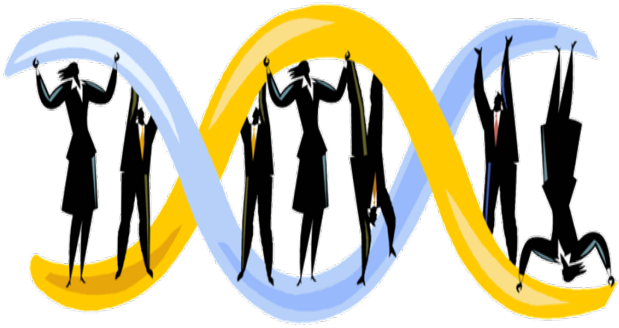

PREDICT-HD

PROTOCOL

2001-2017

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3/15/2021

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INTRODUCTION:

PREDICT-HD was a study initiated by members of the Huntington Study Group (HSG). The grant was written and submitted to the NIH 6-23-1999 and a revised application was prepared for consideration with a response to the reviewers' summary statements in 2000. The program officer requested a response to the summary statements from the second review, after which, NINDS council approved the grant for Notice of Grant Award (NOGA) 9-1-2001. Budget restrictions resulted in the award being less than 50% of that requested requiring a study re-design but we moved forward with a PREDICT-HD orientation meeting.

At that meeting, certain "ethical issues" that had not been addressed by any of the numerous IRB's that had previously approved the grant were raised. Specifically, concerns were raised about the possibility that an individual might, in the course of participating in the study, learn that s/he already had manifest HD. Several additional meetings were scheduled in response to the concerns raised and issues were discussed thoroughly. As a result of the input the following responses occurred: (1) The protocol was changed to accommodate the concerns. A private foundation agreed to cover the expenses of allowing all interested parties to participate in the research, whether or not the investigator felt they had manifest HD. This protocol change was initiated to address concerns that research participants could inadvertently be told they have manifest HD as a consequence of volunteering to be in the study. (2) An additional RO1 grant was submitted to the National Human Genome Research Institute to investigate the ethical, legal, and social implications of living at-risk for HD. The emphasis of the additional submitted grant was to evaluate possible experiences of social stigma and/or genetic discrimination that might occur in this cohort who are healthy but living at 100% risk for a fatal disease. (3) No feedback about research data collected is to be shared with the volunteers. Each participant is encouraged to schedule a separate meeting with a health care professional to address concerns regarding early disease symptoms. (4) An Event Monitoring Committee was established to provide overview for all study events. When all concerns were sufficiently addressed, we redeveloped the case report forms and the informed consent materials and had all new information reviewed again by the Institutional Review Boards at 24 separate sites. Approval for the study was awarded at various times, depending upon each site. A second orientation meeting was held November 1, 2002, after which study enrollment began. From NOGA, the study was delayed by 14 months. Progress continued steadily with weekly Predict Team meetings conducted via teleconference between the primary centers of operation (Iowa for administration, Rochester for data management and HSG coordination, Indiana for cognitive assessment, and Seattle for MRI). Monthly teleconferences were held for Steering, Event Monitoring, and Recruitment Committee meetings. Two new committees were established in 2003: an Executive Committee to address grant renewal and a Publications Committee to develop guidelines for the dissemination of findings.

The first PREDICT-HD grant was funded to study 500 hundred research participants at 20 research sites in the US and Canada over a period of 3 years (2001-2004).

The second PREDICT-HD grant (renewal; 2004-2008) was funded to follow the cohort longer to document more cases of conversion; we were funded to study 625 research participants from 24 HSG sites including Australia. The grant submitted include 38 sites and 10 were to become "backup" sites although 30 of these sites continued to participate in PREDICT-HD.

The third PREDICT-HD grant (2009-2014) was funded to follow over 1000 participants at about 30

sites across six countries. Phenotype measurements were continuously shortened and improved to determine the best measure for each conceptual disease entity with the largest baseline effect size difference from normal. Longitudinal outcomes were assessed differently to determine which measures best tracked disease over time to be used as outcomes in clinical trials. The MRI group was divided into several subgroups to assess various imaging modalities for their usefulness in prodromal HD. FDA-mandated clinical outcomes were advanced in many ways, including more sensitive measures of functional capacity (adding occupational functioning) as well as supporting ancillary grants to develop disease-specific quality of life measures (Carlozzi, U Michigan).

This document is divided into two sections. Section 1 is referred to as the 1.0 version of the study and is considered the 1st half of the study. This section is comprised of the original grant and 5 amendment changes spanning the years from 2001 – 2008. NIH funded the original research in 2001-2004 and renewed the grant for 2004-2008. It should be noted that the 1st amendment to the protocol occurred in 2002 prior to the collection of data. Initial data collection started in September of 2002 and continued through early 2009 for the 1.0 study. Whereas most sites discontinued data collection towards the end of 2008 as they prepared to submit the renewed grant to their IRBs, some sites continued to collect data due to participant retention concerns at which point the study was renewed.

Section 2 is referred to as the 2.0 version of the study and is considered the 2nd half of the PREDICT-HD study. This section is comprised of 6 amendments in addition to the protocol.

This data collection period spans 2009-2014 for all sites and was funded in one 5-year NIH grant renewal.

Though NIH decided to close the parent grant at the conclusion of its third award in 2014, an NIH announcement was posted for competitive review of "PREDICT ancillary grants" to maximize the utility of the cohort prior to closure of the parent grant. To allow data collection in concert with funding up to twelve ancillary PREDICT grants, the University of Iowa continued to collect additional data from 2014-2017 as there were three years of ancillary funding programmatically linked to the PREDICT-HD parent study through NIH. Some significant changes were made to the protocol in 2012 with the addition of the collection of cerebral spinal fluid, PAX gene tubes for RNA analysis, and the reduction of MRI sites to 8 that had Siemens scanners to reduce error variance of the acquired imaging data.

Neurobiological Predictors of Huntington's Disease (PREDICT-HD)

PREDICT-HD

RO1 NS 040068

Twenty sites (n=20) from the **Huntington Study Group (HSG)** with 1.5 GE tesla will enroll 425 persons at-risk for HD and 75 normal controls to characterize the natural history of the pre-manifest period, to develop tools for clinical trials, and to identify markers that will make it possible to test putative neuroprotective therapies that could delay or prevent diagnosis.

Study PI and Chair:
Jane S. Paulsen
The University of Iowa

Steering Committee:
Elizabeth Aylward
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Michael Hayden
Elise Kayson
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Supported by:
The National Institute of Neurological Disorders and Stroke (NINDS) USA

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Indiana University School of Medicine, Indianapolis, Indiana	K. Quaid
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University of Iowa, Iowa City, Iowa	K. Duff
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University of Minnesota; Hennepin County Medical Center, Minneapolis, Minnesota	M. Nance
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Washington University, St. Louis, Missouri	J. Perlmutter

ABSTRACT: THE PREDICT-HD STUDY

OBJECTIVES: The four-year longitudinal study will use volumetric MRI and comprehensive neuropsychological assessment to characterize the preclinical syndrome in HD, to document the rate of change on these variables during the years leading up to diagnosis of HD, and to investigate the relationship among the neurobiologic factors, clinical onset and CAG repeat length. The primary outcome of the proposed work is the identification of MRI and neuropsychological measures which, in concert with the CAG repeat length, can predict age of disease onset better than any other model.

DESIGN: Five hundred subjects will be enrolled for study at 20 research sites in the US and Canada.Two groups will be selected: an age-restricted group (30-55 years) with known CAG repeat length
> 39 (n=425) (CAG-expanded), and an age-commensurate comparison group previously considered at risk (by virtue of having a parent with HD) who do not have CAG expansion (n=75 CAG-normal). This recruitment strategy will significantly enhance the probability of disease onset during the study among the CAG-expanded group. Assuming a 10% annual attrition (censoring) rate [35, 66], about 344 CAG-expanded subjects are expected to complete the 2-year follow-up examinations and 280 CAG-expanded subjects will have completed all MRI and neuropsychological assessments at the end of the study. Of these 280, approximately 85 subjects are predicted to develop clinical (motor) HD during the study, allowing for the first-ever MRI and neuropsychological prospective study of HD onset.

Inclusion Criteria:

(a) Completed predictive testing and known test results with CAG length of one gene >39 (for CAG-expanded group) or both CAG genes are < 30 (for CAG-normal group);
(b) Men and women aged 30 to 55.
(c) Commitment to complete a minimum of 4 yearly evaluations.
(d) Commitment of a companion to attend visits.
(e) Able to undergo MRI

Exclusion Criteria:

(a) Motor exam total score > 10.
(b) Clinical evidence of unstable medical or psychiatric illness.
(c) History of serious alcohol or drug abuse within the previous year.
(d) History of learning disability and/or mental retardation.
(e) History of other CNS disease or event (e.g., seizures, head trauma);
(f) Current or treated within the last 6 months with antipsychotic medications, including the traditional neuroleptics such as haloperidol as well as the atypical antipsychotics risperidone, clozapine, quetiapine and olanzapine.
(g) Treatment with phenothiazine-derivative antiemetic medications such as prochlorperazine, metoclopramide, promethazine and Inapsine on a regular basis (Greater than 3 times per month);
(h) Metallic implants (pacemaker, cardiac defibrillator, vagal nerve stimulator, aneurysm clips, metal shrapnel).

RESEARCH SETTINGS/SITES: To ensure the sample proposed in this study could be obtained successfully,a feasibility survey was constructed and distributed to HSG sites in August 1998. Thirty-seven sites from the United States and Canada indicated that sites were able to identify over 1800 presymptomatic at-risk subjects with a known CAG repeat length, 459 of whom had been tested in the most recent year. Twenty PREDICT sites selected for the proposed project were invited to complete a questionnaire designed to determine approximate numbers of available research subjects. Responses indicated that sites continued to have large numbers of at-risk persons who had completed presymptomatic testing, were confirmed to have CAG expansion in IT 15, and were willing to volunteer in the proposed project. It was encouraging to note that site personnel were well prepared for the proposed study and reported that at least 300 subjects were available for immediate study participation.

TIMELINE: All subjects will be examined annually. Criteria for traditional motor disease diagnosis will be considered at each visit as well as comprehensive cognitive, neuro- psychiatric, functional and motor assessments, with MRI scans every other year in concert with funds. Our rationale for annual assessments is to establish a time interval that provides a balance between the disease development rate and the need to rapidly test experimental compounds. Blood and urine are collected annually whereas MRI evaluations will occur every two years due to extra cost.

SPECIFIC AIMS AND HYPOTHESES

Onset of disease is a vital outcome measure for therapeutic trials involving healthy persons who are at known genetic risk for manifesting disease. Our primary aim is to characterize neurobiological and neurobehavioral markers of Huntington's disease (HD) prior to the development of clinically manifest motor symptoms. If such markers are identified, then treatment should begin no later than the time at which the marker(s) become abnormal, and treatment efficacy in preclinical HD can be quantified as a change in the rate of progression of disease as identified by the marker(s). Completion of this project will facilitate preventive therapeutic trials designed to determine the influence of interventions on the clinical (motor) onset of HD. Findings could result in improved methods for early diagnosis of HD. The general hypotheses to be tested include:

1. Prediction of disease onset will be improved (i.e., beyond that achieved with CAG repeat length and age alone) using measures of brain morphology and cognitive performance.
2. Prediction of disease onset will be further improved (i.e., beyond that achieved with CAG repeat length, age and baseline values) with longitudinal rates of change on measures of brain morphology and cognitive performance.

BACKGROUND AND SIGNIFICANCE

Huntington's disease (HD) is an autosomal, dominant, neurodegenerative disorder that results from an unstable expansion of the trinucleotide repeat CAG in the gene IT-15, or huntingtin [1-8]. HD has a prevalence of 5-10 per 100,000 population. In the United States, there are approximately 30,000 individuals with clinical features of HD and another 200,000 at risk for HD. The clinical features of HD usually emerge in adulthood (mean age of 37 years) with chorea, disorders of voluntary movement, intellectual dysfunction, and psychiatric symptoms. HD is relentless, leading to functional disability and death over a period of 10-30 years.

HD Diagnosis. By tradition, the clinical diagnosis of HD has relied upon the emergence of abnormal motor signs in a person at risk (by virtue of having a parent with HD). The motor signs of emerging HD typically include dyskinesias (chorea, athetosis, dystonia), oculomotor abnormalities (especially slowed volitional saccadic eye movements), and alterations in tone (rigidity), spontaneous movement and alternating movements, alterations in gait (associated arm swing) and reflexes (hyper-reflexia). No single sign is pathognomonic of HD, but the constellation of these extrapyramidal abnormalities, especially their persistence or progression, provides a reliable basis for benchmarking the clinical onset of illness. In the absence of other causes of extrapyramidal dysfunction, such as exposure to neuroleptic medications, motor abnormalities remain the *sine qua non* for the diagnosis of HD.

HD Onset. The age of HD onset is strongly influenced by the length of the glutamine repeat, with longer repeats associated with earlier age of onset [9-13]. The length of the CAG repeat explains only about 50 % of the variance, however, with no explanation for the remaining 50% of the variance in adult age of onset.

We believe that the proposed cognitive and neuroimaging measures will account for a

substantial portion of this remaining variance. For example, based on assumptions from our pilot data regarding pre-diagnostic decline the remaining time until diagnosis may be dramatically stratified by study-intake performance on a single cognitive test.

Pathophysiology of HD. The pathology of HD is characterized by diffuse brain atrophy with severe neuronal loss and gliosis occurring selectively in the caudate nucleus and putamen (basal ganglia) with vulnerability in other regions such as deep layers of the cortex [6, 14-16]. Study of a transgenic mouse model of HD (made using an exon-1 N-terminal fragment) led to the discovery of intranuclear inclusions containing aggregates of huntingtin protein [17, 18]. Intranuclear inclusions and dystrophic neurites that can be labeled with antibodies to the N-terminus of huntingtin or antibodies to ubiquitin have also been identified in brains of HD patients [19, 20] and other mouse models [21, 22]. The inclusions are most dense in the striatum and cerebral cortex, and their density correlates with the CAG repeat length. Although these findings have accelerated research into underlying mechanisms, recent data in humans and animals show that intranuclear aggregates are not causative of neuronal loss; thus, the pathogenesis of cell death in HD remains uncertain [23, 24].

Several studies indicate that changes in the brain precede the manifestation of clinical signs and symptoms. Neuron loss can be detected in the rare individuals with HD CAG expansion who have died and had postmortem brain examination prior to manifest HD onset [23]. Neuroimaging studies using magnetic resonance imaging (MRI) have found that atrophy occurs prior to diagnosis, and the largest study reported basal ganglia atrophy as early as 7 years prior to onset. In addition, the intranuclear inclusions in at least one transgenic mouse model are observed prior to the development of neurological signs. Recent data indicate that receptor changes precede the onset of behavioral phenotype in transgenic mice [25]. In addition, electrophysiological changes with increased intraneuronal calcium clearly precede behavioral and pathological changes in a yeast artificial chromosome (YAC) transgenic mouse model of HD [24]. Although controversial [26], Penney et al. proposed that the striatal pathology develops linearly from birth [27], an assertion based indirectly on relationships among CAG repeat length, neuronal cell loss and age at death. The time-course of brain pathology in relation to the onset of manifest motor signs and symptoms in humans is unknown.

There are other diseases in which neuronal degeneration in humans begins in the presymptomatic period. It is believed that Parkinson's disease patients, for example, do not show clinical movement disorder until 50-70% of substantia nigra dopaminergic neurons are lost [28, 29]. Early detection of cognitive decline is currently being used to identify persons considered "at-risk" for Alzheimer's disease. Defining neurobiological changes in HD may be particularly important since factors that trigger early changes may be different from factors responsible for later disease progression. Although the relationship between CAG repeat length and age at HD onset is robust, it is controversial whether the length of the repeat also influences the rate of progression of HD [27, 30-32]. Should underlying mechanisms of onset and progression vary, therapeutic initiatives to delay age of onset must similarly vary from interventions to slow disease progression. Therapeutic agents that affect onset and progression differently have been identified for other neurodegenerative diseases (e.g., ALS) [33, 34].

Potential Treatments for HD. Efforts are underway to develop clinical treatments that could slow the rate of progression of HD in clinically affected individuals. The "Coenzyme Q10 and Remacemide Evaluation in HD" (CARE-HD) controlled trial (NS-35284) is examining the potential benefits of a mitochondrial electron transfer enhancer and a blocker of NMDA-mediated neurotoxicity in slowing functional decline in HD. CARE-HD is a 30-month study of 347 affected individuals completed in 2001. To date, experimental therapies have been based on rational hypotheses emanating from biochemical advances and our understanding of the selective vulnerability of the striatum in response to endogenous and exogenous insults. More recently, transgenic animal and cell culture-based assays of mutant huntingtin toxicity have been developed and have added support for previously hypothesized interventions. At present, a number of compounds are in development and several smaller-scale clinical trials have been conducted [35] (See Appendices A and B) or are in the process of being organized. For instance, compounds to block the entry of glutamine into the cell body and drugs to delay the aggregation of huntingtin and other aspects of the cellular pathology of HD are in development. Recent studies have shown that inhibition of caspase-1 can slow the behavioral and pathological course in the HD exon-1 transgenic mouse [36]. Additional studies involve inhibition of inflammation and defective transcriptional regulation. In addition, growth factors and surgical transplant of fetal cells are being examined for their utility in replacing cells lost to HD. With the pipeline of rational interventions emerging worldwide from research laboratories and the availability of high throughput screening of compounds in *in vitro* and cell-based assays and additional testing in genetic animal models, prospects are further enhanced for promising therapies for preclinical HD.

Therapeutics in Presymptomatic HD. During the past 50 years, clinical research has emphasized the response of individuals with manifest illness to experimental therapeutics. More recently, new initiatives are shifting the focus from detection and treatment to prediction and prevention. Genetic risk factors are being identified at a rapid pace to allow targeting of preventive interventions to those at the greatest risk. HD is one of many adult-onset disorders for which the genetic mutation predicting future disease can be detected long before signs and symptoms occur. As such, it represents an important opportunity for the medical community to pioneer approaches to delay onset and maintain wellness before disease initiation. The momentum in HD research will likely result in a therapy to delay disease onset or slow disease progression [37]. Unlike other preventive measures (i.e., diet and physical exercise) that have minimal side effects and can be prescribed at any age and for any duration, drugs to delay onset or slow progression of HD may have serious physical and financial repercussions for individuals. If a treatment carries a serious risk of causing cancer, for example, as might be the case for an anti-apoptotic drug, then it will be appropriate to begin treatment in CAG-expanded persons only at the last possible moment to forestall striatal dysfunction. One of the primary aims of the proposed study is to put forth a model in which clinical interventions to delay age of onset can be tested. In contrast to other adult-onset diseases, HD is distinctly suited for the proposed neurobiology and neurobehavioral investigation for several reasons. First, it is caused by a single dominant gene (unlike most Parkinson's disease). Second, neurobiology and neurobehavioral measures are not greatly influenced by aging (unlike Alzheimer's disease).

Furthermore, it has disease manifestations that are directly observable (unlike colon cancer). Finally, there likely exist potential biological and behavioral markers of early disease.

The HSG is currently proposing two studies of presymptomatic individuals at risk for HD. The Prospective Huntington At-Risk Observational Study (PHAROS; Ira Shoulson, PI) will examine a large number of individuals who are unaware of their gene status, whereas the Neurobiological Predictors of Huntington's Disease (PREDICT-HD) study (the current application) will conduct a more intensive examination in fewer persons with known gene status. There is no overlap in the two HSG studies we have developed. PHAROS is an epidemiology study of HD diagnosis with no consideration of neurobiologic markers of disease onset or progression. It is the intent of the HSG to develop research needed to prepare for future clinical trials in individuals at risk for, but presymptomatic, of HD. As more adult-onset genes are identified, the need for accurate and reliable estimates of disease prodrome and phenoconversion (i.e., the transition from health to the disease phenotype) will become of paramount importance.

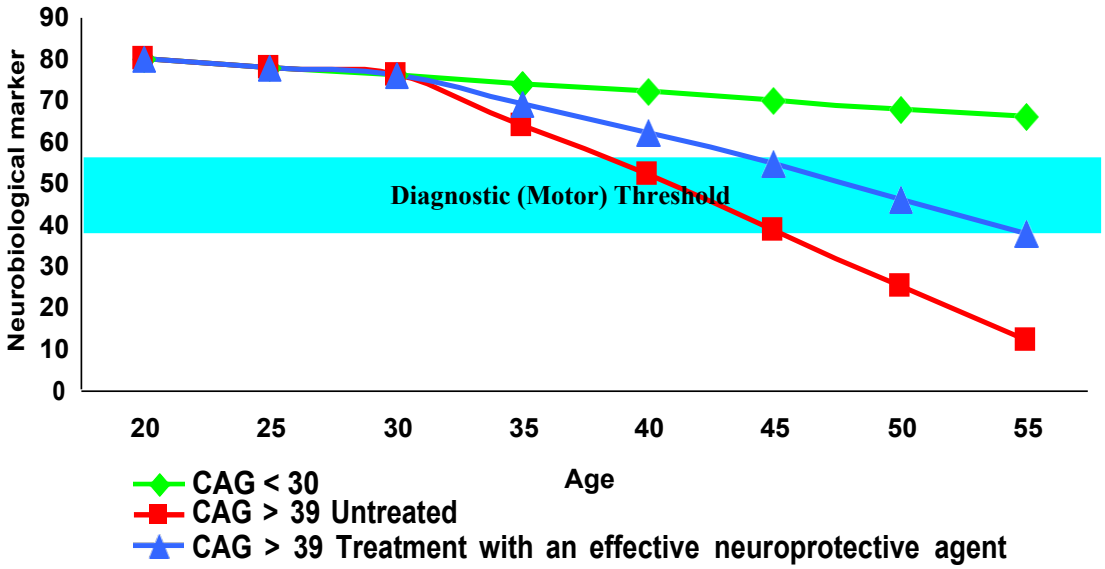
The primary aim of a clinical trial in presymptomatic persons is to determine whether a specific therapeutic intervention can safely delay the age of disease onset. While previous studies have offered useful clues, there is presently no valid and reliable method to determine the effectiveness of any treatment in preclinical phases of HD. No study has prospectively evaluated a substantial sample of CAG-expanded persons prior to and during disease onset. More specifically, no previous MRI or neuropsychological study has prospectively assessed polymerase chain reaction (PCR)-confirmed CAG-expanded persons who have demonstrated conversion to HD while under study. The primary aim of the proposed research is to examine the utility of volumetric MRI and neuropsychologic measures to predict the clinical onset of manifest HD. Although structural neuroimaging and neuropsychological assessment tools have been used widely in research of presymptomatic HD, no previous research has considered these measures as predictors of HD onset.

Structural Neuroimaging Studies. In studies of symptomatic HD, structural neuroimaging measures have been found to be associated with disease duration [38, 39], severity of dementia [40, 41], severity of movement disorder [42, 43] and functional capacity [42, 44, 45]. On longitudinal assessment of HD patients, Aylward et al. [46] demonstrated decline in caudate and putamen volume over a mean inter-scan interval of 21 months, with greater rate of change observed for patients with longer CAG repeat lengths. Aylward et al. [47] also found significant MRI volume reductions for all basal ganglia structures for presymptomatic CAG-expanded individuals, indicating that structural abnormalities are present before onset of symptoms. Furthermore, basal ganglia size was positively correlated with the estimated number of years to onset in presymptomatic CAG-expanded persons, indicating that structural measures may help predict disease onset [48].

Cognitive-Behavioral Studies. More than 30 neuropsychological studies of individuals at risk for HD have been published since the 1970s. Despite mixed findings [49, 50], the evidence is clear that cognitive and behavioral changes can be detected prior to diagnosis in individuals at risk for HD [51-57]. The available studies have varied significantly in terms of the samples and specific cognitive measures utilized, however, limiting comparison across studies. Thus, the magnitude and time-course of early changes in HD are unclear. An overview of the studies

published to date has elucidated optimal approaches to assessment. Cognitive impairment in presymptomatic individuals is most robust when a) the sample is genetically characterized with CAG repeat length; and b) the cognitive tests are well standardized and carefully targeted on specific, known functions of the basal ganglia and/or its connections.

Figure 1. Model for HD Onset



Model for HD Onset. A summary of our model of disease onset and the effects of a hypothetical treatment designed to slow disease onset is shown above in Figure 2. We assume here that the measure (e.g., caudate volume or psychomotor speed) is relatively stable until a point of neurobiologic onset that is prior to clinically detectable and diagnosable HD based on neurologic exam. (A competing hypothesis is that changes begin at birth; methods to distinguish these two possibilities are discussed under post hoc analyses.) As shown in the figure, intervention might result in a delayed onset age (delayed from age 37 to age 42 in the graph above) and/or a slower rate of decline on variables of interest (shown in the blue versus red slopes). Findings of the proposed research project would allow these additional measures of prediction and progression in the preclinical stage, or stage of disease prior to diagnosis, in HD.

Summary. Clinical trials to slow the progression of HD are currently underway. Despitethe imminence of a treatment, there currently exist significant limitations in our ability to test therapeutics in presymptomatic individuals. The purpose of the current study is to identify and characterize neurobiological and neurobehavioral markers of the clinical (motor) onset of HD. The design proposed in this study will address several limitations of presymptomatic research in HD, and findings will help optimize the design of future trials to test preventive therapeutics.

