HD cognitive raters were re-trained and certified on an annual basis to reinforce their standardization of objective cognitive assessments and to maintain quality control of data. An annual video of staff administration was required.

SECTION 2: CHANGES TO INDIVIDUAL COGNITIVE TESTS WITHIN THE BATTERY

The following section documents changes that have been made to trials and blocks within individual cognitive tasks. In cases where the number of items or the number of trials/blocks was reduced, the most sensitive items (upon cross-sectional and longitudinal analysis) were retained, and other items were eliminated because they were largely redundant with the retained variables. 'Year' (of data collection) and 'Visit' are denoted in bold to reduce confusion between the two.

Tapper

1) Starting at **Year 3** of data collection:

In an effort to shorten the **Visit 3** battery, the number of trials in Blocks 4 and 5 was reduced from 6 correct out of a maximum of 12 chances to 5 trials total (a minimum of 5 and a maximum of 5). The number of trials in **Visit 1** data collection was kept the same so that we could continue to collect consistent baseline data.

2) Beginning **Year 6** of data collection

Blocks 1, 3, and 4 (dominant finger speeded tapping, alternate thumbs speeded tapping, and dominant finger paced tapping respectively) were dropped. This left Blocks 2 and 5 (non-dominant speeded finger tapping and alternate thumbs paced tapping respectively). Additionally, a faster paced block was added to compare task sensitivity across speeds in Protocol 2.0 upon transition to the tablet computer (Fast = 3Hz; classic 1.8Hz). Finally, the two paced tapping blocks were order counter-balanced by site, with either the fast then slow block on odd visits (and slow then fast on the evens) or the slow then fast block on odd visits (and fast then slow on the evens)

Tower

1. At the beginning of **Year 2** of the data cut

The Towers tasks (3 and 4 disc) tests were divided into 2 different tasks - originally, they were two blocks of one task. When the Tower task was divided into two separate tasks, a data issue arose with the 4-disk version of Tower for both battery software versions 4.1 and 4.2. There was an error that resulted in the data for the variable "Time to First Move" being invalid for the 1st trial only. Because only one variable was affected, and that variable was being ignored in data analysis anyway, the raw data was left intact, but the data for that variable was deleted in all data cuts.

2. At the beginning of **Year 5** of the data cut

For **Visits 1, 3, and 5**, the Tower task's practice modes were changed. We disabled the practice at the beginning of the 4-disk version and reduced the number of disks used in the practice for the 3-disk version (from 3 to 2). The reason we did this was because some examiners were allowing the participant to practice the full 3 disk solution before starting the test and some were not. By reducing to 2 disks for practice, the participant could learn the rule about large disks not stacking on small disks, but not practice the solution in a meaningful way.

Emotions Recognition

1. At the beginning of Year 2

The Emotions (static and dynamic) tests were broken into 2 different tasks -- originally, they were two blocks of one task.

UPSIT

For the Protocol Amendment 5, the UPSIT was reduced from 40 trials to 20 trials. This was based on findings that the 20 trials showed a similar level of sensitivity to the 40 trials.

SYMBOL DIGIT MODALITIES

DESCRIPTION: The Symbol Digit Modalities Test (SDMT) assesses psychomotor speed and working memory. Participants were presented with a key at the top of the page, which paired the digits 1 through 9 with unique symbols, such as X and =. Below the key, they were presented with the symbols, arranged in rows, and they were required to write below each symbol the digit that corresponded to it.

CITATION OF PUBLICATION OF TEST: Smith, A. (1973). Symbol Digit Modalities Test. Los Angeles, CA: Western Psychological Services.

METHODS FOR PREDICT: The symbol digit modality task was initially administered in the 1.0 study for visits 1-5 from September 2002 – July 2006 and then expanded to all visits through the end of the study. In the 1.0 study, there were initially 4 versions of the form (2, 3, 4, 5). For the duration of the 2.0 study, versions 3 and 4 were used at alternating visits.

TRAINING INSTRUCTIONS:

Symbol Digit Modalities Test (SDMT) (Paper/Pencil Task, Table required)

Materials

Response Sheet (for examinee) (Form 2, 3, 4, or 5)
Pencil (for examinee)
Stopwatch
Scoring Template (for examiner)

Description

This is a test of visuomotor integration, involving visual scanning, tracking, and motor speed. The examinee is given 90 seconds to match symbols and digits as quickly as possible. The key (specifying which symbols are assigned to which numbers) is located at the top of the page.

Note: There are four versions of this test and each one presents the stimuli in a different order. The instructions below are to be filled in with the appropriate responses based on the form that your site is using. You will be using a different form each year, so it will not be useful to fill in the blanks listed in the instructions because these will change each year.

Administration

Place the test form on the table in front of the examinee and say,

Please look at the boxes at the top of the page. Each box in the upper row has a symbol in it, and each below it has a number. Now look at the next line of boxes (point to the first line of boxes without numbers). Notice that the boxes on the top have symbols, but boxes beneath are empty. You are to fill in each empty box with the number that goes with each symbol according to the way they are paired at the top of the page. For example, if you look at the first symbol (point to the first symbol in the row beneath the key), and then look up at the key, you see that this symbol is paired with the number

' ____ ' (indicate the correct response and show the pairing). So, you would write a ' ____ ' (state correct response) in this box (write a ' _ ' in the first box). This next symbol (point to the next symbol) is paired with _____. So you would put a ' ____ ' in this box (write ' ____ ' in the second box). Now what number goes in this box (point to the third box)?

The examinee should say ' ____ '. If the examinee's response is incorrect, explain the error.

When the examinee appears to comprehend the task, say,

Good, now for practice, fill in the boxes up to this double line, and then stop.

Immediately correct any errors made during the practice period, explaining the examinee's error. Repeat the instructions and review the correct coding of the practice boxes as necessary until the examinee understands the task. If the examinee is not able to complete any of the practice items or is clearly unable to comprehend the nature of the task, do not administer the remainder of the test.

Continue with the test by saying,

When I say 'Go', write in the numbers just like you have been doing until I say 'Stop.' Remember to work as quickly as you can, moving from one line to the next without skipping any boxes. If you make a mistake, don't erase it. Just write the correct answer over the mistake. Ready? GO!

Start timing. Do not allow the examinee to skip boxes. At the end of 90 seconds, say, **Stop!** Be sure that the examinee does not continue working after the time limit is reached.

Scoring: The score is the number of correct responses in 90 seconds. Use the scoring template to check responses for accuracy. Do not include the practice items in the total score. Remember to record the Form # on the Cognitive Assessment Summary Sheet (2, 3, 4, or 5).

Symbol Digit Modalities Test (Symbol Digit)

(Paper/Pencil Task, Table required)

Materials

Response Sheet (for participant) (Form 3 for odd numbered visits; Form 4 for even numbered visits)
Pencil (for participant)
Stopwatch
Scoring Template (for examiner)

Task Description

This is a test of visuomotor integration, involving visual scanning, tracking, and motor speed. The participant is given 90 seconds to transcribe matching symbols and digits as quickly as possible. The key (specifying which symbols are assigned to which numbers) is located at the top of the page.

New for 2.0!

NOTE: There are two forms of this test that will be administered at alternating (odd vs. even) visits. The “code” (symbols paired with the numbers) is different for each form. The blanks (i.e., ‘__’) in the instructions below are to be filled in with the appropriate responses based on the form that is being used at this visit.

Administration

Place the test form on the table in front of the participant and say,

Please look at the boxes at the top of the page. Each box in the upper row has a symbol in it, and each box below it has a number in it. Now look at the next line of boxes (point to the first line of boxes without numbers). **Notice that the boxes on the top have symbols, but the boxes beneath are empty. You are to fill in each empty box with the number that goes with each symbol according to the way they are paired at the top of the page. For example, if you look at the first symbol** (point to the first symbol in the row beneath the key), **and then look up at the key, you see that this symbol is paired with the number „_____“** (indicate the correct response and show the pairing).

So, you would write a ‘_____’ (state correct response) **in this box** (write a ‘__’ in the first box). **This next symbol** (point to the next symbol) **is paired with _____**. **So, you would put a ‘_____’ in this box** (write ‘_____’ in the second box). **Now what number goes in this box** (point to the third box)?

The participant should say ‘_____’. Have the participant write in the response. If the participant’s response is incorrect, explain the error.

When the participant appears to comprehend the task, say,

Good, now for practice, fill in the boxes up to this double line (point to the double line), and then stop.

Immediately correct any errors made during the practice period, explaining the participant's error. Repeat the instructions and review the correct coding of the practice boxes as necessary until the participant understands the task. If the participant is not able to complete any of the practice items or is clearly unable to comprehend the nature of the task, do not administer the remainder of the test.

Continue with the test by saying,

When I say 'Go', write in the numbers just like you have been doing until I say 'Stop.' Remember to work as quickly as you can, moving from one line to the next without skipping any boxes. If you make a mistake, don't erase it. Just write the correct answer over the mistake. Ready? GO!

Start timing. Do not allow the participant to skip boxes. At the end of 90 seconds, say, **Stop!** Be sure that the participant does not continue working after the time limit is reached.

Scoring: The score is the number of correct responses in 90 seconds. Use the scoring template to check responses for accuracy. Self-corrected errors are included in the total score as correct responses. Do not include the practice items in the total score. Remember to record the Form # in the tablet eCAS

STROOP COLOR WORD TEST

DESCRIPTION: The Stroop Task assesses processing speed and executive functions. Participants rapidly name colors (Color naming condition), read color names (Word reading condition), and finally name colors while inhibiting the dominant reading response (e.g., correct response to the word “blue” printed in red ink is “red”; Interference condition).

Color Naming - Participants rapidly name the colors of red, green, and blue patches presented on a card for 45 seconds.

Word Reading - Participants read the words red, green, and blue printed in black ink for 45 seconds.

Interference - Participant’s name colors while inhibiting the dominant reading response (e.g., the correct response to the word “blue” printed in red ink) for 45 seconds.

CITATION OF PUBLICATION OF TEST: Stroop, J. R. (1935). [Studies of interference in serial verbal reactions](#). Journal of Experimental Psychology: General, 18(6), 643-662

METHODS FOR PREDICT: The Stroop Color Word Test was administered at every visit throughout the entire study. Participants are given 45 seconds for each test to get as many correct responses as possible. All correct responses were counted with incorrect responses removed leaving the raw score of the task.

TRAINING INSTRUCTIONS:

Stroop Test (Stroop) (*Paper/Pencil Task*)

Materials

Three stimulus cards
Record Form (for examiner)
Stopwatch

Description

This is a test of cognitive flexibility, ability to suppress a habitual response in favor of an unusual one, and selective attention. This test has three parts. First, the examinee names the colors of boxes (red, green, or blue). Next, the examinee reads the names of the colors (“red,” “green,” “blue”) that appear in black print. Finally, the examinee responds to the interference card in which the words are printed in non- corresponding color (e.g., “red” printed in blue ink) with the instructions to ignore the printed words and report only the color of ink in which each word is printed.

Administration

Color Blind Screening: Before starting the Stroop test, you must check the examinee’s ability to discriminate the three colors. Hold the card with the colored rectangles and point to a Red rectangle saying,

Tell me the name of this color.

Repeat with a Blue rectangle and a Green rectangle.

If the examinee is unable to discriminate the colors (Red and Green in particular) discontinue the test.

If the examinee is able to discriminate between the colors, but names a color other than red, blue, or green (i.e., purple for blue), indicate to the examinee that the three colors used in the test are red, green and blue.

If the examinee is able to discriminate the colors but is unable to properly name the colors even after corrected, terminate this test.

If the examinee indicates that he/she is color blind, terminate the test.

Color Naming: Hand the card with the colored rectangles to the examinee and say,

Please look at the boxes in the top line, and name the color of each box, going from left to right; either red, green, or blue.

Continue by pointing to the second line and say,

Begin here and go across the rows from left to right without skipping any. Tell me the colors as quickly as you can. If you finish all the rows before I tell you to stop, immediately start over at the beginning (point to the first rectangle in the test section). GO!

Begin timing and follow along on the Record Form titled 'Stroop Test – Color Naming Card'. Circle any errors and do not count these items in the total score. Say, **stop** after 45 seconds and draw a line on the Record Form after the last item completed by the examinee. If the examinee finished the full page and started over, mark the last item completed and indicate that he/she was working on a second pass.

Scoring: Count the total number of colored blocks correctly named.

Word Reading: Hand the card with the color names printed in black to the examinee and say,

Please read across the top line, telling me the words you see.

If an examinee is truly unable to read the words, discontinue the test. Continue by pointing to the second line and say

Begin here and go across the rows from left to right without skipping any. Tell me the words you see, as quickly as you can. If you finish all the rows before I tell you to stop, immediately start over at the beginning (point to the first word in the test section). GO!

Begin timing and follow along on the Record Form titled ‘Stroop Test – Word Reading Card’. Circle any errors and do not count these items in the total score. Say, **stop** after 45 seconds and draw a line on the Record Form after the last item completed by the examinee. If the examinee finished the full page and started over, indicate the last item completed and that he/she was working on a second pass.

Scoring: Count the total number of words correctly read.

Interference Task: Hand the card with the words printed in different colors to the examinee. Say,

This card has words written in colored ink, but you can see that each word is in the wrong color of ink. For example, here the word ‘Red’ is written in blue ink (point to the first words of the top line), and here the word ‘Green’ is written in red ink (point to the second word of the top line). Please read across the top line, telling me the color of ink that each word is written in. Ignore the words; just tell me the color of ink you see.

Some examinees may be slow to acquire the necessary “cognitive set” and will read the word instead of reporting the ink color. Additional review of the instructions to name ink colors and not read the words may be necessary. Should the examinee fail to show an understanding of the task after several attempts, discontinue the task. Note, however, that most examinees will make one or two errors on the practice line as they acquire the proper “test set.” Do not consider such minor slips to be indicative of failure to comprehend the task.

When it is clear that the examinee understands the task (even if he/she cannot do it flawlessly), continue by pointing to the second line and say,

Begin here and go across the rows from left to right without skipping any. Remember to ignore the words, and simply tell me the colors of ink that you see. GO!

Begin timing and follow along on the Record Form titled ‘Stroop Test – Interference Card’. Circle any errors and do not count these items in the total score. Say, **stop** after 45 seconds and draw a line on the Record Form after the last item completed by the examinee.

Scoring: Count the total number of colors correctly identified.

Stroop Color Word Test (Stroop) (*Paper/Pencil Task*) (*2.0 administration*)**Materials**

3 stimulus cards (color, word, and interference cards) Record
Form (for examiner)
Stopwatch

Description

This is a test of cognitive flexibility, ability to suppress an overlearned response, and selective attention. This test has three parts. First, the participant names the colors of boxes (red, green, or blue). Next, the participant reads the names of the colors ("red," "green," "blue") that appear in black print. Finally, the participant responds to the interference card in which the words are printed in a non-corresponding color (e.g., "red" printed in blue ink) with the instructions to ignore the printed words and report only the color of ink in which each word is printed.

Administration

Color Blind Screening: Before starting the Stroop test, you must check the participant's ability to discriminate the three colors. Hold the card with the colored rectangles and point to a red rectangle saying,

Tell me the name of this color.

Repeat with a blue rectangle and a green rectangle.

If the participant is unable to discriminate the colors (red and green in particular), discontinue the test.

If the participant is able to discriminate between the colors, but names a color other than red, blue, or green (i.e., purple for blue), indicate to the participant that the three colors used in the test are red, green, and blue.

If the participant is able to discriminate the colors but is unable to properly name the colors even after corrected, terminate this test.

If the participant indicates that he/she is color blind, terminate the test.

Note this on the observation form that the test was discontinued, and the reason for terminating the test.

Color Naming: Hand the card with the colored rectangles to the participant and say,

Please look at the boxes in the top line, and name the color of each box, going from left to right; either red, green, or blue.

Continue by pointing to the second line and say,

Begin here and go across the rows from left to right without skipping any. Tell me the colors as quickly as you can. If you finish all the rows before I tell you to stop, immediately start over at the beginning (point to the first rectangle in the test section). GO!

Begin timing and follow along on the Record Form titled “Stroop Test – Color Naming Card.” Circle any errors and do not count these items in the total score. If you circle an error and the participant self-corrects the error, be sure to identify this as a self-corrected error by marking it with “SC”. Say, **stop** after 45 seconds and draw a line on the Record Form after the last item completed by the participant. If the participant finished the full page and started over, mark the last item completed and indicate that he/she was working on a second pass.

Scoring: Count the total number of colored blocks correctly named and record in the tablet eCAS. Self-corrected errors are included as correct items in the total score.

Word Reading: Hand the card with the color names printed in black ink to the participant and say,

Please read across the top line, telling me the words you see.

If the participant is truly unable to read the words, discontinue the test. Continue by pointing to the second line and say,

Begin here and go across the rows from left to right without skipping any. Tell me the words you see, as quickly as you can. If you finish all the rows before I tell you to stop, immediately start over at the beginning (point to the first word in the test section). GO!

Begin timing and follow along on the Record Form titled „Stroop Test – Word Reading Card“. Circle any errors and do not count these items in the total score. If you circle an error and the participant self-corrects the error, be sure to identify this as a self-corrected error by marking it with “SC”. Say, **stop** after 45 seconds and draw a line on the Record Form after the last item completed by the participant. If the participant finished the full page and started over, indicate the last item completed and that he/she was working on a second pass.

Scoring: Count the total number of words correctly read and record in the tablet eCAS.

Self-corrected errors are included as correct items in the total score.

Interference Task: Hand the card with the words printed in different colors to the participant. Say,

This card has words written in colored ink, but you can see that each word is in the wrong color of ink. For example, here the word 'Red' is written in blue ink (point to the first words of the top line), and here the word 'Green' is written in red ink (point to the second word of the top line). Please read across the top line, telling me the color of ink that each word is written in. Ignore the words; just tell me the color of ink you see.

Some participants may be slow to acquire the necessary cognitive set and will read the word instead of reporting the ink color. Additional review of the instructions to name ink colors and not read the words may be necessary.

Should the participant fail to show an understanding of the task after several attempts, discontinue the task. Note, however, that most participants will make one or two errors on the practice line as they acquire the proper "test set." Do not consider such minor slips to be indicative of failure to comprehend the task.

When it is clear that the participant understands the task (even if he/she cannot do it flawlessly), continue by pointing to the second line and say,

Begin here and go across the rows from left to right without skipping any. Remember to ignore the words, and simply tell me the colors of ink that you see. GO!

Begin timing and follow along on the Record Form titled „Stroop Test – Interference Card“. Circle any errors and do not count these items in the total score. If an error is circled and the participant self-corrects the error, be sure to identify this as a self-corrected error by marking it with "SC". Say, **stop** after 45 seconds and draw a line on the Record Form after the last item completed by the participant. If the participant finished the full page and started over, indicate the last item completed and that he/she was working on a second pass.

Scoring: Count the total number of colors correctly identified and record in the tablet eCAS. Self-corrected errors are included as correct items in the total score. The participant does not receive credit for skipped or incorrect items; however, there is no penalty for these responses either.

TRAIL MAKING TEST (PARTS A & B)

DESCRIPTION: The Trail Making Test assesses psychomotor speed and executive functions and involves numeric sequencing followed by alternating numeric and letter sequencing

Trail A - participants connected circles containing numbers in ascending numerical order

Trail B - participants connected circles containing numbers and letters by alternating between numbers and letters in ascending order (e.g., 1-A-2-B, etc.).

CITATION OF PUBLICATION OF TEST: Reitan, R. M. (1958). [Validity of the Trail Making Test as an indicator of organic brain damage](#). *Perceptual and Motor Skills*, 8, 271-276

METHODS FOR PREDICT: The Trail Making Test Parts A & B were administered throughout the PREDICT-HD study. From 2002 through July 2006, the Trail Making tests were administered at visits 1, 3, and 5. From August 2007 through March of 2008 the Trail Making Tests were added to visit 6 and from March 2008 through until the 2.0 study, it was added to visit 7 as well. The Trail Making Tests were administered at every visit for the 2.0 study for all sites. The University of Iowa also administered the Trail Making Tests at every visit starting in March 2008 and continued through the end of PREDICT.

TRAINING INSTRUCTIONS:

Trail Making Test (Parts A & B) (*Paper/Pencil task, Table required*)

Materials

Test Forms A & B (for examinee)

Pencil (for examinee)

Record Form (for examiner) Stopwatch

Description

This test involves several cognitive processes including attention, visual search, cognitive flexibility, and sequencing. The task consists of randomly placed numbers (Part A) or numbers and letters (Part B), that the examinee must connect in sequence by drawing a continuous line with a pencil. Each part begins with a brief sample to instruct the examinee.

Administration

PART A

Practice

Place the Part A Sample on the table in front of the examinee and say,

On this page are some numbers. Begin at number one (point to “1”) and draw a line from one to two (point to “2”), two to three (point to “3”), three to four (point to “4”), and so on, in order, until you reach the end (point to the circle marked “END”). Draw the lines as quickly as you can. Ready? Begin.

Discontinue and do not proceed to the test if the examinee clearly does not comprehend the instructions or cannot complete the sample.

If the examinee makes a mistake on the Sample for Part A, point it out and help her/him correct it. Then tell the examinee to continue from the last correctly sequenced number. When it is clear that the examinee understands the task, proceed to Part A, Test.

Test

Turn the page over and say:

On this page are numbers from one to twenty-five. Do this the same way. Begin at number one (point), draw a line from one (point) to two (point), two to three (point), three to four (point), and so on, in order until you reach the end (point). Remember to work as quickly as you can. Ready? Begin.

Start timing. If the examinee makes a mistake, point it out immediately, return him/her to the last correct circle, and continue the test from that point. Do not stop timing until the examinee has reached the end. If the examinee does not complete the task within 5 minutes, discontinue the task.

Scoring: Record the time (in seconds) needed to complete the task on the Record Form after the examinee completes the trial. If the test is discontinued after five minutes, enter 300 seconds as the score. Indicate on the Record Form that the task was discontinued and indicate the reason for discontinuation.

Record the number of errors made by the examinee, but do not include self-corrected mistakes in this score. A self-corrected error is defined as a mistake caught by the examinee and appropriately corrected without assistance from the examiner.

PART B

Practice

Place the Part B Sample on the table in front of the examinee and say:

This one is similar, except that it has both numbers and letters. Begin at number one (point to "1") and draw a line from one to A (point to "a"), A to two (point to "2"), two to B (point to "b"), B to three (point to "3"), three to C (point to "c"), and so on, in order, until you reach the end (point to "END"). Ready? Begin.

Monitor the examinee's progress. If the examinee makes a mistake, point it out and help her/him correct it. Proceed to the test when it is clear that the examinee understands and is able to perform the task. If the examinee clearly does not comprehend the instructions or cannot complete the sample, discontinue the task.

Test

Turn the page over and say:

This page has numbers and letters again. Do this the same way, going from one (point to "1") to A (point to "A"), A to two (point to "2"), two to B, (point to B), B to three

(point to 3), **three to C** (point to C), **and so on, until you reach the end. Remember, you have to alternate between numbers** (point to “1”) **and letters** (point to “A”). **Do not skip around but go from one circle to the next in the proper order. Draw the lines as quickly as you can. Begin.**

Start timing. If the examinee makes a mistake, point it out immediately, return him/her to the last correct circle, and continue the test from that point. Do not stop timing until the examinee has reached the end. If the examinee does not complete the task within 5 minutes, discontinue the task.

Scoring: Record the time (in seconds) needed to complete the task on the Record Form. If the test is discontinued after five minutes, enter 300 seconds as the score. As in Part A, indicate the reason for discontinuation. Record the number of errors made by the examinee, but do not include self-corrected mistakes in this score. Remember to record the Form # on the Cognitive Assessment Summary Sheet (i.e., 1 or 2).

Trail Making Test (Parts A & B) (*Paper/Pencil task, Table required*) (2.0 Administration)Materials

Test Forms A & B (for participant)

Pencil (for participant)

Record Form (for examiner)

Stopwatch

Description

This test involves several cognitive processes including attention, visual search, cognitive flexibility, psychomotor speed, and sequencing. The task consists of randomly placed numbers (Part A) or numbers and letters (Part B) that the participant must connect in sequence by drawing a continuous line with a pencil. Each part begins with a brief sample to instruct the participant.

Administration**1. Administer Part A***Practice*

Place the Part A Sample on the table in front of the participant and say,

On this page are some numbers. Begin at number one (point to “1”) **and draw a line from one to two** (point to “2”), **two to three** (point to “3”), **three to four** (point to “4”), **and so on, in order, until you reach the end** (point to the circle marked “END”). **Draw the lines as quickly as you can. Ready? Begin.**

Discontinue and do not proceed to the test if the participant clearly does not comprehend the instructions or cannot complete the sample.

If the participant makes a mistake on the Sample for Part A, point it out and help her/him correct it. Then tell the participant to continue from the last correctly sequenced number. When it is clear that the participant understands the task, proceed to Part A, Test.

Test

Turn the page over and say:

On this page are numbers from one to twenty-five. Do this the same way. Begin at number one (point), **draw a line from one** (point) **to two** (point), **two to three** (point), **three to four** (point), **and so on, in order, until you reach the end** (point). **Remember to work as quickly as you can. Ready? Begin.**

Start timing. Be vigilant, closely monitoring the participant's progress. If the participant makes a mistake, cross out the wrong connection, return him/her to the last correct circle, and continue the test from that point. Correct using a short phrase, such as **(This is wrong, go back to here)**. Do not correct the mistake until the participant actually touches the incorrect circle. If they correct their mistake before this happens, it is "self-corrected" and would not count as an actual error. Prompt them to make their line touch each circle if they are not doing so. Do not stop timing until the participant has reached the end. If the participant does not complete the task within five minutes, discontinue the task.

Scoring: Record the time (in seconds) needed to complete the task in the tablet eCAS after the participant completes the trial. If the test is discontinued after five minutes, enter 300 seconds as the score. Indicate on the Record Form that the task was discontinued and indicate the reason for discontinuation.

Record the number of errors made by the participant, but do not include self-corrected mistakes in this score. A self-corrected error is defined as a mistake caught by the participant and appropriately corrected before an incorrect connection is actually made.

2. Administer Part B

Practice

Place the Part B Sample on the table in front of the participant and say:

This one is similar, except that it has both numbers and letters. Begin at number one (point to "1"), and draw a line from one to

A (point to "A"), A to two (point to "2"), two to B (point to "B"), B to three (point to "3"), three to C (point to "C"), and so on, in order, until you reach the end (point to "END"). Ready? Begin.

Monitor the participant's progress. If the participant makes a mistake, point it out and help her/him correct it and direct them to the correct circle. Proceed to the test when it is clear that the participant understands and is able to perform the task. If the participant clearly does not comprehend the instructions or cannot complete the sample, discontinue the task.

Test

Turn the page over and say:

This page has numbers and letters again. Do this the same way, going from one (point to "1") to A (point to "A"), A to two (point to "2"), two to B, (point to "B"), B to three (point to "3"), three to C (point to "C"), and so on, until you reach the end. Remember, you have to alternate between numbers (point to "1") and letters (point to "A"). Do not skip around, but go from one circle to the next in the proper order. Draw the lines as quickly as you can. Begin.

Start timing. Be vigilant, closely monitoring the participant's progress. If the participant makes a mistake, cross out the wrong connection, return him/her to the last correct circle, and continue

the test from that point. Correct using a short phrase, such as **(This is wrong, go back to here)**. Do not correct the mistake until the participant actually touches the incorrect circle. If they correct their mistake before this happens, it is “self-corrected” and would not count as an actual error. Prompt them to make their line touch each circle if they are not doing so. Do not stop timing until the participant has reached the end. If the participant does not complete the task within five minutes, discontinue the task.

Scoring: Record the time (in seconds) needed to complete the task in the tablet eCAS after the participant completes the trial. If the test is discontinued after five minutes, enter 300 seconds as the score. Indicate on the Record Form that the task was discontinued and indicate the reason for discontinuation.

Record the number of errors made by the participant, but do not include self- corrected mistakes in this score. A self-corrected error is defined as a mistake caught by the participant and appropriately corrected before an incorrect connection is actually made

BENTON FACIAL RECOGNITION (FACES)

DESCRIPTION: The Benton Facial Recognition Test assesses visuoperceptual processing and face recognition abilities. Participants viewed an image of a face (frontal view, with either the full face, a partial $\frac{3}{4}$ face, or in darkened conditions) and then selected, from the six alternatives in the multiple-choice response set, the face that matched the target.

CITATION OF PUBLICATION OF TEST: Benton, A. L., & Hamsher, K. (1978). [Multilingual Aphasia Examination Manual](#). Iowa City: University of Iowa.

Benton AL, B A, Sivan AB, Hamsher KS, Varney NR, Spreen O. [Contributions to Neuropsychological Assessment: A Clinical Manual](#): Oxford University Press; 1994.

<https://www.parinc.com/Products/Pkey/108>

METHODS FOR PREDICT: The Benton Facial Recognition test was administered at visits 1, 3, and 5 throughout the 1.0 study in from September 2002-June 2009. It was discontinued in the protocol in the 2.0 study.

TRAINING INSTRUCTIONS:

Facial Recognition Test (FACES) – Short Form (*Paper/Pencil Task, completed while seated at table*)

Materials Stimulus

Booklet

Record Form (for examiner)

Description

This is a test of visual discrimination specific to facial stimuli. For the first 6 items, the examinee is shown a photograph of a person and asked to select the identical photograph from a group of six photos. For items 7 - 13, the examinee is asked to select 3 photographs of the target person, but this time the test photos show a variety of viewpoints.

Administration

Hand the stimulus booklet to the examinee.

For the first 6 items, use the following instruction.

See this woman (point to the single photograph), show me which of these 6 photos shows the same woman.

For items 7-13, use the following instruction.

See this woman (point to the single photograph), she is shown three times here (point to the page with 6 photos). Show me where she is; find three pictures of her.

Scoring: Place a check mark next to the correct items and circle any errors (on the right side of the Record Form). The score is the number of correct responses (out of 27 possible). Record the score in the appropriate location on the Record Form (SF score _____) and the Cognitive Assessment Summary CRF.

DUAL VERBAL WORKING MEMORY TASK (NUMBERS)

DESCRIPTION: The Dual Verbal Working Memory Task (Numbers) is a computerized task in which the participant views a series of colored numbers on the screen one at a time. The participant is instructed to say the color of each number out loud. At the end of the series, a yellow rectangle appears in the middle of the screen and the participant is asked to recall the numbers in the order in which they were presented. The shortest number series consists of 2 numbers and increases by one number every other trial. The test is discontinued when the participant fails to correctly recall the numbers for both trials of any given number series length.