STUDY DESIGN

Procedure: Five hundred subjects will be enrolled for study at 20 research sites in the US and Canada. Two groups will be selected: an age-restricted group (30-55 years) with known CAG repeat length > 39 (n=425) (CAG-expanded), and an age-commensurate comparison group previously considered at risk (by virtue of having a parent with HD) who do not have CAG expansion (n=75 CAG-normal). This recruitment strategy will significantly enhance the probability of disease onset during the study among the CAG-expanded group. Assuming a 10% annual attrition (censoring) rate [35, 66], about 344 CAG-expanded subjects are expected to complete the 2-year follow-up examinations and 280 CAG-expanded subjects will have completed all MRI and neuropsychological assessments at the end of the study. Of these 280, approximately 85 subjects are predicted to develop clinical (motor) HD during the study, allowing for the first-ever MRI and neuropsychological prospective study of HD onset.

Timeline. Based on our pilot data, we anticipate that all subjects will be recruited into the study within the first year. All subjects will be examined at 4 time points (baseline, and follow-up every 12 months thereafter). The Unified Huntington's Disease Rating Scale (UHDRS) [67] will be administered and criteria for disease onset will be considered at each baseline and follow-up visit. The MRI neuroimaging protocol and a comprehensive neuropsychological evaluation will be conducted at 2 time points (baseline and two years).

Subjects.

Inclusion Criteria:

1. A completed predictive testing and known test results with CAG length of one gene >39 (for CAG-expanded group) or both CAG genes are < 30 (for CAG-normal group);
2. Men and women aged 30 to 55;
3. Commitment to complete a minimum of 4 yearly evaluations;
4. Commitment of a companion to attend visits;
5. Able to undergo MRI

Exclusion Criteria:

1. Motor exam total score > 10;
2. Clinical evidence of unstable medical or psychiatric illness;
3. History of serious alcohol or drug abuse within the previous year;
4. History of learning disability and/or mental retardation;
5. History of other CNS disease or event (e.g., seizures, head trauma);
6. Current or treated within the last 6 months with antipsychotic medications, Including the traditional neuroleptics such as haloperidol as well as the atypical antipsychotics risperidone, clozapine, quetiapine and olanzapine;
7. Treatment with phenothiazine-derivative antiemetic medications such as prochlorperazine, metoclopramide, promethazine and Inapsine on a regular basis (greater than 3 times per month);
8. Metallic implants (pacemaker, cardiac defibrillator, vagal nerve stimulator,

aneurysm clips, metal shrapnel).

The only restrictions on concomitant medications involve those with the potential to cause an extrapyramidal movement disorder and thus confound the clinical assessment of subjects. As noted in the Exclusion Criteria, the use prior to screening of traditional dopamine-antagonist antipsychotic medications (such as haloperidol or thioridazine) is prohibited, as is the use of the "atypical" antipsychotic agents' risperidone, olanzapine, clozapine, and quetiapine. A subject exposed to these medications within 6 months prior to screening will not be permitted to enroll. After enrollment, if the subject is started on one of these medications, he/she will be permitted to continue in the study. A new use of one of these restricted medications will be a "Reportable Event."

Reportable Events. The following events must be reported to the HSG Coordination Center and noted on data forms (See Appendix C for sample Case Report Forms).

1. New use of restricted medications (i.e., typical and atypical antipsychotics. phenothiazine-derivative antiemetic agents)
2. Any neurological event (e.g., Traumatic Brain Injury (TBI), seizure, etc.)
3. Pregnancy
4. New visit to a mental health professional
5. New onset of depression
6. Suicide attempt
7. Inpatient hospitalization for any reason
8. Premature withdrawal of subject from study
9. Death

Rationale for including subjects at risk with normal CAG length. Although it has already been demonstrated that presymptomatic CAG-expanded persons, in comparison with CAG-normal individuals, have smaller basal ganglia volumes [47] and poorer performance on neuropsychological tests [53], it will be important to carefully distinguish potential predictors of HD onset from variations that occur in normal individuals. First, for comparisons involving greater abnormality in individuals who are closer to onset, it can be presumed that these individuals will be somewhat older than individuals who are far from onset. If greater abnormalities are observed in the close-to-onset subjects, it will be important to know that these differences are not simply a reflection of normal aging. Second, it will be important to compare longitudinal rates of change between persons with the HD mutation and those without. Although we do not expect much change in basal ganglia volumes, or cognitive performances in the CAG-normal individuals given the relatively young age range we are studying, it will be important to know what portion of the change over time in the CAG-expanded subjects is simply a reflection of normal aging. Third, in individuals who are far from onset, it will be useful to determine whether there is a stage during which basal ganglia volumes and cognitive performances are normal, and if so, at what point abnormalities begin. Without a well-characterized group of CAG-normal comparison subjects, this question cannot be directly addressed. The inclusion of CAG-normal subjects is of additional importance for the hypotheses involving neuropsychological testing, as it is common to observe *improvements* on some tests over time, even within CAG-expanded individuals, due to practice effects. It is possible that CAG-expanded subjects will show a longitudinal decline on neuropsychological

testing, *in comparison with the CAG-normal subjects*, even if a drop in absolute test scores is not observed. Although inclusion of CAG-normal individuals is not important for our primary analyses involving survival techniques, it will be critical to fully characterize significant predictors in a thorough manner in relation to normals. Given the lack of test-retest normative data for many tests, these data are likely to make a significant contribution to the interpretation of the obtained data.

CHARACTERISTICS, SELECTION AND ENROLLMENT OF PARTICIPANTS

Recruitment Plans. First, all study sites will continue to recruit through their established HD Clinics. Second, a letter will be sent to all families on the National Research Roster for Huntington's Disease Patients and Families inviting them to participate in the study. Third, the United States Genetic Testing Group (USGTG) will continue to refer persons seen for genetic testing. Finally, an article and advertisement will be placed in the Huntington's Disease Society of America's newsletter, *The Marker*, and in the Huntington's Society of Canada newsletter, *Horizon* (See letters of support, pp. 258, 264). Potential subjects will be invited to contact one of the study sites for participation consideration. Potential subjects living in rural or distant communities will be offered travel and hotel accommodations near the study site to ease study participation. To assist investigators at each research site with subject recruitment, a flyer describing the study will be developed. Referral fees will be offered to predictive testing centers to assist with resource utilization involved in making potential subjects aware of the PREDICT-HD study. In addition, an Internet web site will be created to allow potential study subjects to review study purposes and criteria, to view the MRI scanner, and to see staged images of "subjects" undergoing evaluations with investigators. Steering committee members and study staff will travel to local and national lay meetings of the US Methods and Measures.

Disease Onset Definition. While HD is a disease comprised of a triad of clinical symptoms (motor, cognitive, and behavioral), its diagnosis has historically relied upon the emergence of motor signs, especially chorea. Thus, the determination of disease onset for the proposed study will adhere with traditional neurology standards and the practice of the HSG. The diagnosis of HD will be determined by an experienced movement disorder neurologist at each site. Training on the standardized motor exam on the UHDRS will be completed with each site investigator. A training videotape will be used to obtain and maintain reliability. A HD Diagnostic Rating Scale (shown below) was designed for this study. A recent reliability study demonstrated very good agreement on the unequivocal diagnosis of HD (confidence=4; kappa=.83). The primary outcome variable used in all analyses will be "HD diagnosis" as defined by reaching a rating of "4" on the HD Diagnostic Rating Scale shown below.

Table 1. HD Diagnostic Rating Scale

HD Diagnostic Rating Scale: To what degree are you confident that this person meets the operational definition of the unequivocal presence of an otherwise-unexplained extrapyramidal movement disorder (e.g., chorea, dystonia, bradykinesia, rigidity) in a person at risk for HD?

0 = normal
1 = nonspecific motor abnormalities (<50% confidence)
2 = motor abnormalities that may be signs of HD – possible HD (50-89% confidence)
3 = motor abnormalities that are likely signs of HD - probable HD (90-98% confidence)
4 = motor abnormalities that are unequivocal signs of HD - definite HD (≥ 99% confidence)

The Unified Huntington's Disease Rating Scale. The UHDRS [67] is a standardized clinical rating scale that assesses four components of HD: motor function, cognition, behavior and functional abilities. The instrument has been used at more than 50 participating HSG sites since July 1994, and data have been collected prospectively on more than 4,000 patients who have definite HD and 500 individuals at risk for HD. The reliability and internal consistency of the four components of the UHDRS have been evaluated and published [67]. Although the entire UHDRS (See Appendix C) will be completed at each study visit, the variables used in the primary survival analyses include a) the standardized neurology exam with the HD Diagnostic Rating Scale (the outcome variable for survival analysis and determination of onset involves a rating of "4"), and b) cognitive assessment of verbal fluency [68], psychomotor speed [69] and disinhibition [70] will be considered potential predictor variables of onset. As suggested by one reviewer, it is also possible to include the intake HD Diagnostic Rating Scale or Motor Exam total score as an additional predictor in survival analyses.

DNA Methodology. HD CAG genotyping will be done as described by Warner et al [71]. Briefly, HD-specific oligonucleotide primers, flanking the HD CAG repeat, are used to specifically amplify the HD CAG repeat from template DNA samples in a polymerase chain reaction (PCR). The resultant, radiolabeled, HD-specific PCR products are displayed on a DNA sequencing gel format, exposed to X-ray film. The size of the HD CAG repeat PCR product, apparent on the autoradiogram, is determined relative to that of known, sequenced, HD CAG-repeat product 'standards'. The HSG conducted a study of interlaboratory variability of CAG length in HD. Findings demonstrated that reliability of CAG reports was very high (r=.97 for expanded alleles and r=.99 for normal alleles [72]).

Process of blood collection and analysis: The process of blood collection and genotype analysis is as follows: 1) Bar-coded blood samples are shipped to Dr. Marcy E. MacDonald's lab at Massachusetts General Hospital and logged into an Excel database for the PREDICT project. Note that this database is on an 'isolated' PC computer that has double password protection, is NOT networked, and is only used by Jayalakshmi Srinidhi, the senior technician who will be doing the work (back-ups are kept in Dr. MacDonald's office, which is locked at all times). 2) DNA is extracted from each sample. 3) Extracted DNA is labeled with the bar- code and is stored in boxes in a cold room. 4) The HD CAG repeat assay (or any other PCR-based assay) is

done by taking a small aliquot of this DNA and performing the genotyping as described above [71]. 5) The results are 'read' into the Excel PREDICT database. 6) The entered results are checked for accuracy by Dr. MacDonald. 7) The autoradiographic results are stored in a locked room and except for bar- code numbers are not labeled in any other way. 8) Data are transferred to the PI and the data coordination center by e-mail or hard copy in the Excel spreadsheet format. 9) Dr. MacDonald and her colleagues have more than 6 years of experience with this and more than a dozen years' experience with other human genetic studies.

In addition, annual blood samples will be collected to determine biological markers. The sample will be evaluated for measures of 8-Hydroxy-deoxyguanosine. The samples will be coded and sent to Dr Flint Beal's lab at Cornell University.

MRI Methodology.

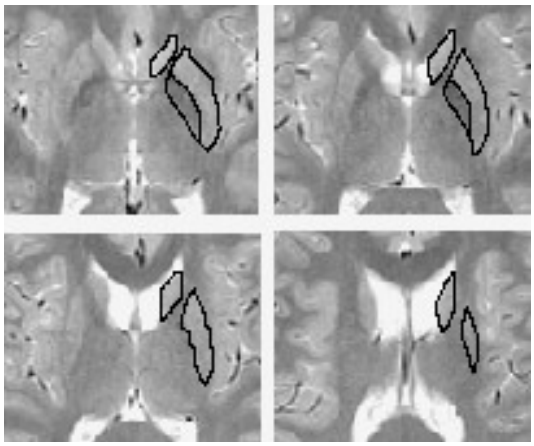
Acquisition of MRI Scans. MRI scans will be obtained at two time points (baseline and 24 months). All scans for this project will be obtained using a standard protocol designed to optimize visualization of the basal ganglia. The T1 sequence is obtained as a 3D volume in the coronal plane using a spoiled GRASS sequence with the following parameters: TE = 6 ms, TR = 20 ms, flip angle = 30°, FOV = 180x180x192 mm, matrix = 256x256x124, NEX=2. The T2 images are acquired using a 2D fast spin-echo sequence in the coronal plane with the following parameters: TE = 85 ms, TR = 4800 ms, slice thickness/gap = 1.8/0.0 mm, FOV = 180x180 mm, matrix = 256x256, NEX = 3, number of echoes = 8, number of slices = 124. All sites will use a General Electric 1.5 tesla scanner. Total scanning time is approximately 30 minutes.
MRI Data Transfer and Processing: Following acquisition of scans by the individual sites, data will be immediately transferred via FTP to Dr. Aylward's lab at the University of Washington. The Research Coordinator in Dr. Aylward's lab will process the scans, using programs individually tailored, as necessary, to make the data compatible with the MEASURE software. Scans will then be archived on CD ROMs. Under the supervision of Dr. Aylward, the Research Coordinator will track the transfer of MRI scans from each site and maintain a log of all scans received. This log will be transmitted on a weekly basis to the Data Coordinating Center in Rochester to make certain that scans have been received from all subjects seen at each site. The Research Coordinator will be trained to assess the quality of scans for measurement and to coordinate rescanning of subjects whose initial scan quality is inadequate. Measurements of caudate, putamen, and total brain volumes will be performed, as outlined below.

MRI Analyses. MRI measures will be performed by Dr. Aylward, or an assistant trained by her, using custom graphics software [73] developed by Patrick Barta, MD, PhD, in the Division of Psychiatric Neuroimaging at Johns Hopkins University School of Medicine. In addition to basal ganglia volumes, volumes of total brain will be obtained to determine whether volume reductions in basal ganglia are over and above generalized brain atrophy. All measurements will be made blind to group status, neuropsychological test results, clinical and genetic variables. Because of the importance of blind ratings for the longitudinal analyses (i.e., raters not knowing whether they are measuring an initial scan or a follow-up scan), measurements for the entire sample will be delayed until all three scans have been completed for each subject, and raters will be blind to order of scans. Initial scans and follow-up scans will be

realigned, if necessary, to ensure that the axial slices are parallel to the line connecting the anterior commissure and the posterior commissure. This will ensure that changes in head tilt between the first and second scans do not interfere with the consistency of the measurements. Although measurement of scans for the purpose of addressing the Specific Aims will be delayed until Year 4, preliminary analyses of a subset of scans will be performed in Years 1-3 in order to address additional questions of interest. These measurements will be redone in the Year 4 analyses, thus providing another opportunity to examine intra-rater and inter-rater reliability.

(a) Basal Ganglia. Volumes of putamen and caudate will be obtained from the axial SPGR series (TR = 18, TE = 3). The rules for defining boundaries of each structure have been previously described [46]. Briefly, measurement of putamen and caudate begins in the most inferior slice in which these structures are clearly separated by the internal capsule. Measurement continues in a superior direction until the body of the caudate is no longer observed. The borders of the caudate are defined laterally by the anterior limb of the internal capsule and medially by the frontal horn or body of the lateral ventricle. The volume of the head of the caudate is based on measures from all slices below the one in which the head and body of the caudate are fused. Measures for body of caudate are not used separately in analyses but are combined with head-of-caudate measures to yield a total caudate volume. The borders of the putamen are defined laterally by the external capsule. At more inferior levels, the medial borders of the putamen are defined by the globus pallidus; at more superior levels, the medial borders are defined by the internal capsule. Area of each structure is outlined manually, using a mouse-controlled cursor, in each slice. Areas within each slice are calculated, summed across slices, and multiplied by slice thickness, resulting in approximate structure volumes. Excellent intra-rater and inter-rater reliabilities for these measures have been established in several previous studies [47, 48].

Figure 2. Outline of caudate and putamen in 4 representative slices



(b) Total brain volume. Total brain volume will be measured using semi-automated thresholding procedures for segmenting brain from cerebrospinal fluid (CSF) and non-brain tissue. This procedure, which employs the 1.5mm axial scans, allows the user to set the contrast such that all pixels above a certain value are highlighted, thus eliminating CSF (which in these images is black). Each individual slice is checked and, when necessary, modified

manually to ensure adequacy of the segmentation process. Intra-rater reliability studies for obtaining brain volumes with this procedure have yielded intraclass correlations of 0.99.

MRI Variations in Software and Hardware. Initial site selection was based on specific scanner details. At present all selected sites will obtain MR images on a 1.5 GE tesla. Over the course of the study, however, it is likely that some of the centers will upgrade their MRI software. Although such changes should affect patients and controls equally, we will make efforts to ensure that any effects on the basal ganglia measurements are accounted for. In order to do this, we will ask centers to scan the MRI phantom (used in pilot studies) before and after the software upgrade. If there are any changes in measurements from the before and after phantom scans (> 1%), we will ask the centers to rescan up to five patients who had been scanned in the month before the software upgrade. If systematic increases or decreases are observed in measurements from these subjects, we will determine the percentage increase/decrease and adjust measurements for all subjects whose scans are acquired after the upgrade. Data analyses will be performed on both the adjusted and unadjusted data. A decision will be made regarding the use of adjusted or unadjusted data depending on which data most closely match those of the other sites. It is expected that minimal changes in basal ganglia volume will result from changes in MRI software. Although less likely, it is also possible that some centers may change their MRI hardware. If a site acquires a new scanner of a different strength or manufacturer, we will ask that efforts be made to identify a nearby facility with a GE 1.5 scanner where PREDICT-HD scans can be performed. A modest amount of travel funds are included in the budget to allow some transfer of subjects to acceptable scanners, if possible. If this is not possible, sites will be asked to follow the procedure outlined above for software upgrades.

Neuropsychology Methodology.

Rationale for Neuropsychological Assessment. Selection of tests for the neuropsychological evaluation in this study was based on the following guiding principles: 1) tests must have demonstrated sensitivity for HD or for damage to the front striatal brain circuits; 2) tests must be psychometrically sound with known validity, reliability, and repeatability; 3) when possible, tests with known sensitivity to differences between at-risk individuals with vs. without CAG expansion will be used; 4) tests must have known effect sizes that are at least medium or large in HD or other relevant groups; 5) the feasibility study or other evidence must support a lack of systematic floor or ceiling effects in the proposed study group; and 6) tests that would distinguish between slowed processing (i.e., slowed learning, perceptual, manipulation, and response selection processes) and motor slowing (i.e., slowed response execution). Based on these principles, we developed a partially computerized battery of tests that combines clinical neuropsychological techniques with experimental techniques from cognitive and movement research. Five overarching cognitive domains were targeted for assessment: 1) working memory; 2) timing and movement sequencing; 3) motor and psychomotor speed; 4) learning and memory; and 5) executive functions, specifically shifting, planning, initiation, and inhibition (See Table 2 below).

Table 2. Neuropsychology measures to be used in PREDICT-HD

Domain	Scientific Rationale	Description	Tests
General Intellect	General intelligence is strongly associated with cognitive and academic functions.	Verbal IQ Nonverbal IQ	WASI – Vocab WASI - Matrix
Working Memory	Deficits in working memory exist after surgical BG lesions or MPTP treatment [74-76]; BG activation detected on PET during working memory task in humans [77]; electrical stimulation of BG during delay disrupted working memory [78]	Auditory Dual Task Working Memory	WAIS-III Letter-Number Sequencing Subtest [79]
		Spatial Working Memory	Dual Verbal Working Memory (DVWM) [80, 81] - **C**
Timing and Movement Sequencing	Gait cycle timing abnormal in HD [82]; Eyeblink classical conditioning shows normal SR learning in HD but abnormal timing of the CR [83]. Reduced motor speed measured with Finger Tapping has been shown in subjects with BG damage [84];Deficits in the execution of abductive movements and control of sequential movements in HD [85]	Timing and Motor Sequencing	Finger Tapping Test *[86]* - **C**
		Movement Sequencing	Buttons Test *[85]*- **C**
Motor and Psychomotor Speed	BG functioning is essential for input-output binding, as shown by EEG activity in humans during sensorimotor integration [87, 88]; Visuomotor abnormalities common in HD using saccade task [89]; reduced psychomotor speed measured with Trail Making Test and Digit-Symbol substitution tests following BG damage [84]; in CAG-Expansion simple and choice reaction time correlates with CAG size [56]	Visuomotor speed and sequencing	Trail Making Test part A [90]
		Visuomotor speed	*****Symbol Digit Modalities Test [69]
		Motor Speed	Simple and Choice Reaction Time *[91]*-**C**

Learning & Memory	Motor learning-Human studies show BG inactivation on PET while performing overlearned task [92]; decreased activation of BG after learning [93]; Primate studies show decreased neuronal firing in BG during learning of arm and hand movements [94]; PET studies of motor sequence control and learning increase rCBF in BG [95, 96]; HD impaired in learning a repeating motor sequence [97]. Verbal learning and memory-in humans with BG lesions there exist deficits in retrieval of stored information [98, 99]; memory and learning deficits associated with damage in the BG [100-101];	Motor learning and sequencing	Serial Reaction Time Task *[97, 102]* – **C**
		Verbal learning and memory	Hopkins Verbal Learning Test Revised [103] (HVLT-R)
Visual Perception	Anatomy studies using virus tracing suggests circuitry from the tail of the caudate to mesial temporal lobe.	Visual Discrimination Emotional Recognition	Visual Discrimination Test (Benton) Faces
Executive Functions	Evidence from studies comparing Parkinson's disease to frontal lesions suggest BG function necessary for shifting from one rule set to another, damage to BG causing inflexibility for shifting to new set [104, 105]; deficits in conceptual reasoning identified with BG [106]; BG in spatial attention and motor planning [107]; reduced frontal volume in HD is related to decreased executive skill performance [108]	Shifting	Set-Shifting Test [91, 109] – **C**
		Shifting	Trail Making Test - Part B [90]
		Planning	Tower Test - **C** [110]
		Initiation	***Verbal Fluency. [111]
		Inhibition	***Stroop Color Word Test [70]

BG = basal ganglia; rCBF = regional cerebral blood flow; **C** = Computerized assessment; SR = stimulus response; CR = conditioned response

* These tests are part of the UHDRS and will be analyzed with, not readministered for, the neuropsychology battery.

Treatment of Potential Confounds.

Neuropsychiatric Symptoms. Neuropsychiatric symptoms, such as depression, can affect cognitive performance, and therefore will be important to consider in the interpretation of cognitive data. Neuropsychiatric evaluations will be obtained in conjunction with the neuropsychological and MRI evaluations and will include the UHDRS Behavioral Section [67]**,** as well as the following self-report questionnaires: Beck Depression and Hopelessness [113] [114] Inventories, the Symptom Checklist-90 [115], the Frontal Systems Behavioral Scale [116], the Yale-Brown Obsessive Compulsive Scale, the Disgust Scale and a substance use survey. We are particularly sensitive to the effects of depression on some of the tasks chosen for the current study. Given that our sample is likely to involve some individuals with depression severe enough to impair cognitive performances, we will make every effort to assess level of depression at every visit and to consider this measure in all cognitive analyses. We will also administer the Life Event Scale and Perceived Stress Scale to obtain ratings of life stress.

Motor and Oculomotor Symptoms. Previous reports have not, in general, found associations between cognitive performance and the severity of the movement disorder in HD [117]. Nevertheless, it is possible that certain motor symptoms may affect cognitive performances prior to manifest HD. For example, saccade velocity and motor stretch reflex abnormalities [56] frequently appear prior to manifest HD, but it is unknown to what extent, if any, these affect performances on tests requiring reaction time or speed of information processing. Several of the computerized tests (i.e., Sequential Button Pressing, Finger Tapping) included in the battery allow a separation of motor skill from the processing time component by recording movement time and down time separately. The Unified Huntington's Disease Rating Scale quantifies 15 motor and oculomotor symptoms, making data available to examine the relationship of clinically rated motor symptoms to cognitive performances. More importantly, it is possible that more sensitive measures of motor dysfunction might be better indicators of imminent HD onset. Therefore, several tests of motor function, such as a version of the Finger Tapping Test [86], are included in the battery to allow us to characterize and partial out the differential contributions of simple speed, dysrhythmia, internal and external timing perception. We are aware that formal assessment of eye tracking may also be sensitive to early changes in CAG-expanded individuals. However, we have elected not to include computerized eye tracking assessment in the current study because measuring eye tracking at 20 sites is expensive and would be premature given a lack of pilot data or indications from the clinical ratings linking motor and oculomotor symptoms with cognitive function. Based on a reviewer's suggestion, it will be possible to include specific items from the UHDRS motor examination as potential "predictors" in the survival analyses. For instance, it might be useful to determine whether subjects who receive an HD Diagnostic Rating of "soft signs" are at increased risk for HD onset.

Demographic characteristics. It is well known that demographic characteristics, such as age, education, and gender have significant associations with performances on many neuropsychological tests [118, 119]. Age tends to have the greatest impact, followed by education, and normative reference sets indicate that across the entire adult age span and a broad range of education, age accounts for 9 to 38 percent of the variance and education accounts for 16 to 29 percent of the variance in performance of the clinical neuropsychological tests in the current battery (see Appendix D for more detail). Given the combination of clinical

and experimental tests in our battery, good normative reference sets are not available for some measures, and therefore, we will be unable to adjust scores for demographic factors using this approach. High levels of education have also been found to mitigate the rate of deterioration in Alzheimer's disease [120], and a similar effect could well occur in HD. Fortunately, the design of the current study limits demographic confounds by restricting age to 30-55 in the subject sample, thus restricting demographically shared variance due to age to less than half that for the full adult age range. Nonetheless, several strategies will be needed in the proposed project to avoid misinterpretation of data secondary to demographic variation. First, education levels must be determined using reliable methods, and will be done by employing the system developed by Heaton and colleagues [118, 119]. Second, demographic variables will be considered at each step of data analysis (e.g., all subgroups will be examined for demographic similarity). When demographics are different between groups of interest, demographic variables will be controlled statistically either by matching or by inclusion of the relevant demographic measures as additional predictors in the models. Third, a CAG-normal group will be recruited and followed throughout the duration of the study. This group will receive the same repeated assessments as the CAG-expanded group and will be matched to the potential converters in demography. Subjects will be available from our normal comparison sample to guide us in determining age- and education-corrected interpretations of our data. We have also examined age and education data available already in the HSG database to help us estimate the potential impact of age and education on our target sample. In the current HSG sample of over 500, at-risk subjects were somewhat equally distributed in ages between the fourth and fifth decades with about 45% in each; only about 10% of subjects were aged greater than 50 years. Because the majority of the sample have ages within a restricted range, our target sample will have much less variability than that shown in normative samples from the entire adult age span. Similarly, over 93% of the HSG at-risk sample had educational levels between 10 and 18 years. Perhaps more importantly, over 98% of the sample had at least 10 years of education, indicating that variance secondary to low education will largely be absent from our sample. Although these analyses relevant to our target sample suggest that our design strategy may minimize variance due to age and education, we will remain vigilant to the potential impact of these and other demographic variables on cognitive performances.

Intelligence. General intelligence has been shown to have effects on many cognitive functions. Among the cognitive domains included in the proposed study, research indicates that working memory, executive functions, and learning and memory are most strongly affected by general intelligence (c.f., [121]). Therefore, we will estimate IQ at intake, and then consider IQ in our statistical analyses in a similar fashion to the methods used for demographic variables detailed above. Because the standard assessment of intelligence in adults (the Wechsler Adult Intelligence Scale, currently 3rd edition; WAIS-III) requires more than one hour to administer, numerous abbreviated methods have been used. Popular approaches include the use of demographic measures to estimate functioning (c.f., [122]-[123]), the use of reading or word pronunciation lists such as the National Adult Reading Test (c.f., [124]), and the use of abbreviated versions of the Weschler Intelligence Scales. All of these approaches are effective in estimating IQ to some extent, although they vary in terms of degree of accuracy, whether they better predict Full Scale, Verbal, or Performance IQs, and how well they work in special

populations (such as demented, learning disabled). These methods share the problem that estimating IQ at either the high or low end of the range is compromised compared to the middle IQ range [125]. We have elected to use an abbreviated Weschler Intelligence Scale approach to assess IQ at intake, the 2 subscale version of the Weschler Abbreviated Scale of Intelligence (WASI; [126]). This recently developed method is brief, is based on a relatively large and well-constructed normative sample, and has demonstrated high correspondence with the WAIS-III. The 2-subtest version of the WASI requires only 15 minutes to administer, and is based on a normative sample of over 2400 individuals. This method uses subtests modeled closely on WAIS-III subtests, but incorporates different items and differing numbers of items. Given the brevity of this approach, and the high correspondence with the current "gold standard" for measuring IQ, the WASI is a very satisfactory method for assessing IQ. It is unknown to what extent any assessment of IQ at study intake may underestimate "premorbid IQ" in subjects who are experiencing cognitive decline secondary to early disease changes prior to manifest motor disease. The ANART [127] will also be administered to provide an assessment of verbal intelligence that might be better correlated with crystallized intelligence prior to possible neurodegeneration. A simple comparison of the current IQ and the premorbid IQ estimate may offer support for one of the models of HD neurobiologic initiation. Subsequently, the WASI [126] and the ANART [127] will be available as measures of current and premorbid IQ for the current study.

Dementia Severity. There are a variety of test instruments designed to estimate the severity of general intellectual decline in dementing populations (e.g., the Mattis Dementia Rating Scale, the Folstein Mini-Mental Status Examination). Frequently, these tests are used to screen groups for cognitive decline and to characterize the overall severity of their cognitive dysfunction. In effect, these instruments briefly sample a wide range of cognitive domains and describe the level of overall decline. We elected not to use this sort of method for assessing dementia severity in the current study for several reasons: 1) approaches to describing deficits in people at risk for HD have been much more effective when they target specific cognitive domains than when they sample broadly across domains; 2) screening instruments utilize only very brief, minimal samples of behavior for each cognitive domain, while our proposed assessment provides in depth assessment of the cognitive domains known to be vulnerable in HD; 3) preliminary data from our own (and others') work suggest that HD subjects fail to reach a level of cognitive decline consistent with dementia until more than 5 years post diagnosis; 4) if desired, a composite severity score could be derived from our data if needed to characterize overall severity of cognitive dysfunction in our study groups; and 5) the functional assessment data from the UHDRS, in conjunction with the neuropsychological data, will be sufficient to identify the development and severity of dementia in our sample.

Standardization and Reliability of Neuropsychological Procedures. Given the importance of neuropsychological measures in the study and the necessity to include data collected by 20 psychometrists, training in and monitoring of testing methods are extremely important for minimizing error variance. Neuropsychological testing procedures will be overseen by Dr. Julie Stout at Indiana University. All examiners will be provided with a test administration manual and in-person training in test administration. Examiners will be required to reach a criterion for accurate administration of the entire battery prior to any data collection and will be required to

submit videotapes for review at Indiana University to identify any drift or errors in test administration procedures. The project will also utilize regular periodic onsite monitoring of data collection to monitor neuropsychological testing procedures.

Neuropsychology Data Reduction. We considered several methods of data reduction approaches to determine which, among several neuropsychological variables of interest, is the most appropriate measure for specific hypothesis testing. There is no universally accepted philosophy, as each of the following strategies has advantages and disadvantages. 1) One of the most popular strategies used when no *a priori* argument exists for the relative importance of specific measures, is to develop an aggregate, or summary score of multiple tests. For instance, in the current study, all raw scores on cognitive tests would be converted to standard scores, based upon the entire study sample. These standard scores could then be combined and equally weighted to result in a "summary cognitive score" for each study subject. This strategy is appropriate to answer a basic question such as "Does cognitive performance, in general, predict HD onset?" 2) A strategy suggested by a reviewer was to exercise a hypothesis-based data reduction process. In general, our approach to neuropsychological assessment is based upon our current understanding about specific brain substrates affected by HD and cognitive-behavioral correlates of these brain structures/functions. For instance, there are five recognized, discrete, parallel circuits uniting regions of the frontal lobe (motor, frontal eye, dorsolateral, orbitofrontal, and anterior cingulate) with the striatum, globus pallidus, and thalamus in functional systems. Each circuit is differentially modulated by two opposing, but parallel pathways: "direct" and "indirect". The neuropsychological assessment battery chosen for the proposed research was based upon the findings from human lesion studies, animal research, and functional imaging studies mapping specific cognitive skills and behaviors onto these circuits. One possible data-driven strategy to assist with data reduction is to choose one test to represent each frontal-striatal circuit. Hypotheses could test whether one of the parallel circuits is most sensitive to early HD, believed to progress from medial to dorsal regions of the caudate. Unfortunately, specific cognitive skills and psychiatric symptoms are less well understood in terms of discrete circuitry dysfunction. The motor system has received the most attention and several movement disorders have been successfully "mapped" onto these circuits. Therefore, data reduction and hypothesis testing at this level might be considered premature. 3) Preliminary descriptive data analyses are often used to select variables for further study. For instance, in the proposed project, a comparison of baseline performances between subjects who later convert to manifest disease and those who do not may suggest which tests to use in the survival analyses. Less circular might be a simple effect size comparison of the CAG-normal with the CAG-expansion subjects on the baseline variables of interest. Such a strategy, however, may be unacceptably insensitive. Given that we assume that some CAG-expansion subjects will be assessed before initiation of pre-diagnostic decline, significant decline in the smaller number of subjects nearer conversion may be masked. 4) Factor analysis is often used to assist in data reduction. Although this strategy is often appealing due to reliance on statistical methods, factors are oftentimes difficult to interpret and result in findings that become difficult to generalize. Follow-up research design is sometimes hampered by difficulties in operationalizing the results for use in new studies. 5) In the absence of *a priori* preferences for certain combinations, variables can be subjected to

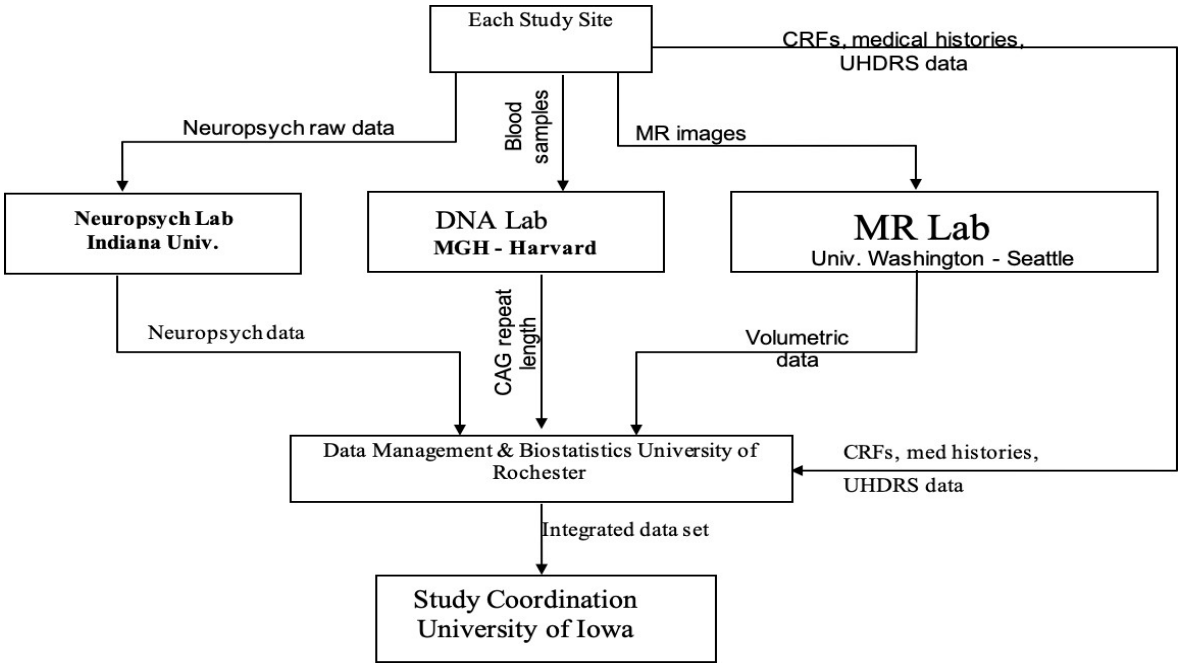
competition in the statistical analyses. For instance, survival analyses might be conducted first with individual cognitive tests as predictors one at a time. (Other known predictors such as CAG length and age would also be included in each model at this step. See Statistical Methods below.) Tests that are significant univariate predictors might then be entered into a competitive model selection procedure. Of concern with this data-driven approach is the potential inflation of nominal statistical significance levels due to the multiple comparisons inherent in model selection. This problem is also inherent in option 3 above.

Based upon our discussion of the challenges in the proposed research we have decided to emphasize option number 5 (although the other options may be adopted at times for conducting secondary, exploratory analyses). Given that several cognitive tests have already been shown to be sensitive to frontal striatal dysfunction, we are most interested in determining which of these are most informative for predicting HD onset. We therefore believe that it is a justifiable *a priori* reason to consider each individual cognitive test as a predictor of HD onset. In exchange, we are willing to accept some elevated risk of type I error (considered at the cognitive-battery-wide level).

Operationalization of this strategy, as well as additional steps to reduce model overfitting and estimate the associated bias are discussed under "Hypothesis testing" (p. 32-197). Some examples of when we may adopt an alternative strategy are discussed under "Post-hoc analyses: Examples of secondary hypotheses and exploratory analyses".

Data Coordination and Management. The coordination and transfer of data among the numerous study sites is of paramount importance to the integrity of the proposed study. Primary data management will occur at the HSG Coordination Center located at the University of Rochester. Over the past several years, the HSG Coordination Center has developed an excellent operation to ensure appropriate data entry, data management, statistical analyses and reporting of data from clinical trial subjects. The chronological flow of data is briefly summarized.

Figure 7. Data Flow



Each study site will send the Case Report Forms (CRFs; see Appendix C) to the Data Control Clerk at the HSG Coordination Center where they are logged into a tracking database, date-stamped, and visually inspected for completion and legibility. Each study site will send the cognitive protocols, the MRI scans and the blood samples to the specialized center as shown in Figure 7. MRI data will be sent via FTP to the University of Washington (i.e., Aylward), blood samples will be sent to Harvard University (i.e., MacDonald) and neuropsychological data will be sent to Indiana University (i.e., Stout). Inspection of hard-copy neuropsychology protocols will occur within 1 week of receipt to assess administration and reliability of scoring. Approved neuropsychology data are forwarded to the HSG Coordination Center. Following analyses, MRI, DNA and electronic data derived from computerized assessment will be forwarded to the HSG Coordination Center electronically, via FTP**.**

Upon receiving CRFs from the site and/or specialized neuropsychological data from Indiana University, the Data Control Clerk will enter each CRF into a computer application called Form Log, which will track the location of the CRF throughout its life span. CRFs will then be packaged for transmission to an off-site vendor, Datrose Inc., for data entry by a double keying technique. CRFs will then be returned from data entry, after which a checking procedure is performed to ensure consistency between the CRFs and electronic records. These electronic records will then be read into the mainframe computer via SAS ACCESS into an INGRES data table. CRFs will then be placed in subject folders where they are maintained.

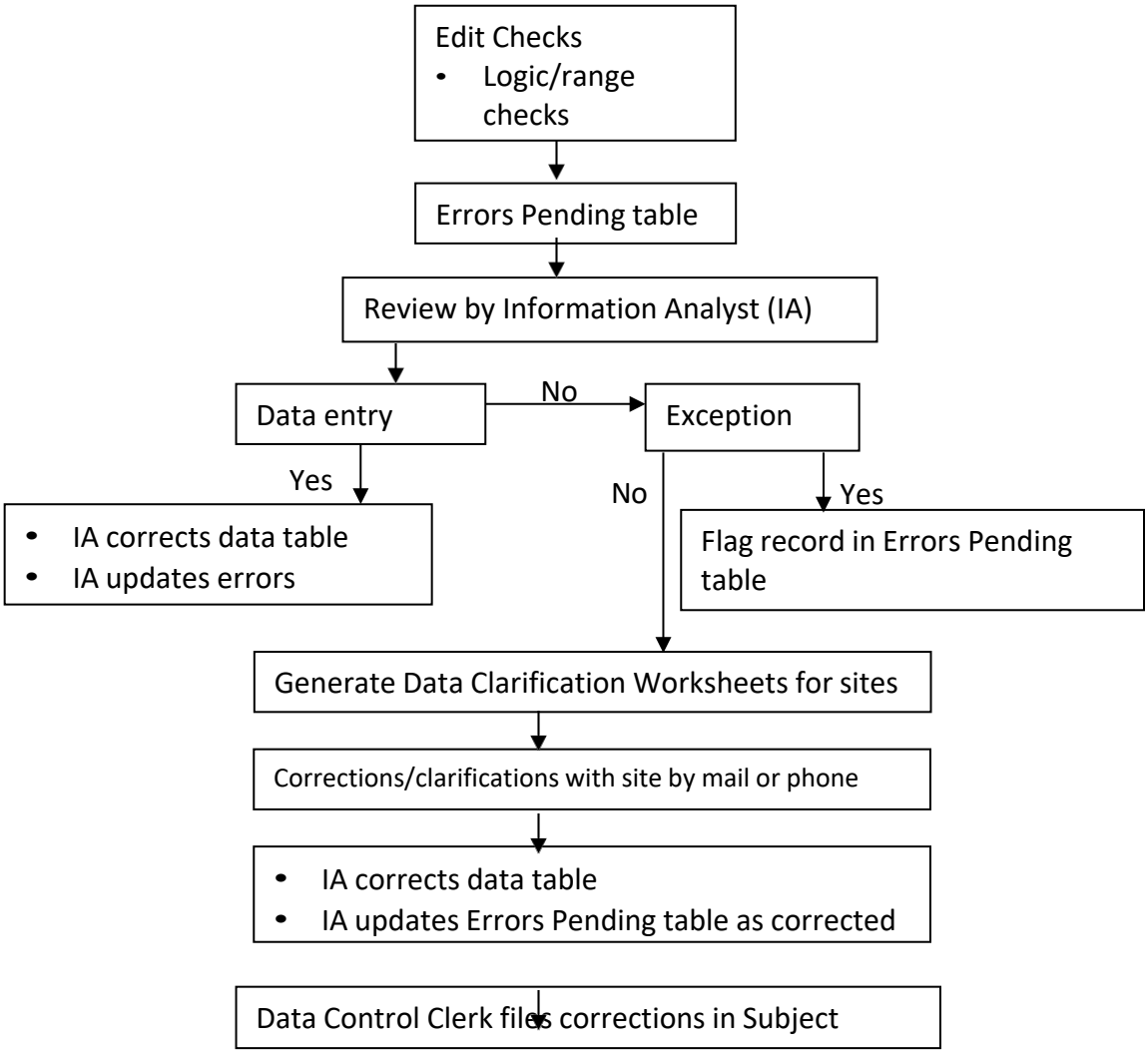
An edit checking and data clarification process will be initiated to ensure accuracy and completeness of the PREDICT-HD database (Figure 3). For example, range-checks, cross-form checks, and logic checks are part of the data clarification. Errors in the data will be identified during visual review, electronic edit checks and on-site study monitor queries and will be listed

on a data clarification worksheet. This worksheet will then be sent to the study sites for considered corrections to the CRF. The worksheet will be signed and dated by the site investigator and coordinator to verify that they have reviewed the queries and made the corrections. Any corrections to the CRF will be maintained at the study site and a photocopy of the corrected copy will be returned to the HSG Coordination Center and date stamped. A record of all queries will be maintained in the Errors Pending Table, separated from the CRF data. Once error corrections are verified, the actual data record will be updated by the Information Analyst using the Errors Pending documentation. Cumulative outstanding error reports will be issued regularly to the PREDICT-HD sites listing the form name, the error found and the original value. This report will also be used by study monitors to verify data corrections at the site.

The HSG Coordination Center will merge the CRF databases with the MRI, DNA and neuropsychology electronic databases and an integrated database will be sent monthly to the University of Iowa, where additional quality control mechanisms are conducted. Finally, data are inspected by the PI and decisions regarding data readiness for hypothesis testing are made.

Data Management Security. The HSG Coordination Center has several provisions in place to maintain integrity, confidentiality and security of subject information. All hard copies of the PREDICT-HD data will be kept in locked, fire-retardant secure cabinets, and the office containing the cabinets will be locked at all times. All personnel who work with the data will sign confidentiality agreements. All data sent to data entry (Datrose Inc.) will be hand-carried and locked in secure cabinets. In addition, the INGRES relational database has journaling capabilities to track changes and personnel who make the changes.

Figure 3. PREDICT-HD Data Clarification Process



Computer System Security. The HSG Coordination Center computer systems and networks are managed by full-time system administrators. All (internal) network traffic is encrypted via network hubs to minimize "eavesdropping" attacks. All PC's run virus protection software full-time and are updated regularly with the latest virus detection strings; the Windows NT server does this as well and has the additional security of scanning all e-mail for viruses before a user can even access them. Both servers have been customized to run the bare minimum of network services in order to minimize potential "back door" attacks, and both servers are updated on a regular basis with the latest vendor recommended software fixes. In addition, other security software runs continuously minimizing other potential attacks (e.g., password "crackers" to detect easily guessable passwords). All accounts are password protected and passwords must be changed on a regular basis. Each study database has three security levels: access to

the database, access to individual tables within a database, and permissions (e.g., read/write vs. read only) to individual tables. Complete backups are run nightly to tape with monthly rotation of backup tapes and monthly off-site tape storage in a bank safety deposit box.

On-Site Monitoring. In compliance with Good Clinical Practice (GCP) guidelines and sound clinical research principles, members of the Steering Committee and study monitors will visit each PREDICT-HD study site to review on-site resources (personnel, space, equipment, milieu) and confirm the presence of required regulatory documents (IRB approval of protocol and subject consents). In addition, study monitors, supervised by the PI and HSG Project Coordinator, will visit each PREDICT-HD site at least yearly to review source documentation materials, neuropsychological assessment practices and to confirm that data clarifications have been accurately completed. This provision will help ensure the integrity of protocol implementation and the accurate and timely collection of data. The study monitor will also review clinical facilities, resources and procedures for evaluating study subjects, and provide reports of protocol compliance to the PREDICT-HD Steering Committee. This provision for annual on-site monitoring is also consistent with FDA guidance's for clinical trial monitoring and will reinforce the confidence of commercial sponsors to test their interventions for preclinical HD using the PREDICT-HD paradigm.

Statistical Analysis

Preliminary Treatment of the Data

Kaplan-Meier curves of drop-out rates among CAG-normal and CAG-expanded subjects will be calculated, and baseline characteristics of dropouts and subjects who complete the study will be compared. Differences in raw and corrected values of imaging and neuropsychological data between centers will be examined and, if appropriate, the results adjusted for any detected systematic differences between centers.

Demographic data such as gender, age at entry to study, and ethnicity will be examined for differences between the CAG-expanded and CAG-normal groups. Comparisons between groups will be adjusted by analysis of covariance for any differences that are found.

For ongoing quality control, descriptive plots and tabulations will be created for all variables, and possible errors or outliers in the data will be identified and queried monthly.

Variables for MRI will include absolute volume of caudate, putamen and total brain. Predictive variables from the comprehensive neuropsychological assessment include letter number sequencing number correct; operation span total; median finger tapping speed; median reaction time; Trails A time to completion, Trails B time to completion; Symbol Digit total; button test number correct; serial reaction time learning rate; HVLT-R list A total 1-5, discriminability; set shift total errors, set shift flexibility errors; Tower total number of moves; COWA total; Stroop color total number correct, and Stroop interference total.

In the event of substantial non-right-censored missing data relevant for a particular test (e.g., missing measurements on an annual UHDRS for a number of subjects), multiple imputation methods [128] will be used to correct the relevant statistical analyses for missing data when a

missing-at-random (but not necessarily missing-completely-at-random) mechanism appears tenable.

Hypothesis testing:

We will use Cox proportional hazards [129] models to test our two primary hypotheses that (1) among CAG-expanded individuals, baseline (intake) measures of cognitive tests and brain volume measures are predictive of the time until HD diagnosis, and that (2) the change over time in these same measures is an additional predictor of time until diagnosis. Since the goal of this study is to improve the prediction of disease onset beyond that already provided by age and CAG length, both of these variables will be controlled for in all models. We will obtain point estimates and significance tests for the hazard ratios associated with baseline cognitive and MRI measures by adding these measures to Cox survival models that already contain age and CAG length as predictors. For example, a typical survival analysis model using a single neuropsychological baseline measure will have the following schematic form:

Years until diagnosis = function of [B_1 age + B_2 (CAG length) + B_3(Baseline Stroop Color Score)]

Age and CAG length will be included in all such models. The significance of a baseline measure as an additional predictor in such models will then be tested. Potential confounders and interactions (described below) will also be included in the models if they appear to be substantial (significant) modifiers of individual models.

We will individually test each of the neuropsychological and MRI measures in such models and will also test the following: (1) the simple sum of standardized scores for neuropsychological batteries; (2) the joint (multiple degrees of freedom) significance of cognitive battery measures, brain volumes, and their combined effect. In cases of jointly significant combinations of measures, we will use backward elimination methods, guided by Aikake's Information Criterion (AIC) as an approximate measure of model complexity, to select parsimonious subsets of predictors [130]. For reasons beyond the scope of this discussion, we are aware that AIC and similar measures are imperfect criteria when model selection is conducted from among multiple candidate variable combinations of the same complexity. The search for improved methods is a topic of vigorous current statistical research and a particular interest of Dr. Langbehn's. We will monitor developments in this area and substitute improved correction methods if available by the end of the study.

Since incident diagnoses will only be determined once per year, we will use the exact likelihood method for tied data in our parameter estimates.

We will check proportional hazard assumptions by testing for time-dependent interactions with the passage of time over the course of the study and by visual inspection of the log(–log(survivor)) estimates. If necessary, the Cox models will be adjusted for significant time-dependent violations of the proportional hazard's assumption if feasible. If this were to prove infeasible, we would switch to alternative models (non-proportional hazard parametric survival models) if an adequate fit could be achieved or to nonparametric Kaplan-Meier models with score tests if necessary [132].

We will control for possible confounding effects of education, intelligence, neuropsychiatric scores, gender, and ethnic background by including these terms in the models if they are statistically significant. In the cases of education, intelligence and neuropsychiatric scores, we will also check for potential interactions with neuropsychological measurements. (Although the neuropsychiatric scores are labeled here as confounders, this is essentially a matter of perspective. In response to a previous reviewer's query, we note that this analysis also constitutes a test of predictive main effects for the neuropsychiatric measures.) Finally, we will also check for site-specific-effects (indicating possible systematic differences in measurement) by testing site-specific main effects and interactions in our models.

Survival curves will be estimated by applying the Cox proportional hazards estimates to the estimated baseline hazard function.

Repeated measures:

Change over time from baseline scores will be incorporated into the Cox survival models as a time-dependent covariate. In the case of neuropsychological measures, these changes will be adjusted for the estimated test-retest practice effects observed in the CAG-normal controls. Baseline measures will also be included in all such models, and the additional predictive effect of change over time, controlling for baseline effects as well as age and CAG will be the primary focus of our hypothesis testing. Note that only subjects who are still in the study and not yet diagnosed at the point of a repeated measure will contribute to this part of the survival analysis.

In our statistical power simulations described below, we noted that two different models of change with repeated measures compete for superior prediction. Deterioration in scores or brain volumes can be incorporated into the models using either the measured amount of change over time or a dichotomous variable that merely indicates whether any decline is occurring. Under high reliability measures (e.g., MRI data) and certain plausible relationships between decline and disease onset, it can be shown that the dichotomous indicator is a more powerful predictor. Having noted this a priori, we will test the significance of change from baseline for high reliability measures with both the continuous and dichotomized versions of the change variable.