CITATION OF PUBLICATION OF TEST: Hale, S., Bronik, M. D., & Fry, A. F. (1997). [Verbal and spatial working memory in school-age children: Developmental differences in susceptibility to interference](#). *Developmental Psychology*, 33, 364-371.

METHODS FOR PREDICT: The Dual Verbal Working Memory Task (Numbers) was administered in the PREDICT-HD study at baseline only. Although the task was computerized, the score was recorded on paper. The sum of all correct trials is recorded on the Cognitive Assessment summary form. In addition, the longest number of correctly remembered numbers is recorded. This is the maximum span.

TRAINING INSTRUCTIONS

Dual Verbal Working Memory Task (Numbers)

(Computer Task)

Materials

Computer

Keyboard (examiner only)

Numbers Record Form (for examiner to record responses) Pencil (for examiner)

Description

1. The Numbers Task requires about 8 minutes to administer.
2. General Task Overview:
 - The Numbers Task consists of a maximum of 22 trials
 - Each trial begins with an asterisk in the middle of the screen. When the participant is ready, the experimenter will press the space bar and the asterisk will disappear. A series of colored numbers are then displayed one at a time. The participant is instructed to say the color of each number out loud. At the end of the series, a yellow rectangle will appear in the middle of the screen. The participant will then be asked to recall the numbers in the order in which they were presented.
 - The shortest number series consists of 2 numbers and the longest consists of 12 numbers. The two practice trials and the first two experimental trials consist of 2 numbers each. The number series length will increase by one number every other trial. That is, the 1st and 2nd trials will both have number series of length 2, while the 3rd and 4th trials will have number series of length 3, etc.
 - **Discontinuation Rule** – The task will be discontinued when the participant fails to correctly recall the numbers for **both** trials of any given number series length. For example, if the participant fails to recall the numbers on **both** trials of length 4, the experiment is discontinued. However, if a participant correctly recalls the numbers

for only 1 of the trials with a length of 4, the experiment proceeds to the next trial, consisting of 5 numbers.

3. This is a difficult task and participants are **NOT** expected to complete all 22 possible trials.
4. When the discontinuation criterion has been met, exit the task by pressing the ***Esc*** (***escape***) key on the keyboard.
5. To use the instructions below, please note that all text in *italics* refers to text shown on the touchscreen. All text shown in **bold** refers to instructions that should be read to the participant.
6. If the participant becomes tired or needs a break, allow a short break ***between*** trials – ***not*** in the middle of a trial.

Note: All data for this task is recorded by the experimenter on the Record Form provided

Administration

Numbers Task Instructions

Step 1: Select the task

1. Select from the Computer Task Menu by touching or clicking the mouse on the button labeled *“Start Numbers Task”*
2. A confirmation screen will appear. At this point you may continue by selecting *“Press Here to Continue”* or exit the task by selecting *“Press Here to Return To Main Menu”*.

Step 2: Enter Participant Information

NOTE: All participant information for this task is recorded on the Numbers Record Form by the examiner – information is not entered into the computer.

1. Record the participant’s three-digit identification number.
2. Record the two-digit participant session number (e.g., 01 for Visit 1, 03 for Visit 3)
3. Record the three-digit testing site identification number.
4. Record the date in the form of month/day/year (e.g., 04/17/02 for April 17, 2002)

Step 3: Administer the Practice Trials

1. A text box will appear that reads *“Press the spacebar to begin practice”*. Read the following instructions to the participant:

For this task, you will be viewing several series of colored numbers on the screen. The numbers will be displayed one at a time. As each number is displayed, please say the color of the number out loud. For example, if a blue 7 appears, please say “blue” out loud. When the series of numbers is complete, a yellow box will appear in the middle of the screen. At that time, you will try to recall all of the numbers that you saw and say them aloud in the order they were presented. So, for example, if you see a blue 7, you will say “blue” and then a red 4, you will say

“red”. Then, when the yellow box appears, you will respond by saying ‘7’, ‘4’. At the beginning of each trial, you will see an asterisk on the screen. Since this task requires a lot of concentration, I will ask you to focus on the asterisk and then to say “begin” when you are ready for the next trial to start. Do you have any questions? [address any questions] Let’s try a couple of practice trials. Remember to focus on the asterisk at the beginning of each trial and say “begin” when you are ready.

2. Arrange the Record form on a clipboard so that you are ready to quickly record the participant’s responses. Make sure that the participant is unable to see the record form. Press the space bar and an asterisk will appear on the screen. When the participant says “begin”, press the spacebar again to start the first practice trial. If the participant does not say anything, give a reminder:

Please say “begin” when you are ready to start.

The colors of each number for each trial are listed on the record form – you can monitor the participant’s progress by following along as they say each color aloud. At the end of each trial, record the participant’s response in the column provided. Check for accuracy and record a ‘Y’ for yes or a ‘N’ for no in the “Correct” column on the record form before proceeding to the next trial.

3. If the participant does not accurately complete the first practice trial, review the instructions before continuing to the second practice trial. To continue, press the space bar to display the asterisk and then press the space bar again when the participant says ‘begin’.

Step 4: Administer the Experimental Trials

1. After the second practice trial, press the space bar again and a text box will appear that reads *“Press the spacebar to begin the experimental trials”*. Read the following instructions to the participant:

Now we will begin the test. Although you saw only two numbers during the practice, the string of numbers will get longer throughout the test. It is important to focus on the screen until you see the yellow box. Remember to focus on the asterisk at the beginning of each trial and to say “begin” when you are ready. Do you have any questions before we start? [address questions]

2. Press the spacebar to display the asterisk. Press the spacebar again after the participant says ‘begin’ to start the trial.
3. At the end of each trial, record the participant’s responses and quickly check for accuracy before continuing.
4. Repeat items 2 and 3 (of Step 4) until the discontinuation criterion is met.
5. It may be necessary to remind the participant to state the colors for each trial. This reminder can be given at any time.
6. Failure to correctly respond to **both** trials of a given length (resulting in two scores of ‘N’ in a row **between** bold lines on the record form) satisfies the discontinuation

criterion.

Step 5: Exit the Numbers Task

1. When the discontinuation criterion has been met, read the following to the participant:

Good Job! You are finished with the Numbers Task

2. Press the escape key on the keyboard to exit the Numbers Task and return to the Computer Task Suite menu.

Step 6: Scoring

Add the total number of correct trials (Do not including the two practice trials) and record this sum on the Numbers Record Form and the Cognitive Assessment Summary Sheet. Also, record the Maximum Span, which is defined as the longest series of numbers correctly recalled; only one of the two items at a particular length is required (i.e., if 8 numbers were recalled correctly only one time, the maximum span would be 8).

LETTER NUMBER SEQUENCING FROM THE WAIS-III (LETTER-NUMBER)

DESCRIPTION: The Letter-Number Sequencing subtest of the Wechsler Adult Intelligence Scale-Third Edition was used to assess auditory-verbal working memory. The examiner read a series of numbers and letters, in mixed order. Participants attempted to repeat back the numbers first in numerical order, followed by the letters in alphabetical order. Three trials were presented at each set length (a total of 2 to 8 letters and number), with increasing set sizes across the task.

CITATION OF PUBLICATION OF TEST: Wechsler D. [Wechsler Adult Intelligence Scale-Third Edition, \(WAIS-III\) administration and scoring manual](#). San Antonio, TX: The Psychological Corporation; 1997

METHODS FOR PREDICT: The Letter Number Sequencing from the WAIS-III was administered at visits 1,3,5, and 7. Please see [Wechsler Adult Intelligence Scale – Third Edition Administration and Scoring Manual for more information](#).

TRAINING INSTRUCTIONS

Letter-Number Sequencing from the WAIS-III (Letter- Number)

(Paper/Pencil Task, verbal only, complete while at computer)

These instructions were reproduced from the Wechsler Adult Intelligence Scale – Third Edition, Administration and Scoring Manual (Copyright 1997 by the Psychological Corporation, a Harcourt Assessment Company) with permission from the Psychological Corporation for the purposes of the Predict HD study only. **DO NOT DUPLICATE THESE MATERIALS OR USE FOR ANY OTHER PURPOSE.**

NOTE: Please see Wechsler Adult Intelligence Scale – Third Edition Administration and Scoring Manual to see how PREDICT-HD administered the Letter Number sequencing.

VERBAL FLUENCY TASKS

DESCRIPTION: Phonemic Verbal Fluency asked participants to say as many words as possible beginning with a specified letter within 60 seconds. Two forms of the task were randomly assigned by site, (B, W, R and L, D, T).

CITATION OF PUBLICATION OF TEST: Benton, A. L., Hamsher, K., Varney, N., & Spreen, O. (1983). [Contributions to Neuropsychological Assessment: A Clinical Manual](#). New York: Oxford University Press

METHODS FOR PREDICT: The Verbal Fluency Task was administered at visits 1,3, and 5 until amendment 3 when it was administered at every visit. The Verbal Fluency Task was discontinued at all sites at the beginning of the 2.0 study. Two forms of the task were randomly assigned by site (B,W,R and L,D,T).

TRAINING INSTRUCTIONS

Verbal Fluency (Fluency) (*Paper/Pencil Task, verbal only, complete while seated at computer*)

Materials

Record Form (for examiner)

Description

This is a test of verbal cognitive flexibility and initiation. The examinee is asked to generate as many words as possible beginning with a specified letter. Time allowed is one minute per letter. The words generated by examinee should be recorded verbatim.

Note: There are two forms: BWR and LDT. These will be counterbalanced by site for each visit and the Record Form will indicate the version you are to administer. Be sure to record the form on the Cognitive Assessment Summary Sheet.

Administration Say:

I'm going to say a letter of the alphabet, and I want you to quickly say all the words you can think of that begin with that letter. For example, if I were to say "P", you could say 'purple, park, potato, etc. However, you are not allowed to say proper nouns, such as 'Patricia' or 'Pittsburg' Also, do not use the same word again with different endings, such as 'park, parking, and parked'. Keep trying until I say stop. You'll have one minute for each letter. Any questions? Your first letter is _____. Start!

Begin timing. Write down all words given by examinee in the order they are produced, even if they are incorrect or repetitions. Note that the Record Form contains 15 second blocks, record responses according to these time blocks. Should the examinee give up before the end of the minute, encourage him/her to generate more words. If the examinee is silent for more than 15 seconds, say, **Remember, tell me more words that begin with the letter _____**(and tell them the letter). Stop the examinee at the end of one minute.

For the 2nd letter, continue by saying,

Now, I would like you to tell me all the words you can think of that start with the letter_.

If necessary, remind the examinee that proper nouns and different verb forms are not allowed. Begin Timing, allowing one minute.

Complete the final letter in the same way.

Scoring: The score is the sum of admissible responses across all three trials. Proper nouns and words not beginning with the specified letter are not counted as correct. If the examinee repeats a word, count only the first occurrence of the word as correct. If multiple forms of a word are given, count only one form toward the examinee's total. Vernacular or commonly accepted slang words (e.g., "munchies") are permissible.

Homonyms (e.g., "see," "sea") are counted separately only if the examinee indicates the alternate usage. Words that are also proper nouns (e.g., "ford") are acceptable only if the examinee indicates the proper usage of the word. It is best to score this task as soon as possible, as the rapid transcription is often sloppy and may be difficult to read at a later time. Remember to record the test version on the Cognitive Assessment Summary Sheet (i.e., BWR or LDT).

UNIVERSITY OF PENNSYLVANIA SMELL IDENTIFICATION TEST (UPSIT)

DESCRIPTION: The University of Pennsylvania Smell Identification Test (UPSIT) assesses olfactory recognition. Participants “scratch and sniff” odor patches and attempt to identify the odors from a 4-choice response set. .

CITATION OF PUBLICATION OF TEST: Doty RL, Shaman P, Kimmelman CP, Dann MS. [University of Pennsylvania Smell Identification Test: a rapid quantitative olfactory function test for the clinic.](#) Laryngoscope. 1984 Feb;94(2 Pt 1):176-8. doi: 10.1288/00005537-198402000-00004. PMID: 6694486.

Sensonics, Inc., Haddon Heights, New Jersey, USA

METHODS FOR PREDICT: The University of Pennsylvania Smell Identification Test (UPSIT) was administered throughout the PREDICT-HD study. Initially, the UPSIT was administered at visits 1, 3, and 5 from 2002 through July 2006. From August 2006 through March 2008, it was added to visit 6. From March 2008 through the end of the 1.0 study it was added to visit 7 as well. Starting in the 2.0 study, the UPSIT was administered to all visits.

NOTE: Smell booklets 1-4 were administered from 2002 through March 2008. Beginning in March 2008 the number of booklets was reduced to 2 (booklets 1 and 3) and sites with IRB approval began to administer booklets 1 and 3. The 2.0 version of the study reduced the number of booklets to 2 for all sites.

The rationale for reducing the number of booklets to 2 due to time constraints and a paper provided by the original creator of the test showed that there were internal consistency reliability ratings between the 10, 20, 30 and 40 items for the UPSIT and that individual UPSIT booklets or their combinations can be used to assess smell function in a reliable manner. See Doty, R.L., Frye, R.E. & Agrawal, U. [Internal consistency reliability of the fractionated and whole University of Pennsylvania Smell Identification Test.](#) Perception & Psychophysics 45, 381–384 (1989).
<https://doi.org/10.3758/BF03210709>

TRAINING INSTRUCTIONS:

Smell Identification Test (Smell) (Paper/Pencil Task, Table required)

Materials

Four Stimulus Booklets
Pencil (for examinee)

Description

This is a brief test used to evaluate smell sensitivity. The examinee is asked to scratch and sniff 40 items presented in 4 booklets consisting of 10 items each. The examiner must complete some questions on the back of Booklet #1 and record the Participant's Identification number on all 4 booklets before beginning the test.

Administration

Step 1. Record relevant information on the back of Booklet #1

On the back of Booklet #1, record the participant's 3-digit ID number on the line designated for NAME:

Do not complete the address information. Skip the next several items.

Ask the question: **Do you suffer from smell and/or taste problems?** Mark the 'yes' or 'no' line. *If the answer is "yes", ask the examinee for an explanation of the problem.*

Ask the question: **Do you smoke?** Mark the 'yes' or 'no' line.

If yes, complete the *If yes*: set of questions.

If no, ask the question **"Have you ever smoked?"**

If yes, complete the subsequent questions.

Step 2. Record the participant ID number on the back of booklets 2 – 4. Step 3. Hand the first booklet and a pencil to the examinee and say:

Beginning with page 1 of this booklet (Booklet 1), use this pencil to scratch the brown label from left to right several times. This will release an odor. Sniff the scraped label and completely fill in the circle corresponding to your smell experience in the column on the right. Erase mistakes completely. If the odor you smell is not represented, mark the closest to your experience. If no smell is present, guess and mark one answer. YOU MUST MARK AN ANSWER FOR EACH QUESTION (EVEN IF YOU SMELL NOTHING) TO MAKE THE TEST VALID.

Set the other 3 booklets (in order) on the table and say:

After answering all 10 questions in the first booklet, complete these other 3 booklets in order (i.e., from 2 to 4).

Step 4. After the participant completes each booklet, check to make sure all items have been completed. If an item was skipped, please bring it to his/her attention and ask the participant to complete it.

Step 5. Use the scoring templates to attain a total score. Record the total score on the CRF.

Step 6. Place the 4 completed booklets in the envelope and include this envelope in the data shipment to IU.

FINGER TAPPING TASK (TAPPER)

DESCRIPTION: Speeded tapping using a computerized response box. Participants tap as quickly as possible for five 10-second intervals.

Paced Tapping involves both tone-paced and self-paced tapping using computerized response box. Participants listened to a tone repeated at 1.8 Hz, and then when ready, began tapping along with the tone. The tone then continued for 11 more taps. After the tone stopped, participants were to continue tapping, at the same rate, until 31 taps had occurred without the pacing tone, at which point the trial ended. This sequence was repeated for five trials.

Block 1 - Speeded Tapping with the dominant index finger holding the hand flat on the response box and pressing a single button

Block 2 - Speeded tapping with the nondominant index finger holding the hand flat on the response box and pressing a single button

Block 3 - Speeded Tapping with alternate thumbs using 2 button box held in the lap

Block 4 - Paced tapping with dominant index finger, holding the hand flat on the response box and pressing a single button

Block 5 - Paced tapping with alternating thumbs using 2 button box held in the lap

CITATION OF PUBLICATION OF TEST: Woodruff-Pak DS, Papka M. [Huntington's disease and eyeblink classical conditioning: normal learning but abnormal timing](#). J Int Neuropsychol Soc. 1996 Jul;2(4):323-34. doi: 10.1017/s135561770000134x. PMID: 9375181.

Paulsen JS, Zimbelman JL, Hinton SC, Langbehn DR, Leveroni CL, Benjamin ML, Reynolds NC, Rao SM. [fMRI biomarker of early neuronal dysfunction in presymptomatic Huntington's Disease](#). AJNR Am J Neuroradiol. 2004 Nov-Dec;25(10):1715-21. PMID: 15569736.

METHODS FOR PREDICT: The speeded and paced tapping trials were administered during the 1.0 Study from 2002 through 2009. The number of trials was reduced from 6 correct trials out of 12 to 5 trials. However, some sites were not able to reduce the number of trials and/or update the software without Amendment approval. These sites recorded the longer version of the tapping trials instead of the shortened version.

TRAINING INSTRUCTIONS

Finger Tapping Task (Tapper) (Computer Task)

Materials

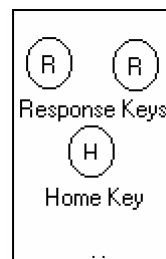
Computer

3-Button Response Box

Speakers

Description

1. The Finger Tapping Task requires about 10-15 minutes to administer
2. General Task Overview:
 - The task consists of five blocks. The five blocks take two forms. The first form occurs in blocks 1, 2, and 3 and involves the participant tapping buttons as quickly as possible. Each of these blocks involves 5 10-second tapping trials. The participant will rest his/her hand flat on the 3-button Response Box with the index finger extended and tap the “home” key (“H” on the diagram below) as quickly as possible. The dominant hand index finger is used in Block 1. The button box is then switched to the other side of the computer stand and the non- dominant hand is used in Block 2. In Block 3, the participant will hold the button box in both hands with his/her thumbs on the two “response” keys (“R” on the diagram below). He/she will again tap as quickly as possible, but this time alternating from left thumb to right thumb with each tap. The second form occurs in Blocks 4 and 5 and involves trials that have the following format: the trial begins with the repeated presentation of a tone at a constant rate; when the participant feels that he/she has a sense of the timing, he/she begins to tap at the same rate as the tone. Once the participant begins to tap, the tone will continue for a few more taps, but is then discontinued. The participant will then attempt to maintain the timing of the tap until the end of the trial. In Block 4, the participant uses the dominant hand index finger to tap in time with the tone. In Block 5, the participant holds the button box in both hands and uses both thumbs to tap in time with the tone – again alternating from left to right with each tap. The participant completes 6 error-free trials of this tone-guided/self-guided tapping sequence for Blocks 4 and 5. There will be a maximum of 12 trials for Blocks 4 and 5.



- a. To use the instructions below, please note that all text printed in *italics* refers to text shown on the touchscreen. All text shown in **bold** refers to instructions that should be read to the participant.
- b. If the participant becomes tired or needs a break, allow a short break *between* blocks or trials (any time a text box is on the screen that must be pressed to continue) – *not* in the middle of a trial.
- c. To exit the task prior to finishing
 - i. Press the *Alt* and *F4* keys at the same time to exit the program at any time during the task.

Note: no data will be saved if the task is exited before completion.

Administration

Finger Tapping Task Instructions

Step 1: Connect the 3-Button Response Box

Dislocate the Response Box cable from the 4-button Response Box, by unscrewing the part of the cable connector closest to the box. It is important that you do not turn the other part of the cable connector. Connect the cable to the back of the 3-Button Response Box by tightening this same section of the connector.

Step 2: Test Tone and Adjust Speaker Volume

1. On the Computer Task Menu, click on the button labeled *“Test Tone”* to determine if the speakers are turned on and functioning properly.
2. Ask the participant if the tone is at a level which can easily be heard. Adjust the volume accordingly.

Step 3: Select the task

1. Select from the Computer Task Menu by touching or clicking the mouse on the button labeled *“Start Tapper Task”*
2. A confirmation screen will appear. At this point you may continue by selecting *“Press Here to Continue”* or exit the task by selecting *“Press Here to Return To Main Menu”*.

Step 4: Enter Participant Information

1. Participant Information Screen appears
2. Enter the participant’s three-digit identification number
3. Enter the two-digit participant session number (e.g., 01 for Visit 1, 03 for Visit 3).
4. Enter the three-digit testing site identification number
5. Select right hand or left hand for the participant’s preferred/dominant hand.
6. Touch or click the mouse on the *“OK”* button to accept participant information. You may also exit the task at this point, if necessary, by touching or clicking on the *“Exit”* button.

Step 5: Administer Block 1

1. A text box will appear that reads *“Press Here to Begin Practice Tapping”*. Instruct the participant as follows:

For the first part of this task, you will rest your dominant hand flat on this 3-button Response Box [point] and tap the lower single button with your index finger as quickly as possible [show the participant the correct button]. Please keep your hand flat – not cupped- with your index finger extended and straight (demonstrate correct hand position). In order to tap the button, lower your finger and depress the button, then immediately release. You will hear a click when the button has been fully depressed. At the beginning of each trial, a tone will sound indicating when you may begin tapping. Continue to tap as quickly as you can until you hear another tone and then stop immediately.

Before we begin, let's try a few practice taps. Place your dominant hand comfortably on the button box with your index finger on the button. Press the text box on the screen with your non-dominant hand to begin the practice.

2. Allow the participant to tap the button a few times just so they are aware of how it feels to tap the button and so they can position their hand comfortably. As they practice, make sure they are tapping correctly. If not, instruct the participant:

Try to fully press and then release the button with each tap.

After they finish practicing:

Good! Now touch "Practice Completed" at the top right corner of the screen and you will begin the test. Position your hand comfortably on the button box. Keeping your hand flat and your index finger extended, tap as quickly as you can until you hear the second tone. Remember to wait for the tone to begin tapping and stop tapping when you hear the tone a second time. When you are ready, use your non-dominant hand to press the button on the screen to begin.

3. At the end of each trial, a text box will appear stating *"Press here to begin free tapping trials. Please use index finger of DOMINANT hand"*. If necessary, remind the participant to press the text box with their non-dominant hand and to leave their dominant hand positioned on the box. Between trials, instruct the participant as follows:

You may begin the next trial by pressing the text box on the screen whenever you are ready.

A total of 5 trials will be completed.

Step 6: Administer Block 2

1. Move the 3-Button Response Box to the participant's non-dominant side.
2. After the completion of Block 1, a text box will appear that reads *"Block 1 complete. Press here to practice with non-dominant hand index finger"*. Instruct the participant as follows:

For the second part of this task, you will again tap on the same button with your index finger. However, this time you will use your non-dominant index finger. Place your non-dominant hand flat on the button box and try a few practice taps.

3. Allow the participant to tap the button a few times just so they are aware of how it feels to tap the button and so they can position their hand comfortably. As they practice, make sure they are tapping correctly. If not, instruct the participant:

Try to fully press and then release the button with each tap.

After they finish practicing:

Good! Now press the “Practice Completed” button at the top right corner of the screen and make sure your non-dominant hand is comfortably positioned on the button box. Remember to wait for the tone to begin tapping and stop tapping when you hear the tone a second time. Keeping your hand flat and your index finger extended, tap as quickly as you can until you hear the second tone. When you are ready, use your dominant hand to press the button on the screen to begin the free tapping trials.

4. At the end of each trial, a text box will appear stating *“Press here to begin free tapping trials. Please use index finger of NON-DOMINANT hand”*. If necessary, remind the participant to press the text box with their dominant hand and to leave their non-dominant hand positioned on the box. Between trials, instruct the participant as follows:

You may begin the next trial by pressing the text box on the screen whenever you are ready.

A total of 5 trials will be completed.

Step 7: Administer Block 3

1. After the completion of Block 2, a text box will appear on the screen that reads *“Block 2 complete//Press here to practice with alternating thumbs*. Read the following instructions:

For the third part of this task, you will again tap as quickly as possible. However, this time, you will hold the button box with both hands and place your thumbs on the 2 top buttons [remove the button box from the stand and demonstrate by holding it in your lap while tapping with alternate thumbs]. You may begin tapping with either thumb, but once you begin, alternate between thumbs with each tap. So, if you start with your right thumb, the 2nd tap would be with your left thumb, then right, left, right, etc. Tell me when you are ready to begin practice, and I will press the button on the screen.

2. Allow the participant to practice. Make sure they are alternating back and forth between thumbs and fully pressing and releasing the button with each tap. Offer reminders if necessary.
 - **Remember to alternate between thumbs with each tap.**
 - **Remember to fully press and release the button with each tap.**

When the participant is finished practicing, the examiner should press *“Practice Completed”* in the upper right-hand corner of the screen.

3. A text box will appear on the screen that reads *Press Here to Begin Free Tapping Trials//next line//Alternate Thumb Tapping Task*. Finish the instructions for this task as follows:

As before, a tone will sound to begin each trial. When you hear the tone, begin tapping, alternating between thumbs, as quickly as possible. Stop tapping as soon as you hear the 2nd tone. Do you have any questions? [address any questions]

Tell me when you are ready, and I will press the box on the screen to start the test.

4. At the end of each trial, a text box will appear stating “*Press here to begin free tapping trial*”. Between trials, instruct the participant as follows:

You may begin the next trial by pressing the text box on the screen whenever you are ready.

A total of 5 trials will be completed.

Step 8: Administer Block 4

1. Place the 3-Button Response Box in the dominant hand position on the Computer Stand.
2. After the alternate thumb fast tapping trials a text box will appear on the screen that reads *Press Here to Begin Tone Tapping Trials. Please use index finger of DOMINANT hand*. Give the participant the following instructions:

For the next part of this task, you will again tap on the lower button with your dominant hand index finger. However rather than tapping as quickly as possible, you will try to tap at the same rate as a tone that will be presented. When the trial begins, you will hear a series of tones. As soon as you feel ready, begin tapping at the same rate with the tone. After a number of taps, the tone will stop, but you should continue to tap at the same rate until the *End of Trial* text box appears on the screen. Do your best to continue tapping at the same rate as the tone. Do you have any questions?

3. Review instructions if the participant appears to have difficulty understanding the task. Otherwise, begin block 2 with the following instructions:

Again, remember that the tone will stop after you have completed a few taps. Please continue to tap without the tone at the same rate until the end of the trial. Place your dominant hand flat on the button box with your index finger extended. As soon as you are ready, please press the text box on the screen with your non- dominant hand to begin.

4. At the end of each trial, a text box will appear stating *Press Here to begin Tone Tapping Trials*. If necessary, remind the participant to press the text box with their non-dominant hand and to leave their dominant hand positioned on the box. Between trials, instruct the participant as follows:

You may begin the next trial by pressing the text box on the screen whenever you are ready.

A total of 6 error free trials (or a total of 12 trials) must be completed for the block to end.

Step 9: Administer Block 5

1. Remove the 3-Button Response Box from the Computer Stand and ask the participant to hold it in his/her lap again.

2. After the dominant hand tone tapping block has ended, a text box will appear on the screen that reads *Press Here to Begin Tone Tapping Trials*//next line//*Alternate Thumb Tapping Task*. Give the participant the following instructions.

For the 5th and final part of this task, you will tap at the rate of the tone as you did before. However, this time you will hold the box and tap with your thumbs, alternating from left to right. When the trial begins, you will hear a series of tones. As soon as you are ready, begin tapping with the tone, alternating between thumbs. As before, the tone will continue for a number of taps and then stop. Please continue to tap without the tone, maintaining the same rate until the text box appears on the screen to end the trial. Do you have any questions? [address any questions]

Let's begin. Tell me when you are ready, and I will start the test.

3. At the end of each trial, a text box will appear stating *Press Here to begin Tone Tapping Trials*. Between trials, instruct the participant as follows:

Tell me when you are ready to begin the next trial and I will press the button on the screen.

A total of 6 error free trials (or 12 total trials) must be completed for Block 5 to end. When this task is finished read the following to the participant:

Good! You have completed the Finger Tapping task.

Return the Response Box to the computer stand.

Step 10: Exit the Task

Press the text box on the screen to return to the Computer Task Suite main menu.

TOWER OF TORONTO (TOWER)

DESCRIPTION: 3- and 4- disk version, based on Saint-Cyr et al., 1988: Both versions of this task display three neutral-colored pegs, labeled A, B, and C. For the 3-disk version, the leftmost peg is stacked with 3 disks of distinct sizes (small, medium, and large), which are arranged in order from largest disk on the bottom to smallest disk on the top. For the 4-disk version, one additional small disk is added to the top of the initial display on the left peg. For both versions the participant is instructed to place the disks in the same order onto the rightmost peg in as few moves as possible by moving only one disk at a time and without placing a larger disk on top of a smaller disk.

CITATION OF PUBLICATION OF TEST: Saint-Cyr, J. A., Taylor, A. E., & Lang, A. E. (1988). [Procedural learning and neostriatal dysfunction in man](#). *Brain*, 111(4), 941-959

METHODS FOR PREDICT: The Tower of Toronto (Tower) was administered at visits 1,3,5, and 7. It was discontinued for the 2.0 study. Data from the task was saved to disc and sent to the Stout lab at Indiana for processing and analysis.

TRAINING INSTRUCTIONS

Tower Task (Tower) (Computer Task)

Materials

Computer

Touchscreen (for response input)

Description

1. The Tower Task requires about 15 minutes to administer.
2. General Task Overview:
 - The Tower Task consists of different sized disks (e.g., small, medium, large) that are stacked on the left of three horizontally arranged pegs. The disks are stacked smallest to largest from the top to the bottom of the peg. Participants are instructed to arrange the disks in the same configuration on the rightmost peg while observing the following rules: (1) only one disk can be moved at a time, (2) a large disk can never be placed on top of a smaller disk. There are two stages to this task that are based on the number of disks to be moved. The first stage consists of 4 attempts to solve a three-disk configuration, and the second stage involves 4 attempts at solving a four-disk configuration.
 - This task is divided into two separate tests on the Computer Task Suite main menu. If the 3-disk version is successfully completed, then the 4-disk version should be administered. If the 3-disk version is not completed (i.e., test was aborted), do not attempt to administer the 4-disk version.
 - For each attempt at the 3-disk task, the participant will have a maximum of 21 moves to solve the task. If not solved within this limit, a text box will appear, the screen will reset to the original configuration and the next trial will begin. For each attempt at the 4-disk task, the participant will have a maximum of 45 moves to solve the task.
3. To use the instructions below, please note that all text in *italics* refers to text shown on the touchscreen. All text shown in **bold** refers to instructions that should be read to the participant.

4. If the participant becomes tired or needs a break, allow a short break **between** trials (any time a text box is on the screen that must be pressed to continue) – **not** in the middle of a trial.
5. To exit the task prior to finishing
 - Press the *Alt* and *F4* keys at the same time to exit the program at any time during the task.

Note: no data will be saved if the task is exited before completion.

Administration

Tower Task Instructions

Step 1: Select the 3-Disk Tower Task

1. Select from the Computer Task Menu by touching or clicking the mouse on the button labeled *"Start Tower Task (3 Disk)..."*
2. A confirmation screen will appear. At this point you may continue by selecting *"Press Here to Continue"* or exit the task by selecting *"Press Here to Return To Main Menu"*.

Step 2: Enter Participant Information

1. Participant Information Screen appears
2. Enter the participant's three-digit identification number
3. Enter the two-digit participant session number (e.g., 01 for Visit 1, 03 for Visit 3).
4. Enter the three-digit testing site identification number
5. Select right hand or left hand for the participant's preferred/dominant hand.
6. Touch or click the mouse on the *"OK"* button to accept participant information. You may also exit the task at this point, if necessary, by touching or clicking on the *"Exit"* button.

Step 3: Administer Practice Trials

1. A text box will appear that reads *"Press Here to Begin Practice For Tower Task"*. Touch or click the mouse on this text box to show the practice screen. Read the following instructions to the participant:

If you look at the screen, you can see that there are three pegs labeled A, B, and C. You will also see that there are three different sized disks stacked on peg A. Notice that the disks are stacked in order so that the largest disk is at the bottom of the peg and the smallest disk is at the top of the peg. In this task, you will be moving the disks from peg to peg. There are two rules that you must follow as you move the disks:

Rule 1: You may only move one disk at a time. Rule 2: You may not stack a larger disk on top of a smaller disk.

The computer will only allow you to move the topmost disk from each peg, so do not try to move a disk that has other disks stacked on top of it. To move a disk, simply touch the disk that you would like to move. Let's say that I want to move the small disk on peg A and stack it on peg B. I would first touch the small disk like this (demonstrate). Notice that when I touched the small disk, it was lifted above peg A. The disk is now activated and ready to be moved to a different peg. To move the activated disk to a new peg, touch the base of the peg where you would like to stack the disk. To put it on peg B, I simply touch the base that says Peg B (demonstrate) and the small disk is stacked on peg B.

Remember that the first rule is that only one disk can be moved at a time and the second rule is that a larger disk cannot be stacked on top of a smaller disk. So, for example, if I were to touch and activate the medium size disk on peg A (demonstrate), and then touch peg B to try to stack the medium disk on the small disk, a buzz sound would occur because I cannot stack a larger disk on top of a smaller disk. The only place that I could stack the medium disk is on peg C or keep it on peg A. Now I would like you to practice moving the disks around the three pegs. (Make sure that the participant is able to accurately move and stack disks).

NOTE: DO NOT EXIT THE PRACTICE SCREEN YET!

Step 4: Administer 3-Disk Tower Task

1. Once the participant demonstrates that he/she can accurately move and stack disks, move the three disks back to peg A and read the following instructions before exiting the practice screen.

Now we will begin the task. Your goal is to move the three disks on peg A over to peg C in as few moves as possible and stack the disks in the same order so that the largest disk is at the bottom of the peg and the smallest disk is at the top of the peg. The important thing is that you complete the task in as few moves as possible – do not worry about how fast you finish. Don't forget the rules.....you may only move one disk at a time, and you may not stack a larger disk on top of a smaller disk. You will attempt this task several times. Between trials, a text box will appear on the screen. You may press that text box and continue as soon as you are ready to begin the next trial. Do you have any questions? [address any questions] Do not allow any further practice after reading this set of instructions. The participant should proceed to Trial 1.

2. If the participant appears to understand the goal of the task, say:

"Touch the *"Done With Practice: Press Here to Begin Trial 1"* bar at the top of the screen to start the first trial. Start as soon as you see the pegs and disks.

3. Between trials, a text box will appear that reads *"Press Here to Begin Trial 2 (3 or 4)"*. If the participant does not continue to the next trial on their own, instruct as follows:

Great job. We are going to do the exact same task. Again, your goal is to move the three disks on peg A to peg C in as few moves as possible and stack the disks in the same order so that the largest disk is at the bottom of the peg and the smallest disk is at the top of the peg. The rules are the same, you may only move one disk at a time, and you may not stack a larger disk on top of a smaller disk. As soon as you are ready, press the text box and begin.

Step 5: Exit the 3-Disk Tower Task

1. At the completion of 3-Disk Trial 4, a text box will appear that reads *"Task Completed, Press Here to Exit"*. Read the following to the participant:

Great! You have finished the first part of the tower task.

2. Touch or click the mouse on the text box to exit the Tower Task and return to the Computer Suite Task menu.

Step 6: Select the 4-Disk Tower Task

1. Select from the Computer Task Menu by touching or clicking the mouse on the button labeled *"Start Tower Task (4 Disk)..."*
2. A confirmation screen will appear. At this point you may continue by selecting *"Press Here to Continue"* or exit the task by selecting *"Press Here to Return To Main Menu"*.

Step 7: Enter Participant Information: Same as for 3 Disk Tower Task Step 8:

Administer the 4-Disk Tower Task

NOTE: A practice screen will appear. Do not allow the participant to practice moving the disks since s/he is already familiar with this process.

1. Read the following instructions to the participant before exiting the practice screen:

Now we are going to make the task a little more challenging. Instead of moving three disks from peg A to peg C, you will be moving four disks. Like before, the disks are stacked so that the largest disk is at the bottom of the peg and the smallest disk is at the top of the peg. Again, your goal is to move the four disks on peg A to peg C in as few moves as possible and stack the disks in the same order so that the largest disk is at the bottom of the peg and the smallest disk is at the top of the peg. The rules are the same, you may only move one disk at a time, and you may not stack a larger disk on top of a smaller disk. As before, you will attempt this task several times.

Between trials, a text box will appear on the screen. You may press that text box and continue as soon as you are ready to begin the next trial. Are you ready to begin the first trial?

Start as soon as the pegs and disks appear.

2. Press the text box on the screen and then touch the button at the top of the screen that reads *“Done With Practice: Press Here to Begin Trial 1”*.
3. The program will immediately launch into Trial 1. Remind the participant to begin if s/he hesitates.
4. If the participant becomes frustrated or states that he/she cannot do the task, encourage him/her to continue trying.
5. Between trials, a text box will appear that reads *“Press Here to Begin Trial 2 (3 or 4)”*. If the participant does not continue to the next trial on their own, instruct as follows:

Great job. You are going to do the exact same task. Again, your goal is to move the four disks on peg A to peg C in as few moves as possible and stack the disks in the same order so that the largest disk is at the bottom of the peg and the smallest disk is at the top of the peg. The rules are the same, you may only move one disk at a time, and you may not stack a larger disk on top of a smaller disk. Are you ready? Press the text box and begin.

Step 9: Exit the 4-Disk Tower Task

2. At the completion of 4-Disk Trial 4, a text box will appear that reads *“Task Completed, Press Here to Exit”*. Read the following to the participant:

Great! You have finished the tower task.

3. Touch or click the mouse on the text box to exit the Tower Task and return to the Computer Suite Task menu.

HOPKINS VERBAL LEARNING TEST (HVLТ-R)

DESCRIPTION: The HVLТ-R requires recall of a series of 12 words over three learning trials, free recall after a delay, and a recognition trial. Raw scores are derived for Total Recall, Delayed Recall, Retention (% retained), and a Recognition Discrimination Index.

CITATION OF PUBLICATION OF TASK – Brandt, J. & Benedict, R. (2001). [Hopkins Verbal Learning Test-Revised: Professional Manual](#). PAR: Florida.

METHODS FOR PREDICT: The HVLТ was administered as part of the Cognitive battery that had three stages during the 1.0 part of the study. The HVLТ was administered at visits 1,3 and 5 from the start of PREDICT through March of 2008 during stage 1 and 2. Starting in March of 2008, the HVLТ was administered at baseline only and continued throughout the remainder of the 2.0 study. In September of 2011, the HVLТ was administered at every visit for a brief period of time at MRI approved sites. The duration of the administration was approximately until August of 2012, but some sites continued beyond due to IRB restrictions. The scoring of the HVLТ is as below:

Total Recall – Sum of trials 1, 2, and 3

Delayed Recall – Score of Trial 4

Retention (% retained) – (Trial 4 / (the higher score of trial 2 or trial 3))*100

Recognition Discrimination Index – recognition hits – total of false positives

German and Spanish versions were administered as well and a description of the development of the forms is provided.

TRAINING INSTRUCTIONS:

Hopkins Verbal Learning Test-Revised (HVLТ-R) (1.0 version)

(Paper/ Pencil Task, verbal only, completed while seated at computer)

Materials

Record Form (for examiner)

Watch (to record clock time)

Description

The test requires the examinee to learn and remember a list of words. The test includes measures of immediate and delayed free recall and delayed recognition memory. There is a 20-25 minute delay interval during which two computerized tasks (Finger Tapping Task and Serial Reaction Time Task) are administered.

NOTE: The timing of the HVLТ-R delay is important for standardization purposes. The two computer tasks that are scheduled to be in the delay interval meet this timing requirement. However, if either the examiner or participant takes a break during this delay, it will be important to adjust the order of the computer tasks and to begin the Delay at the appropriate time. (i.e., Do not take a break, plus administer both tasks – this will result in an extended delay time) If only one task can be completed during the 20-25 minute delay, administer

the second computer task immediately after the HVLT-R delay and continue to administer the remainder of the battery in the standard order.

Administration

TRIAL 1 (Immediate Free Recall)

To begin Trial 1, say:

I'm going to read a list of words to you. Listen carefully, because when I'm through, I want you to tell me as many of the words as you can. You can say them in any order, just say as many of them as you can remember. Are you ready?

Read aloud the stimulus words of TRIAL 1 at an even pace, approximately one word every 2 seconds. After reading the last word on the list say,

Now tell me as many words as you remember. Go ahead.

Write the examinee's responses verbatim, in the order in which they are given (including repetitions), in the column labeled "TRIAL 1" on the Record Form. After the examinee appears to have given his or her last response for the trial, or when the examinee indicates that he or she cannot remember any more words, proceed to TRIAL 2.

TRIAL 2 (Immediate Free Recall)

To begin TRIAL 2, say:

I'm going to read the same list again. Like before, tell me as many of the words as you can remember, in any order. Be sure, to also say words from the list that you told me the first time.

Again, read the list and follow the same procedures for recording as in TRIAL 1. Record the responses in the TRIAL 2 column.

TRIAL 3 (Immediate Free Recall)

To begin TRIAL 3, say:

I'm going to read the same list one more time. As before, tell me as many of the words as you can remember, in any order, including all the words you've already told me.

Read the list and follow the same procedures for recording as in the previous trials. Record the responses in the TRIAL 3 column.

On the Record Form, record the time at which TRIAL 3 is completed.

Scoring: Record the total correct for each of the three trials, as well as the Form# (i.e., 2 or 4) on the Cognitive Assessment Summary Sheet. If a correct item is repeated within a single trial, only count that word once in the trial score.

Hopkins Verbal Learning Test-Revised IHVLT-R Delay) (1.0 version)

(Paper/ Pencil Task, verbal only, completed while seated at computer)

Materials

Record Form (for examiner)

Description

This portion of the HVLT-R is to be completed **20-25 minutes** after the completion of Trial 3. There is a free recall trial and a forced choice recognition trial.

Administration**TRIAL 4**

On the Record Form, document the actual time that you begin TRIAL 4. Say,

Do you remember the list of words you repeated before?

If the answer is "no", remind the examinee that you read the same list three times and I/he was asked to recall the words each time. Say the following:

Tell me all the words you can remember. Go ahead.

Record the examinee's responses in the column labeled "Delayed Recall "rial" on the Record Form using the same procedures as described for the previous trials.

Delayed Recognition Trial

This trial is administered immediately after the Delayed Recall trial. Say the following:

This time I am going to read a longer list of words to you.

Some of these words are from the original list, and some are

not. After reading each word aloud, I'd like for you to respond "Yes" if it was on the original list or "No" if it was not.

Read the words from the Delayed Recognition Trial list in the numerical order listed on the Record Form. Give the examinee as much time as needed to respond. If needed you may use the prompt:

Was horse on the list? Yes, or No?

A response from the examinee is required for every word. If the examinee is not sure, ask for a guess. Record responses on Record Form by circling "Y" for a "Yes" response and "N" for a "No" response.

Scoring: The Delayed Recall Score is the total number of words that were correctly recalled from the original list (maximum = 12). The Recognition Hits score is the number of words from the original list (printed in all caps on the record form) to which the examinee responded "Yes" (maximum= 12). The Related False positive

score is the number of semantically-related items (printed in light shading on the record form) to which the examinee responded "Yes" (maximum= 6).

Hopkins Verbal Learning Test-Revised (HVLTR) (2.0 version)

(Paper/Pencil Task, verbal only, completed while seated at computer)

Materials

Record Form (for examiner) (Form 4 only)

Watch (to record time)

Task Description

The HVLTR requires the participant to learn and remember a list of words.

The test includes measures of immediate and delayed free recall and delayed recognition memory.

NOTE: The timing of the HVLTR delay is important for standardization

purposes. There is a 20-25 minute delay interval during which other tasks (Symbol Digit Modalities Test, Stroop, Trails A & B, Smell ID) are administered. However, if either the examiner or participant takes a break during this delay, it will be important to adjust the order of the filler tasks and to begin the delay at the appropriate time. If 20-25 minutes have *not* passed following the administration of the filler tasks, you may administer Speeded Tapping prior to the HVLTR delay trial. Speeded tapping takes approximately 4 minutes to administer, not including time to set up your tablet. Do NOT administer the ANART prior to the HVLTR delay trial. Do not interrupt any task other than Smell ID to administer the HVLTR delay.

Administration

1. Administer Trial 1 (Immediate Free Recall)

To begin Trial 1, say:

I'm going to read a list of words to you. Listen carefully, because when I'm through, I want you to tell me as many of the words as you can. You can say them in any order, just say as many of them as you can remember. Are you ready?

Read aloud the stimulus words of Trial 1 at an even pace, approximately one word every two seconds. After reading the last word on the list say,

Now tell me as many words as you remember. Go ahead.

Write the participant's responses verbatim, in the order in which they are given (including repetitions and words not from the original list), in the column labeled "TRIAL 1" on the Record Form. After the participant appears to have given his or her last response for the trial, or when the participant indicates that he or she cannot remember any more words, proceed to Trial 2.

2. Administer Trial 2 (Immediate Free Recall)

To begin Trial 2, say:

I'm going to read the same list again. Like before, tell me as many of the words as you can remember, in any order. Be sure to also say words from the list that you told me the first time.

Again, read the list and follow the same procedures for recording as in Trial 1. Record the responses in the Trial 2 column.

3. Administer Trial 3 (Immediate Free Recall)

To begin Trial 3, say:

I'm going to read the same list one more time. As before, tell me as many of the words as you can remember, in any order, including all the words you've already told me.

Read the list and follow the same procedures for recording as in the previous trials. Record the responses in the Trial 3 column.

On the Record Form, record the time at which Trial 3 is completed.

Scoring: Record the total correct for each of the three trials, as well as the Form # in the tablet eCAS. If a correct item is repeated within a single trial, only count that word once in the trial score.

Hopkins Verbal Learning Test-Revised (HVLТ-R Delay) (2.0 Version)

(Paper/Pencil Task, verbal only, completed while seated at tablet)

Materials

Record Form (for examiner) (Form 4)

Description

This portion of the HVLТ-R is to be completed **20-25 minutes** after the completion of Trial 3. You may move speeded tapping ahead of the HVLТ-R

Delay if 20-25 minutes has not passed since the completion of Trial 3. There is a free recall trial and a forced choice recognition trial.

Administration

1. Administer Trial 4 (Delayed Recall)

On the Record Form, document the actual time that you begin Trial 4. Say,

Do you remember the list of words you repeated before?

If the answer is "no", remind the examinee that you read the same list three times and that s/he was asked to recall the words each time. Say the following:

Tell me all the words you can remember. Go ahead.

Record the examinee's responses in the column labeled "Delayed Recall Trial" on the Record Form using the same procedures as described for the immediate recall trial.

4. 2. Administer Delayed Recognition Trial

This trial is administered immediately after the Delayed Recall Trial. Say the following:

This time I am going to read a longer list of words to you. Some of these words are from the original list, and some are not. After reading each word aloud, I'd like for you to respond "Yes" if it was on the original list or "No" if it was not.

Read the words from the Delayed Recognition Trial list in the numerical order listed on the Record Form. Give the examinee as much time as needed to respond. If needed you may use the prompt:

Was bluebird on the list? Yes, or No?

A response from the examinee is required for every word. If the examinee is not sure, ask for a guess. Record responses on Record Form by circling "Y" for a "Yes" response and "N" for a "No" response.

Scoring: The Delayed Recall Score is the total number of words that were correctly recalled from the original list (maximum = 12), please record total number of words in the tablet eCAS.

The Recognition Hits score is the number of words from the original list (printed in all caps on the record form) to which the examinee responded "Yes" (maximum = 12). The Related False positive score is the number of semantically related items (printed in light shading on the record form) to which the examinee responded "Yes" (maximum = 6).

See <https://www.parinc.com/Products/Pkey/130> for more information on form variation.

AMERICAN NATIONAL ADULT READING TEST (ANART)

DESCRIPTION: . The American National Adult Reading Test (ANART) is a brief test used to estimate intellectual ability. The examinee is asked to read aloud a list of 50 irregular words. The National Adult Reading Test (NART) was administered UK sites. The Wortschatztest (WST) was administered at the German site and the Test de Acentuacion (TAP) was administered at the Spanish site.

CITATION OF PUBLICATION OF TASK: GLADSDJO, J., HEATON, R., PALMER, B., TAYLOR, M., & JESTE, D. (1999). [Use of oral reading to estimate premorbid intellectual and neuropsychological functioning](#). *Journal of the International Neuropsychological Society*, 5(3), 247-254. [doi:10.1017/S1355617799533079](#).

Nelson, H. E., & Willison, J. (1991). [National adult reading test \(NART\)](#). Windsor: Nfer-Nelson.

Schmidt, K.-H., & Metzler, P. (1992). [Wortschatztest: WST](#). Weinheim: Beltz.

Del Ser, T., González-Montalvo, J. I., Martínez-Espinosa, S., Delgado-Villapalos, C., & Bermejo, F. (1997). [Estimation of premorbid intelligence in Spanish people with the Word Accentuation Test and its application to the diagnosis of dementia](#). *Brain and cognition*, 33(3), 343–356. <https://doi.org/10.1006/brcg.1997.0877>

METHODS FOR PREDICT: The American National Adult Reading Test (ANART) was administered throughout the entire study. During the 1.0 part of the study, the ANART was administered during stage 1 of the cognitive battery at visits 1,3,5 from the start of the study until July of 2006. During stage 2 of the cognitive battery that started August 2006 through March of 2008, visit 6 was added. For stage 3 of the cognitive battery that was from March 2008 to the beginning of the 2.0 version of the study, the ANART was administered at all visits. Once the 2.0 version of the study began, the ANART was only administered at baseline visits.

All administrations of the ANART/NART were required to be audiotaped (either via analog tape recorder, or digital recording on the table in 2.0). The audiotapes were then sent to a central site for scoring in addition to the scoring done by the evaluator.

The number of errors is recorded on the form and the errors are then translated to a verbal IQ score.

For German participants, the Wortschatztest: WST was administered. This test consists of 42 rows of words in which one word is correct and the rest are distractions. The number of correct answers is recorded on the form and the number of errors is entered into the Cognitive Summary form. It should be noted that the WST asks the participant to determine which word is correct and cross the word out by marking a line through the word. The participant is asked not to guess the correct word. If the participant is unsure, they are asked to leave blank.

For Spanish participants, the Test de Acentuacion was administered. This test consists of 30 unaccented words and the participant is asked to pronounce each word. The number of correct answers is recorded on the form and the number of errors is entered into the Cognitive Summary form.

The WST was administered throughout the 1.0 study as well as the through 2010 of the 2.0 portion of the study.

The TAP was only administered through the 1.0 study through 2008 when the site discontinued participation in the PREDICT study.

Premorbid IQ values provided by Julie Stout's lab when it was located at Indiana University. The values for Spanish participant were not provided and a formula was initially developed but is not added here. Information about the formulas can be provided upon request.

TRAINING INSTRUCTIONS:

American National Adult Reading Test (ANART) (v1.0)

(Paper/ Pencil Task, verbal only, complete while seated at computer)

Materials

Stimulus Card

Record Form/Response Key (for examiner)

Description

This is a brief test used to estimate premorbid intellectual ability. The examinee is asked to read aloud a list of 50 irregular words. The examiner must be familiar with the correct pronunciation of each word as it is necessary to score each item as the participant reads it. The key is located on the Record Form.

Administration

Hand the Stimulus Card to the examinee and say,

Please read slowly down this list of words starting here (indicate 'ache') and continuing down this column and on to the next. After each word, please wait until I say 'Next' before reading the next word. Some of these words are very difficult and there may be words that you do not recognize. Most people are not familiar with many of the words. Please make a guess when you come to a word you are not sure about. Go ahead."

The subject should be encouraged to guess, and all responses be reinforced ("good," "that's fine," etc.). The subject may change a response if he or she wishes to do so but if more than one version is given, the subject must decide on the final choice. No time limit is imposed.

As the participant reads each item, the examiner must check the pronunciation key and determine if the response was correct or incorrect. Record a 'Y' for yes or a 'N' for no in the "Correct" column on the record form before proceeding to the next trial. When the examiner has recorded the score, he/she should say "next" to the participant to indicate that the next item can be read.

Administer all 50 items.

Scoring: Count the errors and record the total number of incorrect responses on the Record Form and the CRF. Slight variations in pronunciation are acceptable when these are due to regional accents.

American National Adult Reading Test (ANART)/National Adult Reading Test (NART) (2.0 version)

(Paper/Pencil Task, verbal only, completed while seated at tablet)

Materials

Tablet

Stimulus Card

Record Form/Response Key (for examiner)

Task Description

The ANART/NART is a brief test used to estimate premorbid intellectual ability. The participant is asked to read aloud a list of 50 irregular words. The examiner must be familiar with the correct pronunciation of each word as it is necessary to score each item as the participant reads it. The key is located on the Record Form.

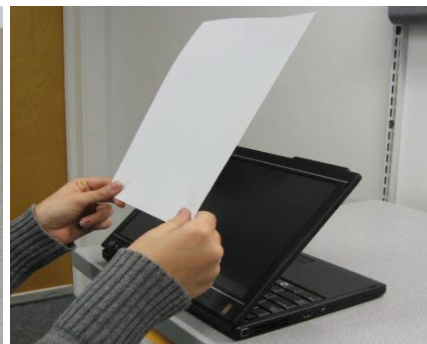
Administration

Step 1: Checking touch/pen settings

1. Double click on SPSync Manager. In the top right corner, select “Pen Settings.” Select “Pen Only”. Do not use the “Touch Only” setting because we do not want the participants to accidentally touch the screen and stop the recording. Once you select “Pen Only”, click “Apply” and then “Done”.

Step 2: Starting the ANART/NART task

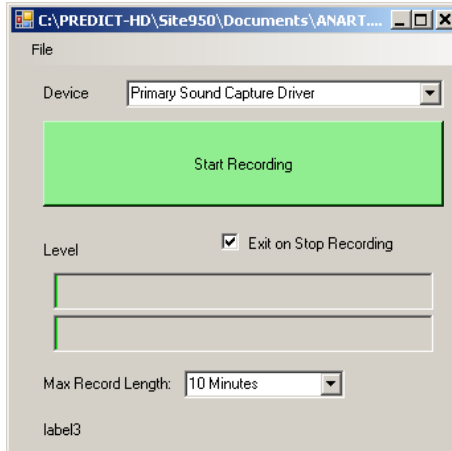
1. Click on ANART/NART Audio Recording in the SPSync Manager bundle list.
2. Gently rotate the screen clockwise 180 degrees and position the screen so that it is slanted at approximately a 45 degree angle. Ensure that the tablet is positioned so that the power button is in the lower left hand corner for the participant. The tablet should be positioned at the edge of the table and centered in front of the midline of the participant. Participant should be seated at a comfortable posture at table.



3. Hand the Stimulus Card to the participant. The participant should hold the Stimulus Card in front of the tablet screen in a way that will not cover the microphones. If the participant has a soft voice, please ask them to speak loudly. Then say,

Please read slowly down this list of words starting here (point to ‘ache’) and continuing down this column and on to the next. After each word, please wait until I say ‘Next’ before reading the next word. Some of these words are very difficult and there may be words that you do not recognize. Most people are not familiar with many of the words. Please make a guess when you come to a

word you are not sure about. (Use the pen to press “Start Recording” on the eANART/NART recorder to record participant’s response.) **“Go ahead.”**



The participant should be encouraged to guess. The participant may change a response if he or she wishes to do so, but if more than one version is given, the participant must decide on the final choice. No time limit is imposed.

As the participant reads each item, the examiner must check the pronunciation key and determine if the response was correct or incorrect. Record a ‘Y’ for yes or a ‘N’ for no in the “Correct” column on the record form before proceeding to the next word. When the examiner has recorded the score, he/she should say “next” to the participant to indicate that the next item can be read. If the examiner is unsure about scoring for particular items, s/he can review the recording later.

Administer all 50 words.

When completed, use the pen to select “Stop Recording” and rotate tablet screen back to laptop mode.

The eANART/NART recorder should be started and stopped as close as possible to when the participant begins and ends the task. Do not use the participant’s name during recording. Warn the participant not to state any personal or identifying information while the recorder is on. Treat all audio recordings as Protected Health Information (PHI).

IMPORTANT: The eANART/NART recorder will not permit you to record more than one recording per visit and will not let you pause and restart the recording. If you start the assessment and need to stop the recording before completing the test, you will need to delete that recording and then record a new audio file. Add a comment on eCAS if multiple recordings were made.

Scoring: Count the errors and record the total number of incorrect responses on the Record Form and the tablet eCAS. Slight variations in pronunciation are acceptable when these are due to regional accents. Audio files with acceptable pronunciations are available. The eANART/NART audio recordings will be pushed to Iowa with the computerized data.

Instructions for the WST and TAP are located on the forms.

EMOTIONS TASK – STATIC VERSION (EMOSTATIC)

DESCRIPTION: The static emotion recognition test assessed facial emotion recognition. Participants viewed photographs of faces expressing one of six extreme emotional expressions or a neutral expression. They then selected the emotion label that identified the expression from a multiple-choice response set which included the words: fear, disgust, happy, sad, surprise, anger, and neutral. A total of 70 trial included ten stimuli per emotion.

CITATION OF PUBLICATION OF TEST:

For stimuli:

Ekman, P., & Friesen, W. V. (1976). [Measuring facial movement. Environmental Psychology and Nonverbal Behavior](#), 1, 56-75

METHODS FOR PREDICT: The Emotions Task-Static Version (Emostatic) was administered at visits 1,3,5,6 and 7. This version of the Emostatic was discontinued at the the beginning of the 2.0 study. A different version of the Emostatic was administered in the 2.0 study and was discontinued at the 2.2 amendment. The two versions of the Emostatic were not combined as data sets due to fundamental programming and data structure differences.

TRAINING INSTRUCTIONS

Emotions Task – Static Version (EmoStatic) (Computer Task)

Materials

Computer

Touchscreen (for response input)

Description

1. This version of the Emotions Task requires about 8 minutes to administer.
2. General Task Overview:
 - a. The Emotions Task – Static Version involves the presentation of photographed faces depicting facial expressions and seven boxes displaying the response options (Anger, Disgust, Fear, Happy, Neutral, Sad, Surprise). The participant is instructed to touch the correct box as soon as s/he decides which emotion is expressed by the person. There are 70 trials.
3. To use the instructions below, please note that all text in *italics* refers to text shown on the touchscreen. All text shown in **bold** refers to instructions that should be read to the participant.
4. If the participant becomes tired or needs a break, allow a short break **between** stages (any time a text box is on the screen that must be pressed to continue) – **not** in the middle of a trial.
5. To exit the task prior to finishing
 - a. Press the *Alt* and *F4* keys at the same time to exit the program at any time during the task.

Note: no data will be saved if the task is exited before completion.

Administration

Emotions Task – Static Instructions Step 1:

Select the task

1. Select from the Computer Task Menu by touching or clicking the mouse on the button labeled *“Start EmoStatic Task??”*
2. A confirmation screen will appear. At this point you may continue by selecting *“Press Here to Continue”* or exit the task by selecting *“Press Here to Return To Main Menu”*.

Step 2: Enter Participant Information

1. Participant Information Screen appears
2. Enter the participant’s three-digit identification number
3. Enter the two-digit participant session number (e.g., 01 for Visit 1, 03 for Visit 3).
4. Enter the three-digit testing site identification number
5. Select right hand or left hand for the participant’s preferred/dominant hand.
6. Touch or click the mouse on the *“OK”* button to accept participant information. You may also exit the task at this point, if necessary, by touching or clicking on the *“Exit”* button.

Step 3: Administer the Practice Block of Emotions Task – Static Version

1. A text box will appear that reads *“Press Here to Begin Practice Block”*. Read the following instructions to the participant:

For this task, you will see a picture of a face on the screen; your job is to decide what emotion the person is feeling based on his/her facial expression. At the same time, you see the face, you will see seven boxes underneath the face and these boxes will include seven response choices. You will select the response that best fits with the face by touching the correct box. There are six emotions to choose from and some faces will show a neutral expression.

We will first start by learning the seven choices. For the practice section, you will first see a purple button at the bottom of the screen. You must press and hold this button until you are ready to respond. After you begin holding the purple button, one of the emotion words will appear in a box in the middle of the screen; at the same time, the seven response words will appear beneath this box. Please remove your finger from the purple button and touch the response that contains the same word as the one presented in the center box. Do you have any questions? [address any questions] Whenever you are ready, press the text box and begin the practice.

2. At the end of the practice, a text box will appear that reads *“Press Here to Start Test”*. Read the following instructions.

For the test section, you will again start by holding your finger on the purple button. This time, a face will appear in the middle of the screen, along with the seven response words.