We will also check for possible substantial interactions between rate of change and baseline scores, CAG length, and age by testing corresponding interaction terms into our time-dependent models. This will provide a test of the null hypothesis that, conditional on imminent diagnosis, the decline in these measures is independent of age or CAG length.

Human Subjects:

All study sites received Institutional Review Board approval from their respective Universities for the first study submission. In addition, the IRB at the University of Iowa has approved the revised protocol. Although some additional sites have also received IRB approval for the revised project, most are currently pending and all will have completed IRB evaluations prior to study review.

1. Subjects: Five hundred (500) research subjects will be enrolled at 20 sites in the United

States and Canada. Two groups will be selected: a group with known CAG repeat length > 39 (n=425), and a comparison group previously considered at risk (by virtue of having a parent with HD) who do not have CAG expansion (n=75). Subjects will range from age 30 to age 55. Although the subjects will be free from neurologic disease (as well as other medical and psychiatric disturbances), it is important to note that they will be within the age range where the emergence of symptoms of Huntington's disease most likely begin. Inclusion and exclusion criteria are as follow:

***Inclusion Criteria*:**

(a) Completed predictive testing and known test results with CAG length of one gene >39 (for CAG-expanded group) or both CAG genes < 30 (for CAG-normal group);
(b) Men and women aged 30 to 55;
(c) Commitment to complete a minimum of 4 yearly evaluations;
(d) Commitment of a companion to attend visits;
(e) Able to undergo MRI.

Exclusion Criteria:

(a) Motor exam total score <10;
(b) Clinical evidence of unstable medical or psychiatric illness;
(c) History of serious alcohol or drug abuse within the previous year;
(d) History of learning disability and/or mental retardation;
(e) History of other CNS disease or event (e.g., seizures, head trauma);
(f) Current or treated within the past 6 months with antipsychotic medications, including the traditional neuroleptics such as haloperidol as well as the atypical antipsychotics risperidone, clozapine, quetiapine and olanzapine;
(g) Treatment with phenothiazine-derivative antiemetic medications such as prochlorperazine, metoclopramide, promethazine and Inapsine on a regular basis (greater than 3 times per month);
(h) Metallic implants.

1. <u>Gender, Minority and Minor Issues</u>. To date, no evidence exists of gender differences in HD. Therefore a 1:1 male: female ratio will be sought. Attention will be paid to recruitment and retention of minority subjects; site selection was partially based upon availability of these populations. Although there are no a priori reasons to hypothesize any differences in the variables of interest, all outcome variables will be analyzed for gender and racial interactions. The proposed study will not involve children. Although HD is a genetic disease that can affect every ethnicity equally, there do exist prevalence differences among different groups. Prevalence estimates for HD in populations of European originvary greatly. The most reliable estimate of prevalence of HD in Caucasians is between 5 and 7 cases per 100,000 total population [140]. Prevalence estimatesin populations other than Western Europeans have been very limited, presumably due to the apparent rarity of the condition in these populations and because of social and cultural circumstances within the surveyed populations. Prevalence estimates that do exist for populations not of Western European

origin have been limited to American Blacks, South African mixed-race Blacks, native South Africans and Japanese. Huntington's disease appears to be quite rare among African and Oriental populations. A survey conducted in South Africa found 11 Africans having Huntington's disease with no evidence of racial admixture. These cases gave an estimated prevalence of only 0.6 cases per million population [141]. Of all the Asian countries, Japan is the only one in which HD has been systematically surveyed. The estimated prevalence of HD inJapan is 4.5 per million [142]. So although quite rare, HD does appear to be present in these populations. The HD Roster consists of 131,995 individuals. Ofthese, 136 (.10%) are American Indian or Alaskan Native; 581 (.44%) are Asian or Pacific Islander; 782 (.59%) are Black, not of Hispanic origin; 1,053 (.79%) are Hispanic; 124,965 (94.67%) are White, not of Hispanic origin; and 4,478 (3.39%)are of other or unknown ethnic origin**. Our goal is to recruit a sample that reflects the epidemiology of HD as well as to recruit minorities at a higher rate than indicated in previous research.** We have made several decisions instudy design to maximize our potential for the recruitment of minorities. When possible, we selected sites with heterogeneity in terms of geographic location and city size. We will focus particular recruitment efforts at sites where minority recruitment may be more fruitful, such as Los Angeles, San Francisco, Atlanta, Baltimore, New York and Houston. We will offer talks and distribute handouts about our study to neurologists and family practitioners in geographic locations more likely to have minority families. Additional effort will be made to inform minority families already identified in the HSG. In addition, we will solicit help with minority recruitment strategies from other professionals, such as consultation with funded research projects aimed at norming neuropsychological instruments for minorities. Given the relatively low prevalence rates of HD in minorities, together with the sampling strategy for the current study, we anticipate that we will recruit a sample representative of HD.

2. The documented demographic breakdowns by state are presented below. To encourage the enrollment of minorities, at least six (6) of our selected sites have minority prevalence greater than the United States average.

Table 3. Demographic Breakdown By State

State	White	Hispanic	Black	Am. Indian	Asian
California	50.5%	28.9%	7.5%	0.9%	12.1%
Colorado	78.7%	13.6%	4.3%	0.9%	2.4%
Connecticut	80.8%	7.3%	9.3%	0.2%	2.5%
Florida	68.6%	13.9%	15.2%	0.5%	1.8%
Georgia	66.7%	2.5%	28.5%	0.2%	2.0%
Indiana	88.2%	2.2%	8.3%	0.2%	0.9%
Iowa	94.6%	1.8%	2.0%	0.3%	1.3%
Kansas	86.7%	4.8%	5.9%	0.9%	1.8%
Maryland	64.8%	3.1%	27.8%	0.3%	4.0%
Massachusetts	84.9%	4.8%	6.4%	0.2%	3.6%

Michigan	81.1%	2.4%	14.3%	0.6%	1.6%
New York	65.4%	10.9%	17.7%	0.4%	5.5%
Texas	55.9%	28.5%	12.3%	0.5%	2.8%
Virginia	72.8%	3.2%	20.1%	0.3%	3.6%
Washington	83.4%	5.5%	3.5%	1.8%	5.8%
Alberta	NA	NA	NA	NA	NA
British Columbia	NA	NA	NA	NA	NA
Ontario	NA	NA	NA	NA	NA
Winnipeg	NA	NA	NA	NA	NA
United States	72.3%	10.2%	12.7%	0.9%	3.9%

3. Rationale for Subject Selection. We are aware that the targeted research sample is comprised of a group of people who potentially will be undergoing a significant amount of life stress (via conversion from health to illness). We are aware that this may raise several additional concerns about the participation of this subject sample in research. Research studies of individuals at risk for genetic disease are not new. What is novel to the proposed research is the sampling strategy, which attempts to oversample individuals in an age range most likely to demonstrate onset during the 5-year study period. In addition, and in contrast to the majority of previous work, the proposed research will examine individuals with known gene status. Without this design factor, however, the proposed study could not be done. Thus, we are utilizing measures for identifying significant distress [113, 114] as well as developing strategies for referral to specialists for assistance.
4. Sources of Research Material: All of the data involved in this study will be collected for research purposes only. Research material consists of a blood sample for DNA analysis, an MRI scan for measurement of volumetric structures within the basal ganglia, and numerous ratings of clinical features, functional abilities, and neuropsychological performances. In addition, a medical and psychiatric history will be taken and updated throughout the study.
5. Recruitment of Subjects and Consent Procedures: There are several potential recruitment sources for the proposed study. Letters will be sent through national and international organizations associated with Huntington's disease. Professionals involved with clinical work or research in Huntington's disease will be invited to recruit individuals from their clinical practices. Finally, the genetic testing centers throughout the United States and Canada will be encouraged to refer individuals who have completed their genetic testing programs. The Site Investigator at each of the 20 research sites will obtain the consent on each research participant. All consent forms will be approved by the PREDICT-HD Steering Committee and each Institutional Review Board. IRB approval has been granted at the University of Iowa prior to submission of this application.
6. Potential Risks and Procedures for Minimizing Risks: The chance of developing HD will not be changed by participating in this study, nor will the progression of

the disease. If a subject has the gene for HD, however, there is a chance that they will develop HD during the course of this study. Although each person will be evaluated periodically, the results of these examinations cannot be shared with subjects. We can offer assistance in arranging for an evaluation outside of the PREDICT-HD study, though, if participants want to know whether they are showing any signs of the illness.

To participate in the PREDICT-HD study, persons at risk must not have significant abnormal motor signs. A movement disorder specialist will conduct a standardized exam to make this determination. If significant abnormal motor signs are not evident then participants will proceed to the Assessment Phase of the study. If significant motor abnormalities are demonstrated the participant will be invited to continue in the Interview Phase that consists of a follow-up telephone interview in one-month post screening to provide support and solicit feedback. Prior to initiation of the screening visit activities the consent form will be gone over in detail so that subjects understand the procedures of the study.

The uncertainties of not knowing when HD will start may cause distress. We will talk with participants at each visit, and if someone feels at any time they could benefit from treatment or support, they can be referred to a specialist.

Confidentiality is a concern in PREDICT-HD. Every possible effort will be made to keep the research information in the strictest confidence, but we cannot absolutely guarantee that accidental disclosure will not happen. We remind subjects that the responsibility for confidentiality rests with everyone: they should think carefully before discussing their role in PREDICT-HD with anyone, since the effects of disclosure on insurance, employment, etc. are not known.

Some people experience nervousness, fatigue, or boredom during the tests of thinking and behavior. Frequent rest breaks are provided, and technicians are trained to offer assurance and to discontinue testing if necessary.

During the collection of blood samples, participants may feel pain at the site on the arm where blood is taken, and bruising may occur. Infections and fainting can also happen, but they are rare. Subjects are told that if they experience faintness, they should lie down immediately to avoid possible injuries and notify study personnel.

Even though the MRI is well lighted, open at both ends, ventilated, and has an intercom, some people undergoing brain scans feel anxious being in it. Subjects may request a mild sedative before the scan if they expect to be uncomfortable.

7. Risks vs. Benefits: Overall, the risks to the subjects are manageable and are reasonable in relationship to the anticipated benefit of information derived from this at-risk population. The knowledge obtained from the ongoing investigation will assist with the development of clinical trials for presymptomatic individuals at risk for HD. Given numerous research papers suggesting that a majority of

neuronal loss has occurred prior to a diagnosis of a neurological illness, the best time to provide clinical trials and intervention is prior to diagnosis of disease. Thus, the proposed research is critical for the initiation of clinical trials in CAG-expanded individuals who are presymptomatic.

8. Confidentiality: The identities of all research subjects will be held in strict confidence to the extent provided by law. No names or other identifying data will be used in any report or publication of this study. A unique code number will identify each subject. All coded data will be maintained in locked file cabinets and/or computers equipped with security programs. The coded research data will be recorded and sent to the HSG Coordination Center at the University of Rochester.

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PREDICT-HD

Neurobiological **PREDICT**ors of **H**untington's **D**isease

OPERATIONS MANUAL

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May 23, 2002

SECTION I

GENERAL INFORMATION

Study Contacts
Clinical Trials Coordination Center (CTCC) Office Closings
Study Personnel

APPENDIX I

New Staff Form
Address List

STUDY CONTACTS

If you have questions regarding the protocol, regulatory issues, payment, or data management please refer to the following list:

Reason to Call	Whom to Call
Protocol questions, Day-to-day study operations, Reportable Events (RE), Notifications, Medical concerns	Project Coordinator Elise Kayson Phone: 585-275-4696 Email: ekayson@mct.rochester.edu
Questions regarding regulatory documents	Assistant Project Coordinator Elaine Julian-Baros Phone: 585-273-2879 Email: ejulian-baros@mct.rochester.edu
CRF questions, Data queries	Information Analyst Connie Orme Phone: 585-275-3506 Email: corme@mct.rochester.edu
Enrollment calls; **Please announce that you are calling for a PREDICT-HD Enrollment.**	**Enrollment Staff** Phone: 585-275-7311 (8:30 a.m. – 4:30 p.m. ET or by special arrangement)
Subcontract, Payment issues	Lynda Sherman Phone: 319-353-4236 Email: lynda-sherman@uiowa.edu

If you have detailed questions regarding Psychological or Cognitive Testing, or MRI Protocol, please contact:

Cognitive data questions, Computer test issues	Julie Stout Phone: 812-855-7608 Email: jcstout@indiana.edu
Psychiatric testing questions	Jane Paulsen Phone: 319-353-4551 Email: jane-paulsen@uiowa.edu
MRI questions	Elizabeth Aylward Phone: 206-221-6610 Email: eaylward@u.washington.edu

OFFICE CLOSINGS FOR 2002 - 2003

The chart below indicates the days and times the Clinical Trials Coordination Center (CTCC), Indiana University (INU), Massachusetts General Hospital (MGH), and Iowa University (IAU) will be closed.

Date	**CTCC Call (585) 275-7311**	**INU**	**MGH**	**IAU**
Monday, May 27, 2002	X	X	X	X
Thursday, July 4, 2002	X	X	X	X
Friday, July 5, 2002	X			
Monday, September 2, 2002	X	X	X	X
Wednesday, November 27, 2002 12 pm EST	X			
Thursday, November 28, 2002	X	X	X	X
Friday, November 29, 2002	X	X		
Tuesday, December 24, 2002 12 pm EST	X			
Wednesday, December 25, 2002	X	X	X	X
Thursday, December 26, 2002	X			
Friday, December 27, 2002	X			
Tuesday, December 31, 2002 12 pm EST	X			
Wednesday, January 1, 2003	X	X	X	X
Monday, January 20, 2003		X		

STUDY PERSONNEL

All study personnel (e.g., investigator, motor rater, coordinator, cognitive tester) in the study will require a staff code, assigned by the CTCC. The Project Coordinator must be notified in advance of a site's intention to change study personnel, and this request must be approved by the PREDICT-HD Steering Committee. If the change is approved, new staff should complete the *New Staff Form* (preceding the Address List) and fax it to the CTCC (fax number and instructions are provided on the form). In addition, the HSG Credentials Committee must approve any investigators who are new or have changed sites. **Please note the importance of study personnel consistency.**

ADDRESS LIST

A study address list follows the *New Staff Form*. Please notify the Project Coordinator at 585-275-4696 if there are any changes in address, email, fax, telephone numbers, or staffing.

SECTION II

PROTOCOL ACTIVITIES

Schedule of Activities

Protocol (insert)

Synopsis (insert)

Amendments (insert)

APPENDIX II

PREDICT-HD Schedule of Activities
PREDICT-HD Schedule of CRF Completion
and Study Activities
Motor Exam Videotaping Outline

PROTOCOL ACTIVITIES

Schedule of Activities

Visit 1 (Screening /Baseline)

The first study visit (Visit 1) will determine whether the participant meets the necessary criteria for participation in the study. If the participant is at-risk for HD, between 30 and 55 years of age, has completed presymptomatic HD testing (and has tested either positive or negative), has never been diagnosed with definite HD, and meets all the necessary criteria they may enter PREDICT-HD. If all study criteria are met during Visit 1 the participant will continue on for the psychiatric, cognitive and MRI assessments. The length of the cognitive examination will be about 3 hours, the length of the psychiatric interview will be about one hour and the brain scan will take about one hour. In addition, a movement disorder specialist will conduct a standardized exam Unified Huntington's Disease Rating Scale (UHDRS) where the participant will be asked to walk heel-to-toe, tap your fingers, stick out their tongue and perform other tasks involving motor (movement) control. They will also be asked during Visit 1 to be videotaped for the cognitive and motor assessment portions of the study to ensure consistency in rating among investigators. These will not be made public and the participant's name will not be disclosed to anyone.

During the Screening/Baseline Visit (Visit 1), the suggested order of the required activities is as follows:

- Obtain consent
- Medical History/Demographics
- Concomitant Medication Review
- Inclusion/Exclusion criteria review

If the participant meets all inclusion/exclusion criteria and is eligible to continue with Screening/Baseline, the suggested order of activities is as follows:

- Confidential Participant Log
- Confidential Companion Participation Log
- UHDRS '99 Part I by Neurologist
- Videotape selected portions of Motor exam for all participants
- Call CTCC for Participant Identification Number
- Obtain DNA sample consent
- Obtain DNA sample
- Cognitive Assessment (see Cognitive Operations Manual for sequence of tests) – **videotape**
- Smell Test
- Psychiatric Assessment (see Section V of PREDICT-HD Operations Manual for sequence of tests)
- UHDRS '99 (IV, V, VI, VII, VIII)
- Family Participation Log

- MRI
- Screening/Baseline confirmation

It is important that the Cognitive Assessment be completed early in the day so that participants will be as alert as possible. Waiting until the end of the day will likely affect the quality of the data by introducing factors such as fatigue, hunger, etc.

Given that each site will be utilizing different arrangements with regard to personnel and locations for the activities listed above, there is some flexibility with regard the order of activities. For example, it is acceptable (and may be preferred by some sites) to complete the Screening Phase on a separate day than the Assessment Phase. If a site takes this approach, all activities included in the Assessment Phase must be completed within 1 month of the Screening Phase. If more than 1 month passes before a participant can be scheduled for the Assessment Phase, then all aspects of the Screening Phase (i.e., consent, medication list, motor exam) must be repeated. If Screening and Assessment are completed on separate days, the order of activities should remain the same for the Assessment Phase, with the Cognitive Assessment occurring early in the day.

Other Assessments and Visits

Please follow *PREDICT-HD Schedule of Activities* and *PREDICT-HD Schedule of CRF Completion and Study Activities* for assessments.

Visit 2

Complete the following activities for Visit 2:

- UHDRS ’99 Part I Motor Assessment (Neurologist)
- Concomitant Medication Review
- Reportable Event Review
- Family Participation Log Review
- Companion Participation Log
- Cognitive Assessments (see Cognitive Operations Manual)
- Psychiatric Evaluations
- UHDRS ’99 Parts IV, V, VI, VII, VIII

Visit 3

Complete the activities listed below:

- UHDRS ’99 Part I Motor Assessment (Neurologist)
- Concomitant Medication Review
- Reportable Event Review
- Family Participation Log Review
- Companion Participation Log
- Cognitive Assessments (see Cognitive Operations Manual)
- Psychiatric Evaluations

- UHDRS ’99 Parts IV, V, VI, VII, VIII
- MRI

Visit 4

Complete the activities below:

- UHDRS ’99 Part I Motor Assessment (Neurologist)
- Concomitant Medication Review
- Reportable Event Review
- Family Participation Log Review
- Companion Participation Log
- Cognitive Assessments (see Cognitive Operations Manual)
- Psychiatric Evaluations
- UHDRS ’99 Parts IV, V, VI, VII, VIII
- Re-consent regarding DNA retention/destruction
- Participant disposition

Premature Withdrawal

If a participant prematurely withdraws, complete the following activities:

- Re-consent regarding DNA retention/destruction
- Complete all activities for Visit 3 if possible
- Participant disposition

APPENDIX II

PREDICT-HD Schedule of Activities
PREDICT-HD Schedule of CRF Completion
and Study Activities
Motor Exam Videotaping Outline

PREDICT-HD SCHEDULE OF ACTIVITIES

	Screening/ Baseline	Assessment Phase Visits		
	Visit 1[1] (0 mo)	Visit 2[2] (12 mo)	Visit 3[1] (24 mo)	Visit 4[2] (36 mo)
Informed consent	X			X
Eligibility criteria	X			
Medical history	X			
General physical exam and Neuro exam	X			
UHDRS '99	X	X	X	X
Concomitant Medication Review	X	X	X	X
Reportable Event Review		X	X	X
Participant Entry Number	X			
Blood draw CAG analysis	X			
Psychiatric Ratings	X	X	X	X
Cognitive Tests	X	X	X	X
MRI	X		X	
Cognitive & Motor Videotaping	X			

[1]Total visit time is approximately 4-8 hours for Visits 1 and 3.

[2]Total visit time is approximately 1-2 hours for Visits 2 and 4.

SECTION III

ENROLLMENT

General Information
Enrollment Calls
Participant ID Number Assignment
Companion ID Number Assignment
Confidential Participant/Companion Log
Screening/Projection Log
Enrollment Projection Report

APPENDIX III

Visit Window Schedule
Sample of Labels
Participant ID Label
Enrollment Verification Report
Confidential Participant Identification Code Log
Confidential Companion Identification Code Log
Screening/Projection Log
Enrollment Projection Report

GENERAL INFORMATION

A participant will be considered to have entered the study via an enrollment call to the Clinical Trials Coordination Center (CTCC).

ENROLLMENT CALLS

When all the appropriate screening/baseline visit tasks have been completed at Visit 1, and the investigator has determined that a person is eligible to participate in the study, he or she may be entered into an on-line Enrollment Module, which generates the 3-digit Participant Identification (ID) number. Labels with a 3-digit code and bar codes will be sent for use on the participant's CRF and serum samples. The barcodes are not the same as the participant's identification number.

CTCC staff will rotate taking enrollment calls for various studies. When the receptionist answers the phone, **please announce that you are calling with a PREDICT-HD enrollment**.

CTCC staff will be available to receive enrollment calls from sites:

- By calling 585-275-7311 weekdays between 8:30 a.m. – 4:30 p.m. (Eastern Time)
- By **pre-arrangement** with the CTCC (with preferably 1-2 days notice), calls can be received at other times to accommodate site-specific scheduling needs
- *Please note dates the office is closed, provided, in Section I. You will be unable to enroll participants on these dates unless special arrangements have been predetermined.*

Who may enroll a participant?

- Either the enrolling Site Investigator or the Site Coordinator (<u>no other site staff will be permitted to enroll participants</u>).

When do I make the enrollment call?

- During the Screening/Baseline Visit (Visit 1) **<u>after</u>** all eligibility criteria are complete.
- Any questions regarding the participant's eligibility should be referred to the Project Coordinator **<u>prior</u>** to placing the enrollment call.

What information do I need to provide?

Information that the caller must have available during the enrollment call includes the following:

- Site number
- Caller's staff code
- Participant's date of birth
- Participants gender
- Participants ethnicity
- Date the consent form was signed
- Knowledge that all inclusion/exclusion criteria have been met
- Motor Score

PARTICIPANT ID NUMBER ASSIGNMENT

The Enrollment Module will generate a Participant ID number for a study participant who meets all eligibility criteria. The Enrollment Module uses the date of enrollment to calculate the participant's follow-up visit window schedule (the dates in which the participant should be seen by the study staff for a given visit). (see Appendix III for sample *Visit Window Schedule*.)

- Locate the Participant ID number on the set of labels and corresponding barcodes (*Sample of Labels* - Appendix III). Enter this number in the space provided on the top of the CRF pages. This number will be used by the HSG Coordination Center to identify the participant for purposes of this study. This number should be entered on all CRF pages. The barcode labels contain a separate embedded number to be used by the lab for identifying the blood samples. Peel off the Participant ID number and place it on the CRF page marked *Participant ID Label*.

NOTE: The participant ID numbers and barcodes are designed such that neither the HSG Coordination Center nor the DNA lab will individually be able to match the numbers to the participant by name.

An *Enrollment Verification Report* (see Appendix III for sample) listing the Participant ID and the visit window schedule will be emailed to the Site Coordinator following the enrollment call. Upon receiving the report, the coordinator should verify that the participant identifiers are correct and file the report in the participant's folder. If an error is found, please contact the CTCC and notify them of the correction to be made.

COMPANION ID NUMBER ASSIGNMENT

A Companion ID number for the study participant's companion will be assigned by the site staff. The companion number will begin with "C" as the prefix to the number and "01" for the first

companion, “02” for the second companion and so on (i.e. C-01 is the first companion. If the participant has a different companion at Visit 2, he/she will be assigned C-02 as his/her number). This number will be used by the HSG Coordination Center to identify the companion for purposes of this study. This number should be entered on all CRF pages that require the companion number.

CONFIDENTIAL PARTICIPANT/COMPANION LOG

Confidentiality of the participants’ identification must remain strict throughout the course of the study. Responsibility for confidentiality rests with both the investigators and participants. Participants should consider carefully before disclosing their participation to anyone.

- Identifying information about a participant such as name, initials, or social security number must never be in the case report form (CRF) binder.
- The signed Consent Form must be kept separate from the CRF binder.
- We are providing you with a *PREDICT-HD Confidential Participant Identification Code Log* (see Appendix III) that should be kept in a locked secure location separate from the CRF binder. When participants are screened/baselined, you may write their initials along with the identification number on the PREDICT Confidential Participant Log. There is also a *PREDICT-HD Confidential Companion Identification Code Log.* The companion name and number should be recorded and if the companion changes, the name and number for the new companion should be listed.

SCREENING/PROJECTION LOG

- **Used to determine projected timelines, the need for additional supplies, monitor schedules, and recruitment difficulties.**
- **Designed to capture information about all participants who signed the Informed Consent and are willing to be screened for PREDICT-HD eligibility.**
- **Reflects site predictions about the number and timing of future enrollments.**
- **Information provided is also used to describe recruitment efforts in reports to the sponsor and IRB annual reports.**
- Fax the updated *Screening/Projection Log* **(see Appendix III) to the PREDICT-HD Data Control Clerk (Fax: 585-461-4594) at the CTCC on a biweekly basis until study enrollment is completed.**
- **In the case of a screening failure, update the log with the reason for the failure.**
- **At the end of the study, send a copy of the log to the CTCC with the final CRFs.**

ENROLLMENT/PROJECTION REPORT (see Appendix III for sample)

- Generated from data entered on the *Screening/Projection Log*.