**Your job is to decide what emotion the person is feeling based on his/her facial expression. You should continue to hold your finger on the purple button until you decide on a response. Then, as soon as you decide, you should quickly move your finger to the response. After a certain amount of time, the face will disappear; you should still respond even after it disappears. Once you touch a response, the screen will clear. Wait for the purple button and then hold it to start the next trial. Do you have any questions? [address any questions]
Whenever you are ready, press the text box and begin the test.**

NOTE: If the participant does not make a response but continues to hold his/her finger on the purple button, the face will disappear after 4 seconds and the response choices will disappear after an additional 4 seconds. In order to continue the participant must remove his/her finger from the button. The participant can then begin the next trial by placing his/her finger back on the purple button.

Step 4: Exit the Emotions Task – Static Version

1. At the completion of 70 trials, a text box will appear that reads *“Task Completed”*. Read the following to the participant:

Good, you have completed the Emotions task!

2. Touch the text box to return to the Computer Task Suite menu.

SECTION 2: DEMOGRAPHICS/GENETICS/MEDICAL HISTORY

INTRODUCTION:

The Clinical Trials Coordination Center in the 1.0 study collected information on the participant through an enrollment call. The site number, callers staff code, participants date of birth, gender, and ethnicity, date the consent form was signed, inclusion/exclusion criteria have been met, and the participant's gene status (negative or positive) were collected during the enrollment call. The demographic information as well as comorbid conditions were also collected on the Medical History and demographics form. Concomitant medications were collected on a separate form and kept in log format. Racial and educational information for European sites were slightly different. Additional items were added as recommendation from the European Huntington's Disease Network.

In the 2.0 study, the enrollment phone call was replaced by electronic submission via the tablet. Demographic and medical history along with concomitant medications were entered through the tablet and submitted to Iowa. A Medical Event form was added to collect yearly information about medical conditions that occurred throughout the 2.0 study.

As part of enhancing the comorbid conditions and concomitant medications, CHDI in conjunction with the Concomitant medications/Co-morbid Conditions team at the University of Ulm helped to categorize and code each condition and medication. As part of the enhancement, duplicate items were removed, and items were recoded. Please also see the Data Dictionary document for more information.

A self-reported CAG along with a sample was collected whenever possible. There are some cases in which the sample collected was damaged during shipping and was unusable. Attempts were made to re-collect samples when possible but in some cases the participant was lost to contact or may have refused re-collection of the sample.

DEMOGRAPHICS:

Label	Instructions
Gender	Self-reported gender
Race	<p>Self-reported race. At the suggestion of the European Huntington's Disease Network, European sites were given additional choices and participants were asked "What is your area of origin?"</p> <p>05=Caucasian (i.e. British, German, Peninsular Spanish, Latin American, French, Italian, Irish, Swedish, etc.)</p> <p>08=African – Black (i.e. area of origin south of the Sahara)</p> <p>09=African – North (i.e. area of origin Sarah or north of the Sarah: e.g. Algeria, Egypt, Morocco, Tunisia, etc.)</p> <p>04=American – Black (i.e. people of African descent whose are of origin is within the Americas: e.g. Canada, Caribbean, Brazil, US, etc.)</p> <p>11=Asian – West (i.e. area of origin in Bangladesh, India, Iran, Iraq, Pakistan, etc.)</p>

	<p>02=Asian – East (i.e. area of origin China, Japan, Korea, etc.) 01=American Indian/Alaska Native 03=Native Hawaiian or other Pacific Islander 06=Mixed (e.g. Asian-white, Black-white, mestizo, etc) 10=Other (i.e. if none of the above categories reflects your area of origin, then please specify as precisely as possible) _____ 07=Unknown or not reported</p>
Ethnicity	<p>Self-reported ethnicity as related to NIH reporting purposes. European sites were instructed to ask “Are you of Spanish origin (e.g., Iberian Peninsula, Cuban, Mexican, Puerto Rican, South or Central America, or other Spanish Origin?)?”</p>
Educational Years	<p>Participants in the US/Canada/and Australia were asked What was the last grade, year in post high school education, or degree participant completed?</p> <p>11 years = GED 13 years = Additional education post-high school (i.e., technical training, some college courses, etc.), but formal degree was not awarded 14 years = 2-yr Associates degree 16 years = 4-yr College degree 18 years = Master’s degree 19 years = JD 20 years = PhD and MD</p> <p><u>UK Qualification Type:</u> 00 = No formal qualifications 12 = GCSE/O-Level/equivalent 14 = Basic vocational qualification (GNVQ/BTEC etc.) OR A-level/AS level 16 = Higher vocational qualification (HND etc.) 17 = University degree 20 = Higher degree (PGDip, MSc, PhD)</p> <p><u>GERMANY Hochster Abschluss:</u> 00 = kein Abschluss 08 = 8. Klasse 09 = Hauptschulabschluss 10 = Mittlere Reife/POS/10. Klasse 12 = Fachhochschulreife 14 = Abitur 17 = FH-Studienabschluss 19 = Hochschul-Studienabschluss</p>

	<u>SPAIN:</u> 00 = Sin estudios 08 = Basicos (8 yos) 09 = O-level (9 yos) 10 = Diploma tecnico 12 = COU 14 = Carrera media 17 = Formacion profesional 19 = Carrera universitaria
Current Occupation	Occupation during most of the participant's career
Highest Occupation	Highest attained occupation by the participant during their career
Weight	Weight in kilograms. Participant's weight to be done via scale instead of self-report.
Height	Height in centimeters. Participant's height measured instead of self-report.
BMI	The BMI calculated
Comorbid Conditions	Participant is asked to describe current conditions or past history and whether the condition is still present. Categories provided are: Dermatologic Ophthalmologic Pulmonary Cardiovascular (including HTN) Gastrointestinal Hepatic Urologic Gynecologic Musculoskeletal Neurologic (other than HD) Endocrine/Metabolic Allergies Other
Self-Reported CAG	Participants were asked to provide a Self-reported CAG as well as a blood sample to provide a lab verified CAG. As newer techniques were available at the beginning of 2.0 all participants that participated in the 1.0 study and enrolled in the 2.0 study were asked to resubmit a blood sample for an update. In the 2.2 amendment, participants were asked to submit a saliva sample as a less invasive way of collecting lab verified CAG. The CAG provided

CONCOMITANT MEDICATIONS

Medication	Record brand name, if unknown, enter generic name for multiple ingredient medications, indicate strength if possible, e.g., carbidopa/levodopa 25/100
Amount per dose	Record total dosage for each administration e.g., 2 tablets of 300 mg is recorded as 600.
Units	Record type of measure, e.g., mg, cc, puffs
Frequency	Record the frequency using the following items: 1 = qd – once a day 2 = bid – twice a day 3 = tid – three times a day 4 = qid – four times a day 5 = qhs – every night at bedtime 6 = cont iv – continuous intravenous 7 = prn – taken as needed 8 = other
Route	Enter route of administration: 1 = IV - intravenous 2 = IM - intramuscular 3 = PO – by mouth 4 = SC - subcutaneous 5 = PR – per rectum 6 = Sublingual – under tongue 7 = Inhaled – self explanatory 8 = Topical – self explanatory 9 = Other
Start Date	Reported start date of medication. If exact date is not known, enter month and year if possible.
Stop Date	Reported stop date of medication. If exact date is not known, enter month and year if possible
Ongoing	Answer yes if medication is still being taken at end of study; enter Ns in the stop date.
Indication	Reason for use, not drug category
Therapy for Reportable Event	Record medication prescribed/not prescribed for Reportable Event.

COMORBIDITY

Category	1 = Cardiovascular 2 = Pulmonary 3 = Neurologic (Other than HD) 4 = Ears/Nose/Throat (ENT) 5 = Gynecologic/Urologic 6 = Reproductive
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	7 = Gastrointestinal 8 = Endocrine/Metabolic 9 = Hemato/Lymphatic 10 = Dermatological 11 = Psychiatric 12 = Musculoskeletal 13 = Allergy/Immunologic 14 = Ophthalmological 15 = Hepatobiliary 16 = Renal 17 = Other
Onset Date	Reported start date of disorder/disease/surgery. If exact date is not known, enter month and year if possible
Date Resolved	Reported stop date of disorder/disease/surgery. If exact date is not known, enter month and year if possible
Enter and Specify disorder or disease	Name of disorder/disease/disorder

SECTION 3 FUNCTIONAL

INTRODUCTION:

The Functional assessment section was added to the protocol to produce and further refine functional measurements found to be insensitive in the premanifest HD population. This was in response to government regulatory agencies requiring accurate measures of functionality as endpoints for clinical trial models. To better characterize the disease path and earliest HD changes, measure was refined and/or piloted with the aim of increasing sensitivity of detection.

In addition, the Total Functional Capacity (TFC), Functional Assessment Summary (FAS) and the Independence Scale (IS) were modified and/or removed from the protocol. Analysis of the Independence Scale determined that it was not a sensitive early indicator of HD and was removed from the protocol. Decisions were made to discontinue the items in the functional assessment measures where all PREDICT participants had scored at ceiling. Only items showing range in PREDIT-HD were maintained; specifically, The Functional Assessment Summary was reduced to questions 43,44,46,49, and 50. The Total Functional Capacity scale was reduced to questions 70 and 71 initially in the 2.0 study but all questions were reintroduced during the 2.2 amendment. Scoring for the TFC was imputed for the missing items to keep scoring continuous over the course of the study.

FUNCTIONAL ASSESSMENT SUMMARY (FAS)

DESCRIPTION: The functional assessment summary is comprised of yes/no questions in the modified UHDRS '99. The functional rater is asked to determine if the participant is able to perform the daily task based on their impression of disability due to any cause, whether cognitive or physical.

CITATION OF PUBLICATION OF TEST: [Unified Huntington's Disease Rating Scale: reliability and consistency](#). Huntington Study Group. Mov Disord. 1996 Mar;11(2):136-42. Doi: 10.1002/mds.870110204. PMID: 8684382.

METHODS FOR PREDICT: The functional assessment summary was administered in full during the 1.0 study and then reduced to questions 43, 44, 46, 49 and 50 for the rest of the study.

TRAINING INSTRUCTIONS

FUNCTIONAL ASSESSMENT (#43-67)

The functional assessment consists of three principal sections. In the first series of questions, which may only be answered YES (1) or NO (2), the clinician must judge whether the subject has the capacity to perform the task, not if the subject actually performs the task. This assessment is based on the clinician's impression of disability due to any cause, whether cognitive or physical.

General Guidelines for Administration of Functional Assessment checklist (items 43 through 67)

1. Because insight may be impaired in people with HD, it is best to interview an informant in addition to the subject. Sometimes it is helpful to have the subject sitting in front of the informant. In that case, if an informant disagrees with the subject, he/she can nod his head yes/no without the subject's knowledge. Alternatively, you may want to interview the subject and the informant separately. If there is disagreement between the subject and informant, the investigator must use his/her judgment to determine the most likely answer.
2. The time frame for the answers to these questions is the day of the assessment. It is not the time since the last visit or performance over the last week or month.
3. Functional capacity should be judged according to the investigator's opinion of the subject's capacity to perform the activity rather than the actual performance of this activity. If the subject or informant reports that the subject never does or does not want to do the activity, ask: *"Could they do it if they had to?"* The investigator might also ask what would happen if the subject were alone and had to complete the task? For example, if the spouse says that the subject has never managed the monthly finances, the investigator should ask, "If you (informant) were away for a week, would the monthly bills be paid, or would they pile up until you came home?"
4. Impairment of any of the functional activities may be based on any cause, i.e., cognitive impairment, physical impairment, or psychiatric impairment. For example, chorea might impair someone's ability to do housework. Not doing housework might also be due to cognitive impairment such as inability to plan and organize the activity, or psychiatric impairment such as severe apathy associated with lack of initiative.
5. In general, if there is some doubt about the accuracy of the response, ask for specific examples of the ability or inability to perform a given activity. Include enough probes to determine the reason for the problem.

6. An informant or a subject may report that he/she has always had difficulty with the activity, i.e., the subject has always had difficulty managing monthly finances without any help. To help the informant determine whether the subject could perform this activity unassisted, the probe might be: *“Compared to today, do you think he/she could have managed the monthly finances better a year ago?”* Alternatively, the probe could be, *“Do you think he/she could have managed the monthly finances better before he/she had some of the symptoms/signs of HD?”* These probes, which highlight change in function may help the informant determine the subject’s capacity to perform the activity at the present time.
7. For many of the responses, the key feature is the ability to do these activities without any help, i.e., alone. Therefore, if the subject has some difficulty doing the laundry, i.e., it takes longer to put the clothes in the washing machine, but the subject can do the laundry unassisted, the answer to the question *“Could the subject do his/her own laundry (wash/dry) without help?”* is yes. If the subject folds the laundry but does not use the washer or dry, the answer would be no. If there is some doubt, to probe further, the investigator can ask the caregiver, *“If you were away for a week, would the subject do his/her laundry?”*
8. All answers should be answered yes or no. Only use “U” or “N” as specified.

Guidelines for Specific Functional Assessment Questions

- #43** If the subject is no longer able to work at the job, he/she had for the majority of his/her life, answer “no”. For example, if the person worked in a fast-food chain as a cashier, and after developing HD was forced to leave that job and worked in a less demanding job, the answer would be “no” to gainful employment in accustomed work. If the subject is a homemaker who never worked for pay, the probe for this person might be: *“Can the subject manage the household today as well as he/she always has, or must they have assistance to do so?”* If assistance is now required, the answer would be “no”.
- #44** Gainful employment means that the person is paid for their services. This is judged as potential capacity, not whether the person is actually working.
- #45** Volunteer or non-gainful work means the person is not paid for their services.
- #46** Refer to General Guidelines #6.
- #47** Shopping for groceries without help means going into the store and obtaining groceries without assistance. If the subject requires help carrying bundles, but can otherwise handle the task, the answer is “yes.”
- #48** The person should be able to go to a store and come back with the correct change.
- #49** Supervising children means physically as well as cognitively caring for children who could not otherwise be left alone. This does not mean infants.
- #50** Operating an automobile safely and independently means the subject can drive without others feeling afraid to drive with the subject and showing good judgment. If the person has

never learned how to drive, the answer should be “N” (Not Applicable) since it is difficult to judge potential in this situation.

- #51** Housework activities might include cooking, vacuuming, dusting, taking out the trash, and doing dishes. If a subject never did any housework, ask about picking up after themselves (e.g., doing light dusting or making the bed) and hanging up his/her clothes. Housework might also extend to light yard work if that was the subject’s responsibility.
- #52** If the subject only folds laundry and does nothing else, the answer is “no”.
- #53** Preparing meals can include making a sandwich, heating up soup, or using the microwave, as long as the person does it himself/herself. A probe might be, *“if the subject were left alone, would he/she be able to prepare his/her own meals?”*
- #54** Using a telephone without help means the ability to make outgoing calls and answer the telephone.
- #55** If the subject has the pills in a dispenser but he/she is able to remember to take them by himself/herself, then the answer is “yes”. If the subject cannot physically handle medications without assistance, the answer is “no.”
- #56** If the subject cannot cut his/her own food without assistance, then the answer to ability to feed himself/herself without help is “no”.
- #57** If the subject must have clothes laid out but he/she can dress properly (i.e., enough to be presentable), the answer is “yes”.
- #58** If the subject requires assistance getting into the shower/tub, but then bathes himself/herself, the answer is “yes.”
- #59** Public transportation includes bus and train. If there is no public transportation the question should be, *“if public transportation were available, could he/she use it without assistance?”*
- #60** Walking to places in the neighborhood without help implies not getting lost. A probe might be, *“would he/she be able to find his/her way home if he/she was out on one of the streets in the neighborhood?”*
- #61** Falling should occur at least once a week for a “no” answer. A one-time fall does not indicate a “no” answer.
- #62** Required use of a walker or a cane is “help”. In other words, if the subject cannot walk without an assistive device, the answer is “no”.
- #63-66** Self-explanatory.

- #67** Care at home implies only whether the person is capable of living at home, rather than in the equivalent of institutional care.

INDEPENDENCE SCALE

DESCRIPTION: The Independence Scale is intended to assess the ability of the subject to function independently in activities of daily living across the full spectrum of the disease since the last visit. The scale makes inquiry of a general level of functioning representative of the capabilities of the subject as judged by the investigator. By using specific tasks as benchmarks, this scale attempts to quantify a subject's general level of function. However, in some instances these tasks may not pertain to the experiences of a particular subject, and the clinician will have to make a judgment as to the ability of the subject to perform that task if he or she were required to do so.

CITATION OF PUBLICATION OF TEST: [Unified Huntington's Disease Rating Scale: reliability and consistency](#). Huntington Study Group. Mov Disord. 1996 Mar;11(2):136-42. doi: 10.1002/mds.870110204. PMID: 8684382.

METHODS FOR PREDICT: The independence scale was administered throughout the span of the 1.0 study. The independence scale was dropped from the battery after analysis of the scale revealed limited sensitivity as an indicator to early HD.

TRAINING INSTRUCTIONS

INDEPENDENCE SCALE (#69)

Guidelines for administration of the Independence Scale

The Independence Scale is intended to assess the ability of the subject to function independently in activities of daily living across the full spectrum of the disease since the last visit. As with the Total Functional Capacity (TFC), it is best to interview an informant in addition to the subject. The scale makes inquiry of a general level of functioning representative of the capabilities of the subject as judged by the investigator. By using specific tasks as benchmarks, this scale attempts to quantify a subject's general level of function. However, in some instances these tasks may not pertain to the experiences of a particular subject, and the clinician will have to make a judgment as to the ability of the subject to perform that task if he or she were required to do so.

It is acceptable to score a subject as intermediate between two levels (e.g., 75) when the subject maintains some attributes of the upper level but not others.

100 No special care needed.

The subject shows no decline in ability to perform at pre-disease levels in any sphere of activity. This score is generally reserved for an assessment of persons at risk and asymptomatic.

90 No physical care needed if difficult tasks are avoided.

The subject functions at an apparently unimpaired level in employment, interpersonal relationships, and personal finances so long as he or she is not confronted with an unusual challenge or high-stress circumstance.

- 80 Pre-disease level of employment changes or ends; cannot perform household chores to pre-disease level; may need help with finances.
- Subjects who have been gainfully employed are not able to continue in the same position and must either stop working altogether or accept a position of lesser responsibility. For subjects who have generally not worked outside the home, the ability to manage and perform their daily tasks (such as grocery shopping, cleaning and home maintenance, and childcare), is lessened. The ability to oversee income tax preparation and more complex aspects of personal finances (e.g., investment or retirement plans) will also lessen at this stage for subjects who have been involved in these activities previously.
- 70 Self-care maintained for bathing; limited household duties (cooking and use of knives); driving terminates; unable to manage finances.
- Some aspects of personal hygiene and other activities of daily living may be impaired although the basic capacity to bathe remains. Generally, employment or supervision of household chores will have ceased and, although the individual is still at home, his or her ability to perform household duties is limited. Tasks requiring manual and cognitive dexterity such as cutting food or using a stove are impaired. By this time the subject has or should have stopped driving and can no longer manage his/her finances although still able to use money for simple purchases.
- 60 Needs minor assistance in dressing; food must be cut for subject.
- The subject can no longer function with total independence for basic tasks of dressing and eating. Modifications to the home may include a change to clothes that are more easily put on and removed or use of finger foods or foods that can be eaten with a spoon alone as opposed to knife and fork.
- 50 24-hour supervision appropriate; assistance required for bathing, eating, toileting.
- The subject may not necessarily reside in a nursing facility or chronic care facility, but such a placement would not be considered inappropriate. In accordance with such a placement, the subject would benefit from supervision and assistance for essential activities of daily living.
- 40 Chronic care facility needed: limited self-feeding, liquefied diet. The subject either resides in a chronic care facility or is cared for in manner consistent with such placement at home. The subject is able to eat finger foods or can use utensils only with greater difficulty. The texture of food items may have been modified to include softer or pureed foods.
- 30 Subject provides minimal assistance in own feeding, bathing, toileting. The subject requires significant assistance with all activities but is still able to sit in a chair.
- 20 No speech; must be fed. The subject provides no assistance for any activities. There is no recognizable speech, although the subject may vocalize.
- 10 Tube fed; total bed care. The subject is never out of bed and requires total care, for all personal care and can be appropriately considered a candidate for tube feeding although this may not actually have been instituted.

TOTAL FUNCTIONAL CAPACITY (TFC)

DESCRIPTION: The Total Functional Capacity (TFC) is comprised of questions 70-74 of the Unified Huntington's Disease Rating Scale. Questions cover occupation, finances, domestic responsibilities, perform activities of daily activities, and level of care.

CITATION OF PUBLICATION OF TEST: Shoulson I, Kurlan R, Rubin A, Goldblatt D, Behr J, Miller C, Kennedy J, Bamford K, Caine E, Kido D, Plumb S, Odoroff C: Assessment of functional capacity in neurodegenerative movement disorders: Huntington's disease as a prototype, in *Quantification of Neurologic Deficit*, T Munsat (ed), Butterworths, Stoneham, MA., pp. 271-283, 1989.

[Unified Huntington's Disease Rating Scale: reliability and consistency](#). Huntington Study Group. Mov Disord. 1996 Mar;11(2):136-42. doi: 10.1002/mds.870110204. PMID: 8684382.

METHODS FOR PREDICT: The total functional capacity scale was administered throughout the PREDICT-HD study. The scale was presented in full during the 1.0 study and during the 2.2. amendment until the end of the study. At the beginning of the 2.0 study through the 2.2. amendment, the number of questions was reduced to questions 70 and 71 with the missing items imputed to provide a total functional capacity score. The rationale behind the removal of some questions was due to time constraints and that the questions removed were not statistically significant to the overall score in this particular participant population. The questions were re-inserted in the 2.2 amendment until the end of the study. The rationale was that the questions did not add significant time to the battery.

TRAINING INSTRUCTIONS

FUNCTIONAL CAPACITY (#70-74)

Guidelines for Assessing (Total) Functional Capacity (TFC)

The HD Functional Capacity (HDFC) Scale, also referred to as Total Functional Capacity (TFC) or the Shoulson-Fahn scale, was designed so that a health professional experienced with HD could evaluate a subject based on a brief interview involving the subject and a close family member or friend familiar with the subject's functioning. The scale has undergone extensive validity and reliability testing in large populations of HD subjects [1].

The HDFC scale focuses on assessment of the subject's capacity rather than actual performance. This places the emphasis on the clinician's judgment and does not require rigorous documentation of performance. The examiner is required to arrive at a clinical rating of the subject's capabilities - a judgment that the clinician commonly makes in the day-to-day evaluation of disability. An examination of the subject's actual motor or cognitive performance is only required to the extent that it aids in arriving at a realistic assessment of the subject's capabilities. Accordingly, the TFC should take into account a global assessment of the subject's motor and cognitive capabilities but does not require formal assessment of motor or cognitive performance.

On the basis of a 5-10 minute interview, the clinician rates the subject in each of the 5 categories according to what the subject is judged capable of doing. The scale should reflect current capacity

and should be assessed independent of prior examinations. The subject may overestimate capacity, and the interview involving family or friend helps to confirm actual function.

Guidelines for Specific Functional Capacity Questions

#70 Engagement in Occupation

The subject's capacity to engage satisfactorily in gainful or voluntary work is assessed regardless of whether or not the subject is actually working. *Normal* refers to gainful employment, actual or potential, with usual work expectations. *Reduced Capacity* refers to full or part-time gainful employment with lower-than-usual work expectation (relative to the subject's training and education), but with satisfactory performance. *Marginal* refers to a capacity only for part-time employment, actual or potential, with low work expectations. *Unable* refers to a subject who would be unable to work, even with considerable assistance and oversight.

#71 Capacity to Handle Financial Affairs

Functional capacity is assessed by surveying the subject's involvement in personal and family finances including balancing a checkbook, paying bills, budgeting, shopping, etc. *Normal* capacity refers to satisfactory handling of these basic financial tasks. *Requires slight assistance* refers to mild difficulties that would require the assistance/oversight of a family member or financial advisor. *Requires major assistance* refers to a subject who would require extensive supervision in handling routine financial tasks. *Unable* refers to a subject who would be unable to carry out these financial tasks, even with considerable assistance and oversight.

#72 Capacity to Manage Domestic Responsibilities

This category refers to the subject's capacity to carry out routine domestic tasks such as cleaning, laundering, dishwashing, table setting, cooking, lawn care, answering mail, maintaining a calendar, etc. *Normal* capacity refers to a full capacity without assistance. *Impaired* refers to a less than normal capacity, requiring some assistance or supervision. *Unable* refers to marked incapacity requiring major assistance.

#73 Capacity to Perform Activities of Daily Living

This category refers to the traditional areas of "activities of daily living", including eating, dressing and bathing. *Normal* refers to full capacity. *Minimal impairment* refers to impaired capacity requiring only slight assistance. *Gross tasks only* refers to requiring moderate assistance and supervision. *Total care* refers to major incapacity requiring total assistance and supervision.

#74 Level of Care

This category refers to the most appropriate care environment to meet the subject's capacity, whether at *home*, at *home or chronic care facility*, or *full skilled nursing care (24-hour-a-day supervision)*.

V. CLINICAL SUMMARY (#80)

- #80** To answer this question the examiner must take into account all aspects of the UHDRS (Motor, Cognitive, Behavioral and Functional components) and to decide with a confidence level $\geq 99\%$ whether the subject has manifest HD.

WORLD HEALTH ORGANIZATION (WHO) DISABILITY ASSESSMENT SCHEDULE (WHODAS II/2.0 36/12)

DESCRIPTION: The WHODAS 36 is comprised of 36 questions that provides a profile of functioning across six activity domains as well as a general disability score. The WHODAS 12 is a shortened version of the WHODAS 36 with that provides a general disability score comparable to the WHODAS 36.

CITATION OF PUBLICATION OF TEST:

Ustün TB, Chatterji S, Kostanjsek N, et al. [Developing the World Health Organization Disability Assessment Schedule 2.0](#). Bulletin of the World Health Organization. 2010 Nov;88(11):815-823. DOI: 10.2471/blt.09.067231.

METHODS FOR PREDICT: The WHODAS 36 was introduced to the PREDICT-HD battery during the 2.0 study. The WHODAS 36 was administered to all participants as well as their companions if applicable. The WHODAS 36 was discontinued in favor of the shortened 12 item version. The scoring provided is based on simple calculation rules provided in the WHDOAS manual. WHODAS 12 scores are provided for all participants that have WHODAS and answered the required number of questions for scoring, while scores for the 36-question survey are provided where applicable. For items that are missing, the mean of the other items are used to assign a score to the missing item. Scores for the 36-question survey are provided where applicable. If 2 items or less are missing from the whole measure and are not from the same domain, the mean of the other items within the domain are used to assign a score to the missing items. If the respondent was not working and the respondent has answered the 32-item WHODAS 2.0, then the score can be used as is.

TRAINING INSTRUCTIONS

WHO-DAS II

Description:

The World Health Organization Disability Assessment Schedule II (WHODAS II) has been under development by WHO (World Health Organization) for several years. Available versions include self-administered, interviewer-administered, and proxy-reported.

The WHODAS II provides a profile of functioning across six activity domains, as well as a general disability score. This information can be used to

- Identify needs
- Match patients to interventions
- Track functioning over time
- Measure clinical outcomes and treatment effectiveness

The PREDICT-HD 2.0 battery includes the following Domain Reviews from the WHO-DAS II:

1. Understanding and Communicating
2. Getting Around
3. Self-Care
4. Getting Along with People
5. Life Activities
6. Participation in Society

Administration (Participant):

Please refer to the WHODAS manual for expanded instructions related to administration guidelines, details about specific questions and test scenarios for training purposes.

Administration (Companion):

Please refer to the WHODAS manual for expanded instructions related to administration guidelines, details about specific questions and test scenarios for training purposes.

WHODAS 2.0 (12-item version, self-administered)

Description:

These questions are adapted from the WHODAS II. The World Health Organization Disability Assessment Schedule II (WHODAS II) has been under development by the WHO (World Health Organization) for several years. Available versions include self-administered, interviewer-administered, and proxy-reported.

The WHODAS II provides a profile of functioning across six activity domains, as well as a general disability score. This information can be used to

- Identify needs
- Match patients to interventions
- Track functioning over time
- Measure clinical outcomes and treatment effectiveness

The PREDICT-HD 2.2 battery includes the following Domain Reviews from the WHO-DAS II:

1. Understanding and Communicating (Cognition)
2. Getting Around (Mobility)
3. Self-Care
4. Getting Along with People
5. Life Activities (Household and Work/School Activities)

6. Participation in Society

Administration:

Both the participant and companion WHODAS 2.0 forms are self-report. They should read the instructions and complete the form in its entirety.

Participant instructions: “This questionnaire asks about difficulties due to health conditions. Health conditions include diseases or illnesses, other health problems that may be short or long lasting, injuries, mental or emotional problems, and problems with alcohol or drugs.

Think back over the past 30 days and answer these questions, thinking about how much difficulty you had doing the following activities. For each question, please circle only one response.”

Companion instructions: “This questionnaire asks about difficulties due to health conditions experienced by the person about whom you are responding in your role as friend, relative or carer. Health conditions include diseases or illnesses, other health problems that may be short or long lasting, injuries, mental or emotional problems, and problems with alcohol or drugs.

Think back over the past 30 days and, to the best of your knowledge, answer these questions thinking about how much difficulty your friend, relative or carer had while doing the following activities. (Note: the questionnaire uses the term “relative” to mean “friend”, “relative” or “carer”.) For each question, please circle only one response.”

SECTION 4: MOTOR ASSESSMENT

DESCRIPTION: The motor assessment is part of the Modified Unified Huntington's Disease Rating Scale '99 (UHDRS '99) and assesses various motor features of Huntington's Disease. The areas are oculomotor function, dysarthria, chorea, dystonia, gait and postural stability. Each area assessed is standardized and is on a scale of 0-4.

CITATION OF PUBLICATION OF TEST: [Unified Huntington's Disease Rating Scale: reliability and consistency](#). Huntington Study Group. Mov Disord. 1996 Mar;11(2):136-42. doi: 10.1002/mds.870110204. PMID: 8684382.

METHODS FOR PREDICT: The motor assessment section of the Modified UHDRS was administered throughout the entire study and is considered one of the core assessments in the battery. The Diagnostic Confidence Level is one of the outcomes of the motor assessment that is used in clinical settings onset of HD diagnosis. In addition, several scores are derived from the individual items. Scoring is as follows:

Total Oculo Score: Sum of ocular pursuit, saccade initiation, and saccade velocity

Total brady score: Sum of dysarthria, tongue protrusion, finger taps, pronate/supinate hands, Luria, bradykinesia, gait, tandem, retropulsion

Total rigidity score: Degree of resistance in movement in both arms (0=absent to 4=severe for each arm)

Total dystonia score: Degree of sustained abnormal posturing/movement in trunk and extremities (0=absent to 4=prolonged for each of 5 areas)

Total chorea score: Degree of rapid abnormal involuntary movements/contractions in face, trunk, and extremities (0=absent to 4=prolonged for each of 7 areas)

Total Motor Score: Sum of 31 motor items (UHDRS1-UHDRS15)

TRAINING INSTRUCTIONS

I. INTRODUCTION

Neurobiological Predictors of Huntington's Disease (PREDICT-HD) is a prospective, multicenter, observational study of people who are at risk for Huntington's disease (HD) by virtue of having (or having had) a parent with HD.

One aim of the study is to characterize the transition from health to illness ("phenoconversion") in a cohort of participants at risk for HD, and to determine a rate for that transition. One outcome variable will be time to phenoconversion, judged to have occurred when the Motor Rater (MR) is 99% confident that the participant has motor abnormalities that are unequivocal signs of HD (i.e., HD diagnosis confidence level of 4 on item 17 of the Unified Huntington's Disease Rating Scale '99 [UHDRS '99]).

The MR will perform the motor UHDRS at baseline and every 12 months. MRs have been selected on the basis of their knowledge in evaluating patients with HD, their experience in controlled clinical trials, and their skills in carrying out the UHDRS examination. In operational terms, MRs should function as “UHDRS rating machines”, while maintaining appropriate clinical sensibilities with research participants and their families.

II. RESPONSIBILITIES OF THE MOTOR RATER (MR) IN PREDICT-HD

a. PREDICT-HD Protocol, UHDRS '99 Motor Assessment and UHDRS '99 Motor Assessment Guidelines

All MRs should review the latest version of the PREDICT-HD protocol. MRs are responsible for familiarizing themselves with the motor portion of the UHDRS '99 and particularly with the revised “HD Diagnosis Confidence Level.” The MR should review the updated UHDRS '99 Guidelines for completion of the motor UHDRS.

b. Inter-Rater Reliability Training

For purposes of assessing inter-rater reliability, videotapes showing patients at various stages of illness onset will be used to train each MR. The MRs will view the videotapes and, using the form provided, rate each patient shown on

“the tape according to the “HD diagnosis confidence level.” The MR will complete this task at a single sitting without replaying the tape, changing ratings, or soliciting the input of other clinicians.

Note: The same rater should be used to perform motor assessments (i.e., Section 1 of the UHDRS) throughout this study. The consistent use of one rater will increase the reliability of the data.

c. Performing the motor exam

The interaction with the participant can be accomplished by saying to the participant, “Hello, Mr./Mrs. _____. I'm Dr. _____. First I'm going to do the motor examination.”

III. PRECAUTIONS

The MR will see participants every 12 months. **No other clinician may substitute for the MR. It is the responsibility of the MR to ensure availability at every visit.**

V. COMMUNICATION REGARDING PREDICT-HD

If the MR has any questions about the PREDICT-HD protocol, this manual, the videotape training, or the role and responsibilities of the MR, these should be directed to:

Elise Kayson, MS, RNC, Project Coordinator

Phone: 585-275-4696

Email: elise.kayson@ctcc.rochester.edu

or

Jane Paulsen, PhD, Principal Investigator

Phone: 319-353-4551

Email: jane-paulsen@uiowa.edu

EXAMINATION GUIDELINES FOR THE MODIFIED UNIFIED HUNTINGTON'S DISEASE RATING SCALE '99 (UHDRS '99)

I. MOTOR ASSESSMENT

- #1 OCULAR PURSUIT** - Ocular pursuit should be assessed over a range of approximately 20° with a target passing slowly at $\leq 10^\circ$ per second, which corresponds to about 2 seconds for moving an object from one shoulder to the other.
- #2-3 SACCADIC INITIATION AND VELOCITY** - Saccadic initiation should be tested over a 20° range, as for ocular pursuits. Saccadic movement should be elicited by a sound (snapping fingers) or movement (wiggle fingers), but not by a verbal command to look to the right or left. Saccadic velocity should be tested at a larger range of approximately 30° so as to be able to detect incomplete range.
- #4-5 DYSARTHRIA AND TONGUE PROTRUSION**
Self-explanatory.
- #6 FINGER TAPS** - Subject taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately.
- #7 PRONATE/SUPINATE HANDS** - This task requires the subject to alternately hit the palmar and dorsal surface of one hand against the palm of the opposite hand. Use the palm of the opposite hand as a target, instead of some other surface such as the subject's leg or the table surface. The subject should do this task as quickly as possible over a 5-second interval. The task is graded according to the degree of slowing and irregularity.

- #8 LURIA – FIST-HAND-PALM SEQUENCING THREE STEP** - Say *“Can you do this?”* Examiner puts hand into fist on flat surface (or in lap) and sequences as follows: fist, side, flat (DO NOT SAY THIS OUT LOUD). Watch to make sure that subject can mimic each step. Continue to practice Luria 3-step for 1-2 minutes. When subject is able to join you then say, *“Very good, now keep going; I am going to stop.”* Rest hand and start timing subject’s sequences. A sequence is considered correct only if it is unaided by examiner model and in the correct order. Count completed sequences and score. If subject was unable to complete any sequences over a 10-second period, then continue as follows. Say *“Now let’s try it again. Put your hands like this. FIST, SIDE, FLAT.”* Watch to make sure the subject can mimic each step. Using the verbal labels, begin the sequences again and ask the subject to *“Do as I do, Fist, Side, Flat”* (repeat this as you continue). Continue to perform Luria 3-step. When subject is able to join you say, *“Very good; now keep going, I am going to stop.”* Rest hand and start timing subject’s sequences. A sequence is considered correct if it is unaided by examiner model and in the correct order. Count completed sequences and score as above.
- #9 RIGIDITY-ARMS** - Rigidity is judged on passive movement of the arms with the subject relaxed in the sitting position.
- #10 BODY BRADYKINESIA** - Observe the subject during spontaneous motion such as walking, sitting down, arising from a chair, and executing the tasks required during the examination. This rating reflects the examiner’s overall impression of bradykinesia.
- #11-12 MAXIMAL DYSTONIA (TENDENCY TOWARD A POSTURE, POSTURING ALONG AN AXIS) AND MAXIMAL CHOREA (MOVEMENT)** - Observe the subject during the examination, i.e., no particular maneuvers are required to illicit these features. Maximal dystonia and chorea are typically observed during demanding motor tasks such as tandem gait. Both dystonia and chorea are rated by specific regions. “BOL” refers to buccal-oral-lingual. Facial dystonia includes blepharospasm, jaw opening and closing. When rating dystonia (question #11) BOL, and facial dystonia should be included in your assessment of the truncal region.
- #13 GAIT** - Observe the subject walking approximately ten yards as briskly as they can, then turning and returning to the starting point.
- #14 TANDEM GAIT** - The subject is requested to walk ten steps in a straight line with the foot placed (accurately but not quickly) such that the heel touches the toe of the other foot. Deviations from a straight line are counted.
- #15 RETROPULSION PULL TEST** - The subject’s response to a sudden posterior displacement produced by a pull on the shoulder while the subject is standing with eyes open, and feet slightly apart is assessed. The shoulder pull test must be done with a quick, firm tug after warning the subject. The test may be repeated if the subject did not have sufficient warning or did not understand the test. The subject

should be relaxed with feet apart and should not be leaning forward. If the examiner feels pressure against his/her hands when placed on the subject's shoulders, the examiner should instruct the subject to stand up straight and not lean forward. The examiner should instruct the subject to take a step backward to avoid falling.

Examiners must catch subjects who begin to fall. To prevent either individual from falling to the floor, examiners should brace themselves with one foot back and/or stand between subject and a wall. However, adequate room is needed to test retropulsion and recovery. Subjects should be told that taking one step backwards is acceptable.

#16 WEIGHT - Self-explanatory.

#17 DIAGNOSTIC CONFIDENCE LEVEL

0 = normal (no abnormalities)

1 = non-specific motor abnormalities (less than 50% confidence)

2 = motor abnormalities that *may* be signs of HD (50 - 89% confidence)

3 = motor abnormalities that are *likely* signs of HD (90 - 98% confidence)

4 = motor abnormalities that are *unequivocal* signs of HD (\geq 99% confidence)

The diagnosis of HD is based on the unequivocal presence of an otherwise unexplained extrapyramidal movement disorder (e.g., chorea, dystonia, bradykinesia, rigidity) in a subject at risk for HD.

The grade assigned by the investigator represents a level of confidence for the diagnosis of HD in a particular subject. Grade 1 represents a < 50% confidence level for a particular subject who may have non-specific motor abnormalities. Such abnormalities could include mild clumsiness or slowness that might be normal findings, or non-specific changes such as distal weakness. Grade 2 implies a 50 - 89% confidence level and should be assigned to a subject with suggestive but not definitive clinical findings. Such findings could include mild slowness and clumsiness with minimal non-specific oculomotor abnormalities. Grade 3 should be assigned to a subject that has motor abnormalities that are likely signs of HD (90 - 98% confidence). Such abnormalities could include intermittent movements that could represent chorea in the setting of mild motor slowing. Grade 4 should be assigned only to a subject with an unequivocal extrapyramidal movement disorder in the presence of a confirming family history or known positive gene test, when the examiner is \geq 99% confident (only errs 1 in 100 such instances) that the subject has HD. Such findings would include the presence of definite chorea or dystonia, usually with accompanying motor slowing.

SECTION 5: PSYCHIATRIC

INTRODUCTION:

The Psychiatric assessment section was part of the 1.0 and 2.0 protocol. The initial 1.0 study Psychiatric assessment battery consisted of the Symptom Checklist 90 revised (SCL90R), Frontal System Behavioral Scale (FrSBe), Beck Depression Inventory II (BDI-II), Beck Hopelessness Scale (BHS), Perceived Stress Scale (PSS), Haidt Disgust Scale (Haidt), Leyton Inventory (Leyton), Unified Huntington Disease Rating Scale Behavioral (UHDRS BEH), and Life Events Scale (LES). The Leyton was administered up until Amendment 3 and then was dropped in favor of the Schedule of Compulsions, Obsessions, and Pathological Impulses (SCOPI) form (see Protocol document for more information). The Substance Use Form (SUF) was added at Amendment 4.

The 2.0 study kept the SCL90R, FrSBe, UHDRS BEH), and SUF. The BDI-II, BHS, PSS, Haidt, LES, and SCOPI were all removed from the initial 2.0 study. The Columbia Suicide Severity Rating Scale (CSSRS), HD Behavioral Scale comprised of the Starkstein Apathy Scale and Snaith Irritability Scale (HDBS), and Structured Interview for Behavior in HD (SIB-HD) were added.

At Amendment 2, the UHDRS Behavioral form was added to the protocol as a comparison to the SIB-HD. Both the SIB-HD and UHDRS Behavioral form were removed at Amendment 3. It was determined that the SIB development portion was complete.

At Amendment 4, The BDI-II was re-inserted as a review of depression data revealed that it was a better measure to use. The Problem Behaviors Assessment short form (PBA-s) was introduced as well as it is specifically designed to address the most common behavioral and psychiatric manifestations in HD. The SUF and HDBS were removed as a version of the SUF was inserted into the Environmental and Family History Questionnaire (EFHQ) and the HDBS was removed due to participant burden. The SCL90r and FrSBe measures were reduced from 90 items to 28 and 23 down to 18 respectively as data analyses revealed clear differences between items sensitive in the pre-HD population versus those items that were not.

The SUF was re-inserted into the battery after quality control processes and participant feedback showed insufficient data for statistical analyses capabilities and participant burden was too high.

SYMPTOM CHECKLIST 90 REVISED (SCL90-R)

DESCRIPTION: The Symptom Checklist 90 Revised is a 90 items questionnaire used to assess psychological problems. The test helps to measure 9 primary symptom dimensions and is designed to provide an overview of a patient's symptoms and their intensity at a specific point in time.

CITATION OF PUBLICATION OF TEST: Derogatis, Leonard R.; Savitz, Kathryn L. (2000). "[The SCL-90-R and the Brief Symptom Inventory \(BSI\) in Primary Care](#)". In Maruish, Mark Edward (ed.). Handbook of psychological assessment in primary care settings. Mahwah, NJ: Lawrence Erlbaum Associates. pp. 297–334. ISBN 978-0-8058-2999-0. OCLC 42592750

METHODS FOR PREDICT: The Symptom Checklist 90 Revised was administered throughout the PREDICT-HD study. The full 90 questions were administered up to the 2.2 amendment. Item analysis of the SCL90r was done, and a subset of questions showed promise as a reduced measure within the SCL90r for HD disease progression. The number of questions were reduced to 28 in an attempt to determine if a reduced measure was viable, however, further analysis was halted in 2014 as the study ended for all sites except for the University of Iowa.

TRAINING INSTRUCTIONS

SYMPTOM CHECKLIST-90-R (SCL-90-R)

Description:

The SCL-90-R is a self-report symptom inventory consisting of 90 items and is intended to reflect the psychological symptom pattern of community, medical and psychiatric respondents. Each checklist item is rated from 0-4 in terms of distress (0 = not at all; 4 = extremely). The SCL-90-R is then scored and interpreted on nine primary symptom dimensions (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism) as well as three global indices of distress (global sensitivity index, positive symptom distress index, and positive symptom total).

Administration:

This test will be administered to both the participant and the participant's companion at each visit (V1 – V4). For the companion administration, when the instructions are read, please inform the companion that they are answering in terms of how often the behaviors occur in the participant (**not the companion**).

The SCL-90-R typically takes between 12 and 15 minutes to complete, and the time for administrative instructions is 2 to 5 minutes. The SCL-90-R will be administered to both the PREDICT-HD participant and their companion individually. The following instructions should be read to the respondent: **NOTE: Due to copyright permissions, portions of the administration instructions have been removed.**

The following instructions should be read to the Companion: **NOTE: Due to copyright permissions portions of the instructions have been removed.**

LEYTON INVENTORY (LEYTON)

DESCRIPTION: The Leyton Obsessional Inventory is a self-report inventory consisting of 20 items designed to measure obsessive behaviors.

CITATION OF PUBLICATION OF TEST: Flament MF, Whitaker A, Rapoport JL, Davies M, Berg CZ, Kalikow K, Sceery W, Shaffer D. [Obsessive Compulsive Disorder in Adolescence: An Epidemiological Study](https://doi.org/10.1097/00004583-198811000-00018). Journal of the American Academy of Child & Adolescent Psychiatry. 1988;27(6):764-71.
<https://doi.org/10.1097/00004583-198811000-00018>

METHODS FOR PREDICT: The Leyton Inventory was administered from 2002 to prior to the approval of the third amendment of PREDICT which spans from May 2004 through March 2005. After which the Leyton Inventory was discontinued.

The Leyton Inventory is scored as follows:

The scale contains the following:

Yes/No Questions

1 = Yes

0 = No

Interference Questions

0 = Wastes none of my time

1 = Wastes a little of my time

2 = Wastes some of my time

3 = Wastes a lot of my time

The Yes/No answers are added together, and the Interference questions are also added together. The participants are further divided into groups called the High Yes/Low interference group, High Interference group, and negative group. The scoring criteria for each group is as follows:

Yes score ≥ 15 and Interference score ≤ 10 = High Yes/Low interference group

Interference score ≥ 25 = High Interference group

All other scores are considered the negative group.

TRAINING INSTRUCTIONS

LEYTON INVENTORY (LEY)

Description:

The Leyton Obsessional Inventory is a self-report inventory consisting of 20 items designed to measure obsessive behaviors.

Administration:

The Leyton typically takes about 5 - 7 minutes to complete and will be administered at Visits 1-4. The Leyton should be administered to both the participant and the companion. The following instructions should be read to the participant: *"Please mark "Yes" or "No" to the following questions. If you answer*

“Yes” to any of these questions, mark the number (0 - 3) to indicate how much time you spend on each habit, according to this scale: (0 = wastes none of my time, 1 = wastes a little of my time, 2 = wastes some of my time, 3 = wastes a lot of my time).” The instructions for the companion are as follows: “Please mark “Yes” or “No” to the following questions as they pertain to the PREDICT participant. If you answer “Yes” to any of these questions, mark the number (0 - 3) which describes how each habit affects the HD participant, according to this scale: (0 = wastes none of his/her time, 1 = wastes a little of his/her time, 2 = wastes some of his/her time, 3 = wastes a lot of his/her time).”

FRONTAL SYSTEMS BEHAVIOR SCALE (FRSBE)

DESCRIPTION: The FrSBE was designed to identify and quantify behavioral problems associated with frontal lobe dysfunction. This scale assesses behavior related to frontal systems damage. It also quantifies behavioral changes over time by including both baseline (retrospective) and current assessments of behavior.

CITATION OF PUBLICATION OF TEST: Grace, J., & Malloy, P. F. (2001). [FrSBe Frontal System Behaviour Scale: Professional manual](#). Lutz, FL: Psychological Assessment Resources, Inc

METHODS FOR PREDICT: The Frontal Systems Behavior Scale (FrSBe) was administered throughout the PREDICT-HD study. The full 46 question scale was administered up through the 2.2 amendment of the study. Item analysis of the FrSBe was done and a subset of questions showed promise as a reduced measure within the FrSBe for HD disease progression. The number of items were reduced to 36 in an attempt to determine if a reduced measure was viable, however, further analysis was halted in 2014 as the study ended for all sites except for the University of Iowa.

TRAINING INSTRUCTIONS

FRONTAL SYSTEMS BEHAVIOR SCALE (FrSBe)

Description:

The FrSBe is designed to provide a measure of three frontal systems-associated behavioral syndromes: apathy, disinhibition, and executive dysfunction.

Administration:

NOTE: Due to copyright permissions portions of the administration instructions have been removed.

The FrSBe takes about 10 minutes to administer. The FrSBe will be administered to both the PREDICT-HD participant and their companion individually.

The following instructions should be read to the **Participant**: **NOTE:** Due to copyright permissions portions of the administration instructions have been removed.

The following instructions should be read to the **Companion**: **NOTE:** Due to copyright permissions portions of the administration instructions have been removed.

BECK DEPRESSION INVENTORY II (BDI-II)

DESCRIPTION: The BDI-II is a 21-item self-report instrument measuring the severity of depression in adults and adolescents ages 13 and older.

CITATION OF PUBLICATION OF TEST: Beck, A.T., Steer, R.A., & Brown, G.K. (1996). [Manual for the Beck Depression Inventory-II](#). San Antonio, TX: Psychological Corporation.

METHODS FOR PREDICT: The BDI-II was administered every year from the start of the study through the end of the 1.0 phase of PREDICT when it was discontinued for the 2.0 phase of the study. The BDI-II was re-introduced into the PREDICT 2.0 phase starting in September of 2011 at Iowa and at all participating sites. Starting dates of the administration of the BDI-II vary based on IRB approval at each site. Raw scores are derived as the following:

BDI-II Total – Sum of all 21 items

Scoring is based on 0-3 scale

Questions 16 and 18 allow have a different scale that includes letters, 1a, 1b,2a,2b,3a,3b. Options 1a and 1b are set to 1

Options 2a and 2b are set to 2

Options 3a and 3b are set to 3

BDI -Total scoring range is 0-63

Per NDA scoring guidelines, missing items can be imputed by following guidelines established in the data dictionary. The total number of missing items must be less than 5. If there are less than 5 missing items, the score is imputed by taking the integer median of the non-missing items, bdi1 through bdi21.

TRAINING INSTRUCTIONS

BECK DEPRESSION INVENTORY – II (BDI-II)

Description:

The BDI-II is a 21-item self-report instrument for measuring the severity of depression in adults and adolescents ages 13 and older.

Administration:

The BDI-II typically takes 5 to 10 minutes to complete. It will be administered at Visits 1-4. The following instructions should be read to the respondent:

NOTE: Due to copyright permissions portions of the administration instructions have been removed.

Screening for Referral

For the purpose of screening for major depression, the following interpretation of scores should be used: 0-13 = minimal; 14-19 = mild; 20-28 = moderate; 29-63 = severe.

NOTE: *Participants admitting to suicide ideation (item 9) and hopelessness (item 2 – pessimism) with a rating of 2 or 3, or a BDI score greater than 13 should be referred to a mental health professional. Participants should be closely scrutinized for suicide potential (see Suicide Risks Assessment Pocket Card). This is considered a Reportable Event (Suicide Risk) and sites must notify the CTCC.*

BECK HOPELESSNESS SCALE (BHS)

DESCRIPTION: The BHS is a 20-item scale for measuring the extent of negative attitudes about the future (pessimism).

CITATION OF PUBLICATION OF TEST: Beck, A. T., Weissman, A., Lester, D., & Trexler, L. (1974). [The measurement of pessimism: The hopelessness scale](#). *Journal of Consulting and Clinical Psychology*, 42, 861–865. 10.1037/h0037562.

METHODS FOR PREDICT: The BHS was administered at visits 1-4 from the start of PREDICT through the end of the 1.0 phase. Most sites discontinued the BHS in 2008 but some sites discontinued the BHS earlier due to IRB considerations. The BHS was discontinued in the 2.0 study. The BHS is scored as follows:

The 20 True/False questions are scored 1 or 0 with 9 keyed as FALSE and 11 keyed TRUE to indicate endorsement of pessimism. The scoring range is 0-20.

Scoring is 1 = True, 0 = False except for questions that are keyed False in which 1 = True and 0 = False

Questions 1,3,5,6,8,10,13,15, and 19 are keyed False

Questions 2,4,7,9,11,12,14,16,17,18, and 20 are keyed True

General guidelines for interpretation of the score is as follows:

0-3 = minimal

4-8 = mild

9-14 = moderate,

Greater than 14 = severe

Per NDA scoring guidelines, missing items can be imputed by following guidelines established in the data dictionary. The total number of missing items must be less than 5. If there are less than 5 missing items, the score is imputed by taking the integer median of the non-missing items, bhs1 through bhs2. In addition, the NDA scoring guidelines indicate that the scores in the dataset provided should be reverse scored where needed. The data set that we have provided have the scores already scored as indicated above so no additional scoring is needed.

TRAINING INSTRUCTIONS

BECK HOPELESSNESS SCALE: (BHS)

Description:

The BHS is a 20-item scale for measuring the extent of negative attitudes about the future (pessimism) as perceived by adolescents and adults.

Description and Content of the Scale

The BHS consists of 20 true-false statements that assess the extent of negative expectancies about the immediate and long-range future. Each of the 20 statements is scored 1 or 0. Of the 20 true-false statements, 9 are keyed FALSE and 11 are keyed TRUE to indicate endorsement of pessimism about the future. The item scores are summed to yield a total score that can range from 0 to 20 with higher scores indicating greater hopelessness. The 20 statements of the BHS and the corresponding responses which indicate hopeless cognitions are: **NOTE: Due to copyright permissions assessment questions and scoring information have been removed.**

Administration:

The BHS typically takes 5 to 10 minutes to complete and will be administered at Visits 1-4. The following instructions should be read to the respondent:

NOTE: Due to copyright permissions assessment questions and scoring information have been removed.

Interpretation of Scores:

The general guidelines for interpretation are **0-3 = minimal, 4-8 = mild, 9-14 = moderate, greater than 14 = severe**. If statements 1, 3, 5, 6, 8, 10, 13, 15, 19 are answered with a FALSE, one (1) point is awarded for each of those endorsements. If statements 2, 4, 7, 9, 11, 12, 14, 16, 17, 18, 20 are answered with a TRUE, one (1) point is awarded for each of those endorsements.

Since the BHS score produces only an estimate of the overall severity of a person's negative attitude about the future, it is clinically important to be aware of other aspects of psychological functioning displayed by a participant, especially the levels of depression and suicidal ideation. Beck, Steer, Kovacs, and Garrison (1985) reported that BHS scores of 9 or more were predictive of eventual suicide in depressed suicidal ideators followed for 5-10 years after hospital discharge. Hopelessness has also been found to be a better predictor of suicidal intent than depression per se (Beck, 1986).

NOTE: *Participants describing moderate to severe levels of hopelessness (as reflected by scores of 9 or greater) should be referred to a mental health professional and evaluated further for suicide potential (see Suicide Risk Assessment Pocket Card). This is considered a Reportable event (Suicide Risk) and Sites must notify the CTCC.*

HAIDT DISGUST SCALE (HAIDT)

DESCRIPTION: The Haidt Disgust Scale (HDS) is a 32-item scale designed to measure an individual's level of dislike or disgust for a variety of statements.

CITATION OF PUBLICATION OF TEST: Haidt J, McCauley C, Rozin P. Individual differences in sensitivity to disgust: [A scale sampling seven domains of disgust elicitors. Personality and Individual Differences](#). 1994;16(5):701-13. doi: [https://doi.org/10.1016/0191-8869\(94\)90212-7](https://doi.org/10.1016/0191-8869(94)90212-7). Also see <http://people.stern.nyu.edu/jhaidt/disgustscale.html>

METHODS FOR PREDICT: The Haidt Disgust Scale was administered at visits 2-4 from the start of PREDICT through the end of the 1.0 phase. The HDS was discontinued in the 2.0 study. The HDS is scored as follows:

Section 1:

1 = True

0 = False

Section 2:

0 = not disgusting at all

1 = slightly disgusting

2 = very disgusting

To calculate the Disgust Scale, the number of True responses is counted with the exception of questions 2, 9 and 13. The number of False responses is counted for questions 2, 9, and 13. The number of True responses and False responses are added together to get the score of part one. The ratings for questions 17-32 are added up and divided by 2. This is the score of part 2. The scores from part 1 and 2 are added together to give an overall score between 0 -32. The dataset provided contains the reverse responses for questions 2,9, and 13.

TRAINING INSTRUCTIONS

THE HAIDT SCALE (HAI)

Description:

The HAIDT Scale is designed to measure an individual's level of dislike or disgust for a variety of statements.

Administration:

This test will be administered in Visits 2–4. The following instructions should be read to the respondent:

“For the first section, please mark ‘1’ for true or ‘2’ for false to respond to the following statements. In the second section, please rate ‘0’, ‘1’, or ‘2’ as to how disgusting you would find the following experiences (‘0’ = not disgusting at all, ‘1’ = slightly disgusting, and ‘2’= very disgusting).”

PERCEIVED STRESS SCALE (PSS)

DESCRIPTION: The Perceived Stress Scale (PSS) is a 14-item scale designed to assess how unpredictable, uncontrollable, and overloaded the respondent finds his/her life. It is designed to measure the degree to which a person appraises situations in their personal life as stressful.

CITATION OF PUBLICATION OF TEST: Cohen, S., Kamarck, T., & Mermelstein, R. (1983). [A Global Measure of Perceived Stress](#). *Journal of Health and Social Behavior*, 24(4), 385-396. Retrieved December 22, 2020, from <http://www.jstor.org/stable/2136404>

METHODS FOR PREDICT: The PSS was administered at visits 1-4 from the start of PREDICT through the end of the 1.0 phase. The PSS was discontinued in the 2.0 study. The PSS is scored as follows:

- 0 = never
- 1 = almost never
- 2 = sometimes
- 3 = fairly often
- 4 = very often

Questions 4,5,6,7,9, and 13 are reversed scored.

Questions 1,2,3,8,10,11,12, and 14 are scored normally

The dataset provided has the scores for questions 4,5,6,7,9 and 13 already reversed.

TRAINING INSTRUCTIONS

PERCEIVED STRESS SCALE (PSS)

Description:

The Perceived Stress Scale is designed to measure the degree to which situations in a person's life are appraised as stressful. The 14 items are designed to assess how unpredictable, uncontrollable, and overloaded the respondent finds his/her life.

Administration:

The Perceived Stress Scale will be completed at Visits 1-4. The following instructions should be read to the respondent, emphasizing the phrasing in italics: *"These questions ask about your feelings and thoughts during the last month. You are asked to indicate how often you felt or thought a certain way."*

PROBLEM BEHAVIORS ASSESSMENT SHORT FORM (PBA-S)/ UHDRS BEHAVIORAL ASSESSMENT (UHDRS BEH)

DESCRIPTION: The Problem Behaviors Assessment Short Form (PBA-s) is an 11-item brief semi-structured interview covering the most common behavioral and psychiatric manifestations in HD. This measure is intended to be answered by the participant and a knowledgeable informant (i.e., spouse or caregiver) together.

The UHDRS Behavioral is part of the Modified Unified Huntington's Disease Rating Scale '99 (UHDRS '99). The UHDRS Behavioral was the precursor to the PBA and consists of 11 items that are administered in a semi-structured interview.

CITATION OF PUBLICATION OF TEST: Craufurd, David, Thompson, Jennifer & Snowden, Julie. (2001). [Behavioral Changes in Huntington Disease](http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=ovfte&NEWS=N&AN=00010291-200110000-00004). *Neuropsychiatry, Neuropsychology, & Behavioral Neurology*, **14**(4), 219-226. Retrieved from <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=ovfte&NEWS=N&AN=00010291-200110000-00004>. (Original version)

(1996), [Unified Huntington's disease rating scale: Reliability and consistency](https://doi-org.proxy.lib.uiowa.edu/10.1002/mds.870110204). *Mov. Disord.*, 11: 136-142. <https://doi-org.proxy.lib.uiowa.edu/10.1002/mds.870110204>

METHODS FOR PREDICT: The Modified Unified Huntington's Disease Rating Scale '99 Behavioral (UHDRS Behavioral) was originally administered at visits 1-4 and was expanded to all visits from the start of PREDICT-HD through June 2009. The UHDRS Behavioral was discontinued at the start of the 2.0 part of the study and was re-introduced in 2010 until 2011. In 2011, the Problem Behavioral Assessment Short Form was administered in place of the UHDRS Behavioral and was administered for the rest of PREDICT. The UHDRS and the PBA were developed by investigators familiar with HD clinical care from the Huntington Study Group (HSG) and the European HD Network (EHDN), respectively. There were a few items deleted from the former, and scoring options were extended in the PBA. Since PREDICT-HD was a longitudinal study and the differences between the scales were minor, we opted to merge these scales to facilitate longitudinal hypothesis testing throughout the study. If desired, the scales can be separated by investigators using these data. The PBA annotated an additional "worse" rating.