- Distributed on a regular basis to sites so all are able to see where they rank in enrollment status relative to other sites.
- Principal Investigator, Steering Committee, and monitors also receive this report.

APPENDIX III

Visit Window Schedule
Sample of Labels
DNA Blood Tube Label
Enrollment Verification Report
Confidential Participant Identification Code Log
Confidential Companion Identification Code Log
Screening/Projection Log
Enrollment Projection Report

SECTION IV

CASE REPORT FORM (CRF) INSTRUCTIONS

General Description of Case Report Forms (CRFs)
CRF Distribution
Submitting CRFs to the CTCC
Timeframe for Submitting CRFs
Overview of Data Processing at the CTCC
Data Clarification Process
General Directions for Completion of CRFs
Directions for Completion of Specific Forms

APPENDIX IV

CRF Order Form
CRF Transmittal Log
CRF Mailing Labels
Staff/Study Related Duties Log
Data Clarifications Worksheet
Missing Forms Report
Medical History/Demographics (sample)
Family Participation Log (sample)
Reportable Event Log (sample)
Participant Site Transfer Form (sample)
Schedule of CRF Completion and Study Activities
Sample Set of Case Report Forms (sample)

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* (see Appendix IV for sample) 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 CTCC 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 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 CRFs 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. Mailing Labels will be provided for the CTCC and Indiana University.

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 any 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 a 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 the 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 ball point pen. Remember that you must press hard when completing the original to make 2 (two) legible copies beneath. Each participant CRF binder contains a cardstock 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

0	0	9	8

Right 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 (REs) , 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 participant Visit 1 will be assigned the number C01. 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 new companion's number would be "C02". 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 "C01" and that will be his number only. If another companion comes for Visit 2, he/she will be assigned another number, i.e. "C02", 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 "C01").

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 the initials and the date will not be misinterpreted as being part of the corrected entry. If participants and companions make a correction, have them date and initial if possible.

All persons entering data on the CRFs must fill out the *Staff/Study Related Duties Log* (see Appendix IV). The 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.

DIRECTIONS FOR COMPLETION OF SPECIFIC FORMS

Medical History/Demographics (see example)

Comorbid Conditions (Question 18-30):

- List only one disorder, disease, or surgery per line and confine comments to a single line.
- Avoid abbreviations.
- Only significant items (as determined by the investigator based upon how recent and how severe the disorder, disease, or surgery) should be listed. If more than 4 significant history entries are required in any given category, the additional items should be listed in the "other": (Question #30) category.

Reportable Event Log (see Section IX for full details)

- The Reportable Event Log is used to notify the CTCC about <u>any</u> Reportable Events that occur during the course of the trial.
- **Do not use "UU" in any dates on the Reportable Events Log. The month, day and year MUST be filled in.**
- Please note that the Investigator's signature is required on the Reportable Events Log.

FAMILY PARTICIPATION LOG

<u>*The Family Participation Log*</u> (see Appendix IV) needs to be completed at each participant visit. List the participant number for any first-degree relative(s) (e.g., brother, sister) who is/are participating in PREDICT-HD at your site. A copy of the <u>*Family Participation Log*</u> should be sent to the CTCC at each visit. Send the original white NCR page to the CTCC at the end of the study.

PARTICIPANT SITE TRANSFER FORM

Please first contact the CTCC Project Coordinator if a transfer is to occur. The current site coordinator must contact the new site coordinator regarding the participant's course in the study. The study binder will be copied by the current site for their records, and the original binder with the original CRFs will be sent to the new study site. A copy of all study

documentation including a copy of the signed consent must be forwarded to the new site. *The Participant Site Transfer Form* (see Appendix IV) must be completed by the new site.

NOTE: The participant must be re-consented at the new site using the new site's consent prior to any visit activities occurring at the new site.

Teleform® Surveys

Please complete per directions on form and make corrections as indicated.

APPENDIX IV

CRF Order Form
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Schedule of CRF Completion and Study Activities
Sample Set of Case Report Forms

SECTION V

PSYCHIATRIC ASSESSMENTS

Symptom Checklist – 90 (SCL – 90)
The Leyton Inventory (LEY)
Frontal Systems Behavior Scale (FrSBe)
Beck Depression Inventory-II (BDI - II)
Beck Hopelessness Scale (BHS)
Substance Use Form (SUF)
Rozin Scale (ROZ)
Perceived Stress Scale (PSS)
UHDRS '99 – Part III

PSYCHIATRIC ASSESSMENTS

Below are the instructions for administering each of the psychiatric tests. A brief description of each test is included along with the procedure for administering the test.

There is also a section to screen high-risk items on the Beck Depression Inventory II, the Beck Hopelessness Scale and UHDRS 99 Part III.

NOTE: Standard administration requires that identical verbiage be used at each site.

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 PREDICT-HD Participant: "*Below is a list of problems people sometimes have. Please read each one carefully and blacken the circle that best describes how much that problem has distressed or bothered you/the PREDICT-HD participant during the past 7 days including today. Blacken the circle for only one number for each problem and do not skip any items. If you change your mind, follow the directions on the form for making corrections. Read the example before beginning, and if you have any questions, please ask them now.*"

The following instructions should be read to the Companion: "*Below is a list of problems people sometimes have. Please read each one carefully and blacken the circle that best describes how much that problem has distressed or bothered the PREDICT-HD participant during the past 7 days including today. Blacken the circle for only one number for each problem and do not skip any items. If you change your mind, follow the directions on the form for making corrections. Read the example before beginning, and if you have any questions, please ask them now.*"

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-HD participant. If you answer, 'Yes' to any of these questions, mark the number (0 - 3) that describes how each habit affects the 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 is designed to provide a measure of three frontal systems-associated behavioral syndromes: apathy, disinhibition, and executive dysfunction.

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 in column 1 they are answering in terms of how often behaviors occur in the participant (not the companion). However, in column 2, the Companion will rate his/her own level of distress (not the participant's).

The FrSBe takes about 10 minutes to complete. The FrSBe will be administered to both the PREDICT-HD participant and their companion individually. The following instructions should be read to the **Participant**: "*Below is a list of phrases used to describe someone. In column 1, rate how frequently each of these behaviors occurred in (you/the PREDICT-HD participant) during the past 2 weeks. In column 2, rate the level of distress that you/the PREDICT-HD participant experienced as a result of each of these behaviors or characteristics.*" The following instructions should be read to the **Companion**: "*Below is a list of phrases used to describe someone. In column 1, rate how frequently each of these behaviors occurred in the PREDICT-HD participant during the past 2 weeks. In column 2, rate the level of distress that you (the companion) experienced as a result of each of these behaviors or characteristics.*"

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: "*This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the one statement in each group that best describes the way you have been feeling during the past two weeks, including today. Blacken the circle beside the statement you have picked. If several statements in the group seem to apply equally well, blacken the highest number. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) and Item 18 (Changes in Appetite).*"

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) or hopelessness (item 2 - pessimism) with a rating of 2 or 3, or a BDI-II 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). Sites must notify the CTCC and complete the Suicide Risk Form.***

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 that indicate hopeless cognitions are: Please refer to **Pearson Assessments** for more information.

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: *"This questionnaire consists of 20 statements. Please read the statements carefully one by one. If the statement describes your attitude for the past week including today, darken the circle with a 'T' indicating TRUE in the column next to the statement. If the statement does not describe your attitude, darken the circle with an 'F' indicating FALSE in the column next to the statement. Please be sure to read each statement carefully."*

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

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). The sites must notify the CTCC and complete the Suicide Risk Form.*

SUBSTANCE USE FORM (SUF)

Description:
The Substance Use Form is designed to quantify substance usage both within the past six months and over the individual's lifetime.

Administration:
The Substance Use Form takes 5 to 10 minutes to complete and will be administered at Visits 1-4. The following instructions should be read to the respondent: "*Below is a list of several kinds of drugs that people use. Use the key for items 1-14 for both the left and right columns. In the left column of boxes, indicate '0' if you have never used the drug. For alcohol, indicate the number of times in your lifetime that you have been intoxicated (drunk). For all other drugs, mark the number of times in your lifetime that you have used the drug. In the right column, using the key, mark the number of times in the past 6 months you have been intoxicated on alcohol or you have used the drugs listed. Put '0' = never used, '1' = 1 – 10 times, and '2' = more than 10 times.*

THE ROZIN SCALE (ROZ)

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

Administration:
This test will be administered for 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 is designed to measure the degree to which a person appraises situations in their personal life 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*: "These questions ask about your feelings and thoughts during the past month. Using the key, you are asked to indicate how often you felt or thought a certain way."*

UHDRS '99 – Part III

Please follow directions on the CRF for the participant and companion. UHDRS '99 Part III will

be completed at Visits 1-4.

NOTE: If question #28a and 28b are scored 3 or 4 this is considered a Reportable Event (Suicide Risk) and must be reported to the CTCC and the *Risk Form* must be completed. The participant should be referred to a mental health professional and evaluated further for suicide potential (see Suicide Risk Assessment Pocket Card).

SECTION VI
COGNITIVE ASSESSMENTS

WASI-Vocabulary Subtest (WASI – Vocab)
WASI-Matrix Reasoning (WASI – Matrix)
Symbol Digit Modalities Test (Symbol Digit)
Stroop Color Word Test (Stroop)
Trail Making Test (Trail Making)
Facial Recognition Test (Faces)
Dual Verbal Working Memory (Numbers)
Smell Identification Test (Smell ID)
Hopkins Verbal Learning Test- Revised
(Immediate and Delayed Recall)
Finger Tapping Task (Tapper)
Tower Task (Tower)
Emotion Recognition Test (Emotions)
WAIS –III Letter-Number Sequencing (Letter-Number)
American National Adult Reading Test (ANART)
Verbal Fluency (Fluency)

For instructions regarding the Cognitive Testing Battery, please refer to the Cognitive Operations Manual.

EXAMINATION GUIDELINES

FOR THE

MODIFIED UNIFIED HUNTINGTON'S DISEASE RATING SCALE '99

June 11, 1999

PRODUCED AND REVISED BY THE HUNTINGTONSTUDY GROUP

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EXAMINATION GUIDELINES FOR 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 ≤ 10° per second, which corresponds to about 2 seconds for moving an object from one shoulder to the other.

#2-3 SACCADE INITIATION AND VELOCITY – Saccade initiation should be tested over a 20° range, as for ocular pursuits. Saccade 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. Saccade 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 learning 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% cconfidence)
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 (≥ 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 ≥ 99% confident (only errs 1 in a 100 such instances) that the subject has HD. Such findings would include the presence of definite chorea or dystonia, usually with accompanying motor slowing.

II COGNITIVE ASSESSMENT

General testing guidelines and instructions for administration and scoring will be found in the **PREDICT-HD Cognitive Operations Manual.**

III. BEHAVIORAL ASSESSMENT (#25-35)

Guidelines for Administration of Behavioral Assessment and scoring are found in **Section V of the PREDICT-HD Operations Manual.**

IV. 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.

V. 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 of 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 great 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.

VI. 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* refer 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)*.

VII. 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.

References:

1. 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.

THE PREDICT-HD STUDY
AMENDMENTS TO FIRST GRANT 2001-2004

PROTOCOL OVERVIEW:

This section provides a brief overview of the protocol changes for the PREDICT-HD study. For more detailed information please refer to the appropriate amendment section.

1.0 STUDY:

The initial 1.0 protocol was taken from the original research plan submitted to NIH as a grant proposal in 1999 and revised for NIH submission in 2000. The first grant was funded for 3 years, 2001-2004.

AMENDMENT 1:

Prior to data collection, the protocol was amended in July 2002. A summary of the modifications are listed below:

1. Inclusion criteria for PREDICT-HD were initially written as exclusion of persons with a total motor score (TMS) greater than 10; More specifically, any potential research participant for PREDICT with a TMS > 10 were excluded from enrollment into the study. At our study start-up meeting, persons from the lay and professional communities of HD protested the ethical conduct of the proposed, NIH-funded, study. Despite having been peer-reviewed, revised, resubmitted, scored, funded, and IRB-reviewed at 20 sites, persons challenged the PREDICT investigators that the study of healthy persons with a future risk for disease would cause harm and was akin to "putting a gun to their heads".

   The start-up meeting was concluded with a promise to cease the study until agreements among interested parties could be reached. NIH, the HSG, and 20 site investigators and coordinators met many times and requested assistance from ethicists and attorneys to assure that the study could proceed in a safe and respectful manner.

   This amendment was developed prior to study start-up. All interested participants would be enrolled, regardless of diagnostic status, to avoid disclosure of diagnostic status being provided to a research volunteer without request for the information. This decision was made after worldwide deliberation of ethical principles for research and the basic premise to "do no harm". Since our sites all involved experienced HD researchers, it was agreed that all persons volunteering who had undergone a predictive test for HD would be enrolled, regardless of diagnostic status, to avoid disclosure of diagnostic status being provided to a research volunteer without request for the information. More specifically, we

became aware that some persons desired study enrollment despite the fact that they had been (or were found to manifest) the movement disorder consistent with diagnosed, manifest HD, and were not presymptomatic according to study guidelines.

Unawareness, or anosognosia, had been documented in diagnosed HD and no previous study had characterized this disease sign through the spectrum of disease from gene-carrier to disability. Since our sites all involved experienced HD researchers, we considered this modification most safe to begin the first study of persons at certain risk of a future fatal disease. Scientifically, we added a companion to the research study for each enrolling participant to obtain an additional report of observed signs and symptoms (in addition to self-report from the gene-expansion carrier).

An Ethics Committee was developed and implemented to review every informed consent and protocol revision of the study to continue to prioritize the balance of risk versus benefit in the research. A Certificate of Confidentiality was obtained from the Federal Government to further protect privacy of participants.

2. Blood samples were to be collected annually and saved for future research if agreed to by the participant.
3. The Yale Brown Obsessive Compulsive Scale was removed and replaced with The Leyton Obsessional Inventory.
4. The University of Pennsylvania Smell Identification Test (UPSIT) was added.

AMENDMENT 2:

1. The main modifications to the protocol were updating the cognitive battery for visit 2.
2. Inclusion/eligibility requirements were expanded to broaden the age range and exclusion criteria for exclusion of mental retardation or severe cognitive impairments were clarified. The most important study amendment was that age was now decreased to recruiting all adults, rather than the beginning enrollment plan which emphasized only the 5 years around the “average age at onset”.
3. Audio-taping of the American National Adult Reading Test (ANART) at year 1 for each participant per site was added to improve measure validity.
4. An addition was made to review reportable events at each visit to document potential adverse events (e.g., depressed mood, suicidal ideation) associated with presymptomatic persons being studied.
5. To better characterize the entire spectrum of disease from gene-carrier through diagnosed manifest HD (according to criteria developed in Venezuela) we recruited all persons who had undergone presymptomatic testing independently of this research study and were self-reported to be “presymptomatic.”
6. Persons could be enrolled without a companion present if the companion agreed to be contacted for data collection at a specified time near the participant’s visit.

AMENDMENT 3:

The following items affecting data/sample collection were modified in Amendment 3

1. MRI scans were updated as appropriate throughout the study to acquire new sequences to maximize brain imaging outcomes. The first amendment added T2/PD and later amendments added DTI and rsfMRI.
2. ANART audio taping was to be done at years 1 and 3 for each participant per site to improve scoring reliability and validity.
3. Dual Verbal Working Memory (Numbers) was discontinued as the difficulty level of the task failed to allow for the level of sensitivity necessary for the longitudinal study.
4. The Schedule of Obsessions, Compulsions and Pathological Impulses (SCOPI) replaced the Leyton Obsessional Inventory. Recent research had indicated a dimensional approach was more desirable than a categorical approach. This was the second modification in our attempts to quantify the perseverative thinking and behaviors that were reported secondary to subtle executive dysfunction.
5. Questions 5 and 16 on the Life Experiences Scale were modified due to review and feedback that indicated questions were poorly understood and not being answered correctly.
6. Visit 3 Cognitive Battery was added.
7. A **telephone contact (TC)** was added at 6-month intervals to facilitate retention. Permission to release contact information to the PI at Iowa was added to provide centralized retention including newsletters, study updates and other retention materials.

1. Updated **Schedule of Activities** provided to all sites.

	Visit 1 month 0	**TC 6mos**	**Visit 2 month 12**	**TC 18 mos**	**Visit 3 month 24**	**TC 30 mos**
Informed consent	x		x		x	
Eligibility criteria	x					
Medical history	x					
General physical exam and Neuro exam	x					
Participant HD History			x		x	
UHDRS '99	x		x		x	
Concomitant Medication Review	x		x		x	
Reportable Event Review	x		x		x	
Participant Entry Number	x					
Blood draw for CAG analysis	x					
Blood draw for biomarkers	x		x		x	
Cognitive tests	x		x		x	
Cognitive[1] & Motor[2] Videotaping	x		x		x	
MRI	x				x	
Psychiatric ratings	x		x		x	
Telephone Contact		☎		☎		☎

Neurobiological Predictors of Huntington's Disease (PREDICT-HD)

PREDICT-HD
4-7 RO1 NS 040068

Thirty-eight sites (n=38) from the **Huntington Study Group (HSG)** will enroll 625 persons at-risk for HD and normal controls to characterize the natural history of the pre-manifest period, to develop tools for clinical trials, and to identify imaging and biofluid markers that will make it possible to test putative neuroprotective therapies that could delay or prevent diagnosis.

Steering Committee

Jane S. Paulsen	Study PI and Chair
Elizabeth Aylward	Brain Imaging
Mark Guttman	Site Investigator
Michael Hayden	Genetics
Elise Kayson	Data and Clinical Trial Coordination Center (CTCC)
Karl Kieburtz	Director, CTCC
Douglas Langbehn	Statistician
Martha Nance	Predictive testing and recruitment
David Oakes	Senior Statistician
Christopher Ross	Motor Ratings
Julie Stout	Neuropsychology
Ira Shoulson	Huntington Study Group Chair

Supported by:
The National Institute of Neurological Disorders and Stroke (NINDS) USA and the HighQ Foundation, Inc.

PREDICT-HD
NIH Grant Request for Renewal 2004-2008

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CLINICAL SITES PARTICIPATING IN THE STUDY – 38 sites in application

Site Name	*Site Investigator*
Baylor College of Medicine, Houston, Texas	J. Jankovic, W. Ondo
Cambridge Centre for Brain Repair, Cambridge, UK	R. Barker
Cardiff University, Cardiff, Wales	A. Rosser
Clinica de la Concepcion, Fundacion Jimenez Diaz, Madrid, Spain	Garcia deYebnes
Clinical Genetics Centre, Aberdeen, Scotland, UK	S. Simpson
Colorado Neurological Institute, Denver, Colorado	R. Kumar and L. Seeberger
Columbia University Medical Center, New York City, New York	P. Mazzoni and K. Marder
Emory University School of Medicine, Atlanta, Georgia	R. Jones
Graylands Hospital, Selby-Lemnos & Special Health Care Services, Perth, Australia	P. Panegyres
Harvard University / Massachusetts General Hospital, Boston, Massachusetts	D. Rosas
Hereditary Neurological Disease Center, Wichita, Kansas	W. Mallonee
Hospital Ram'on y Cajal, Madrid, Spain	J. Garcia De Yebenes
Indiana University School of Medicine, Indianapolis, Indiana	K. Quaid
Johns Hopkins University, Baltimore, Maryland	A. Rosenblatt, C. Ross
Leiden University Medical Center, the Netherlands	R. Roos
Manchester University, Manchester, UK	D. Craufurd
Massachusetts General Hospital, Charlestown, MA	D. Rosas
National Hospital for Neurology and Neurosurgery, London, UK	T. Warner, S. Kloppel, S. Tabrizi
Royal Melbourne Hospital and St. George's Health Service, Melbourne Australia	P. Chua / D. Ames
Ruhr-University of Bochum, Germany	P. Kraus
University of Alberta, Edmonton, Alberta, Canada	W. Martin
University British Columbia, Vancouver, British Columbia, Canada	L. Raymond
University of Calgary, Calgary, Alberta, Canada	O. Suchowersky, S. Furtado
University of California Davis, Davis California	V. Wheelock
University of California Los Angeles Medical Center, Los Angeles, California	S. Perlman
University of California San Francisco, San Francisco, California	M. Geschwind
University of Iowa, Iowa City, Iowa	H. Paulson
University of Kansas	R. Dubinsky
University Medical Center, Nijmegen, The Netherlands	H. PH Kremer
University of Melbourne, Normandy House, VIC Australia	E. Chiu,
University of Michigan	R. Albin
University of Minnesota; Hennepin County Medical Center, Minneapolis, Minnesota	M. Nance
University of Rochester, Rochester, New York	P. Como
University of Toronto/Centre for Addiction & Mental Health, Markham, Ontario, Canada	M. Guttman
University of ULM, Ulm, Germany	B. Landwehrmeyer, S. Trautman
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Washington University, St. Louis, Missouri	J. Perlmutter
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ABSTRACT

Although treatments in animal models for HD have proven successful, and several clinical trials are underway in persons with manifest HD, there currently exists no methodology in which to test experimental therapeutics prior to diagnosis of manifest motor disease. The Predict-HD study is designed to provide essential methodology for the initiation of preventive clinical trials in Huntington's disease (HD). Early identification of neurological disease is imperative so that intervention using protective, gene therapy, and regenerative strategies can be initiated at high levels of life quality and prior to the occurrence of irreversible cellular injury. The Predict-HD study has successfully recruited nearly 500 healthy participants who had previously undergone genetic testing for the HD expansion. Annual measures of brain imaging and cognitive performance are obtained in concert with other demographic, clinical and genetic information. Findings already suggest a remarkable convergence of the first detectable decline in brain morphology, motor skill, and cognitive ability at about 15 years priorto traditional motor diagnosis. This is notably earlier than had generally been suspected and representsa major advance in our understanding of HD. With completion of the requested 3-year continuation of the Predict-HD study we will have longitudinal observations that allow us to 1) test and refine the model of early HD changes suggested by our baseline data; 2) determine which measures of functional decline are concurrent with measurable brain morphology changes; and 3) better understand the relationships among striatal and cortical changes, DNA repeat length, and clinical phenotype in HD. Completion of PREDICT-HD will result in a methodology and a cohort that can be readily applied to presymptomatic treatments as they become available. In addition to the contribution this will make towards early intervention in HD, our findings are likely to improve our understanding of the functional pathophysiology of other neurodegenerative and genetic illnesses.

STUDY OBJECTIVES

SPECIFIC AIMS

Huntington's disease (HD) is an autosomal-dominant, neurodegenerative disorder of the basal ganglia and associated circuitry that produces an insidious decline in motor, cognitive, and psychiatric functioning, resulting in a diminished quality of life and premature death. HD is typically diagnosed with the onset of motor symptoms, although individuals at risk for the disorder may present with cognitive and/or psychiatric symptoms as much as a decade prior to diagnosis. At present, there are no FDA-approved treatments that slow or prevent disease progression, although several agents have proven effective in animal models of HD[9 16] and are in various stages of clinical trials.[10 13 17] Ideally, preventive treatments would be initiated at or before the earliest signs of disease, but there currently exist no measures by which to assess the efficacy of an intervention in persons with the HD mutation prior to onset of manifest motor dysfunction.

Predict-HD is a prospective, longitudinal study of participants who have undergone predictive testing for HD but are currently healthy. The study obtains volumetric MRIs, neurocognitive assessments, psychiatric rating scales, diagnostic evaluations, and demographic information to better characterize the transition from health to disease.

The primary aim of this study is to establish measures that can predict diagnosis with enough precision that the efficacy of experimental therapeutics initiated prior to traditional diagnosis can be adequately evaluated.

Hypotheses to be tested include:

1. Prediction of disease onset (defined by motor diagnosis} will be improved (i.e., beyond that achieved withCAG repeat length and age alone) using measures of brain morphology and cognitive performance; and

2. Refined markers of presymptomatic disease progression will be characterized using standardized measuresof *imaging,* cognitive performances, motor ratings and psychiatric symptoms.

BACKGROUND

Although the gene mutation responsible for HD is present at birth, HD is typically an adult-onset disorder diagnosed with the manifestation of an unequivocal movement disorder. It is well-established that other indicators of HD are often present in individuals at-risk for HD as much as a decade prior to diagnosis. For example, at least two studies suggest that minor motor signs are evident a few years prior to diagnosis,[2] [24] numerous studies have shown cognitive impairments in pre-HD (the period of time prior to diagnosis in persons at-risk with the gene mutation).[6] [25,] [29] and psychiatric disturbances are prevalent prior to diagnosis.[8] [30] [31] A total of seven studies have evaluated volumetric MRI in pre-HD[32] [36] with the most recent reports suggesting that striatal volume loss is evident nine to eleven years prior to estimated onset.[37] Recent fMRI studies collected in concert with the Predict-HD study suggested that basal ganglia hypoactivation coupled with task-specific alterations of anterior cingulate activation were apparent in presymptomatic HD participants before MRI volume loss or cognitive impairment were evident.[38] [39]

Although there is no current intervention to delay the onset or slow the progression of HD, a number of agents have already shown some therapeutic benefit in HD mouse models.9-15 40.41 In addition, several compounds are currently being tried in HD patients with manifest illness, including Co-enzyme Q10, minocycline, creatine, riluzole, remacemide, ethyl-EPA, amantadine and paroxetine. Growth factors and surgical transplant of fetal cells are also being examined for their utility in replacing cells lost to HD. Most recently Davidson and colleagues at the University of Iowa demonstrated for the first time that gene therapy delivered to the brains of living mice can prevent the physical symptoms and neurological damage caused by triplet repeat disorders.

Although the first treatments for early HD are likely to involve a combination of protective compounds, future treatments are likely to involve gene therapy and neurosurgery. There is little doubt that these more invasive treatments will demand careful consideration of the optimal time to initiate intervention Completion of Aim 2 will help optimize the best time for therapeutic intervention to maximize functional capacity and avoid side effects of treatments.

Current efforts to treat HD are being conducted in individuals with manifest illness. However, advances in genetics and technology are beginning to facilitate an obviously desirable shift from treatment following diagnosis to prevention of disease.

Preliminary results from our research have already made it apparent that detectable decline in neurobiological function begins considerably earlier than the point at which such deficits lead to obvious clinical signs and symptoms. At present, all clinical trials of experimental therapeutics are initiated at or after a movement disorder specialist gives this diagnosis and the potential restraint of further decline is therefore limited.

Earlier intervention might result in a dramatically delayed onset and preservation of much higher functional levels (shown in the blue versus red slopes). Findings from the ongoing Predict-HD research project will help us develop and implement measures of prediction and progression in this preclinical stage of HD progression. This, in turn, will allow us to substantially improve clinical trial design by being able to stratify presymptomatic, gene-expanded individuals by their risk of progressing to the point of traditional diagnosis during the course of the trial. It may also allow the development of more sensitive clinical trials using outcome markers that both precede and are causally related to substantial functional decline. Since HD is one of the few adult-onset disorders for which indicators of disease are detectable long before disability occurs, it represents an important opportunity for the medical community to pioneer approaches to delay onset, or diagnosis.

Based upon these estimates, a 5-year clinical trial would require a sample size of approximately 2,500 to 3000 gene-tested participants to detect a 20% delay in onset with alpha= .05and power= 80%. (This is the proposed effect in clinical trials currently being contemplated in diagnosed patients.) Given that it is estimated that less than 10% of the at-risk population is tested in North America, these numbers exceed the possible sample and make a clinical trial infeasible.

Predict-HD should significantly increase efficiency (in terms of sample size and cost) of all future clinical trials in this cohort. For instance, completion of the Predict-HD study will increase the feasibility of successful HD preclinical trials in two ways:

(1) Traditional trial: A traditional trial continues to use delay of motor symptom onset (i.e., diagnosis) as the outcome. Our baseline data suggest that cognitive performance and basal ganglia volume (in addition to subtle motor abnormalities) are very strong indicators of time to motor diagnosis. As such, they would substantially reduce the sample sizes needed for such trials. The basic principle is this: The more accurately the specific date of diagnosis for each untreated participant can be estimated, the easier it is to detect a deviation from that estimate due to a treatment. We have strong reason now to believe that some of our measures will contribute very markedly to these individualized prognostic estimates. Even further decreases in sample size could be achieved if this prognostic information were used to limit trial participation only to those at highest risk of motor diagnosis during the trial.

(2) As a proxy for disease onset: If one has scientific justification to assume that slowing the deterioration of a marker is an acceptable proxy for slowing disease development, then the markers themselves become candidate outcome measures for clinical trials. If feasible, this would be a tremendous advantage.

Since our baseline data suggest that functional decline typically begins 10-20 years before motor diagnosis (See Progress Report and Figures 5 and 6, p. 282 and 284), it seems highly

desirable, in theory, to implement preventive treatments at or before this period. A traditional trial using motor diagnosis as the outcome could take at least 10-20 years to complete. In contrast, our preliminary baseline data suggest that treatment modifications to the rate of marker change would be detectable over 4-8 years using realistic sample sizes, even far from the point of motor diagnosis. Furthermore, it seems probable that the average rate of decline for most of these candidate markers accelerates somewhat after the first few years of decline (See Figure 6, p. 284). Detection of treatment effects on marker decline in this slightly later period could be achieved with dramatically smaller sample sizes. We cannot confirm these projections or design such trials, though, without the longitudinal data that completion of Predict-HD will give us.

The above-described advantages rely on careful quantification of the relationships between the proposed markers and motor diagnosis. The only way this can be done is via longitudinal observation of people known to be at risk for HD because they carry the GAG-expansion mutation.

Predict-HD is a prospective, longitudinal study of imaging and cognitive measures designed to predict motor diagnosis in 500 persons who have undergone testing forthe HD mutation. Predict-HD is being conducted at 24 sites throughout the United States, Canada and Australia. Award notice for NS 40068 was granted on September1, 2001. Despite budgetary reductions at the request of the reviewers, we suffered additional administrative budget cuts (i.e., deletion of year 4) so that the award was less than 50% of the amount initially estimated for the project.
The first 6 months were used to hire personnel, develop case report forms, develop informed consent and other IRB materials, establish a database, develop brochures and slide presentations for recruitment, build computer stations for the cognitive assessment, program the cognitive tasks and develop a software platform to make cognitive assessment, scoring and data management as automatic as necessary, finalize site selection, purchase supplies, and train the motor and cognitive raters toadequate consistency. A Predict-HD orientation meeting was scheduled for May 2002, after which study initiation was scheduled to begin immediately.

At that meeting, certain "ethical issues" that had not been addressed by any of the numerous IRB's that had previously approved the grant were raised. Specifically, concerns were raised about the possibility that an individual might, in the course of participating in the study, learn that they already had manifest HD. Several additional meetings were scheduled in response to the concerns raised and issueswere discussed thoroughly. As a result of the input the following responses occurred: (1) The protocol was changed to accommodate the concerns. A private foundation agreed to cover the expenses of allowing all interested parties to participate in the research, whether or not the investigator felt they had manifest HD. This protocol change was initiated to address lay members' concerns that volunteers could inadvertently be told they have manifest HD as a consequence ofvolunteering to be in the study. (2) An R01 grant was submitted to the National Human Genome Research Institute to investigate the ethical,

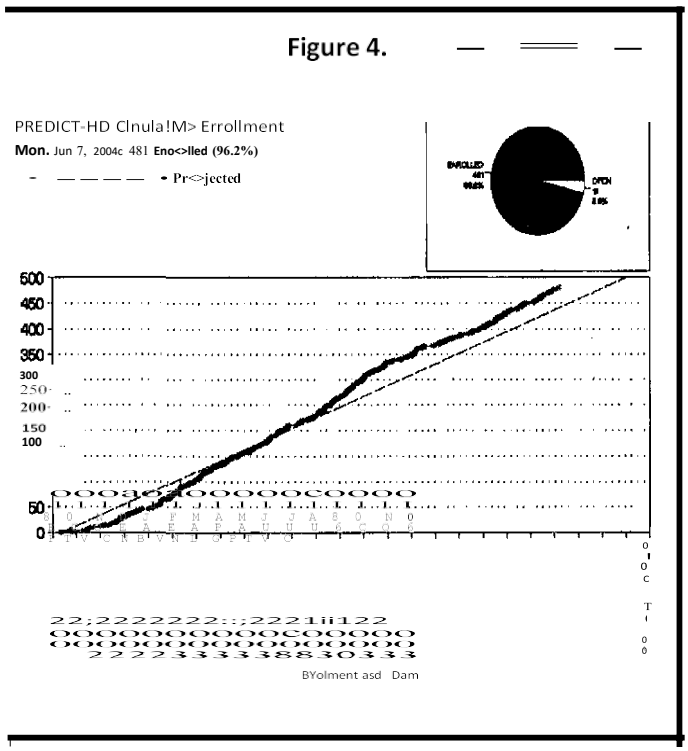
legal, and social implications of living at-risk for HD. The emphasis of the submitted grant is to evaluate possible genetic discrimination that might occur in this cohort who are healthy but living at 100% risk for a fatal disease. (3) No feedback about research data collected is to be shared with the volunteers. Each participant is encouraged toschedule a separate meeting with a health care professional to address concerns regarding early disease symptoms. (4) An Event Monitoring Committee was established to provide overview for all study events (See Appendix 3A). When all concerns were sufficiently addressed, we redeveloped the case report forms and the informed consent materials and had all new information reviewed again by the Institutional Review Boards at 24 separate sites. Approval for the study was awarded at various times, depending upon each site. A second orientation meeting was held November 1, 2002, after which study enrollment began. Progress has continued steadily since then. Weekly Predict Team meetings are conducted via teleconference between the primary centers of operation (Iowa for administration, Rochester for data management and HSG coordination, Indiana for cognitive assessment, and Seattle for MRI). Monthly teleconferences are held for Steering, Event Monitoring, and Recruitment Committee meetings (Please see letters of support for consultants, p. 330-344). Two new committees were established over thepast year: an Executive Committee to address grant renewal and a Publications Committee to develop guidelines for the dissemination of findings).

At the time of this writing, the data management center had processed over twelve thousand case report forms that involved the processing of 1,603,961 data points. Of the 12,118 case report forms received, 81% were received in a timely manner (within 2 weeks), 88% were error free and on average there were 0.11 errors per form accordingto the Site Performance Statistics. To date there have been 4,027 data queries, 3,185queries have been reconciled and 842 are still outstanding and need resolution per the Database Statistics Report. The excellent timeliness and quality of the data is particularly impressive, given the size and complexity of the Predict-HD project.

Of those participants enrolled in the study to date, nine percent required a waiver on eligibility criteria to enroll. The largest proportion of these waivers was predictive DNA test results not in our range of inclusion (viz., 40 or greater).Subsequent to this finding, an amendment was made to allow CAG repeat lengths of 39 in the study. Analyses of our separate international collaborative database linking CAG lengths to age of onset[54] indicated that this should have minimal impact on the outcome of the study. The second most prevalent waiver for protocol deviation was the absence of a companion at the visit (11%). With this discovery, an additional amendment was created to allow capture of companion consent and data via mail. Other waivers granted for study entry included participants with metallic implants that would not impact brain MRI, lack of parental history of HD, and participants having a history ofspecial education (waivers were only granted when a member of the cognitive team suggested enrollment after a careful review of the educational history).

Recruitment of the study sample was the primary emphasis in the first two years of the project. Although all study sites were HD specialty clinics, healthy at-risk participants do not typically attend movement disorder clinics. Given the unique characteristics of the target sample and the need to ensure measures to protect confidentiality of genetic information, novel recruitment strategies were implemented,and new efforts were made to protect privacy of participants and research materials. Weekly Enrollment and Projections reports were compiled and forwarded to all Recruitment and Team Committee members to address the individual progress and needs of each Predict site. Recruitment activities included the following: (a) Contacts from the local HD community were identified in every US state, Canadian province,and Australian region (See letters of support from lay organizations, p. 350-353); (b)brochures were developed, over 3,000 of which have been distributed (c) 38 informational talks were given in person by the PI, the chair of the recruitment committee, and site investigators (See Appendix 2C for recruitment talk schedules);
(d) over 24 media events (i.e., radio, television, newspapers) were used to inform the public (See Appendix 2D for media schedule); (e) slide show materials were developed for specific professional organizations and their membership (i.e., genetic counselors, neurologists, family practitioners; see Appendix 2E); (f) lay organizations were contacted for attendance permission at local and national events; (g) surveys were distributed to solicit opinions from potential recruits about study design and implementation; (h) additional funds were awarded by the High Q Foundation for travel;
(i) solicitations were mailed to over 100,000 persons on mailing lists related to HD (see example of brochure mailed from HDSA in Appendix 2F); U) brochures were distributed at 62 different HD community events; (k) personalized charts were produced for each site to enable them to track recruitment efforts and results (See Appendix 2G for example of individualized recruitment chart); (I) individualized alterations were made in the recruitment protocol to best meet the specific needs of each site (i.e., additional raters were trained or computer systems were purchased when these factors limited recruitment); (m) postings were put on Web sites and senton LISTSERVES. Recruitment far surpassed expectations.

Four-hundred and ninety-six participants have enrolled to date in the Predict-HD study. As shown in Figure 4, rates of enrollment have been steady and relativelyrapid compared to other studies of persons at genetic risk. At many sites, volunteers were coming in faster than staff personnel could manage them



A data cut was made on March 15, 2004 to allow data analyses in preparation for this competing renewal. Data have been analyzed for the first 412 participants. The sample sizes reported throughout the progress report
vary somewhat due to the times required to process each type of data. A summary of the data processed for this proposalis shown in Table 3 below:

Table 3. Predict-HD March 15, 2004 data cut.

Total number in database 3-15-04	*Number of demographic CRFs*	*Number of psychiatric CRFs*	*Number of cognitive protocols*	*Number of DNA analyzed*	*Number of MRI scans processed*
412 (367+, 45-)	367+, 45-	359+, 45-	365+, 42-	288+, 24-	214+,21-

+ denotes participants with CAG expansion – represents participants with two normal alleles

Age of research participants ranges from 26 to 76 with a mean age of 42 (SD=9.9). Over 97 % of the sample is white (1.5% Latino, 2% multiracial), 91% are right-handed, and 62% are female. Sixty-nine percent are currently married although 29% have been divorced or widowed. Ninety-two percent completed at least a high school education. Fifty-six percent of participants obtained some college or associate degree and an additional 21% obtained Masters degrees or higher. A majority (78%) of the participants were currently employed in professional (37%), managerial (28%), crafts (5%), service (6%), or laborer (2%) roles. In order to eventually obtain a sample that included a comparison cohort of participants without the expansion, sites were asked to enroll one participant with a CAG repeat length in the normal range (e.g., less than 30) for every 7 participants enrolled with a CAG repeat length in the HD range (i.e., greater than or equal to 39). Forty-five of the first 412 participants whose data have been

analyzed had no CAG expansions in the HD gene whereas the CAG expansions in the remaining sample ranged from 39 to 62, with an average of 42. Ten percent of participants reported having symptoms that concerned them as possibly related to HD and several were taking compounds believed to possibly slow disease development. Table 4 compares the diagnostic confidence ratings based upon the motor exam for participants with and without the gene expansion. Briefly, 9 participants (2%) were diagnosed with definite HD, and their data have been excluded from further analysis. Nineteen participants (5% of gene- expanded individuals) were rated as "probable HD" whereas 16% (n=58) were considered to have "possible HD". (For these ratings, "possible" and "probable" refer to the confidence with which the motor evaluator would consider a declaration that the stage of clinical diagnosis has been reached.) The majority of all participants were rated as having soft motor signs (n=159, 45%) or no motor signs (n=117, 33%). Of participants without gene expansion, 62% were considered to have no signs whereas 31% were found to have minor motor abnormalities {"soft signs"). Seven percent of participants without gene expansion were diagnosed with possible HD and none were considered to have probable or definite HD.

Cognitive Assessment

The baseline Predict-HD cognitive assessment consists of ten paper-and-pencil neuropsychology tests and ten touch-screen computerized tasks. All tasks were chosen for their probable sensitivity to presymptomatic HD by: 1)targeting specifically those cognitive functions associated with basal ganglia-frontal brain circuits and using tests that have shown effects in presymptomatic HD; and 2) using testing techniques that augment data sensitivity because they are reliable and they sample data continuously at high levels of accuracy and precision (i.e computerized assessment of reaction times). Thus, the battery is based on neurobiological, cognitive science, and statistical considerations that provide us with the maximum benefit. Table 6 is a brief summary of the cognitive domains targeted in the assessment, and details are provided in the Cognitive Assessment Manual which is included in the Appendix 4A. Descriptive statistics for the cognitive variables are shown by diagnostic level

Table 6. Cognitive Assessment: Domains Targeted and Tests Used
Working Memory: WAIS-Ill Letter-Number Sequencinq Subtest; Dual Verbal Workinq Memory Task
Timing and Movement Sequencing: Tone and Self-Paced Tapping Task; Sequential Button Pressing Task
Motor and Psychomotor Speed: Trail Making Test-A; Symbol Digit Modalities; Speeded Finger Tapping, Simple and Choice Reaction Time
Learning and Memory: Serial Reaction Time Task; Hopkins Verbal Learning Test - Revised
Executive Functions: Contextual Shift Task; Trail Makinq Test-B; Tower Task; Controlled Oral Word Association; Stroop Test
Face and Emotion Recognition: Benton Facial Recognition Test; Emotion Recognition - Static (identification of Ekman &Friesen facial expressions); Emotion Recognition - Dynamic
Other: American National Adult Reading Test (estimate of intellectual ability); The Smell Identification Test

For the purposes of this application, we analyzed all available baseline cognitive data (365

CAG-expanded and 42 comparison participants) to establish whether the Predict cognitive assessment appeared to be yielding potential markers of prediagnostic variability in our CAG-expanded sample. More specifically, our goals were to establish whether the baseline cognitive data related to: 1) variability in our estimates of expected time to onset based on CAG repeat length and age;[54] and, 2) variations in striatal volumes measured from MRI. An additional question weaddressed in these baseline analyses was whether the baseline cognitive assessment data were sufficiently uncorrelated with the striatal volumes.to be able to improve the prediction of onset over and above what could be predicted with striatal volumes alone.

For the majority of computerized cognitive tasks we used a multivariate outcome regression (MAVOVA) strategy. (The exception was the two Emotion Recognition Tasks, which required a logistic regression approach due to the response distributions). In correspondence to the two goals above, we developed two models that were then tested with the data from each computerized cognitive test. For the first model (goal 1) the predictor variable of primary interest was probability of onset in 5 years based upon CAG repeat length and current age. Additional predictor variables were included to control for potential confounds (age, education, gender, estimated IQ from the ANART score) and to simultaneously consider additional variables associated with HD prognosis (presence/absence of any CAG expansion and parent age at onset). Within this multivariate model, we examined the individual effects of eachof these variables, and we also tested the combined effects of: 1) the prognostic variables, by calculating the joint significance of gene expansion presence, probability of onset in 5 years, and parent's age of onset; and 2) general intellectual capacity, by examining the joint effect of education (years) and estimated baseline IQ. The model for goal 2 was similar to the first model except that the prognosis variables were replaced with separate estimates of caudate and putamen volume effects on cognitive function. For this second model, we included estimates of the joint effects of striatal volumes by testing the combined effects of these two variables. For these analyses, effect sizes were computed as Cohen's F,[55] For the paper/pencil cognitive tasks, because each task only yields a small number of variables, we used a simultaneous multiple regression analysis strategy. The strategy for examining the independent variables was implemented by constructing two models, one focused on estimated time to onset, and the other including the striatal volumes, in the same fashion (and with the same additional predictor variables) as the two **MAN**OVA models described for the computerized tasks. For these analyses, effect sizes were computed as standardized B.[55] (See Table 7 below and Appendix 4B).

Results of these analyses indicated many significant associations between cognitive data and prognostic indices (model 1 analyses). We summarize the significant findings from these analyses as effect sizes **(SM, MED, LG** indicate small, medium and large effect sizes, corresponding to at least 1%, 9%, and 25% of adjusted variance accounted for by the domain of interest respectively) by cognitive domain and provide the full results of these

Table 7. Baseline Cognitive Data: Effect Sizes for Associations with Probability of Onset in Five Years
Timing and Movement Sequencing: variability in paced alternating thumb tapping without tone **LG,** variability in paced alternating thumb tapping with tone pacing **MED;** sequential button pressing, advance location cuing condition, initiation andmovement rates and variability, **all SM**
Motor and Psychomotor Speed: Trail Making Test, part **A MED;** Symbol Digit Modalities Test **LG;** speeded tapping non-dom.hand **LG;** speeded tapping dom. hand **MED;** simple reaction time rate and variability **SM;** 2-choice response movement rate andvariability **SM**
Learning and Memory: Serial Reaction Time Task response rate variability after interference **MED;** Hopkins Verbal Learning Test (HVLT)- Revised total learning and delayed recall, both **MED;** HVLT recognition discriminability **MED;** Serial Reaction Timeresponse rate after interference **SM**
Executive Functions: Verbal Fluency **MED;** Stroop Test Interference **MED;** Trail Making Test, part B **SM;** Tower Task-3 disk version **SM**
Working Memory: Dual verbal working memory **SM**
Face and Emotion Recognition: Benton Facial Recognition **SM;** Emotion Recognition Static for Anger, Fear, Sadness **SM;**Emotion Recoqnition Dynamic for Anger, Disgust, Fear **SM**
Other: Smell Identification Test (olfaction) **MED**

MANOVAs and multiple regressions in the Appendices 4C and 4D.[55]

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The results summarized in this table, along with the full results described in Appendices 4C and 4D, indicate that 17 of the 20 tests in our cognitive assessment battery show significant associations with our estimates of time to onset. Therefore, the data show that, with respect to goal 1 above, the baseline cognitive data appear to be sensitive to HD-related variability in our prediagnosed sample.

Cognitive data from several tests were also significantly associated with striatal volumes. We summarize the significant findings from these analyses as effect sizes by cognitive domain and provide the full results of theseMANOVAs and multiple regressions in Appendices 4E and 4F.

Table 8. Baseline Cognitive Data: Effect Sizes for Associations with Striatal Volumes
Timing and Movement Sequencing: variability in paced alternating thumb tapping without tone **SM** (caudate), variability inpaced alternating thumb tapping with *tone* pacing **SM** (caudate)
Motor and Psychomotor Speed: Trail Making Test, part A **MED** (caudate); simple reaction time rate **SM** (putamen); 2-choice response movement rate **SM** (outamen)
Learning and Memory: Serial Reaction Time Task response rate variability after interference **SM** (caudate); Hopkins Verbal Learning Test (HVLT)- Revised total learning and delayed recall, both **MED** (caudate);
Executive Functions: Tower Task-3 disk version **SM** (caudate)
Working Memory: WAIS-Ill Letter-Number Sequencing Subtest **MED** (caudate)
Face and Emotion Recognition: Benton Facial Recognition **SM** (caudate); Emotion Recognition Static for Disgust **SM** (putamen); Emotion Recognition Dynamic for Anger, **MED** (caudate)

Other: none

The results summarized in this table, along with the full results from Model 2 analyses displayed in Appendices 4E and 4F, indicate that 12 of the 20 tests in our cognitive battery show significant associations with striatal volumes. Thus, with respect to the second goal above, there is a large set of cognitive variables that are associated with striatal volumes. At the same time, additional analyses (not shown) indicate that the cognitive measures show association with estimated probability of onset even after controlling for striatal volume, demonstrating that cognitive measurements are not redundant with MRI data withrespect to HD prognosis.

In summary, we have already obtained strong evidence that the variability in performance of our cognitive assessment battery is related to estimated time to HD onset. Further, despite a controversy in the preclinical literature about the existence of cognitive decline prior to HD diagnosis, our data provide definitive evidence that carefully focused cognitive assessment can reliably yield data that are significantly associated with other HD onset predictors (GAG-based prognosis and striatal volume). Our findings to date suggest we are garnering solid evidence that the Predict-HD cognitive assessment will prove effective for predicting outcomes. The addition of longitudinal cognitive data will be critical for the refinement of specific cognitive ability measures as clinical markers of prediagnostic progression and HD onset. The effectiveness of the cognitive battery is likely due to: a) the design of the battery, which specifically targets cognitive functions related to basal ganglia-frontal brain circuits, b) our psychometric approach, which relies heavily on computerized testing and reaction times, and, c) the degree to which we have been successful in standardizing the equipment, materials, and examiner testing techniques for the Predict-HD cognitive assessment.

MRI

Of the 364 participants for whom we had received enrollment forms at the time of the March 15 data cut, we had obtained scans for 358. There are 2 participants for whom MRI have been unobtainable due to claustrophobia, 2 for whom data were corrupted or lost at the sites, and 53 that have not yet been received in our lab. For the remaining 301 scans, all have been processed and the quality has been assured. We have measurements for 224 of these scans, and have 77 more that are ready to be measured. Of these, the mean volume for caudate is 8.63cc (s.d. = 1.57) and the mean volume for putamen is 8.16cc (s.d. = 1.73), Measurement of scans is moving along at a reasonable pace. We anticipate processing all incoming scans in a timely fashion.

The graph below (Figure 5) shows that MRI-based volumes of the basal ganglia are significantly associated with estimated years to onset based on age and CAG in the Predict-HD sample. This analysis extends previous findings[56] and suggests that the relationship between these two measures is clearly nonlinear. This model raises the question of whether those more than14 years or so from onset can be shown to have any detectable

difference from non-GAG-expanded control participants. These findings reinforce the idea that intervention in the far-from-onset group might be different from interventions in the close-to-onset group. Clearly, it also reinforces the idea that assessment of interventions will need to be different in the two groups. Since Figure 5 is a cross-sectional analysis with years-to-onset estimates based on CAG repeat lengths and current age, longitudinal analysesof the Predict- HD cohort will be critical to verify the rate at which striatal volume diminishes in the pre-clinical period prior to manifest motor disease.

This analysis is based on 214 GAG-expanded predict participants with both a CAG length report and striatal volume available. This is a nonlinear least squares regression fit based on a 4 d.f. restricted cubic spline of years to expected onset. The significance of the model is $p < .0001$. The statistical significance of the nonlinear element of the model is $p = .005$. The adjusted percent of variance explained in this model is .267. Age and gender are additional significant predictors of striatal volume. However, after adjusting for these two variables, the residual variance attributable to the Years to Expected Onset is essentially unchanged and the shape of the non-linear curve, including the marked change in slope at 14-15years, is not substantially affected.

Cortical surface analyses were conducted on a subset of Predict-HD participants. Findings suggest that Predict-HD participants showed significantly altered cerebral cortex morphology with enlargement of gyral surface area, thickened gyral cortex, yet thinner than normal sulcal cortex. These changes manifest in global alterations in gyral and sulcal shape with broadened gyral crowns and flattened sulcal fundi in the Predict-HD participants. Enlargement of brain tissue or more specifically, cerebral cortical gray matter, is a phenomenon common to several neurodevelopmental brain disorders. Findings from this study indicate that there may be abnormal development in the pathophys[i]ology of HD and that clearly, the neuropathology is widespread in the cerebrum rather than exclusively affecting the striatum. The above studies are an important step forward in expanding our knowledge of the neurobiology of HD. However, several key questions remain unanswered. First, the trajectory of these structural changes over time will be vital information to help determine the etiology of these abnormalities. For instance, is cortical enlargement present years before onset or is cortical volume normal until close to onset when it begins degeneration and "swells"? These two scenarios would lead to two different patterns of change in structure over time. The ongoing study in a prospective, longitudinal design is vital to the progress in understanding the neurobiology of this devastating disease. The grant continuation will allow one more year of MRI acquisition and will facilitate cortical surface analyses of some Predict-HD scans.