Scoring for both the PBA and UHDRS Behavioral are as follows:

Group Domain Scores:

Depression: (depressed mood severity X frequency) + (suicidal ideation severity X frequency) + (anxiety severity X frequency)

Irritability/Aggression: (irritability severity X frequency) + (angry or aggressive behavior severity X frequency)

Psychosis: (delusions/paranoid thinking severity X frequency) + (hallucinations severity X frequency)

Apathy: (apathy severity X apathy frequency)

Executive Function: (perseverative thinking or behavior severity X frequency) + obsessive-compulsive behaviors severity X frequency)

Where items overlapped between the PBA and UHDRS Behavioral forms the PBA variable name was used. Items from the UHDRS Behavioral form that are not found in the PBA are listed in the dataset as separate items. The items are uhdrsb_27a (Frequency Low Self-Esteem/Guilt), uhdrsb_27b (Severity Low Self-Esttem/Guilt) pbax_36a (Confusion)

uhdrsb_q37 (Dementia), pbax_37a (Dementia altered performance), uhdrsb_q38 (showing signs of depression), uhdrsb_q39 (is pharmacotherapy warranted for depression), and uhdrsb_q40 (is pharmacotherapy warranted for irritability).

TRAINING INSTRUCTIONS

PROBLEM BEHAVIORS ASSESSMENT-SHORT FORM (PBA-s) (2.0 Version)

The PBA-s is an 11-item brief semi-structured interview covering the most common behavioral and psychiatric manifestations in HD. This measure is intended to be answered by the participant and a knowledgeable informant (i.e. spouse or caregiver) together. Immediately following the interview, the coordinator should briefly re-interview the informant to elicit any additional information which could not be discussed openly in the presence of the participant.

Administration:

PBA-s ratings should be based on all available information including the clinician's impression from observation of the patient together with report of the patient and a knowledgeable informant. If possible, try also to interview the relative without the patient present before completing these ratings.

Rate the patient's average behavior over the past 4 weeks, using the general guidelines below together with the detailed scoring criteria and examples specified in the accompanying manual. If the symptom has NOT been present in the past 4 weeks, or the rating for the past month does not adequately reflect symptom severity in the interval since the patient's last assessment, use the third box on the form to rate the WORST level of severity during the interval since patient was last seen.

Scoring:

Each symptom is rated for severity on a 5-point scale according to detailed

scoring criteria below.

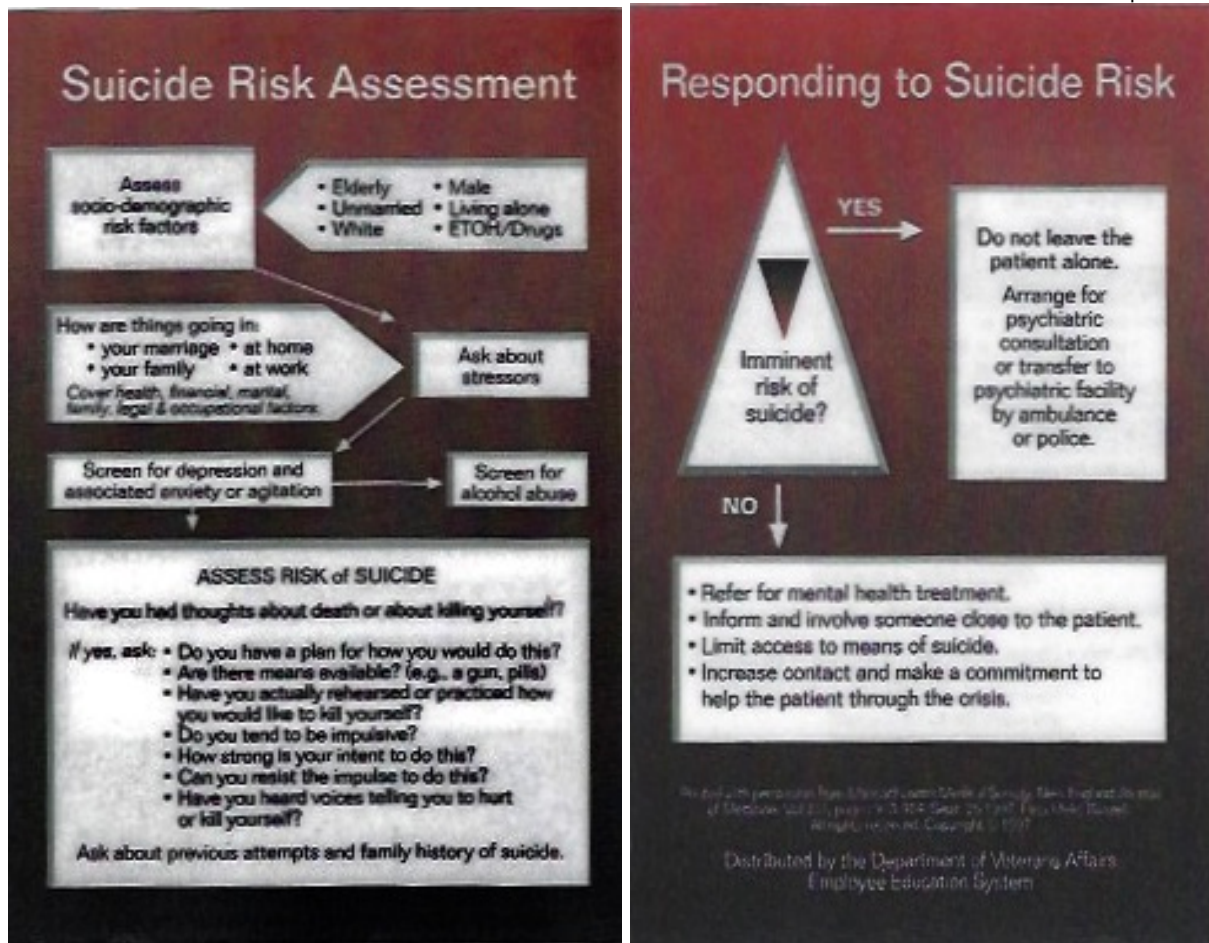
Severity	Frequency
0 = absent	0 = never / almost never
1 = slight, questionable	1 = seldom (less than once/week)
2 = mild (present, not a problem)	2 = sometimes (up to 4 times a week)
3 = moderate (symptom causing problem)	3 = frequently (most days / 5, 6 or 7 times a week)
4 = severe (almost intolerable for carer)	4 = daily / almost daily for most (or all) of day
8 = unable to assess because condition too advanced (e.g., mute and immobile)	8 = unable to assess because condition too advanced (e.g., mute and immobile)
9 = not known or no reliable informant	9 = not known or no reliable informant

UHDRS '99 - Part III (1.0 version)

Please follow directions on the CRF for the participant. UHDRS '99 Part III will be completed at Visits 1-4.

NOTE: Remember to crosscheck the scores of the BDI and the BHS with the individual scores for UHDRS Part III Questions 25a, 25b (Depressed Mood) and 28a, 28b (Suicidal Thoughts) prior to the participant completing the visit.

Participants endorsing a rating of ≥ 3 on either Question 25a or 25b or a rating of ≥ 2 on either Questions 28a and 28b should be advised to see a mental health professional and be evaluated further for suicide potential (see Suicide Risk Assessment Pocket Card). If the respondent has any of the above ratings this is considered a Reportable Event (Suicide Risk). Sites must notify the CTCC, complete the Reportable Event Form and Suicide Risk Form.



UNIFIED HUNTINGTON'S DISEASE RATING SCALE '99 (UHDRS '99 III)

Description of measure:

The UHDRS '99 III is a structured interview designed to measure the frequency and severity of various behaviors and moods.

Who gives this measure?

Visit Coordinator.

Who takes this measure?

The participant.

How long does this measure take?

10 to 20 minutes depending on responses.

How has this changed in PREDICT-HD 2.1?

The same measure was given in the original PREDICT protocol. It had been dropped in the 2.0 protocol. However, the 2.1 protocol adds the measure back in, for the participant only, not the companion.

Administration:

This interview is to be conducted at every visit. It requires you to rate the **frequency** and **severity** of each behavior identified for the past month. Frequency and severity should be **uniquely** assessed as independent qualifiers of positively affirmed behavioral symptoms. Frequently occurring behaviors do not necessarily indicate a high severity rating (e.g., presence of anxiety may be constant but mild in impact). Severity is indicative of the behavior's impact on the individual's ability to carry out daily activities. The following instructions should be read to the participant:

I will now ask you about experiences that most individuals have at some point in life. I will ask you to help me gauge how frequently and severely these experiences occur.

SECTION 7: LABORATORY SPECIMEN MANAGEMENT

1.0 STUDY

A. DNA SAMPLES

- Laboratory analysis of DNA samples will be performed by Marcy MacDonald's Laboratory.
- Each site will be provided all the necessary materials to collect the required specimens, including labeling and shipping supplies.
- All laboratory supplies will be shipped to you from the HSG Coordination Center. Please contact Elise Kayson (585-275-4696) if you need more supplies or have any questions.

***NOTE: Personnel at MacDonald's Lab have been instructed not to respond to any site questions for confidentiality purposes.**

BLOOD SAMPLE TUBES

- The blood sample tubes are yellow-topped (ACD solution) vacutainer tubes. Two (2) tubes per participant are required.

DNA BLOOD SAMPLE HANDLING

The following are directions for management of DNA blood samples:

- Blood samples for DNA analysis will be collected at the Screening/Baseline visit (Visit 1) after all eligibility criteria have been verified and consent procedures completed.
- 2 yellow-topped (ACD solution) vacutainer tubes (10 ml of blood per tube) are required per participant. Gently invert the tube to ensure mixture of the solution in the tube and the blood.
- Vacutainer tubes must be properly labeled with the designated participant barcode label and the site number. Locate the set of five labels (see Sample of Labels Appendix X), which corresponds to the participant ID number given to you at the enrollment call. The labels are designed in five sections. A barcode label will be placed on each tube collected. Place the remaining barcodes, one designated for the PREDICT Blood Sample Laboratory Requisition (see Appendix X) and one extra label if unused on the PREDICT Blood Sample Laboratory Requisition form. The label with the participant ID number will be placed on the CRF page marked Participant ID Label (see Appendix X).
- **ONLY THE SITE NUMBER SHOULD BE WRITTEN ON THE TUBES. NO OTHER IDENTIFYING INFORMATION SHOULD BE WRITTEN ON THE TUBES.**

RETENTION/DESTRUCTION OF DNA SAMPLES

- Ensure the appropriate labels are affixed to the DNA Blood Sample Laboratory Requisition. In addition, for each participant's sample, you must complete the DNA Sample Consent CRF page and check the appropriate boxes indicated on the form as to whether: **1) the sample should be retained for future HD related research purposes or 2) destroyed after initial DNA CAG_n analysis. This information should be transcribed from the participant's consent form.**
- At the conclusion of the study (or earlier if the participant prematurely withdraws) the participant will be asked again to determine if they wish to have their DNA sample retained or destroyed. This information must be entered on the Participant Disposition CRF page.

STORAGE OF DNA SAMPLES

- DNA²⁰⁰⁴ Blood samples should be stored at either -20°C or -70°C in a secure DEEP FREEZE FREEZER until shipment. It is recommended that the temperature of the freezer be monitored using a max-min thermometer to avoid temperature fluctuations. **The samples cannot be kept in a refrigerator freezer. Refrigerator freezers are only -4°C.** As the blood tubes are fragile, ensure that samples are stored away from the freezer door. ***Do not allow samples to thaw after freezing.***

SHIPMENT OF DNA SAMPLES

- **Frozen blood samples should be batch-shipped twice a year to the MacDonald Lab.**
- Frozen blood samples must be shipped on dry ice. **Do not allow samples to thaw.** Frozen samples must be placed in the Styrofoam containers in a plastic bag, appropriate shipping box, and packed with dry ice. If you have difficulty obtaining dry ice in your institution, contact your local ice cream store, they usually have dry ice.
- All blood samples should be shipped via courier service (e.g., overnight priority Fed-Ex, Airborne). Samples must be shipped **Monday** or **Tuesday** overnight priority. **DO NOT SHIP SAMPLES IF THE NEXT DAY IS A HOLIDAY.**
- If a sample should break prior to shipment, place the frozen tube into a 50ml blue cap screw top falcon tube and keep in freezer (do not allow to thaw) until ready to ship. If the bar code is unreadable, copy the code from the Lab Requisition and attach it to the falcon tube. If the glass is shattered, you may have to obtain another sample.
- If a sample tube is broken or the barcode is unreadable when it arrives at the lab, the lab will request another blood sample. You must call Elise Kayson (585-275-4696) if this occurs.

NOTE: If you do not have a Deep Freeze Freezer, the samples must be shipped at room temperature the **SAME DAY OF COLLECTION** if possible. Do NOT freeze or refrigerate prior to shipment. The samples should be placed in the cardboard box mailers provided and placed in the FedEx biological (plastic) shipping sleeves prior to shipment.

If samples cannot be shipped the same day, do not freeze, keep at room temperature. Ship those samples drawn on Wednesday – Friday on the following Monday. Samples can be kept at room temperature for several days, but there will be less DNA to extract and a higher chance of needing to repeat a blood draw.

- All laboratory specimens should be sent to the following address:

Ms. Lakshmi Srinidhi
Molecular Neurogenetics Unit, Room 6102
Massachusetts General Hospital
Building 149, 13th Street
Charlestown, MA 02129
Phone: (617) 726-5726
Fax: (617) 726-5736

B. ANNUAL BLOOD SAMPLES

Annual blood samples will be collected to determine biological markers. The sample will be evaluated for measures of 8 Hydroxy-deoxyguanosine and stored for discovery and validation of future biological markers. The samples will be coded and sent to Flint Beal's laboratory.

Materials to collect the samples will be shipped to you.

BLOOD TUBE HANDLING

- 1 (one) purple topped (EDTA) Vacutainer tube (10 ml of blood) is required per participant.
- Once the blood sample is obtained the tube needs to be gently inverted 7 times (to mix sample) and then spun in a refrigerated centrifuge (+ 4 C°) at 4000 rpm for 10 minutes. Remove plasma immediately. The plasma should be extracted from the

tube and at least 1.0 ml should be transferred to 3 cryovials. **Freeze immediately at – 20 to -70 C°.**

- The cryovials must be labeled appropriately with the SITE NUMBER, PARTICIPANT ID NUMBER, AND VISIT NUMBER (i.e., V1, V2, V3, V4) using a Sharpie® pen. DO NOT put any other identifying information on the label. Complete the Blood Sample Laboratory Requisition

STORAGE OF SAMPLES

- Samples should be stored in the small fiberboard box (provided to you) at – 20 to -70 C° in a secure DEEP-FREEZE FREEZER until shipment. It is recommended that the freezer's temperature be monitored using a max-min thermometer to avoid temperature fluctuations. **The samples cannot be kept in a refrigerator freezer. Refrigerator freezers are only -4°C.** As the blood tubes are fragile, ensure that samples are stored away from the freezer door. Do not allow samples to thaw after freezing.

SHIPMENT OF SAMPLES

- **Frozen blood samples should be batch-shipped ONCE A YEAR to the ESA Lab.**
- Frozen blood samples must be shipped on dry ice. **Do not allow samples to thaw.** The frozen samples in the fiberboard box should be placed in the polyfoam bioshipping box and packed with dry ice. If you have difficulty obtaining dry ice in your institution, contact your local ice cream store; they usually have dry ice.
- All blood samples should be shipped via courier service (e.g., overnight priority fed-ex, Airborne). Samples must be shipped **Monday or Tuesday** overnight priority. **DO NOT SHIP SAMPLES IF THE NEXT DAY IS A HOLIDAY.**
- If a sample tube is broken and unusable or the ID code is unreadable when it arrives at the lab, the lab will request another blood sample. You must call Elaine Julian-Baros at (585) 273-2879 if this occurs.

BLOOD TUBE SHIPPING

Please call ESA when samples are being shipped so they can be alert for their arrival. The samples should be shipped to:

Attn: Misha Bogdanov, MD, PhD
 ESA Inc.
 22 Alpha Road
 Chelmsford, MA 01824
 Phone : 978-250-7180
 Fax : 978-250-7065

C. LABORATORY SPECIMEN MANAGEMENT

Methods for collection, processing, transport, assay, and archiving of samples DNA and RNA Injury Markers (Bedford VA Medical Center Laboratory)

In prior work at Dr. Matson's laboratories¹ and in a number of other studies of biomarkers, significant differences have been seen among clinical sites and among samples acquired at different times. The principal target compounds 8- hydroxy 2'deoxyguanosine (8OH2'dG) and 8-hydroxy guanosine (8OHrG) are highly stable in biological matrices. If sample preparation techniques are adapted to a range of acquisition and archiving conditions, their levels will not be affected by unusual time temperature profiles during processing. However, if the sample set is to be of general use to the research community acquisition and archiving across multiple sites must be addressed. We have used the protocols outlined below to minimize clinical site variations. All samples will be suitable for 8OH2'dG, 8OHrG and 8OHG under this protocol.

There will be variability in the utility of the samples. For instance, samples centrifuged at 3000xg in a standard clinical centrifuge will have higher levels of serotonergic metabolites and other markers of platelet and white blood cell metabolism. Each site will record the processing variables used. The sample set proposed for acquisition is a highly valuable resource for any further studies of biomarkers or mechanism, particularly in view of the emerging multiparameter analytical technologies in proteomics and metabolomics. It is critical that it be defined such that artifacts introduced by clinical acquisition variables can be addressed by specific selection of samples based on their processing in any further use of the samples.

DNA damage marker 8-hydroxy 2'deoxyguanosine (8-OH2'dG) and RNA damage marker 8-hydroxy guanosine (8OHrG) specimen management is being performed at the Bedford VA Medical Center (VMAC) under the direction of Wayne Matson, PhD. We plan to obtain a single set of blood and urine samples from all consenting PREDICT participants to measure plasma and urine 8- OH2'dG and 8OHrG concentrations. Flash frozen whole blood, processed for analysis from the frozen state provides little opportunity for clinical acquisition variability. The process of plasma acquisition in which all aliquoting operations are performed in the archiving laboratory minimizes clinical site variation. Note Heparin is suggested as the anticoagulant for plasma because it will be used in the NIST/NIH plasma standard under development.

Bedford VA Medical Center (VMAC) under the direction of Wayne Matson, PhD will work with the HSG coordination center to develop operations procedures for the clinical sites that cover all aspects of sample acquisition, labeling, processing, storage, shipment, and record keeping. These will be included as a supplement for the site operations manual.

COLLECTION

URINE SAMPLE PROTOCOL

Urine samples will be collected via clean catch method. 50cc of urine will be collected and aliquoted into 50 ml screw top polypropylene vials, frozen on dry ice and stored at -70°C to -80°C until shipment. The tubes will be labeled with a barcode. A separate label with the same barcode should be affixed to the *Biomarker Sample Laboratory Requisition Form* (Appendix 7A).

PLASMA SAMPLE PROTOCOL

There are two tubes: TUBE 1 a plastic 4ml red top vacutainer and TUBE 2 a plastic 10ml green top heparin vacutainer. The tubes will be labeled with a barcode. A separate label with the same barcode should be affixed to the *Biomarker Sample Laboratory Requisition Form* (Appendix 7A).

Draw Two Tubes From The Subject:

Tube 1 Plastic 4ml Red Top Vacutainer

Tube 2 Plastic 10ml Green Top (Heparin) Vacutainer

TUBE 1

- 4ml red top vacutainer is drawn
- Immediately freeze on dry ice
- Transfer tube to -70°C to -80°C freezer. Tube should be in a freezer box, and the box should be in a freezer compatible zip lock bag. Maintain in freezer until shipment.

TUBE 2

- 10 ml green top (Heparin) vacutainer is drawn. Invert tube 4 times to mix anticoagulant.
- Place on ice until centrifugation (recommended maximum time on ice is 45 minutes).
- The green top vacutainer is centrifuged according to a time/g force schedule depending on the capabilities of the laboratory. **NOTE:** The highest time/g force is the preferred method. Record the g force used on the *Biomarker Sample Laboratory Requisition Form*.

- Centrifuge TUBE 2 in a refrigerated centrifuge at 4°C according to the following centrifuge dependent schedule below. Note both swing rotor and slant rotor centrifuge heads are acceptable.

g force	Time (minutes)
8000xg	20 minutes
7000xg	25 minutes
5000xg	35 minutes
3000xg	45 minutes

- The tube is then immediately frozen and maintained at -70°C to -80°C until shipment. TUBE 2 should be in a freezer box, and the box should be in a freezer compatible zip lock bag.

TRANSPORT

- Samples will be shipped to the Bedford VA Medical Center Laboratory archiving laboratory on dry ice using Fedex overnight delivery. With each shipment send a copy of the *Biomarker Sample Laboratory Requisition Form* (Appendix 7A) with the barcode affixed. Do not provide any information on subject identity. Samples will be shipped according to the following site specific

schedule:

- Sites with -70 to -80°C freezers should ship every two months
- Sites with -20 to -40°C freezers should ship every three weeks
- If a sample should break prior to shipment, place the frozen tube into a 50ml blue-cap screw-top falcon tube and keep in freezer (do not allow to thaw) until ready to ship. If the bar code is unreadable, copy the code from the Biomarker Sample Laboratory Requisition Form (Appendix 7A) and attach it to the falcon tube. If the glass is shattered, you may have to obtain another sample.
- If a sample tube is broken and unusable or the barcode is unreadable when it arrives at the lab, the lab will request another 8OH2'dG and 8OHrG blood sample. You must call Elise Kayson (585-275-4696) if this occurs.
- All laboratory specimens should be sent to the following address:

Bedford VA Medical Center
 Attention: Wayne Matson
 Edith Nourse Rogers Memorial Hospital and Bedford VA Medical Center 200 Springs Road
 Room 125 Bldg 70
 Mail Stop 152
 Bedford, MA 01730

Please phone 781-687-2866 and leave a message the day your samples are shipped out so the lab is aware that they are to be received.

Be certain that you ship out your samples on a Monday, Tuesday or Wednesday. Do not ship samples if the next day is a holiday.

RETENTION/DESTRUCTION OF 8OH2'DG AND 8OHRG SAMPLES

Ensure the appropriate labels are affixed to the PHAROS 8OH2'dG and 8OHrG Biomarker Sample Laboratory Requisition Form (Appendix 7A). In addition, for each participant's sample, check the appropriate box indicated on the 8OH2'dG and 8OHrG Biomarker Sample Consent form (Appendix 7A) as to whether, **1) the sample should be retained for future HD related research, or 2) destroyed after initial 8OH2'dG and 8OHrG analysis. This information should be transcribed from the participant's consent form.**

ASSAY

Measurements of 8OH2'dG and 8OHrG on the carbon column switching systems (CCS) use the same mobile phase set with slightly different timing conditions for maximum resolution and specificity. While it is possible in standards and control subjects to measure both in the same assay, the increased complexity introduced by a disease makes simultaneous assay risky because of the possibility of sample specific interferences. Thus we will sequence assays with specific conditions.

URINE SAMPLES

The Bedford VA Medical Center Laboratory will ensure that samples are sub- aliquoted in a single step by thawing to 0°C, mixing thoroughly and immediately refreezing in 2 ml screw top polypropylene vials. Urine samples from archived sub aliquots are thoroughly mixed to include any precipitates formed on storage. We have found^{2,3} that a significant portion of the 8OH2'dG and 8OHrG can co-precipitate with aggregates formed during storage. The urine is diluted 1:1 with mobile phase A. 8OHrG is analyzed first typically in a 24-hour run as it is the least stable of the three analytes (degradation of signal after 48 hours at room temperature is about 5-8%). Creatinine is assayed from the same auto-sampler vial in a rolling sequence removing the tube from the CCS platform to the Liquid Chromatography with Electrochemical Detection (LCECA) UV and Florescent detectors (UV/F) instrument. The tube is then sequenced to the CCS for 8OH2'dG measurements (8OH2'dG in buffer is stable at room temperature for over a week). 8OHG measurements are made on the CCS with a different mobile phase buffer set on a separate aliquot of urine.

PLASMA SAMPLES

At the Bedford VA Medical Center Laboratory, the frozen plasma/buffy coat/packed RBC are expelled to a -80°C plate under nitrogen and the plasma, buffy coat and packed RBC are dissected aliquoted and archived. Plasma aliquots of 0.4 to 1 ml (1ml is standard) are processed using our standard SPE protocol². The initial eluent from the column is archived for 8OHG measurements. The final preparation of 0.12 ml containing 8OH2'dG and 8OHrG is first assayed on the CCS for 8OH2'dG using 0.020 ml and then for 8OH2'dG using 0.070 ml aliquots. Plasma assays are controlled by standards plasma pools and spiked pools to assess the recovery and precision of the preparative steps, and by standards to control instrument variables.

ARCHIVING

The blood and urine samples will be inventoried and archived at the Bedford VA Medical Center. Eventually the samples may be transferred to Coriell Laboratory in New Jersey as we have done in our other HSG studies.

References

- 1) Rozen S, Cudkowicz ME, Bogdanov M, Matson WR; Kristal BS, Beecher C, Harrison S, Vouros P, Flarakos J, Vigneau-Callahan KE, Matson T, Newhall K, Beal MF, Brown RH Jr, Kaddurah-Daouk R. "Metabolomic Analysis and Signatures in Motor Neuron Disease" *Metabolomics* 2005, 1, 101-108.
- 2) Bogdanov MB, Beal MF, McCabe DR, Griffin RM, Matson WR. A Carbon Column-Based Liquid Chromatography Electrochemical Approach To Routine 8-Hydroxy-2'-Deoxyguanosine Measurements In Urine And Other Biologic Matrices: A One-Year Evaluation Of Methods. *Free Radical Biology & Medicine*. 27,5/6,647-666,1999.
- 3) Bogdanov MB, Matson WR, Acworth IN. The Use of HPLC/EC for Measurements of Oxidative

DNA Damage. In: Cutler, R.G.; Rodriguez, H., eds. *Critical Reviews of Oxidative Stress and Aging*, volume 1. NJ: World Scientific; 203-221; 2003.

D. CAG GENOTYPING/GENOTYPING FOR OTHER GENETIC POLYMORPHISMS

The following procedure and language is added to the Research Design and Methods section.

- a. CAG Genotyping/Genotyping for other Genetic Polymorphisms. Establishment of lymphoblastoid cell lines for all enrolled PREDICT participants who agree to provide a blood draw, at the first follow-up visit post amendment 5 approval, for this purpose.

All PREDICT subjects will have one (1) blood specimen (10ml) collected. Nucleated cells will be immortalized from this blood specimen to create a lymphoblastoid cell line. The cell line DNA will be available for HD CAG genotyping and other HD genetic research, such as genotyping for the CAGn and other polymorphisms that may modify disease features. This research will be performed in a research lab and therefore the results are experimental data. Under no circumstances will the results be reported to the sites or to the subjects.

Coriell Institute for Medical Research will be the company receiving the blood samples which will be processed into plasma, lymphocytes and lymphoblastoid cell line for the PREDICT study. The following process will be utilized for the collection and processing for the cell line and obtaining DNA for genotyping at the CAG or for other authenticated genetic polymorphisms:

- One yellow top tube of blood (10 ml) will be collected and shipped (*at room temperature on the same day of collection*) by overnight courier with the site number and subject number for identification purposes.
- Coriell will assign a unique identifier to the sample.
- Coriell will process the blood samples to produce plasma, lymphocytes, and a lymphoblastoid cell line and will store these for future HD research.
- For each lymphoblastoid cell line, Coriell will produce lymphoblastoid cell line DNA.
- Routine quality control studies will be conducted to estimate the quality and integrity of the DNA.
- All activities will be documented by Coriell.
- Coriell will send an aliquot of the lymphoblastoid cell line DNA to a laboratory at Massachusetts General Hospital (MGH) where genotyping for the HD CAG repeat will be performed at the Genomics facility (Molecular Neurogenetics Unit, Massachusetts General Hospital) under the supervision of Marcy MacDonald, PhD who, with her collaborators identified the CAG expansion of the mutant HD gene and who has considerable experience with the analytic technique.

HD researchers will be able to request coded lymphoblastoid cell lines and/or coded lymphoblastoid cell line DNA from Coriell. Samples will be identified only by the Coriell identification number assigned by Coriell Institute for Medical Research.

E. SPECIMEN REPOSITORY

Blood –If the subject agrees to have blood samples stored in the specimen repository, 2 tubes of blood (total volume - 20 ml) will be collected at each visit.

The blood will be sent to Coriell Institute for Medical Research and processed for storage in the PREDICT specimen repository. This blood will be used to store plasma, lymphocytes, and lymphoblastoid cell lines for future HD research. Cell lines will only be created one time. If for any reason the cell line fails, frozen lymphocytes can be used to make another cell line. When the cell line is created, because the HD CAG size may be different than in the blood DNA, an aliquot of the lymphoblastoid cell line DNA will be sent to MGH to be used in the genotyping for HD CAG repeat number, and authenticated polymorphisms in other genes previously shown to modify timing or expression of disease features. For the purposes of genotyping, MGH will receive DNA from the cell line that is identified only by the Coriell identification number assigned by Coriell Institute for Medical Research. The other portion of the lymphoblastoid cell line will be stored for future research in Huntington's disease. The following process will be performed for the creation of samples for the repository:

- One (1) yellow top tube (10 ml) and one (1) purple top tube (10 ml) of blood will be collected and shipped by overnight courier (*at room temperature on the same day of collection*) with the site number and subject number for identification purposes.
- Coriell will assign a unique identifier to the sample.
- Samples will be processed including appropriate testing for viability and contamination.
- All activities and testing will be documented by Coriell.

Coriell will oversee the repository based on strict guidelines set forth by the PREDICT Steering Committee.

F. CYTOKINE PROJECT.

Levels of the potent NMDA receptor agonists QUIN and 3-HK, endogenous metabolic products of the kynurenine pathway, are increased in the cortex and striatum of YAC 129 HD animals [71]. Similar increases in QUIN and 3-HK levels have been detected in the neocortex and neostriatum of early grade HD brains [72]. These changes in the brain would predict that alterations of cytokines would be present in HD plasma. Immune activation has been found in patients with HD [73]. A recent study shows increased levels of inflammatory markers such as IL6, IL8, IL10, TNF-alpha and clusterin in plasma from HD patients at early stages of the disease that increase with progression [74]. We hypothesize that immune activation occurs early in HD and that levels of cytokines/chemokines correlate with symptoms and signs of HD. We plan to examine alterations in inflammatory mediators, their potential role in disease pathogenesis, and their utility as biomarkers of disease progression in a subset of the PREDICT-HD cohort.

Collection and Shipment Protocol to be determined.