MRI reliability: Although most components of image acquisition and processing have gone very smoothly, we have been challenged with changes in institutional MRI hardware and software. We therefore undertook an investigation of possible effects of such changes at the beginning of the study to assess the reliability of imaging variables across sites. In addition to scanning persons across different scanners we also compared test-retest

reliability differences in volumetric outcomes for the basal ganglia. We found minimal variation with 1-2 percent variation in caudate and 1-3 variation in putamen. The reliability of this process actually appears to be around .95-99, which suggests that the additional slight impact of different scanner models may actually be undetectable.) Our best estimate, made with high precision (see estimation intervals) was that the use of various scanner models would reduce the reliability of basal ganglia estimates by less than 1%. Combining multiple overlapping reliability analyses, we concluded that the measurements were close enough on these three scanners to justify using any of them; as long as the same scanner is used for all longitudinal scans on the same participant. We are aware that scanner changes are likely to further challenge the longitudinal data analyses collected in the Predict-HD study. We will continue to conduct small studies of inter-subject and inter-scanner reliability to document variance when possible. For instance, if a site changes scanners mid-stream in the study, we will require that 5 participants undergo the Predict-HD protocol on both scanners. Data will be analyzed by the study biostatistician and any substantial effects will be taken into account in all longitudinal analyses.

Consistency of relationships to the estimated time until HD diagnosis.

Cross-Sectional Analyses of the Relationships Between Various Predict-HD Measures and the Expected Years to Onset Based On CAG Repeat Length and Age illustrates the relationships between a number of the potential markers being used in Predict-HD and the expected years to onset based on Langbehn et al.[54] These markers, along with numerous others, all converge to suggest that detectable biological and functional changes typically begin in HD gene carriers between 10 and 20 years prior to clinical diagnosis of the disease.

Dissemination of findings. Seventeen abstracts have been published and 17 Predict-HD presentations have been made at national and international professional meetings. Importantly, findings have been presented across disciplines at meetings for neurology, psychiatry, neuropsychology and neurosciences.

Summary of Progress Report. We have implemented a study of biological and behavioral markers of disease in persons who have a dominant gene but are currently considered healthy. We have established 24 sites with materials and testing supplies, trained personnel for motor, psychiatric and cognitive ratings, established a MRI protocol, and standardized operations manuals (See Appendix 6B). We have successfully recruited and enrolled over 490 participants who have undergone genetic testing for the HD expansion. We have conducted analyses of the motor, psychiatric, and cognitive evaluations, DNA and MRI scans on 412 participants. We have completed at least one annual examination on over 200 of these participants. We have created a database of over 1.6 million data points, with double data entry errors less than 0.05% and specific data queries less than 1%. We have submitted one additional RO1 to examine ethical, legal, and social issues in the presymptomatic period of HD. We have received two National Research Service Awards (NRSA) from NIH to support graduate students who are devoting their research

training to the Predict project. We have completed two studies to address inter- scan variability using MRI volumes. We have made 17 presentations and prepared 7 papers for publication.

STUDY DESIGN

Overview: The three-year longitudinal study continuation will use volumetric MRI and comprehensive cognitive assessment to characterize the preclinical syndrome in HD, to document the rate of change of these variables during the years leading up to diagnosis of HD, and to investigate the relationships among the neurobiologic factors, clinical onset, and CAG repeat length. The primary outcome of the proposed work is the identification of MRI and neuropsychological measures which, in concert with the CAG repeat length, can predict age of motor diagnosis and characterize rate of disease development in pre-clinical HD.

Procedure: A total sample of 600 participants will be followed for longitudinal study at up to 27 research sites in the US, Canada, Europe, and Australia. Two groups will be followed: healthy individuals with known CAG repeat length

	Original grant			Renewal grant		
N	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
Baseline	270	500	600			
Follow-up 1		256	475	570		
Follow-up 2			244	451	544	
Follow-up 3				232	428	518
Follow-up 4					220	407
Follow-up 5						210

39 (n=525) (GAG-expanded), and an age-commensurate comparison group previously considered at risk (by virtue of having a parent or sibling with HD) who do not have CAG expansion (CAG 30; n=75 GAG-normal). Given the dates of participant recruitment and assuming a5% annual attrition (censoring) rate,[72 73] about 518 GAG-expanded participants are expected to complete 3 years of follow-up examinations, 407 will complete 4 years of exams, and 210 will complete 5 years of follow-up.

Timeline. All participants are examined at baseline and every 12 months thereafter. The Unified Huntington's Disease Rating Scale (UHDRS),[74] an abbreviated cognitive and psychiatric evaluation, and criteria for disease onset (motor diagnosis) are assessed at each visit. The MRI neuroimaging protocol and a comprehensive cognitive evaluation are performed every two years (year one, year 3) and will be continued in year 5. Our rationale for the number and timing of assessments was based on consideration of a balance between frequent evaluations (to enable capture of the conversion from wellness to manifest motor disease) and longer follow-up (to maximize changes in variables of interest). In addition, we wanted to schedule visits with enough frequency to maintain study retention but not so frequent as to be perceived as too time-consuming to potential participants or to result in excessive familiarity with neuropsychological tests.

CHARACTERISTICS, SELECTION AND ENROLLMENT OF PARTICIPANTS

Participants. The following eligibility criteria are considered for study inclusion. A CAG repeat size of at least 39 was chosen based upon available data demonstrating that some individuals with repeat lengths between 35 and 39 may have incomplete penetrance over a normal human lifespan.[53 54]

Inclusion Criteria:

Completed predictive testing with CAG 39 (expanded group) or CAG 30 (normal group); Men and women aged 18 and older.

Commitment of an informant to enhance retention.

Exclusion Criteria:

Clinical evidence of unstable medical or psychiatric illness; History of serious alcohol or drug abuse within the previous year; History of learning disability and/or mental retardation;History of other CNS disease or event (e.g., seizures, head trauma).

Current or previous treatment with antipsychotic medications, including the traditional neuroleptics as well astheny atypical antipsychotics.

Treatment with phenothiazine-derivative antiemetic medications such as prochlorperazine, metoclopramide, promethazine and Inapsine on a regular basis (greater than 3 times per month).

Pacemaker or metallic implants.

Methods and Measures.

Disease Onset Definition. While HD is a disease comprised of a triad of clinical symptoms (motor, cognitive, and behavioral), its diagnosis has historically relied upon the emergence of motor signs, especially chorea. Thus, the determination of disease onset for the proposed study will adhere with traditional neurology standards and the practice of the Huntington Study Group (HSG). An experienced movement disorder specialist at each site determines the diagnosis of HD. Training on the standardized motor exam is completed with each site investigator once per year. A training videotape is also used to obtain and maintain reliability in-between training meetings. A recent reliability study demonstrated very good agreement on the unequivocal diagnosis of HD.75 A primary outcome variable will be "HD diagnosis" as defined by reaching a rating of "4" on the HD Diagnostic Rating Scale in Table 12 shown below.

Table 12.

HD Diagnostic Rating Scale: To what degree are you confident that this person meets the operational definition of the unequivocal presence of an otherwise-unexplained extrapyramidal movement disorder (e.g., chorea, dystonia, bradykinesia, rigidity) in a person at risk for HD?
0 = normal
1 = nonspecific motor abnormalities (<50% confidence)
2 = motor abnormalities that may be signs of HD - possible HD (50-89% confidence)
3 = motor abnormalities that are likely signs of HD - probable HD (90-98% confidence)
4 = motor abnormalities that are unequivocal signs of HD - definite HD (<: 99% confidence)

The Unified Huntington's Disease Rating Scale. The UHDRS[76] is a standardized clinical rating scale that assesses four components of HD: motor function, cognition, behavior and functional abilities. The instrument has been used at more than 50 participating HSG sites since July 1994, and data have been collected prospectively on more than 8,000 patients who have HD. The reliability and internal consistency of the four components of the UHDRS have been evaluated and published.[76] Although the entire UHDRS (See Appendix 6C) will be completed at each study visit, the variables used in the primary statistical analyses include a) the standardized neurology exam with the HDDiagnostic Rating Scale (the outcome variable for survival analysis and determination of onset involves a rating of "4, definite HD"), b) cognitive assessment of verbal fluency,[77] psychomotor speed[78] and disinhibition[79]as potential predictor variables of HD diagnosis; and c) behavioral assessments of neuropsychiatric symptoms (i.e., depression) that may impact cognitive performance and/or prove predictive of disease features or onset in and of themselves.

DNA Methodology. HD CAG genotyping will be done as described by Warner et al.[80] Briefly, HD-specific oligonucleotide primers, flanking the HD CAG repeat, are used to specifically amplify the HD CAG repeat from template DNA samples in a polymerase chain reaction (PCR). The resultant radiolabeled, HD-specific PCR products are displayed on a DNA sequencing gel format and exposed to X-ray film. The size of the HD CAG repeat PCR product, apparent on the autoradiogram, is determined relative to that of known, sequenced, HD GAG-repeat product 'standards'. The HSG conducted a study of interlaboratory variability of CAG length in HD and demonstrated that reliability of CAG reports was very high (r=.97 for expanded alleles and r=.99 for normal alleles).[81] Dr. MacDonald and her colleagues have more than 10 years of experience with HD and more than a dozen years' experience with other human genetic studies.

Predicted Mean Time Until Manifest HD Onset. Predicted time until onset was calculated using a formula reported by Langbehn et al. on the basis of 2,298 affected and 615 presymptomatic gene-expanded HD cases registered at 40 different care centers throughout the world (primarily North America and Europe, see Appendix 1A).[5] The analyzed sample was limited to those with CAG lengths between 41 and 56. Those with lower repeat lengths were excluded because of evidence that the registered participants represented an atypical sample of the whole population with those lengths. We excluded those with

lengths> 56 due to their rarity. Convergent, evidence-based, population genetic models of anticipation in trinucleotide repeat mutations[82] suggested that those participants analyzed were a reasonably representative sample of the entire population in that CAG range.

Backup Participant Sites. Ten sites are interested in participating in Predict-HD. Two to four sites will be chosen as primary sites and the remainder will be back up sites.

Site Name	MPA#	Site Investigator	Cognitive Rater	Coordinator
Cambridge Centre for Brain Repair, Cambridge, UK	**N/A**	R. Barker	K. Shiels	R. Barker
Clinica de la Concepcion, Fundacion Jimenez Diaz, Madrid, Spain	**N/A**	J. Garcia de Yebenes	M. Fatas	A. Martinez-Descals
Leiden University Medical Center, Leiden, Netherlands	**N/A**	R. Roos	M. Witjes-Ane	R. Roos
National Hospital for Neurology and Neurosurgery, London, UK	**NIA**	S. Tabrizi	S. Henley	S. Tabrizi
Ruhr-University of Bochum, Bochum, Germany	**N/A**	P. Kraus	M. Finger	J. Andrich
School of Medicine, University of Aberdeen, Aberdeen, Scotland	**N/A**	S. Simpson	F. Summers	S. Simpson
St. Mary's Hospital, Manchester UK	**N/A**	D. Craufurd	J. Snowden	E. Howard
University Medical Center, Nijmegen, Netherlands	**N/A**	H. Kremer	Unknown	Unknown
University of Ulm, Ulm, Germany	**N/A**	B. Landwehrmeyer	C. Sorg	D. Ecker
University of Wales College of Medicine, Cardiff, Wales	**N/A**	A. Rosser	J. Naji	J. Naji
Hospital Henri Mondor, Creteil Cedex, France	**N/A**	A. Bachoud-Levi	Unknown	Unknown

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PREDICT-HD

Neurobiological PREDICTors of Huntington's Disease 2004-2008

OPERATIONS MANUAL

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Leigh Beglinger
Kevin Biglan
Noelle Carlozzi
Cathy Covert
Kevin Duff
Mark Guttman
Michael Hayden
Elaine Julian-Baros
Elise Kayson
Bernhard Landwehrmeyer
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Martha Nance
David Oakes
Connie Orme
Jane Paulsen
Christopher Ross
Lynda Sherman
Julie Stout
Stacie Vik

May 6, 2004

SECTION I

GENERAL INFORMATION

Study Contacts
Office Closings
Study Personnel

APPENDIX I

New Staff Form
Address List

STUDY CONTACTS

If you have questions regarding the protocol, regulatory issues, payment,or data management please refer to the following list:

Reason to Call	Whom to Call
Protocol questions, Day-to-day studyoperations, Reportable Events (RE), Notifications, Medical concerns and questions regarding regulatory documents	**Project Coordinator Assistant** **Kay Meyers** Phone: 585-275-3507 Email: kay.meyers@ctcc.rochester.edu **Project Coordinator** **Elaine Julian-Baros** Phone: 585-273-2879 Email: elaine.julianbaros@ctcc.rochester.edu **Project Coordinator** **Elise Kayson** Phone: 585-275-4696 Email: elise.kayson@ctcc.rochester.edu
CRF questions, Data queries	**Information Analyst** **Cathy Covert** Phone: 585-275-7161 Email: cathy.covert@ctcc.rochester.edu
Enrollment calls: **Please announce that you are calling for a PREDICT-HD Enrollment.**	**Enrollment Staff** Phone: 585-275-7311 (8:30am–4:30pm ET or by special arrangement)
Subcontract, Payment issues	**Christine Anderson** Phone: 319-353-5829 Email: christine-m-anderson@uiowa.edu **Brenda McAreavy** Phone: 319-353-4236 Email: brenda-mcareavy@uiowa.edu
Recruitment and Retention	**Stacie Vik** Phone: 319-353-3716 Email: Stacie-vik@uiowa.edu **Christine Anderson** Phone: 319-353-5829 Email: christine-m-anderson@uiowa.edu

If you have detailed questions regarding Psychological or Cognitive Testing or MRI Protocol, please contact:

Cognitive data questions, Computer test issues	**Noelle Carlozzi** Phone: 812-855-0318 Email: ncarlozzi@indiana.edu
Psychiatric testing questions	**Kevin Duff** Phone: 319-335-6640 Kevin-duff@uiowa.edu **Jane Paulsen** Phone: 319-353-4551 Email: jane-paulsen@uiowa.edu
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OFFICE CLOSINGS FOR 2008 - 2009

The chart below indicates the days and times the Clinical Trials Coordination Center (CTCC), Indiana University (IU) and University of Iowa (UI) will be closed for 2008-2009. **Please note these dates are subject to change and will be updated yearly.**

Date	CTCC	Indiana Univ.	Univ. Iowa
Tuesday, January 1, 2008	X	X	X
Monday, January 21, 2008		X	X
Friday, March 14, 2008	X		
Monday, May 26, 2008	X	X	X
Friday, July 4, 2008	X	X	X
Monday, September 1, 2008	X	X	X
Wednesday, November 26, 2008	Closed at Noon		
Thursday, November 27, 2008	X	X	X
Friday, November 28, 2008	X	X	X
Wednesday, December 24, 2008	Closed at Noon		
Thursday, December 25, 2008	X	X	X
Friday, December 26, 2008			X
Wednesday, December 31, 2008	Closed at Noon		
Thursday, January 1, 2009	X	X	X

STUDY PERSONNEL

All study personnel (e.g., Investigator, Motor Rater, Coordinator, Cognitive Tester) in the study will require a staff code, assigned by the CTCC. The Project Coordinator must be notified in advance of a site's intention to change study personnel, and this request must be approved by the PREDICT-HD Steering Committee. If the change is approved, new staff should complete the *New Staff Form* (preceding the Address List) and fax it to the CTCC (fax number and instructions are provided on the form). In addition, the HSG Credentials Committee must approve any Investigators who are new to the HSG or have changed sites. **Please note the importance of study personnel consistency.**

ADDRESS LIST

A study address list follows the *New Staff Form*. Please notify the Project Coordinator at 585-275-4696 if there are any changes in address, email, fax, telephone numbers, or staffing. The address list will be updated as needed to reflect new information and will be distributed by email.

APPENDIX I

New Staff Form
Address List

CLINICAL TRIALS COORDINATION CENTER
NEW OR CHANGE STAFF FORM

Incoming Staff Member:

Last name:_____First Name: _____

Academic Credentials: MD_____PHD_____RN_____Other_____

Address: *Information will be used for mailing labels, study address lists, and entered in our database*

Institution Name: _____Site #_____

Street: _____

_____

City: _____State:_____Zip:_____

Phone:_____Fax: _____

Email address: _____

Shipping Address (Fed-EX, UPS, Etc) If Different Than Mailing_____

Start Date:_____Role:_____Invest____Coord_____Data Entry___Other_____

Studies: 1) _____ 2) _____ 3) _____

4) _____ 5) _____ 6) _____

If you are replacing a current staff member, complete the section below. Include each study. If you are not replacing anyone, skip this section.

Outgoing Staff Member:_____Staff Code: _____

Leaving Department/ Institution:_____Yes_____No_____End Date: _____ Role_____

Studies: 1) _____ 2) _____ 3) _____

4) _____ 5) _____ 6) _____

** If the outgoing staff member is currently listed as your site's referral contact person on the HSG website listing (www.huntington-study-group.org) please provide the following information for your new contact person:

1) Name
2) Phone #
3) E-mail address (optional)

**** IF LEAVING DEPARTMENT/INSTITUTION:**

Most journals are now requiring written authorization of individuals listed as authors or acknowledged on manuscripts. If you want your name to appear in any future articles regarding studies in which you have participated, please provide your forwarding information

Address:_____

E-mail:_____

Phone: _____

PREDICT-HD Cross Reference Index (155 constituents comprising 178 roles)

Name	Staff No	Site/Group
ABHIJIT AGARWAL MBBS MPH	2425	Recruitment Committee (RC) *MEMBER*
ABHIJIT AGARWAL MBBS MPH	2425	Johns Hopkins University (028) *COORDINATOR*
JAVIER ALEGRE MD	2647	Hospital Ramón y Cajal (176) *MOTOR RATER*
DAVID AMES MD	2992	St. George's Health Service (144) *INVEST/MOTOR RATER*
CHRIS ANDERSON	3093	Consultants (CON) *CONSULTANT*
THOMASIN ANDREWS MD BSC MRCP	2651	National Hospital for Neurology and Neurosurgery (177) *MOTOR RATER*
ELIZABETH AYLWARD	1002	Steering Committee (SC) *MEMBER*
ROGER A BARKER BA MBBS MRCP	2653	Cambridge Centre for Brain Repair (178) *INVEST/MOTOR RATER*
KATRIN BARTH	2860	University of Ulm (175) *COORDINATOR/NEUROPSYCH*
KATRIN BARTH	2860	Recruitment Committee (RC) *MEMBER*
STACEY BARTON MSW LCSW	2975	Washington University (027) *COORDINATOR/NEUROPSYCH*
MONICA BASCUNANA GARDE	2801	Hospital Ramón y Cajal (176) *COORDINATOR/NEUROPSYCH*
KATHLEEN BAYNES PHD	1178	University of California Davis (061) *NEUROPSYCH*
LEIGH BEGLINGER PHD	2524	Consultants (CON) *MRI CONSULTANT*
LEIGH BEGLINGER PHD	2524	University of Iowa (024) *MOTOR RATER*
BERNADETTE BIBB PHD	2058	Westmead Hospital (054) *NEUROPSYCH*
KEVIN BIGLAN MD	1389	Steering Committee (SC) *MEMBER*
JONATHAN BISSON	2833	Cardiff University (179) *SUPPORT STAFF*
ROBI BLUMENSTEIN	2559	Steering Committee (SC) *MEMBER*
KEITH BOURGEOIS	0171	Biostatistics (BIO) *BIOSTATISTICS*
JASON BRANDT PHD	0634	Consultants (CON) *CONSULTANT*
MAGGIE BURROWS RN BA	2779	National Hospital for Neurology and Neurosurgery (177) *COORDINATOR/NEUROPSYCH*
NOELLE E CARLOZZI PHD	2904	Consultants (CON) *CONSULTANT*
DAVID CAUGHLIN BS	3986	Consultants (CON) *CONSULTANT*
AMY CHESIRE	1330	Recruitment Committee (RC) *MEMBER*
AMY CHESIRE	1330	University of Rochester (001) *COORDINATOR*
EDMOND CHIU MD	2050	St George's Health Service (144) *INVEST/MOTOR RATER*
PHYLLIS CHUA MD	2051	Royal Melbourne Hospital (159) *INVEST/MOTOR RATER*
PETER COMO PHD	0278	University of Rochester (001) *INVESTIGATOR/NEUROPSYCH*
MICHAEL CONNEALLY PHD	0670	Consultants (CON) *CONSULTANT*
CARMELA CONNOR BP MP DP	2145	Graylands, Selby-Lemnos & Special Care Health Services (156) *ADMIN INVESTIGATOR*
WILLIAM CORYELL MD	2595	Ethics Committee (EC) *MEMBER*
CATHERINE COVERT	1985	Clinical Trials Coordination Center (999) *CTCC-DATA MANAGEMENT*
DAVID CRAUFURD MD	2661	University of Manchester (181) *INVESTIGATOR*
RACHELLE DAR SANTOS BSC	4084	University of British Columbia (048) *NEUROPSYCH*
JOJI DECOLONGON MSC	1294	University of British Columbia (048) *COORDINATOR/NEUROPSYCH*
PHILLIP DINGJAN BA	2074	Royal Melbourne Hospital (159) *NEUROPSYCH*
PHILLIP DINGJAN BA	2074	St. George's Health Service (144) *NEUROPSYCH*
NICHOLAS DOUCETTE BA	3008	University of Iowa (024) *NEUROPSYCH*
RICHARD M DUBINSKY MD	0470	University of Kansas Medical Center (029) *INVEST/MOTOR RATER*
ANN DUDLER	2943	Consultants (CON) *CONSULTANT*

KEVIN DUFF PHD	2525	University of Iowa (024) *NEUROPSYCH*
DAVID EIDELBERG MD	1075	Consultants (CON) *CONSULTANT*
MACKENZIE ELBERT BS	3101	University of Iowa (024) *COORDINATOR/NEUROPSYCH*
DIANE ERICKSON RN	4079	Colorado Neurological Institute (052) *COORDINATOR*
CHERYL ERWIN JD PHD	2596	Ethics Committee (EC) *MEMBER*
MARTA FATAS	2645	Hospital Ramón y Cajal (176) *NEUROPSYCH*
SARAH FURTADO MD PHD FRCPC	1620	University of Calgary (030) *CO-INVEST/MOTOR RATER*
JUSTO GARCIA DE YEBENES MD	2646	Hospital Ramón y Cajal (176) *INVEST/MOTOR RATER*
NELLIE GEORGIOU-KARISTIANIS	2052	St. George's Health Service (144) *NEUROPSYCH*
MICHAEL D GESCHWIND MD PHD	1659	University of California San Francisco (073) *INVEST/MOTOR RATER*
CHRISTINE GIAMBATTISTA BSW	2539	The Centre for Addiction and Mental Health (039) *COORDINATOR/NEUROPSYCH*
ANITA GOH RN	3165	St. George's Health Service (144) *NEUROPSYCH*
CAROLYN GRAY RN CCRC	0471	University of Kansas Medical Center (029) *COORDINATOR/NEUROPSYCH*
JANE GRIFFITH RN	2055	Recruitment Committee (RC) *MEMBER*
JANE GRIFFITH RN	2055	Westmead Hospital (054) *COORDINATOR*
MARK GUTTMAN MD	0480	Steering Committee (SC) *MEMBER*
MARK GUTTMAN MD	0480	The Centre for Addiction and Mental Health (039) *INVEST/RATER/NEUROPSYCH*
MIRA GUZIJAN MA	2520	University of California San Francisco (073) *COORDINATOR/NEUROPSYCH*
MIRA GUZIJAN MA	2520	Recruitment Committee (RC) *MEMBER*
JACKIE HAMILTON MSC	2660	Clinical Genetics Centre Aberdeen (180) *NEUROPSYCH*
OLIVIA JANE HANDLEY PHD BS	2658	Cardiff University (179) *NEUROPSYCH*
JOAN M HARRISON RN	0414	Emory University School of Medicine (032) *COORDINATOR*
MICHAEL HAYDEN MD PHD	0637	Steering Committee (SC) *MEMBER*
ELIZABETH HOWARD MD	2663	University of Manchester (181) *MOTOR RATER*
CHRISTINE HUNTER RN CCRC	0439	Baylor College of Medicine (007) *COORDINATOR/NEUROPSYCH*
JOSEPH JANKOVIC MD	0122	Baylor College of Medicine (007) *INVEST/MOTOR RATER*
ARIK JOHNSON MD	2434	UCLA Medical Center (050) *COORDINATOR/NEUROPSYCH*
HANS JOHNSON PHD	3119	Consultants (CON) *CONSULTANT*
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ANDREW JUHL BS	2955	Consultants (CON) *MRI CONSULTANT*
ELAINE JULIAN-BAROS CCRC	1492	Clinical Trials Coordination Center (999) *CTCC-PROJ COORDINATOR*
ELAINE JULIAN-BAROS CCRC	1492	Recruitment Committee (RC) *MEMBER*
ELISE KAYSON MS RNC	0749	Steering Committee (SC) *MEMBER*
ELISE KAYSON MS RNC	0749	Ethics Committee (EC) *MEMBER*
ELISE KAYSON MS RNC	0749	Recruitment Committee (RC) *MEMBER*
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ANGELA KOMITI	2267	Royal Melbourne Hospital (159) *COORDINATOR/NEUROPSYCH*
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CHRISTEL LEMMON PSYCH	2994	St. George's Health Service (144) *NEUROPSYCH*
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NICHOLE MURACO	2819	Clinical Trials Coordination Center (999) *CTCC-MEETING PLANNING*
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MARTHA NANCE MD	0818	Steering Committee (SC) *MEMBER*
MARTHA NANCE MD	0818	Hennepin County Medical Center (071) *INVEST/RATER/NEUROPSYCH*
DAVID OAKES PHD	0279	Steering Committee (SC) *MEMBER*
DAVID OAKES PHD	0279	Biostatistics (BIO) *BIOSTATISTICS*
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JANE PAULSEN PHD	0462	Ethics Committee (EC) *MEMBER*
JANE PAULSEN PHD	0462	Recruitment Committee (RC) *MEMBER*
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JULIE STOUT PHD	1159	Recruitment Committee (RC) *MEMBER*
JULIE STOUT PHD	1159	Ethics Committee (EC) *MEMBER*
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TERRY TEMPKIN RNC MSN	0933	University of California Davis (061) *COORDINATOR*
CLAUDIA TESTA MD PHD	1515	Emory University School of Medicine (032) *MOTOR RATER*
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ERGUN UC MD	1340	University of Iowa (024) *MOTOR RATER*
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TOM WARNER MD PHD	2649	National Hospital for Neurology and Neurosurgery (177) *INVEST/MOTOR RATER*
PAULA WASSERMAN MA	1690	Columbia University Medical Center (002) *COORDINATOR*
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JOE WEBER BS	2277	Clinical Trials Coordination Center (999) *CTCC-DATA MANAGEMENT*
CHRISTINE WERLING	2781	Consultants (CON) *CONSULTANT*
MELISSA WESSON MS	1129	Indiana University School of Medicine (045) *COORDINATOR/NEUROPSYCH*
MARGARET WETZEL BS	2618	University of California San Francisco (073) *NEUROPSYCH*
VICKI L WHEELOCK MD	0593	University of California Davis (061) *INVEST/MOTOR RATER*
MONICA WILLIAMS BA	2198	St. George's Health Service (144) *SUPPORT STAFF*