G. CHOLESTEROL PROJECT.

Recently, we determined that the mRNAs levels for key genes of the cholesterol biosynthetic pathway were severely diminished in cortex and striatum from HD transgenic mice [75] as well as in post-mortem brains from HD patients and in primary fibroblasts taken from HD patients [76]. One potential molecular mechanism for this is that mutant huntingtin interferes with the activity of SREBPs, the transcription factors that regulate the expression of SRE-controlled genes involved in the cholesterol biosynthetic pathway [76]. As a pilot we conducted an analysis of cholesterol metabolism in 55 HD patients, 14 pre-HD participants,

and 180 controls. Findings suggested that levels of cholesterol, the cholesterol precursors lanosterol and lathosterol, and 240HC were abnormal and associated with estimated probabilities of motor diagnosis as well as striatal volumes in HD. We plan to measure these plasma levels of desmosterol, lathosterol and lanosterol and indicators of body cholesterol synthesis and plasma levels of 240HC as an indicator of brain cholesterol catabolism in a subset of the PREDICT- HD cohort.

Collection and Shipment Protocol to be determined.

LABORATORY SPECIMEN MANAGEMENT: DNA (UPDATE)

DNA SAMPLES

- Laboratory analysis of DNA samples will be performed by Marcy MacDonald's Laboratory at Massachusetts General Hospital.
- CAG genotyping and other authenticated genetic polymorphisms will be obtained.
- Samples will be used to produce plasma, lymphocytes and a lymphoblastoid cell line which will be stored for future HD research.
- Each site will be provide all of the necessary materials to collect the required specimens.
- All laboratory supplies will be shipped to you from your site assistant at the University of Iowa. Please contact your site assistant via e-mail and list out the required number of DNA kits needed.

NOTE: Personnel at MacDonald's Lab have been instructed not to respond to any site questions, for confidentiality purposes.

DNA BLOOD SAMPLE TUBES

- The DNA blood sample tubes are yellow-topped (ACD solution) Vacutainer tubes. Two (2) tubes per participant are required.



DNA BLOOD SAMPLE HANDLING

The following are directions for management of DNA blood samples:

- Blood samples for DNA analysis will be collected at the Screening/Baseline visit (Visit 201) after all eligibility criteria have been verified and consent procedures completed.
- DNA samples are also drawn at the first initial visit for every participant entering 2.0 from the original study.
- 2 yellow-topped (ACD solution) Vacutainer tubes (10 ml of blood per tube) are required per participant. Gently invert the tube to ensure mixture of the solution in the tube and the blood.
- Vacutainer tubes must be properly labeled with the designated participant barcode label and the site number. Locate the set of three labels that corresponds to the participant ID number and visit number provided by your site assistant. The labels are designed in three sections. Place one barcode label on each tube collected. Place the remaining barcode on the *DNA Blood Sample Laboratory Requisition*.
- If the correct barcodes have been mistakenly used for another visit or misplaced, please use blank barcodes. Fill in the site ID, subject ID and visit ID on the barcode and then place on the tubes and CRF as usual.

RETENTION/DESTRUCTION OF DNA SAMPLES

- Ensure the appropriate label is affixed to the *DNA Blood Sample Laboratory Requisition*
- Samples will be stored and maintained for future research at MGH indefinitely or until the sample is depleted.

STORAGE OF DNA SAMPLES

- DNA blood samples should be kept at room temperature.

SHIPMENT OF DNA SAMPLES

- Samples should be shipped at room temperature on the same date of draw, if possible. If shipping on the same date of draw is impossible, leave at room temperature and ship the next business day.
- Samples should arrive at MGH within 72 hours of the draw to be viable.
- Overnight priority shipments should be arranged; international sites must ship via two-day mail.
- Holiday shipments to the US should be avoided; site assistants will keep sites updated on these dates.
- Samples should be placed in the white styrofoam tube holder that is supplied. Place the foam box in the biosample bag and ship via FedEx if possible.
- Enclose with the sample shipment the original *DNA Blood Sample Laboratory Requisition* form (maintaining a photocopy of this CRF in your blood binder).
- Shipping labels are currently not provided to sites. Please ship and seek reimbursement from the University of Iowa by submitting a receipt to your site assistant.

- Site coordinators should send an email notification to Lakshmi at MGH (mysore@chgr.mgh.harvard.edu) listing the participant #, site #, visit # and date of draw along with the FedEx tracking number so that she can anticipate the arrival of samples.
- All DNA blood specimens should be sent to the following address:

Ms. Jayalakshmi S. Mysore
Center for Human Genetic Research
Richard B. Simches Research Center
Massachusetts General Hospital
185 Cambridge Street
5th Floor CPZN 5300-D2
Boston, MA 02114
Phone (617)-726-5726
Fax (617)-643-3202

2.0 STUDY: LABORATORY SPECIMEN MANAGEMENT (2.0/2.1 AMENDMENTS)

PLASMA, URINE, & WHOLE BLOOD

Within the 2.0 protocol, the biosample procedures have been updated to include urine sample collection in addition to the normal yearly plasma samples. Plasma samples will be used to conduct more sophisticated analyses, such as metabolomics, proteomics lipidomics, and mass spectroscopy. Samples will be evaluated to measure the DNA injury markers (such as 8-OH2'dG) and the RNA injury markers (such as 8OHrG). All samples will be kept indefinitely for future research at the Coriell Institute for Medical Research.

Researchers who have had their research reviewed by an Institutional Review Board will be able to request coded plasma samples following approval by the principal investigator and the PREDICT-HD Steering Committee.

COLLECTION PROCEDURES

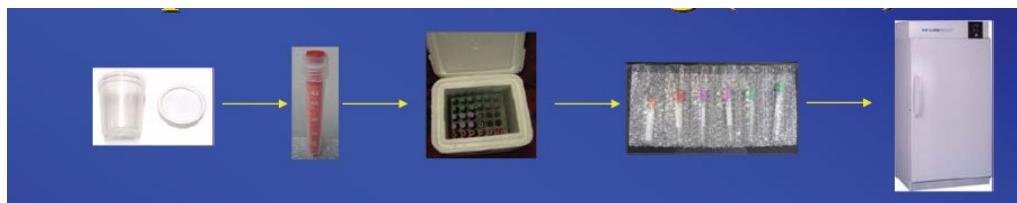
IMPORTANT: Prior to beginning biosample collection, be sure that your freezer block has been in the freezer for at least 2 hours or more prior to removing it from the freezer to conduct sample procedures for urine and plasma. The freezer block does not need to remain in the freezer at all times. Also note that the metal freezer block will only maintain a temperature of -70°C to -80°C for 4-5 hours at room temperature.

URINE SAMPLE PROTOCOL

Urine samples will be collected via clean catch method. 50ml of urine will be pipette into a **50ml screw top polypropylene vial**, frozen on dry ice and stored at -70°C to -80°C until shipment.



An additional 5ml of urine will be pipette into an **orange screw top tube**, flash frozen in the freezer block and transferred to the -70°C to -80°C freezer until ready for shipment. All tubes must be labeled with participant #, site #, visit # and date of collection.



Complete the *2.0 Biomarker Sample Laboratory Requisition (see Appendix XI)* with all pertinent details relating to the urine collection (i.e. time of collection, etc). Maintain these CRFs in your blood binder (no photocopy needs to be sent to Iowa or Coriell at this time).

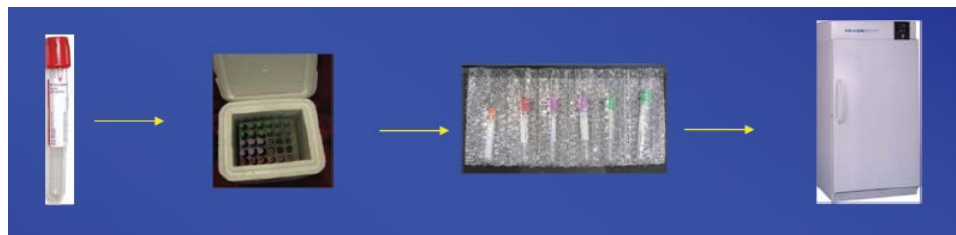
PLASMA SAMPLE PROTOCOL

Draw five tubes from the participant:

1. Plastic 5ml Red Top Whole Blood
2. Plastic 6ml Green Top (Lithium Heparin) Vacutainer
3. Plastic 6ml Green Top (Lithium Heparin) Vacutainer
4. Plastic 6ml lavender top (K2EDTA) Vacutainer
5. Plastic 6ml lavender top (K2EDTA) Vacutainer

TUBE 1:

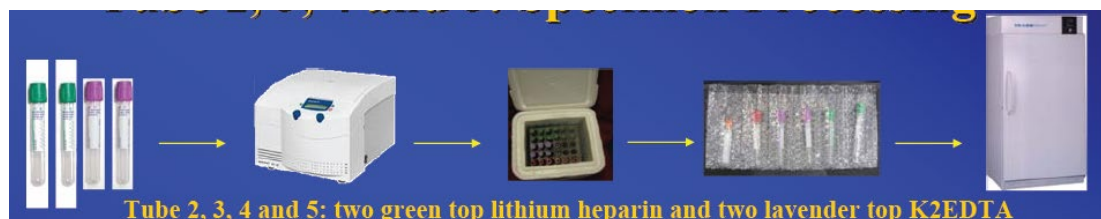
- 4ml red top vacutainer is drawn
- Immediately place in the freezer block for flash freezing (no spinning required)
- Transfer tube to -70°C to -80°C freezer. Tube should be in a freezer box or tube pouch until ready for shipment.
- Document date, time of draw, time frozen and storage temperature on the *Biomarker Sample Laboratory Requisition* form.

**TUBE 2, 3, 4 & 5:**

- Two 6 ml green top (Heparin) vacutainer and two 6ml lavender top (K2EDTA) vacutainer are drawn.
- Invert tubes 4 times to mix anticoagulant. (if you are drawing multiple participant samples, you may keep the tubes in an ice/water 0°C for no longer than 40 minutes before centrifuging.
- Centrifuge TUBE 2, 3, 4 & 5 in a refrigerated centrifuge at 4°C according to the following centrifuge dependent schedule below. Note both swing rotor and slant rotor centrifuge heads are acceptable.
NOTE: The highest time/g force is the preferred method.

g force	Time (minutes)
8000xg	20 minutes
7000xg	25 minutes
6000xg	35 minutes
<6000xg	40 minutes

- The tubes are then immediately flash frozen in the metal freezer block and maintained at -70°C to -80°C until shipment.
- Document date, time of draw, time frozen, storage temperature and spin rate on the *Biomarker Sample Laboratory Requisition* form.
- Send a copy of the *Biomarker Sample Laboratory Requisition* form to your Site Assistant with all other visit paperwork after each visit.



STORAGE OF PLASMA AND URINE SAMPLES

- Samples must be sent no later than 2-3 months after draw in -70°C to -80°C freezer
- Samples must be sent no later than every 6 months after draw in -20°C freezer
- After every **2 sets** of participant biosamples collected in **US**, they should be sent to Coriell
- After every **5 sets** of participant biosamples collected in **EU/Aus/Can**, they should be sent to Coriell

SHIPPING PROCEDURES

NOTE: There are different guidelines for US and International Sites below. Please reference the correct section.

U.S. SHIPMENTS OF 2.0 BIOMARKERS TO CORIELL

1. Ensure all tubes are correctly labeled (4-digit participant ID and 3-digit visit ID).
2. Place tubes into 6-compartment bubble pouch (provided in the Coriell kits), then wrap the bubble pouch around the 50 ml falcon tube.
3. Place samples into biohazard bag (also provided in the Coriell kits) along with absorbent material, seal bag, and place sealed bag into white pouch.
4. Place white pouch into Styrofoam shipping container, making sure container holds no more than 2 participants' worth of samples.
5. Pack dry ice around samples as thoroughly as possible. **Dry ice should fill all remaining space, saving room only for the Styrofoam container lid.**
6. Place Styrofoam lid on snugly; **do NOT seal Styrofoam box with tape.**
7. Place copy of electronic inventory form on top of styrofoam box.
8. Seal outer cardboard shipping box with tape along top middle flap seam; **do NOT seal cardboard edges fully with tape.**
9. Affix outer cardboard container with all provided shipment warnings; pay special attention to the sticker asking for dry ice amount.
10. Affix pre-printed FedEx shipping label to top of outer cardboard box.
11. Provide e-mail notification to Coriell contact prior to shipment, including FedEx tracking number and all other required information about the samples being shipped. The electronic inventory form contains 3 tabs. Be sure to complete the tab labeled "Site Info" as well as the tab labeled "Sample Info for 2.0 shipment".
12. Email the completed form to Karen Reeves (Kreeves@Coriell.org) and Cc Rod Corriveau (Rcorrive@Coriell.org) and Kelli Thumma (kelli-thumma@uiowa.edu).
13. **Ship overnight Mon-Thurs; do not ship on Fridays, weekends or holidays (holiday schedule will be provided)**
14. **Samples obtained Friday should be held and shipped immediately on Monday**

Plasma and urine samples should be shipped to:

Karen Reeves
Coriell Institute for Medical Research
403 Haddon Avenue
Camden, NJ 08103-1559

**Australian, Canadian, and European
Shipments of 2.0 biomarkers to Coriell**

1. Ensure all tubes are correctly labeled (4-digit participant ID and 3-digit visit ID).
2. Place tubes into 6-compartment bubble pouch (provided in the Coriell kits), then wrap the bubble pouch around the 50 ml falcon tube.

3. Place samples into biohazard bag (also provided in the Coriell kits) along with absorbent material, seal bag, and place sealed bag into white pouch.
4. Place white pouch into Styrofoam shipping container, making sure container holds no more than 5 participants' worth of samples.
5. Pack dry ice around samples as thoroughly as possible. **Dry ice should fill all remaining space, saving room only for the Styrofoam container lid.**
6. Place Styrofoam lid on snugly; **do NOT seal Styrofoam box with tape.**
7. Place copy of electronic inventory form on top of styrofoam box.
8. Seal outer cardboard shipping box with tape along top middle flap seam; **do NOT seal cardboard edges fully with tape.**
9. Affix outer cardboard container with all provided shipment warnings; pay special attention to the sticker asking for dry ice amount.
10. Affix pre-printed FedEx shipping label to top of outer cardboard box.
11. Provide e-mail notification to Coriell contact prior to shipment, including FedEx tracking number and all other required information about the samples being shipped. The electronic inventory form contains 3 tabs. Be sure to complete the tab labeled "Site Info" as well as the tab labeled "Sample Info for 2.0 Shipment".
12. Email the completed form to Karen Reeves (Kreeves@Coriell.org) and Cc Rod Corriveau (Rcorriveau@Coriell.org) and Kelli Thumma (kelli-thumma@uiowa.edu).
13. **Ship overnight Mon-Thurs; do not ship on Fridays, weekends or holidays (holiday schedule will be provided)**
14. **Samples obtained Friday should be held and shipped immediately on Monday**

Plasma and urine samples should be shipped to:

Karen Reeves
Coriell Institute for Medical Research
403 Haddon Avenue
Camden, NJ 08103-1559

SPECIAL PROCEDURES FOR DIFFICULT DRAWS

For some individuals, providing five tubes of blood may be unfeasible. In this case, we ask that you obtain as many of the following samples in this order:

1. Yellow top DNA tube for MGH
2. Yellow top DNA tube for MGH
3. Red top whole blood for Coriell
4. Purple top whole blood for Coriell
5. Green top whole blood for Coriell
6. Purple top whole blood for Coriell
7. Green top whole blood for Coriell

LABORATORY INFORMATION:*HOURS OF OPERATION*

Coriell operates from 9 AM to 5 PM Eastern Time, Monday through Friday.

HOLIDAY SCHEDULES

Please note that courier services may observe a different set of holidays. Please be sure to verify with your courier's schedule prior to any holiday.

Frozen samples must be shipped so that expected arrival at Coriell occurs Tuesday – Thursday (please plan accordingly as transit times may vary between sites).

Ambient samples may be shipped Monday – Friday (preferably Monday – Thursday) provided they are received at Coriell within 5 days of collection.

Weekend/holiday delivery must be arranged in advance with Coriell.

*Additional information about shipping restrictions will be provided as necessary.

2.0 STUDY: LABORATORY SPECIMEN MANAGEMENT (2.2) PLASMA, URINE, WHOLE BLOOD, CSF, RNA

Biological specimens are a prime study focus with several researchers eager to analyze new components of plasma, DNA, CSF, etc.; thus, we must make all efforts to continually replenish our invaluable samples so that the possibility of new discoveries can be achieved.

COLLECTION PROCEDURES

SPECIMEN COLLECTION KITS AND SUPPLIES

Research specimen collection kits will be provided to you by NINDS Repository at Coriell Institute for Medical Research with most of the materials needed for the urine, blood, RNA and CSF collection, as well as shipping labels and pre-filled FedEx Airway Bills to send samples back to the NINDS Repository.

The University of Iowa will provide saliva kits and waybills for shipments back to the UI. The saliva sample must be shipped with the remaining visit materials.

BLOOD COLLECTION ORDER

BLOOD AND PLASMA SAMPLE PROTOCOL AT BASELINE/INITIAL 2.2 VISIT

1. RNA PAXgene tubes (Two, 2.5 ml)
2. 10ml Yellow-top ACD tube
3. Plastic 5ml Red Top Whole Blood
4. Plastic 6ml Green Top (Lithium Heparin) Vacutainer
5. Plastic 6ml Lavender top (K2EDTA) Vacutainer
6. Plastic 6ml Green Top (Lithium Heparin) Vacutainer
7. Plastic 6ml Lavender top (K2EDTA) Vacutainer

BLOOD AND PLASMA SAMPLE PROTOCOL AT FOLLOW UP VISIT

1. RNA PAXgene tubes (Two, 2.5 ml)
2. Plastic 5ml Red Top Whole Blood
3. Plastic 6ml Green Top (Lithium Heparin) Vacutainer
4. Plastic 6ml Lavender top (K2EDTA) Vacutainer
5. Plastic 6ml Green Top (Lithium Heparin) Vacutainer
6. Plastic 6ml Lavender top (K2EDTA) Vacutainer
7. Plastic 6ml Green Top (Lithium Heparin) Vacutainer
8. Plastic 6ml Lavender top (K2EDTA) Vacutainer

SPECIMEN COLLECTION KITS BASELINE KIT COMPONENTS

Type of sample	Tube type	# of tubes in the kit	Tubes sent to Coriell	Tubes stay at site
RNA	2 (2.5ml) PAXgene tubes	2		
DNA	1 (8.5 ml) yellow-top ACD solution vacutainer tubes	1		
Whole-blood	plastic 5ml red top whole blood	1		
Plasma	plastic 6ml green top lithium heparin vacutaine	2		
Plasma	plastic 6ml lavender top K ₂ EDTA vacutainer	2		
Urine	50ml polypropylene vial	1		
Urine	5ml orange screw top tube	1		
Urine	Collection Cup	1		

FOLLOW-UP KIT COMPONENTS

Type of sample	Tube type	# of tubes in the kit	Tubes sent to Coriell	Tubes stay at site
RNA	2 (2.5ml) PAXgene tubes	2	2	0
Whole-blood	plastic 5ml red top whole blood	1	1	0
Plasma	plastic 6ml green top lithium heparin vacutaine	3	Up to 3	0
Plasma	plastic 6ml lavender top K ₂ EDTA vacutainer	3	Up to 3	0
Urine	5ml orange screw top tube	1	1	0
Urine	50ml polypropylene vial	1	1	0
Urine	Collection Cup	1	0	1

CSF KIT COMPONENTS

Type of sample	Tube type	# of tubes in the kit	Tubes sent to Coriell	Tubes stay at site
Whole- blood for CSF screening	plastic 3ml lavender top K ₂ EDTA	1	0	1
	plastic 5ml green PST	1	0	1
	plastic 3ml light blue Na Citrate	1	0	1
CSF	2ml purple top microcentrifuge tube for routine lab testing	1	0	1
CSF	15ml conical polypropylene tube	1	N/A	N/A
CSF	2ml microcentrifuge tubes for CSF aliquoting (1.5 ml aliquot. A total of 8-10 aliquots will be obtained)	10	all	0
CSF	Cardboard Cryobox	1	1	0

LUMBAR PUNCTURE KIT CONTENTS

Quantity	Kit Component
1	Sprotte Spinal Needle, 24G x 90 mm
1	Introducer needle, 1mm x 30mm
1	22G x 1.5 in. Needle
4	Plastic Syringes (5 ml, Luer Lock)
1	Plastic Syringe (3 ml, Luer Lock) with 25G x 5/8 in. Needle (Attached)
1	Needle stick pad
1	Adhesive bandage
1	Fenestrated Drape
2	Towels
6	Gauze Sponges
3	Sponge Applicators
1	Lidocaine HCl (1%), 5 ml
1	Povidone-Iodine Solution, 0.75 oz

Sites must supply the following phlebotomy equipment:

- Dry ice
- Gloves
- Alcohol wipes
- Butterfly needles
- Tourniquet
- Gauze Pad
- Bandage
- Microcentrifuge tube rack
- Sharps bin and lid
- Crushed Ice
- Pipettes and pipette tips

FASTING BLOOD DRAW: OPTIONAL PROCEDURE

- All participants should be informed of the option to complete a fasting blood draw prior to the day of the visit
- If the participant agrees, they must fast for a period of 12 hours. If participant forgets to fast, blood and CSF samples can still be obtained
- Blood should be drawn immediately after consenting using the 2.2 consent
- If CSF sample will be obtained, the participant should be instructed to fast after Day 1 of PREDICT-HD visit CSF samples obtained immediately in the morning of Day 2. **For participants that are unwilling to fast, or have minimal availability for a two-day visit, it is possible to do the pre-screen activities right away in the AM, followed by a late afternoon LP (pending on- site physician availability)
- Participants will need to be provided a snack and/or rest period following the blood draw to ease any discomfort or difficulties
- Coordinators should record whether a fasting blood and/or CSF procedure(s) was/were completed via the CSF Collection Laboratory form and Biomarker Sample Requisition Form

COLLECTION OF SALIVA

Saliva samples will be collected for all NEW participants (at Baseline Visit) for the purpose of CAG analysis. For participants who have experienced past difficulties with DNA samples being viable, they may be asked to provide a saliva sample either at home (via mail-in kit) or at their next scheduled visit.

Participants should not eat, drink, smoke or chew gum for 30 minutes before giving their saliva sample.

An ORAGENE Discover (ORG-500) kit will be provided by the University of Iowa. These kits should arrive pre-labeled. If they are not, **please write the participant ID, Visit #, Site #, gender, initials and date on the label supplied using a permanent marker and affix to the outside of the tube.**

The coordinator or participant should remove the contents of the kit, review the collection instructions and keep the kit at room temperature at all times.

HELPFUL TIPS:

****Ensure you secure a private location/room for the participant to provide their saliva sample.**

****If a participant is experiencing difficulty salivating, begin a conversation about food and inquire about their favorite foods. Additionally, you could provide picture stimuli to help him/her. If needed, allow the participant to return to a private location to provide the sample.**

Step 1: Participants need to refrain from talking. It is better for the participant to drop down the head and let the saliva run naturally to the front of the mouth; hold for a while and spit into the provided tube. Participants will spit into the collection tube for approximately 2-5 minutes. Should the participant cough up mucus as saliva is collected, instruct them to spit it in a sink/trash can/etc then await the next saliva collection opportunity.



Step 2: After the participant has filled the saliva to the designated fill line, the coordinator or participant should close the funnel lid (you will hear a loud click). The liquid in the lid will mix with the saliva.

Step 3: Hold the tube upright and unscrew the funnel from the tube.

Step 4: Place the small screw cap on the tube and tightly close. Shake for 5 seconds.



Step 5: Place the closed tube into the bio-specimen bag and seal.

Step 6: Place the bio-specimen bag into the padded envelope and mail to the University of Iowa with the remaining visit materials:

PREDICT-HD
The University of Iowa 200 Newton Road
1185 Westlawn Iowa City, IA 52242 (319) 353-4523

AMBIENT YELLOW-TOP ACD

BLOOD SAMPLES

- Samples may be used to produce plasma lymphocytes and a lymphoblastoid cell line which will be stored for future medical research.
- Each site will be provided all of the necessary materials to collect the required specimens.

All bio-specimen collecting supplies except saliva collecting tubes will be shipped to you from the NINDS Repository. To order bio-specimen collection kits, please contact PREDICT Management Team at University of Iowa. Please allow at least **three-week turnaround time**.

AMBIENT YELLOW-TOP ACD BLOOD SAMPLE TUBE

- One (1) ACD blood sample will be collected at the Screening/Baseline visit (Visit 201) after all eligibility criteria have been verified and consent procedures completed.



- Gently invert the tube to ensure mixture of the solution in the tube and the blood.
- Using a permanent black ink marker, ACD tube must be properly labeled with the designated participant ID number, visit number, site number, visit date.
- Under 2.2, the previous barcode labels have been discontinued, thus writing essential information on the tube is important (as above). *If you still have barcodes on-site, please return to the University of Iowa with your next UI shipment.
- Coordinators must complete the designated ACD tube section on the NINDS Repository/Coriell Sample Record Shipping Form prior to shipping sample; also specify whether fasting occurred.

RETENTION/DESTRUCTION OF YELLOW-TOP ACD BLOOD SAMPLES

- Sample will be stored and maintained for future research at the NINDS Repository at the Coriell Institute for Medical Research indefinitely or until the sample is depleted.

SHIPMENT OF YELLOW-TOP ACD BLOOD SAMPLE

- Blood sample should be shipped to the NINDS Repository at room temperature on the same date of draw for priority overnight delivery. **Do not freeze blood.**
- **Ambient blood samples may be shipped Monday – Friday (preferably Monday – Thursday) provided they are received at Coriell within 5 days of collection.**
- Insert the blood sample into the foam-lined ambient shipping container and ship at room

temperature according to kit instructions. If sample cannot be shipped the same day as collected, hold at room temperature until shipping

can be arranged. **Sample must be received at Coriell within 5 days of being collected.**

- Holiday shipments to the US should be avoided; Holidays are listed on the Home Page of the SharePoint site and in Appendix XI. Shipping during US holidays may result in ruined samples and payment penalties.

FROZEN LABORATORY SPECIMEN MANAGEMENT: PLASMA, URINE, RNA, CSF & WHOLE BLOOD

Within the 2.0 protocol, the biosample procedures have been updated to include urine sample collection in addition to the normal yearly plasma samples. Plasma samples will be used to conduct more sophisticated analyses, such as metabolomics, proteomics, lipidomics, and mass spectroscopy. Samples will be evaluated to measure the DNA injury markers (such as 8- OH2'dG) and the RNA injury markers (such as 8OHrG). All samples will be kept indefinitely for future research in the NINDS Repository at the Coriell Institute for Medical Research. Within the 2.2 protocol amendment, the sample collection has been expanded to include the possible collection of saliva, RNA and/or CSF.

Researchers who have had their research reviewed by an Institutional Review Board will be able to request coded samples following approval by the principal investigator, the PREDICT-HD Executive Committee and NINDS.

RNA PAXGENE SAMPLES

Two (2) 2.5ml RNA samples (totaling 5ml) should be obtained early in the collection process (before plasma, etc.). **Please be sure to have a designated location where both tubes can be placed UPRIGHT and stored for a period of 24 hours at room temperature prior to freezing in a -70 or -80 freezer.**

INSTRUCTIONS FOR PAXGENE TUBES:

1. Store PAXgene™ Blood RNA Tubes at room temperature 64⁰ F -77⁰ F (18°C to 25°C) before use. Write the participant #, site #, visit # and date of collection on the PAXgene RNA tubes prior to blood draw using a permanent black marker. **Label tubes prior to specimen collection.**



2. Using a blood collection set and a holder, collect blood into the first of the two PAXgene™ Blood RNA Tubes using your institution's recommended procedure for standard venipuncture technique. The following techniques shall be used to prevent possible backflow:
 - a. Place donor's arm in a downward position.
 - b. Hold tube in a vertical position, below the donor's arm during blood collection.
 - c. Release tourniquet as soon as blood starts to flow into tube.
 - d. Make sure tube additives do not touch stopper or end of the needle during venipuncture.
3. Allow at least 10 seconds for a complete blood draw to take place in each tube. **Ensure that the blood has stopped flowing into the tube before removing the tube from the holder.** The PAXgene™ Blood RNA Tube with its vacuum is designed to draw 2.5ml of blood into the tube. Record time of draw on Biomarker Sample Laboratory Requisition form.
4. **CRITICAL STEP:** Immediately after blood collection, gently invert/mix (180 degree turns) the PAXgene™ Blood RNA Tube 8 – 10 times.
5. REPEAT STEPS 2 TO 4 for the second PAXgene™ Blood RNA Tube to be collected.
6. **CRITICAL STEP:** Incubate the PAXgene™ Blood RNA Tubes **UPRIGHT at room temperature (18°C to 25°C) for 24 hours.** Record time and date of draw on Biomarker Requisition form.

❖ *If blood is drawn on a Friday and you are unable to return on Saturday to place tubes in the freezer, transfer the tubes as late as possible before leaving on Friday. **Samples must sit at room temperature for a minimum of 2 hours.***
7. After **24 hours** at room Temperature, transfer the two PAXgene tubes to -70 or **-80°C freezer.** Keep the two **PAXgene™ Blood RNA Tubes at -80 °C** until you ship on dry ice. Both tubes are to be shipped to Coriell. Complete remainder of the Biomarker Sample Laboratory Requisition form.

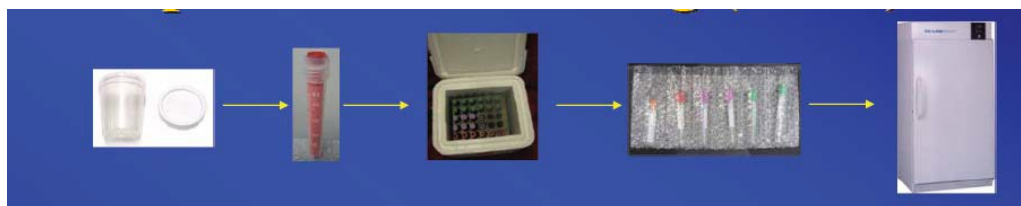
IMPORTANT: Prior to beginning bio-sample collection, be sure that your freezer block has been in the freezer for at least 2 hours or more prior to removing it from the freezer to conduct sample procedures for urine and plasma. The freezer block does not need to remain in the freezer at all times. Also note that the metal freezer block will only maintain a temperature of -70°C to -80°C for 4-5 hours at room temperature.

URINE SAMPLE PROTOCOL

Urine samples will be collected via clean catch method. 50ml of urine will be pipetted into a **50ml screw top polypropylene vial**, frozen on dry ice and stored at -70°C to -80°C until shipment.



An additional 5ml of urine will be pipetted into an **orange screw top tube**, flash frozen in the freezer block and transferred to the -70°C to -80°C freezer until ready for shipment. All tubes must be labeled with participant #, site #, visit # and date of collection. **Label tubes prior to specimen collection.**

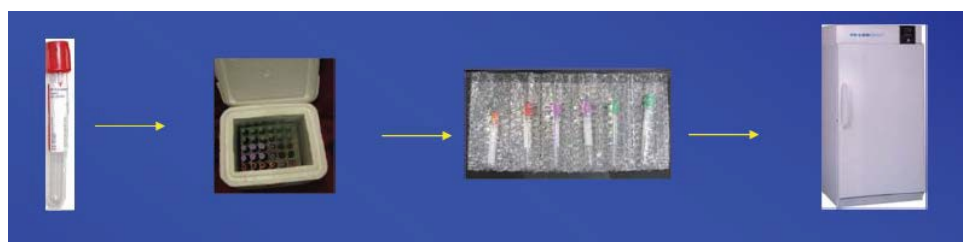


Complete the *2.2 Biomarker Sample Laboratory Requisition* (see Appendix XI) with all pertinent details relating to the urine collection (i.e., time of collection, etc.). In the future, the Biomarker Sample Laboratory Requisition form will be entered via the web and/or laptop/tablet. Sites will be prepped to be able to scan and upload the form via the web. Until the site has been trained, they may continue to send the paper Biomarker Sample Laboratory Requisition form via mail.

IMPORTANT: Prior to beginning bio-sample collection, be sure that your freezer block has been in the freezer for at least 2 hours or more prior to removing it from the freezer to conduct sample procedures for urine and plasma. The freezer block does not need to remain in the freezer at all times. Also note that the metal freezer block will only maintain a temperature of -70°C to -80°C for 4-5 hours at room temperature.

*WHOLE BLOOD AND PLASMA SAMPLES PROTOCOL**Red-top 5ml tube:*

- Whole Blood 5 ml red top vacutainer is drawn
- Immediately place in the freezer block for flash freezing (no spinning required)
- Transfer tube to -70°C to -80°C freezer. Tube should be in a freezer box or tube pouch until ready for shipment.
- Document date, time of draw, time frozen and storage temperature on the *Biomarker Sample Laboratory Requisition* form.

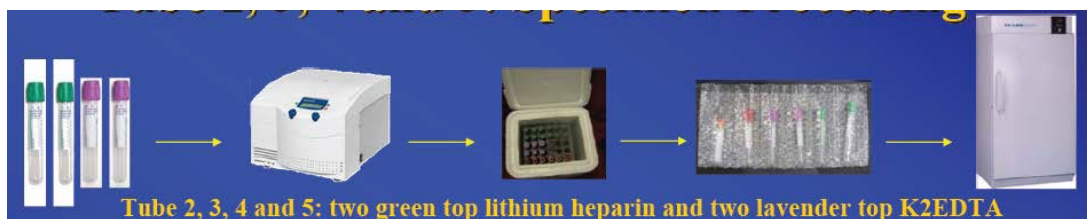
*Four (4) plasma tubes (Baseline) or Six (6) plasma tubes (at Follow up):*

- Two 6 ml green top (Heparin) vacutainer and two 6ml lavender top (K2EDTA) vacutainer are drawn at baseline visits. [Three tubes of each are drawn at follow-up visits.]
- Invert tubes 4 times to mix anticoagulant. (if you are drawing multiple participant samples, you may keep the tubes in an ice/water 0 °C for no longer than 40 minutes before centrifuging.
- Centrifuge TUBE 2, 3, 4 & 5 in a refrigerated centrifuge at 4°C according to the following centrifuge dependent schedule below. Note both swing rotor and slant rotor centrifuge heads are acceptable.
NOTE: The highest time/g force is the preferred method.

g force	Time (minutes)
8000xg	20 minutes
7000xg	25 minutes
6000xg	35 minutes
<6000xg	40 minutes

- The tubes are then immediately flash frozen in the metal freezer block and maintained at -70°C to -80°C until shipment.

- Document date, time of draw, time frozen, storage temperature and spin rate on the *Biomarker Sample Laboratory Requisition* form.
- Send a copy of the *Biomarker Sample Laboratory Requisition* form to the University of Iowa with all other visit paperwork after each visit.



** Tubes 6 & 7 will be processed for follow-up visits as well.

STORAGE OF PLASMA AND URINE SAMPLES

- Samples should be stored in -70°C to -80°C freezer until shipment to the NINDS Repository. Samples should be shipped within 2 weeks (US sites) and 4 weeks (international sites) after draw (See “Shipping Procedures” section).

SHIPPING PROCEDURES

NOTE: There are different guidelines for US and International Sites. Please reference Appendix XI.

COLLECTION OF CEREBROSPINAL FLUID (CSF)

Within the 2.2 protocol, CSF collection is an important aspect that NINDS/NIH has requested be incorporated into the PREDICT-HD study in order to examine possible biomarkers unique to CSF that are most closely associated with the disease, hopefully creating a powerful means to measure response to treatments under development now and in the future.

Site personnel will carefully review the 2.2 consent which explains the potential risks, side effects and procedures for the lumbar puncture procedure with participants. Participants, themselves, can only consent to this study component; their legal authorized guardian cannot. For participants willing to undergo a LP, the site coordinator and MD should complete all necessary pre- screen recommendations to ensure safety. For some sites, their ethics boards or MD’s may request additional screening protocols; please follow their requirements as well.

PRE-SCREEN PROCEDURES

- ✓ Medication review: all current medications should be documented on the Concomitant Medication Log and MD should verify that the participant is not taking any anti-coagulants (such as warfarin and heparin) and/or anti-platelets (such as aspirin). Participants taking these CANNOT undergo a LP.
- ✓ Physical and Neuro exams: The site investigator, or other designated personnel, should ensure that the participant does not have any medical conditions that would preclude undergoing the procedure.
- ✓ Blood pre-screen labs: 10 ml of the blood will need to be collected and analyzed on-site prior to the LP.
 - plastic 5ml light green PST
 - plastic 3ml light blue Na Citrate
 - plastic 3ml lavender top K2EDTA

The study coordinator will complete the top portion of the CSF Screening Blood Samples form indicating time of collection and time samples were sent to their local lab for analyses.

Necessary on-site labs include:

- Sodium (Na)
- Potassium (K)
- Chloride (Cl)
- Carbon Dioxide (CO₂)
- Blood Urea Nitrogen (BUN)
- Glucose
- Calcium (Ca)
- Creatinine (Crn)
- Bilirubin Total
- Albumin
- Total Protein
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline Phosphatase (ALKP)
- Uric Acid
- Prothrombin time (PT)
- Partial Thromboplastin Time (PTT)
- White Blood Cell Count (WBC)
- Red Blood Cell Count (RBC)
- Hemoglobin (Hb)
- Hematocrit (HCT)
- Platelet Count (PLT)

The study coordinator should request lab results prior to the end of the visit day, insert values into the CSF Screening Blood Samples form and provide to their MD/Site Investigator. Abnormalities in lab values may preclude participation, in particular increased PT/PTT and/or low platelets.

After all pre-screen steps are complete, the MD will decide if he/she supports participant's safety to undergo a LP. The MD MUST sign off on the CSF Screening Blood Samples form prior to the LP.

SETTING UP FOR THE LP

Site coordinators will be supplied with LP kits which can be provided to the LP physician. On an over bed table, remove the contents of the LP kit from outer plastic packaging, leaving the contents wrapped in their sterile drape. Leave everything wrapped until the person performing the LP is seated and begins examining the subject.

Feel the outside of the LP kit (still wrapped up) to determine which end contains the spongy swabs. Turn this end toward the person performing the LP and begin unwrapping the kit.

Touch only the outside of the paper wrapper. When you grab an edge to unfold it, touch only the folded under portions of the outside of the wrapper. Also, don't let the outside of the wrapper touch any part of the inside. If you touch any part of the inside of the paper wrapper, or if any non-sterile object or outside of the wrapper touches any part of the inside of the wrapper, throw the kit away and start over. If you are in doubt as to whether something touched the inside of the paper wrapper, throw the kit away and start over.

MAINTAINING THE STERILE FIELD

Keep in mind that there is usually a lot of staff in the room during an LP, and a big part of assisting with the LP is keeping the field sterile, and keeping people away from it, and reminding people to be careful around it. If anybody touches the inside of the paper wrapper or any part of the contents of the kit, throw the kit away and start over. If you are in doubt as to whether someone touched the kit, throw it away and start over. Also, you are the monitor for whether the person performing the LP has broken sterility – usually by touching something not sterile with a sterile gloved hand. Feel free to be the boss of people if need be. Be assertive.

TIPS FOR CLINICIANS PERFORMING LUMBAR PUNCTURE

Optimizing patient comfort and minimizing risk of adverse events.

1. Talk the patient through the procedure -no surprises.
2. Use of a Sprotte 24g atraumatic spinal needle and careful technique are optimal for reducing post-LP headache risk. A pencil point spinal needlesuch as Spinocan, 22g or 24g may also be used.
3. Use adequate local anesthesia. Use the 25g 1/2" needle and inject lidocaine to raise a skin wheal. Then inject lidocaine using the pattern of a square -first the center and then to all 4 corners. If the subject is thin, do not insert the deep infiltration needle OR the spinal introducer all the way. Use only about 2/3 of their length (to prevent entering the subarachnoid space with anything other than the 24g pencil point spinal needle).
4. Increasing fluid intake immediately after LP is helpful.
5. Be sure to give post-LP care instructions verbally to subject (see below).

DETAILED LUMBAR PUNCTURE PROCEDURE

Remember, CSF is processed at Room Temperature [64°F 77°F (18°C to 25°C)].

Also, a portion of the CSF must be sent to your clinical lab and analyzed within 4 hours of collection.

1. Label participant ID, specimen type (CSF), Visit #, Site # and Date on the collection and aliquot tubes (per section 6.2). Prepare at least 10 aliquot tubes based on the collection of 15mls of CSF.
2. Place aliquot tubes on ice prior to procedure so they are pre-cooled. **Label all aliquot tubes prior to placing on ice.**
3. Perform lumbar puncture using the atraumatic technique.
4. Collect CSF into syringes. After the LP has begun and fluid is being collected, take the first 1-2 mls of CSF from the first syringe and place in the CSF labs tube (PURPLE TOP). **Do not freeze this sample.**

❖ Send at room temperature to local clinical lab for basic CSF analyses. NOTE: Sample must be analyzed within 4 hours of collection.

- Cell count (erythrocytes first)
- Total protein
- Glucose

5. Collect remaining 15mLs of CSF and transfer to 15 mL conical polypropylene tubes at room temperature, mix gently by inverting 3-4 times. Record time of draw (i.e., once collection is complete) on the Lumbar Puncture data form.
6. Within 15 minutes of collection, spin the remaining CSF sample down at 2000 x g for 10 minutes at **Room Temperature** [64°F 77°F (18°C to 25°C)].
 - Equivalent rpm for spin at 2000 x g = _____
 - While centrifuging record the time of centrifuge start on the Biomarker Sample Requisition form.
7. Pipette (micropipette preferred) 1.5 ml of supernatant directly into labeled, pre-cooled 2-ml microcentrifuge tubes (clear-top, 2 ml microcentrifuge tubes). provided in the kit. This will yield, on average, 8-10 aliquot tubes per participant.
8. Freeze aliquots immediately following processing by transferring to **-80°C Freezer**. If samples cannot be immediately transferred to **-80°C Freezer**, prepare a sufficient amount of dry ice for immediate freezing. Store all samples at **-80°C Freezer** until you ship on dry ice. Complete the remainder of the Biomarker Sample Laboratory Requisition form and ensure timely entry of data.

POST-LP CARE INSTRUCTIONS FOR PARTICIPANTS

IMMEDIATELY FOLLOWING THE SPINAL TAP:

1. You will have a 60-minute rest period during which time your vitals will be taken, and you will be provided a light snack if you fasted the evening before.
2. You should continue with increased fluid intake.
3. You should not do any tiring activity for the next 24 hours. This includes things as such:
 - a. Lifting
 - b. Bending
 - c. Housework
 - d. Gardening
 - e. Vigorous Exercise like jogging or bicycling
 - f. Sexual activity
4. You are able to travel in a car or plane the same day of the procedure unless you experience severe side effects
5. If necessary, the study coordinator can arrange for suitable transportation service to your hotel or home if you are unable to drive for any reason.
6. You will receive a follow-up phone call within 3 days of your spinal tap to ask about any post-ST side effects. If you experience any symptoms or require further healthcare consultation, please alert your site investigator using the contact information below.

POTENTIAL SIDE EFFECTS YOU MAY EXPERIENCE:

Mild to moderate headache following lumbar puncture usually appears after 6+ hours and typically resolves within 3-4 days. 30% of individuals are likely to experience a mild to moderate headache.

- Treatment for mild to moderate headache:
 - First, always lie flat and rest. In many cases, this simple task helps relieve the headache.
 - Limit physical activity as much as possible
 - Oral fluids and caffeine are helpful. Drinking a soft drink (e.g., Mountain Dew) is preferable to coffee
 - Tylenol should be used for symptomatic relief. If you cannot tolerate Tylenol, then ibuprofen should be used. **AVOID ASPIRIN**. If they do not relieve the headache, a doctor may prescribe Tylenol with Codeine or similar analgesic.

Severe headache: 0.5% of individuals experiences a severe headache.

- If you have a severe headache, severe back pain, nausea, vomiting, visual disturbances, etc. we encourage you to seek consultation from your local physician or emergency room.

Fever can be controlled using Tylenol or ibuprofen. If your fever doesn't subside within 24 hours, please call the study investigator for further assistance.

Redness at the Spinal Tap Area occurs and usually goes away with time and healing.

[**COORDINATORS: Feel free to copy and paste these post-LP instructions into a handout for participants to take home; along with the site personnel contact information.]

FOLLOW UP PHONE CALL AFTER LP

REPORTABLE EVENTS FOLLOWING CSF LP

SECTION 8: MRI

INTRODUCTION:

MRI collection occurred throughout the PREDICT-HD study. In the 1.0 study, MRI's were collected at odd visits when possible. The scanner type varied across sites and a traveling phantom was used to help calibrate MRIs across sites. The Tesla strength was 1.5 and consistent across the study.

During the 2.0 study a mixture of 1.5 and 3.0 Tesla strength MRIs were introduced. Sites were encouraged to locate a 3.0T scanner for participant scans. However, many sites were unable to secure use. As a result, and to help reduce cost in the study, the number of sites collecting MRI's was reduced to 8. Those sites were selected based on a number of factors including quality of scans submitted and cost factors. Throughout the 2.0 study, a traveling phantom was used to help calibrate MRIs across the sites. When the study ended for sites in August 2014, the University of Iowa continue to collect scans to help supplement an ancillary study using PET technology. After the ancillary study was completed, MRI collection was discontinued.

MRI PROTOCOL (1.0)

All images are requested to be obtained on a 1.5 Tesla GE magnet using the parameters listed below. Sites with a phased array neurovascular coil should use this coil instead of the standard quadrature head coil because of increased SNR (24 m).

Following the scan, make a note regarding the scans obtained, any repeats, any problems, any comments on the participant and on the acquisition on the MRI CRF.

The following MRI scanner settings in the table below include that of the original MRI protocol and amendment 3 additional MRI scan time (Coronal Variable Echo (T2/PD)).

MRI SCANNER SETTINGS

	Sagittal Localizer *	Axial 3D Volumetric SPGR	Coronal Variable Echo (T2/PD)
TR	500	18	3000
TE	11	3	28
FOV	24	24	26
Thickness	3	1.5	3.0
Gap	1.5	0	0
Matrix	256 x 192	256 x 192; 3/4 phase FOV	256 X 192
NEX	1	2	1
Flip angle	90	20	90
# of slices	19	124	64 (or enough to cover whole brain)
Bandwidth	15	15	N/A
Inferior SAT pulse	None	None	None
Prescan options	Autoshim	Autoshim	Autoshim
Scan time	1:44	11:07	~6 minutes

***Note:** It is not essential for the sagittal parameters to match exactly.

MRI SOFTWARE/HARDWARE CHANGES

If a site has an MRI software upgrade, they should contact Dr. Elizabeth Aylward at University of Washington **BEFORE** the upgrade. She will send them a phantom, which will need to be scanned before and after the upgrade so that comparisons can be made on volumetric measurement. Sites should also scan one person (this can be a participant or any other volunteer) before and after the upgrade so that comparisons can be made.

If there is a difference of >1% in volumetric measures for the phantom or participant, the site will be asked to rescan 5 participants who were scanned within the month before the software upgrade. (If systematic increases or decreases are observed in measurements from these subjects, Dr. Aylward will determine the percentage increase/decrease and adjust measurements for all participants whose scans are acquired after the upgrade.)

If a site changes MRI hardware, scans **MUST** continue to be done on a GE 1.5T scanner. If the new scanner is also a GE 1.5T scanner, procedures should be the same for switching software as above. If a GE 1.5T scanner is no longer available, arrangements will have to be made to have the scans done at another nearby location or to have participants travel to another study site to be scanned.

SCHEDULING

MRI scans are to be completed at the Screening/Baseline visit (Visit 1) and Visit 3. The scans need to be done no more than one month before or after the neuropsychological testing is completed for the Screening/Baseline and Visit 3. The MRI Form (see Appendix XI) must be completed at each scan and sent to the CTCC.

If the participant is not scanned within this time frame, the study site must contact the CTCC Project Coordinator via phone. Each month an MRI Transmittal Log (see Appendix XI) will need to be updated by the University of Iowa and the University of Washington and sent via email to the CTCC.

SPECIAL REQUIREMENTS

Prior to the participant's MRI scan, ensure that all eligibility criteria have been met and that the participant does not have any metal implants/fragments or implanted metal devices (e.g., pacemaker, cardiac defibrillator, aneurysm clips). If a female participant becomes pregnant during the study, perform the required MRI scans after the delivery of the fetus.

DATA TRANSFER

Sites are to transfer MRI data to Jane Paulsen at the University of Iowa. A permanent archival copy (CD, magnetic tape, etc.) of each participant's MRI scan should be stored at the site. (See Appendix XI for detailed requirements for MRI data transfer and checklist for sending MRI data to the University of Iowa). The T1 imaging data will be relayed to the Washington site by the University of Iowa.

The University of Iowa will maintain a long-term archive of all raw and processed data collected on a secure data storage system. The data storage system is designed to ensure the integrity of the data through power and media redundancies by employing various RAID technologies. In addition, the data storage system will undergo nightly incremental and periodic archival backups to magnetic tape.

QUESTIONS

Any questions or concerns that may arise with regards to MRI scan settings, MRI data transfer, or MRI protocol questions can be addressed to:

Elizabeth Aylward, PhD
 University of Washington
 Department of Radiology
 Box 357115
 Seattle, WA 98195
 Phone: 206-221-6610
 Fax: 206-543-3495
 Email: eaylward@u.washington.edu

OR

Leigh Beglinger, PhD
 University of Iowa
 Psychiatry Research
 1-321 Medical Education Building
 Iowa City, IA 52242
 Work Phone: 319-335-8765
 Secretary's Phone: 319-353-5829
 Fax Number: 319-353-3003
 Email: leigh-beglinger@uiowa.edu

REQUIREMENTS FOR PREDICT HD MRI DATA AND TRANSFER

- Scans must be sent in .dcm or .MR format. We have had sites send files in other formats, which then require our group to find a way to convert scans into .dcm format. This conversion process leads to several potential problems. For example, it makes it very difficult to retrieve the header data that includes information on the image acquisition parameters and PREDICT HD subject ID number.

- Scans must be sent as a series of labeled folders (directories). We have had sites send scans as individual slices, without a containment/ organizing folder, and no identifying information (i.e., no Predict HD subject ID number or site number).

- Each subject's MRI should be sent in a uniquely identifiable folder identified by Site ID, "Predict-HD", subject ID number and date of the scan. Without this information in the folder names, we do not know that this is a PREDICT HD MRI. Furthermore, header information is also sometimes incomplete, particularly if the data were sent in an incorrect file format. Determining the identity of these images takes quite a bit of time, which could be avoided with correct labeling of the materials.

- Inside each subject's uniquely identifiable folder should be subfolders containing separate types of scan series. An example of this would be to have a subfolder titled 3DSPGR, which would contain only the 124 slices of the SPGR series. Sites should send 1 to 4 series: always the 3D SPGR, and T2/PD and one or two "scout" series.

- Data from the 3D SPGR and T2/PD series must include the entire brain. We have received incomplete structural image data sets. Missing data files have occurred both with CD transfer and with ftp. It is very simple and straightforward to check each data set for completeness prior to sending the images by viewing them.

- Headers must not include any identifiers that compromise subject confidentiality, such as a person's name or social security number. This information is usually entered into the scanner by the imaging technician. Specific information that should NOT be in the header includes patient initials, name, social security or other personal identifying number, and date of birth. Instead, please ask the imaging technician to enter the PREDICT HD subject ID number in the subject or

patient ID field (e.g., PREDICT 142). This is sufficient information for the University of Washington and Iowa and is the best protection of confidentiality for the participant.

- SPGR scans must conform to the following structural format:

- 1.5mm thickness with no gap (this usually results in a series with 124 slices; on some scanners, the number of slices can be between 120-128, which is OK as long as the whole brain is covered with the correct thickness and gap).
- TR=18 TE=3 NEX = 2 Flip-angle= 20 FOV=240
- Note that the lack of conformity occurs most in the NEX parameter.

AND

- Additional MRI Protocol (Coronal variable echo (T2/PD))

- 3.0mm thickness with no gap (this usually results in a series with 64 slices; on some scanners the number of slices may be greater than 64, which is OK as long as the whole brain is covered with the correct thickness and gap).

TR=3000 TE=28 Eff-TE2=96 NEX=1 Flip-angle= 90

Echo-Train-Length=8 FOV=26 Phase-FOV=1.0

Freq=256 Phase=192 Freq-Direction=S/I

MRI PROTOCOL – 1.5T & 3.0T (2.0 STUDY 2.0/2.1)

HOW TO CHOOSE BETWEEN 1.5T AND 3.0T SCANNERS:

If a site has only a 3.0T scanner available, then the staff at that site should acquire PREDICT MRI scans at 3.0T strength.

If a site has only a 1.5T scanner available, then the staff at that site should continue to acquire PREDICT MRI scans at 1.5T strength.

If a site has both a 1.5T and 3.0T scanner available, then the staff at that site should transition from collection of 1.5T to 3.0T PREDICT MRIs—assuming the dependable availability of the 3.0T scanner. To properly transition, staff at such sites should:

- adhere to the protocol for MRI hardware changes (below, under “MRI Hardware Changes”).
- ensure that participants with previous 1.5T PREDICT scans have at least two longitudinal 1.5T scans collected from them before transferring to collection at the 3.0T level.
- ensure that all new participants have only 3.0T scans collected from them.
- ensure that once 3.0T scans are being collected on a participant, no further 1.5T scans be collected on them.

OBTAINING THE MRI PROTOCOL:

The correct MRI protocol for the scanner used at any particular site varies according to that site’s scanner make, scanner model, and console software package. To obtain the correct PREDICT MRI protocol for a specific site’s scanner, contact your Site Assistant and provide the following information:

- Scanner make (GE, SIEMENS, Phillips, etc.),

- scanner model (Avanto, Signa, Tims Trio, etc.),
- and the scanner console software version.

MRI SOFTWARE CHANGES

If a site will have an MRI software upgrade, then the Site Coordinator should contact their Site Assistant **BEFORE** the upgrade. The Site Assistant will schedule an ADNI phantom to be shipped to the site, where it will need to be scanned before and after the upgrade so that comparisons between the volumetric measurements can be made. Phantom scans should then be sent to the Site Assistant (**see**: Appendix XI).

MRI HARDWARE CHANGES

If a site will change MRI hardware, then procedures are similar to software upgrades, as explained above. The Site Coordinator should contact their Site Assistant **BEFORE** the hardware is changed. The Site Assistant will schedule an ADNI phantom to be shipped to the site, where it will need to be scanned on the new hardware before any participants are. Phantom scans should then be sent to the Site Assistant (**see**: Appendix XI).

MRI SCHEDULING

MRI scans are to be completed at the Screening/Baseline visit and at all 24-month interval follow-ups (**see**: Schedule of Events).

Scans need to be done no more than one month before or after the neuropsychological testing is completed for the associated visit. If the participant is not scanned within this time frame, the study site must contact the Site Assistant.

If for some reason a scan is not completed at a designated scanning visit (**see**: Schedule of Events), then that participant will need to be scanned at their next visit. After, the participant should continue being scanned at the designated scanning visits, as per the Schedule of Events.

- *If a participant is pregnant during a visit requiring an MRI scan, do not schedule her for an MRI. Instead, collect an MRI at her next visit.*
- *If a participant misses a visit requiring an MRI scan, collect an MRI at the participant's next visit.*

SPECIAL REQUIREMENTS

Prior to the participant's MRI scan, ensure that all eligibility criteria have been met and that the participant does not have any metal implants/fragments or implanted metal devices (e.g., pacemaker, cardiac defibrillator, aneurysm clips, etc.).

DATA TRANSFER

Sites are to transfer MRI data to the University of Iowa. A permanent archival copy of each participant's MRI scan should be stored at the site. The University of Iowa will maintain a long-term archive of all raw and processed data collected on a secure data storage system.

REQUIREMENTS FOR PREDICT HD MRI DATA AND TRANSFER:

- Scans must be sent in DICOM (.dcm) or MR (.mr) format.
- Scans must be sent as a series of labeled directories.
- Scans, *when possible*, must include whole-brain coverage.
- Scan headers should include helpful, non-confidential identifiers, such as the date and participant number.
- Headers must NOT include identifiers that compromise confidentiality, such as a person's name and address.

QUESTIONS

Any questions or concerns that may arise with regards to MRI scan settings, MRI data transfer, or MRI protocol questions can be addressed to your Site Assistant.

MRI PROTOCOL –3T SIEMENS SCANNERS (2.2 AMENDMENT)

The PREDICT-HD 2.2 MRI protocol allows for ONLY 3T Siemens MRI scanners to be utilized.

SCAN REQUIREMENTS

Siemens 3T scans are required and are the only accepted scan for the PREDICT-HD study

3T SCAN REQUIREMENTS FOR PREDICT-HD NON-IOWA SIEMENS SITES:

Localizer	50 sec
T1	5 min 20 sec
T2	6 min 50 sec
Resting State FMRI	6 min 15 sec
DWI-64	12 min
T1	5 min 20 sec

3T SCAN REQUIREMENTS FOR IOWA AS PREDICT-HD:

Localizer	0:50
T1 MPRAGE	5:20
T2 Space	6:50
Resting State FMRI (Functional/Connectivity)	6:15
T2 Map	6:35
DTI 64 Directions	12:01
T2 Map	10:15
T1rho	08:40

NOTE: A good T1, T2, + DWI scan is mandatory for payment; any other sequence of images may be replaced in order to get at least one good image of each mandatory sequence. However, scan sequences should only be replaced in the event of an anomaly. Since HD is a movement disorder, segments of the scan can be invalidated by participant movement. The minimal PREDICT-HD MRI 3T protocol of providing at least one good T1 scan was specifically designed to last under one hour in duration and is integral to the site reimbursement allocation.

Resting State-FMRI instructions: Instruct the participant to lie quietly with eyes closed and try not to fall asleep. Please note that all visual and auditory stimuli should be turned off during PREDICT-HD scan sessions.

PREDICT-HD 2.2 MRI RECORD FORM:

An MRI Record form will be provided to all PREDICT-HD imaging sites (see Appendix XII). This form contains basic information regarding the PREDICT- HD visit scan session and should be filled out by the MRI technician. The site coordinator or valid data-entry person will later transcribe the information online. This information will be used by the Iowa data management team to verify scan session metadata.

DESIRED SLICER PRESCRIPTION (DTI IMAGE):



***NOTE:** A QA/QC review will be performed at The University of Iowa on MRI scans for image quality. If the scan does not pass this review, the site may be asked to rescan the participant. Sites will not be reimbursed for poor quality

scans. Scans are typically assessed for QA within two weeks of receipt at The University of Iowa.

OBTAINING THE MRI PROTOCOL:

The correct MRI protocol for the scanner used at any particular site varies according to that site's scanner make, scanner model, and console software package. To obtain the correct PREDICT-HD MRI protocol for a specific site's scanner, contact the CSM Team with the following information:

- scanner make (SIEMENS),
- scanner model (Verio, Skyra, TIM Trio),
- scanner console software version (syngo B17, etc.).

MRI SOFTWARE CHANGES

ADNI phantoms do not need to be scanned before and after software changes or upgrades. Contact CSM with updated software info. Once data (from the first session after new software) is transferred please notify CSM immediately with scan session info so that image quality may be assessed.

MRI HARDWARE CHANGES

ADNI phantoms do not need to be scanned before and after hardware changes or upgrades. Contact CSM with updated hardware info. Once data (from the first session after new hardware) is transferred please notify CSM immediately with scan session info so that image quality may be assessed.

MRI SCHEDULING

MRI scans are to be completed at the Screening/Baseline visit and at ALL subsequent follow-up visits (**see:** Schedule of Events).

Scans need to be done no more than one month before or after the neuropsychological testing is completed for the associated visit. If the participant is not scanned within this time frame, the study site must contact CSM to discuss.

- *If a participant is pregnant* at the time of her next visit, please contact the CSM team. A CSM member will work with you to determine how best to proceed. Depending on the participant's due date in relation to the visit

window, we may suggest a delayed visit. However, in some instances, we will recommend that the visit be completed within window, skipping the MRI.

SPECIAL REQUIREMENTS

Prior to the participant's MRI scan, ensure that all eligibility criteria have been met and that the participant does not have any metal implants/fragments or implanted metal devices (e.g., pacemaker, cardiac defibrillator, aneurysm clips, etc.).

DATA TRANSFER

Sites are to transfer MRI data to the University of Iowa using the XNAT Uploader tool. A permanent archival copy of each participant's MRI scan should be stored at the site. The University of Iowa will maintain a long-term archive of all raw and processed data collected on a secure data storage system (XNAT).

REQUIREMENTS FOR PREDICT HD MRI DATA AND TRANSFER:

- Scans must be sent in DICOM, making sure that files are PACS compliant.
- Scans must be sent as a series of labeled directories.
- Scans must include whole-brain coverage.
- Scan headers should include all, non-confidential identifiers meta- data, including the scan date and participant number.
- Headers **MUST NOT** include identifiers that compromise confidentiality, such as a person's name and address.

QUESTIONS

Any questions or concerns that may arise with regards to MRI scan settings, MRI data transfer, or MRI protocol questions can be addressed to the CSM Team: predict-management@uiowa.edu.