JENNIFER WILLIAMSON MS	1656	Columbia University Medical Center (002) *SUPPORT STAFF*
DANIEL WILLINGHAM PHD	1324	Consultants (CON) *CONSULTANT*
MARY WODARSKI BA	2114	University of Rochester (001) *NEUROPSYCH*
JOANNE WOJCIESZEK MD	0334	Indiana University School of Medicine (045) *MOTOR RATER*
MARK WOODMAN B SC	2700	Graylands, Selby-Lemnos & Special Care Health Services (156) *COORDINATOR/NEUROPSYCH*
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SECTION II

PROTOCOL ACTIVITIES

Schedule of Activities Video and Audio Taping Activities
Protocol (insert)
Synopsis (insert)
Amendments (insert)

APPENDIX II

PREDICT-HD Schedule of Activities PREDICT-HD Schedule of CRF Completionand Study Activities

PROTOCOL ACTIVITIES

SCHEDULE OF ACTIVITIES

Visit 1 (Screening/Baseline)

The first study visit (Visit 1) will determine whether the participant meets the necessary criteria for participation in the study. If the participant isat risk for HD, is 18 years old or older, has completed presymptomatic HD testing (and has tested either positive or negative), has never been diagnosed with definite HD, and meets all the necessary criteria, they may enter PREDICT-HD. If all study criteria are met during Visit 1 the participant will continue on for the psychiatric, cognitive and MRI assessments. The length of the cognitive examination will be about 2 hours, the length of the psychiatric interview will be about 1 hour, and the brain scan will take about one hour. In addition, a movement disorder specialist will conduct a standardized exam, Unified Huntington's Disease Rating Scale (UHDRS) where the participant will be asked to walk heel-to-toe, tap your fingers, stick out their tongue and perform other tasks involving motor (movement) control. To ensure consistency in rating among investigators one participant per year will be asked during each visit to be videotaped for the cognitive portion. Each participant each year will be asked to be videotaped for the motor assessment portions of the study. These tapes will not be made public, and the participant's name will not be disclosed to anyone.

During the Baseline Visit (Visit 1), the suggested order of the requiredactivities is as follows:

- Obtain consent
- Medical history/demographics
- Concomitant medication review
- Inclusion/Exclusion criteria review

If the participant meets all inclusion/exclusion criteria and is eligible to continue with Screening/Baseline, the suggested order of activities is as follows:

- Confidential Participant Log
- Confidential Companion Participation Log
- Call CTCC for Participant Identification Number
- CTCC Unique ID
- Blood sample consent
- Obtain DNA sample
- Obtain Blood and Urine Samples for Biomarker
- Cognitive assessment (see Cognitive Operations Manual forsequence of tests)

- Videotape Cognitive Exam (selected participant)
- UHDRS '99 Part I by Neurologist
- Videotape Motor Exam
- ANART Audio tape
- UHDRS '99 (IV, V, VI, VII, VIII)
- Psychiatric Assessment (see Section V of this manual forsequence of tests)
- Family Participation Log
- MRI
- Screening/Baseline confirmation
- Reportable Event Review –discuss with participant events thatshould be reported
- Subsequent Visit Information Form
- Confidential Visit Evaluation
- Telephone Contact Form (6 months after visit)
- Biannual Retention Activity Record

NOTE: It is important that the Cognitive Assessment be completed earlyin the day so that participants will be as alert as possible. Waiting untilthe end of the day will likely affect the quality of the data by introducing factors such as fatigue, hunger, etc.

Given that each site will have different personnel and location arrangements for the activities listed above, there is some flexibility to the order of activities. If more than 1 month passes before a participantcan be scheduled for the assessments, then all aspects (i.e., consent, medication list, motor exam) must be repeated.

Other Assessments and Visits

Please follow *PREDICT-HD Schedule of Activities* and *PREDICT-HD Schedule of CRF Completion and Study Activities* for a complete listing ofassessments.

Visit 2, 4 and 6

Complete the following activities:

- Concomitant Medication Review
- Reportable Event Review
- Family Participation Log Review
- Participant HD History
- Companion Participation Log
- Obtain Biomarker Samples
- Cognitive Assessments (see Cognitive Operations Manual)
- Cognitive video tape (selected participant)

- UHDRS ‘99 Part I Motor Assessment (Neurologist)
- Motor video tape
- UHDRS ‘99 Parts IV, V, VI, VII, VIII
- Psychiatric Evaluations
- Subsequent Visit Information Form
- Confidential Visit Evaluation
- Telephone Contact Form (6 months after visit)
- Biannual Retention Activity Record

Visit 3, 5 and 7

Complete the activities listed below:

- Concomitant Medication Review
- Reportable Event Review
- Family Participation Log Review
- Companion Participation Log
- Obtain Annual Blood Sample
- Cognitive Assessments (see Cognitive Operations Manual)
- Cognitive video tape (selected participant)
- UHDRS ‘99 Part I Motor Assessment (Neurologist)
- Motor video tape
- UHDRS ‘99 Parts IV, V, VI, VII, VIII
- Psychiatric Evaluations
- MRI **(visit 3 and 5 only)**
- ANART Audiotape
- Subsequent Visit Information Form
- Confidential Visit Evaluation
- Telephone Contact Form (6 months after visit)
- Participant HD History
- Biannual Retention Activity Record

Premature Withdrawal

- Prior to a participant prematurely withdrawing, the site must notify via email Elaine Julian-Baros at the CTCC and Stacie Vik atthe University of Iowa for guidance.
- If a participant prematurely withdraws, complete all activities forVisit 7 if possible.
- Participant disposition and Reportable Event Log **must** reflect thewithdrawal.
- This is considered a Reportable Event. The CTCC **must** be notifiedvia telephone or email and the event must be noted on the Reportable Event log.

VIDEO AND AUDIO TAPING ACTIVITIES

Cognitive Exam Videotaping
Please refer to the Cognitive Operations Manual Section Overview ofAssessment Guidelines for complete instructions.
(Please note that all European cognitive recordings must be received inDVD or CD format)

ANART Audio Taping
Please send the audiotapes along with the participant data form (YellowNCR page) to Indiana University. Please send the White original NCR page to the CTCC.

Please refer to the Cognitive Operations Manual Section Overview ofAssessment Guidelines for complete instruction.

Motor Exam Videotaping
To ensure high inter-rater reliability among the study sites, consistent administration and scoring of the Motor Assessment is essential.
Specific instructions are provided to facilitate inter-site consistency. In addition, each examiner must complete a training video and test prior toseeing any participants.

Who is required to rate the participant and how often?
Each Motor Rater is required to videotape each Predict HD participantevery year. The purpose of recording the Motor Assessment with a participant is to ensure standardized administration across sites, and tomake it possible to characterize the reliability of the motor data across sites and across time. Every examiner must be videotaped. If the examiner changes, the new motor examiner must be videotaped as well during the year with a participant.

Video camera preparation
Make sure to check the video camera prior to starting the session. In particular, be sure that the sound is clearly audible and comprehensible with the arrangement planned for the participant and examiner. Positionthe camera so that both the examiner and participant are in view.
Remember to move the camera as the assessment shifts if necessary.Recording the entire Motor Assessment may require more than one videotape; be sure to change videotapes as needed.

If possible, record videos in NTSC (National Television System Committee) format, the analog television system used in the US, and Canada. If NTSC format is not available, please include the format on thelabel (i.e. PAL, PAL60).

Multiple participants can be recorded on the same tape.

Each **tape or segment** must begin by identifying the participant with thefollowing information: 1) Site Number, 2) Participant Number, 3) Visit Number and 4) Date of Visit.

Helpful Hints:

- Some sites show the top of the completed CRF, some use a white board, others print an identifying form, and some simply write theinformation on a small piece of paper that the participant holds before the camera.

- Review tapes before sending to insure video quality. Make sure that the participant is clearly visible throughout the entire exam.

- Rewind tapes before sending.

- If sending videos on CDs or DVDs, please send as a data file in MPEG format. Separate participants into individual files if possible.

- Each **tape or disk** must be clearly labeled with the followinginformation in the order the participants appear on the tape:
  Site Number Participant Number(s)Visit Number(s)
  Date of Visit(s)

Motor Videos should be sent in protective packaging.

Where should I send the motor video and CRFs?
Please send the motor videotapes along with the participant data form (Yellow NCR page) to the University of Iowa to Ann Dudler, The University of Iowa, Department of Psychiatry, 1-309A MEB, Iowa City, IA 52242.

Please send the White original NCR page to the CTCC.

PREDICT-HD MOTOR VIDEOTAPING PROCEDURE

Participant is seated at start of taping.

View	Time (secs)	Details
WHOLE BODY	10	Sitting with feet on the floor, resting palms on arms of chair.
OCCULAR PURSUIT, SACCADE INITIATION, SACCADE VELOCITY,	10	"Please look at my nose. Now, without moving your head, use your eyes to indicate which of my two hands I am moving" (complete15 taps, be sure to randomize sequence so you don't just go from left to right in a pattern).
DYSARTHRIA	20	The participant sits at ease without speaking for 10 seconds. "Please repeat these phrases after me". "No Ifs, Ands, or Buts" "LaLaLaLaLaLaLa" "Kitty, Kitty, Kitty, Kitty"
TONGUE PROTRUSION	5	"Open your mouth and stick out your tongue, for 5 seconds."
FINGER TAPS	10	"Please tap your index finger and thumb together as fast as you can with your right hand. Now try theleft hand."
PRONATE/SUPINATE HANDS	10	"Please do as I do." (Place one palm up and one palm down on your legs or table, rotate them 180 degrees or flip them in sequence). Now you keep going and I will stop.
LURIA	20	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).

RIGIDITY - ARMS	10	Rigidity is judged on passive movement of the arms with thesubject relaxed in the sittingposition.
BRADYKINESIA - BODY	5	Observe the subject during spontaneous motion such as walking, sitting down, arising from a chair, and executing the tasks required during the examination.
MAXIMAL DYSTONIAAND CHOREA	5	Maximal dystonia and chorea are typically observed during demanding motor tasks such as tandem gait. Facial dystonia includes blepharospasm, jaw opening and closing.
GAIT	20	"Now I want you to walk up and down the hall to the spot and back." (Walk 10 feet and back)
TANDEM WALKING	20	"Please walk in a line with your feet touching heel-to-toe, like walking on a tightrope." (Count 10 steps)
RETROPULSION PULL TEST - Standing, unaidedif possible. The internal malleoli are 5 cm apart. Arms are down at the subject's side	30	"Stand up straight without leaningforward with your eyes open and feet slightly apart, I am going to pull on your shoulders. You can take a step backwards to avoid falling back if you need to."
MINI MENTAL SCREEN	60	"Please spell the word 'world'. Please spell the word 'world' backwards." (Allow two tries) "Now start at 100 and count backwards by 7s." (discontinue after the first 5 answers)

APPENDIX II

PREDICT-HD Schedule of Activities PREDICT-HD Schedule of CRF Completionand Study Activities

PREDICT-HD SCHEDULE OF ACTIVITIES

	Visit 1 month 0	TC 6mos	Visit 2 month 12	TC 18 mos	Visit 3 month 24	TC 30 mos	Visit 4 month 36	TC 42 mos	Visit 5 month 48	TC 54 mos	Visit 6 month 60	TC 66 mos	Visit 7 month 72
Informed consent	x		x		x		x		x		x		x
Eligibility criteria	x												
Medical history	x												
General physical exam and Neuro exam	x												
Participant HD History			x		x		x		x		x		x
UHDRS '99	x		x		x		x		x		x		x
Concomitant Medication Review	x		x		x		x		x		x		x
Reportable Event Review	x		x		x		x		x		x		x
Participant Entry Number	x												
Unique ID number[4]	x		x		x		x		x		x		x
Blood draw for CAG analysis	x												
Markers of DNA and RNA Damage	x		x		x		x		x		x		x
Blood for CAG Genotyping[3]	x		x		x		x		x		x		x
Specimen Repository	x		x		x		x		x		x		x
Cognitive tests	x		x		x		x		x		x		x
Cognitive[1] & Motor[2] Videotaping	x		x		x		x		x		x		x
MRI	x				x				x				
Psychiatric ratings	x		x		x		x		x		x		x
Telephone Contact													

[1] Cognitive videotaping on a selected participant per year

[2] Motor videotaping on each participant per year

[3] To be collected at the first follow-up visit **only** post amendment 5 approval

[4] To be issued at the first follow-up visit post amendment 5 approval

DRAFT

PREDICT-HD
SCHEDULE OF CRF COMPLETION AND STUDY ACTIVITIES

FORM/ACTIVITY	LEVEL #	SCREENING/BASELINE	MAINTENANCE VISITS											
		MONTH 0	MONTH 6	MONTH 12	MONTH 18	MONTH 24	MONTH 30	MONTH 36	MONTH 42	MONTH 48	MONTH 54	MONTH 60	MONTH 66	MONTH 72
		VISIT 1	T1	VISIT 2	T2	VISIT 3	T3	VISIT 4	T4	VISIT 5	T5	VISIT 6	T6	VISIT 7
Obtain Informed Consent		X												
Participant Identification Code Log		X												
Companion Identification Code Log		X		X		X		X		X		X		X
Study Staff/Study Related Duties Log		X		X		X		X		X		X		X
Inclusion/Exclusion (INEXB)	76	X												
Demographics (EU-Demo)[5]	03	X												
Medical History/Demographics (DEMO)	04	X												
Participant HD History (HDHX)	78			X		X		X		X		X		X
Concomitant Medication Log (CMED)	06	X		X		X		X		X		X		X
UHDRS'99 (I) (UHDRS)	08	X		X		X		X		X		X		X
Motor Assessment Video (CONSENT)	14	X		X		X		X		X		X		X
Participant ID Code Call CTCC		X												
Participant Unique ID Number[4]		X		X		X		X		X		X		X
UHDRS'99 (IV, V, VI, VII, VIII)	08	X		X		X		X		X		X		X
Biomaker Sample Consent	10	X												
Participant ID Label (PTID)	12	X												
Blood Draw for CAG Analysis		X												
Markers of DNA and RNA Damage		X		X		X		X		X		X		X
Blood for CAG Genotyping[6]		X		X		X		X		X		X		X
Specimen Repository		X		X		X		X		X		X		X
DNA Blood Sample Laboratory Requisition		X												
Biomarker Sample Laboratory Requisition		X		X		X		X		X		X		X
MRI (MRI)	56	X				X				X				
Family Participation Log (FAM)	18	X		X		X		X		X		X		X
Screening/Baseline Confirmation (SCCONF)	20	X												
Signature Form (SIG)	22	X		X		X		X		X		X		X
Reportable Event Log (RE)	86	X		X		X		X		X		X		X
Participant Disposition (DISP)[1]	26													X
Participant Site Transfer Form (STF)[2]	28													
Autopsy Form (AP)[3]	30													
Cover Page (COV)[1]	32													X

[1] Complete At Final Visit or if participant prematurely withdraws. C = Computerized

[2] Complete if participant transfers to another Predict site

[3] Complete if participant dies and autopsy is performed.

[4] To be issued at the First Follow-up Visit Post Amendment 5 approval.

[5] European sites only

[6] To be collected at Initial Visit or First Follow-up Visit ***ONLY*** Post Amendment 5 approval.

DRAFT

PREDICT-HD
SCHEDULE OF CRF COMPLETION AND STUDY ACTIVITIES

FORM/ACTIVITY	LEVEL #	SCREENING/BASELINE	MAINTENANCE VISITS											
		MONTH 0	MONTH 6	MONTH 12	MONTH 18	MONTH 24	MONTH 30	MONTH 36	MONTH 42	MONTH 48	MONTH 54	MONTH60	MONTH 66	MONTH 72
		VISIT 1	T1	VISIT 2	T2	VISIT 3	T3	VISIT 4	T4	VISIT 5	T5	VISIT 6	T6	VISIT 7
Symptom Checklist-90 (SCL-90P) (Participant)	34	X		X		X		X		X		X		X
Symptom Checklist-90 (SCL-90C) (Companion)	36	X		X		X		X		X		X		X
Frontal Systems Behavioral Scale Revised (FRSBEP) (Participant)	42	X		X		X		X		X		X		X
Frontal Systems Behavioral Scale Revised (FRSBEC) (Companion)	44	X		X		X		X		X		X		X
Beck Depression Inventory-II (BDI-II)	46	X		X		X		X		X		X		X
Beck Hopelessness Scale (BHS)	48	X		X		X		X		X		X		X
Substance Use Form (SUF)	50	X		X		X		X		X		X		X
Haidt Scale (HAIDT)	52			X		X		X		X		X		X
Schedule of Compulsions, Obsessions and Pathological Impulses Participant (SCOPI-P)	80	X		X		X		X		X		X		X
Schedule of Compulsions, Obsessions and Pathological Impulses Companion (SCOPI-C)	92	X		X		X		X		X		X		X
Life Experiences Scale (LES)	84	X		X		X		X		X		X		X
Perceived Stress Scale (PSS)	58	X		X		X		X		X		X		X
UHDRS - Part III (UHDRSP) (Participant)	60	X		X		X		X		X		X		X
UHDRS - Part III (UHDRSC) (Companion)	62	X		X		X		X		X		X		X
Suicide Risk Assessment (SRA)	64	X		X		X		X		X		X		X
Cognitive Assessment Summary Sheet (Visit 1) (CAS1)	66	X												
Cognitive Assessment Summary Sheet (Visit 2) (CAS2)	68			X										
Cognitive Assessment Summary Sheet (Visit 3) (CAS3)	70					X								
Cognitive Assessment Summary Sheet (Visit 4) (CAS4)	72							X						
Cognitive Assessment Summary Sheet (Visit 5) (CAS5)	94									X				
Cognitive Assessment Summary Sheet (Visit 6) (CAS6)	96											X		
Cognitive Assessment Summary Sheet (Visit 7) (CAS7)	98													X
Cognitive Assessment Video (CAV) (SelectedParticipant)	74	X		X		X		X		X		X		X
Telephone Contact Form (TC)	88		X		X		X		X		X		X	
Subsequent Visit information Form (SVI)	82	X		X		X		X		X		X		X
Bi-Annual Retention Activity Record (BRAR)	90	X	X	X	X	X	X							
Bi-Annual Retention Activity Record (BRAR)	91							X	X	X	X	X	X	X
Confidential Visit Evaluation	99	X		X		X		X		X		X		X
Symbol Digit Modalities Test (Symbol Digit)		X		X		X		X		X		X		X
Stroop Color Word Test (Stroop)		X		X		X		X		X		X		X
Trail Making Test (Parts A & B, Trails)		X		X		X		X		X		X		X
Smell Identification Test (Smell ID) (UPSIT; 20 items only Smell)		X		X		X		X		X		X		X
Dual Verbal Working Memory (Numbers)	C	X												
Hopkins Verbal Learning Test-Revised, Immediate Recall (HVLT Immediate and Delayed)		X				X				X				X
Finger Tapping Task (Block 2)	C	X		X		X		X		X		X		X
Hopkins Verbal Learning Test Revised (HVLT-R)		X				X				X				X
Emotion Recognition Task-Static Version (EMOSTATIC)	C	X	X	X	X	X	X	X	X	X	X	X	X	X
Simple/Choice RT Task (Chooser)	C	X		X		X		X		X		X		X
American National Adult Reading Test (ANART)		X				X				X				X
ANART Audiotaping (All participants)		X		X		X		X		X		X		X
Set Shifting Task (Shifter)	C	X				X				X				X
Controlled Oral Word Association (Verbal Fluency)		X		X		X		X		X		X		X
Abbreviated Buttons Task (Block 1 & 3, Buttons)	C	X		X		X		X		X		X		X

[1] Complete At Final Visit or if participant prematurely withdraws. C = Computerized

[2] Complete if participant transfers to another Predict site

[3] Complete if participant dies and autopsy is performed.

8/31/07
(Amend # 5)

SECTION III

ENROLLMENT

General
Information
Enrollment Calls
Unique ID Number
Participant ID Number Assignment
Companion ID Number Assignment
Confidential Participant/Companion Log
Screening/Projection Log
Enrollment Projection Report

APPENDIX III

Visit Window Schedule/ Enrollment Verification Report
Sample of DNA Blood Tube Labels
Participant ID Label
Confidential Participant Identification Code Log
Confidential Companion Identification Code Log
Screening/Projection Log
Enrollment Projection Report

GENERAL INFORMATION

A participant officially enters the study when the site phones an enrollment call to the Clinical Trials Coordination Center (CTCC).

ENROLLMENT CALLS

When all the appropriate screening/baseline visit tasks have been completed at Visit 1, and the Investigator has determined that a person is eligible to participate in the study, he or she may be entered into an on-line Enrollment Module by the CTCC, which generates the 4-digit Participant Identification (ID) number. Labels with a 4-digit code and bar codes will be sent prior to enrollment for use on the participant's CRFs and blood samples. The barcodesare not the same as the participant's identification number.

To enroll a participant, you must call the CTCC. CTCC staff rotate taking enrollment calls for various studies. When the receptionist answers the phone, **please announce that you are calling with a PREDICT-HD enrollment**.

CTCC staff will be available to receive enrollment calls from sites:

- Call 585-275-7311 weekdays between 8:30 a.m. – 4:30 p.m. (Eastern Time)
- By **pre-arrangement** with the CTCC (with preferably 1-2 days' notice), calls can be received at other times to accommodate site-specific scheduling needs
- *Please note dates the office is closed, provided in Section I. You will be unable to enroll participants on these dates unless special arrangements have been predetermined.*

Who may enroll a participant?

- Either the enrolling Site Investigator or the Site Coordinator (<u>no other site staff will be permitted to enroll participants</u>).

When do I make the enrollment call?

- During the Screening/Baseline Visit (Visit 1) **<u>after</u>** all eligibility criteria are complete.
- Any questions regarding the participant's eligibility should be referred to the Project Coordinator **<u>prior</u>** to placing the enrollment call.

What information do I need to provide?

You must have the following information available during the enrollment call:

- Site number
- Caller's staff code
- Participant's date of birth
- Participant's gender
- Participant's ethnicity
- Date the consent form was signed
- Knowledge that all inclusion/exclusion criteria have been met
- Participant's gene status (negative or positive)

NOTE: You must have permission from the CTCC to enroll a genenegative participant.

PARTICIPANT ID NUMBER ASSIGNMENT

The Enrollment Module will generate a Participant ID number for a study participant who meets all eligibility criteria. The Enrollment Module uses the date of enrollment to calculate the participant's follow-up visit window schedule (the dates in which the participant should be seen by the study stafffor a given visit). (See Appendix III for sample *Visit Window Schedule*.)

- Locate the Participant ID number on the set of labels and corresponding barcodes (*Sample of DNA Blood Tube Labels* - Appendix III). Enter this number in the space provided on the top of each CRF page. This number will be used by the HSG Coordination Center to identify the participant. The barcode labels contain a separate embedded number to be used by the lab for identifying the blood samples. Peel off the Participant ID number and place it on the CRF page marked *Participant ID Label*.

NOTE: The participant ID numbers and barcodes are designed such that neither the HSG Coordination Center nor the DNA lab will individually be able to match the numbers to the participant by name.

An *Enrollment Verification Report* (see Appendix III for sample) listing the Participant ID and the visit window schedule will be emailed to the Site Coordinator following the enrollment call. Upon receiving the report, the coordinator should verify that the participant identifiers are correct and file the report in the participant's folder. If an error is found, please notify the CTCC.

COMPANION ID NUMBER ASSIGNMENT

A Companion ID number for the study participant's companion will be assigned by the site staff. The companion number will begin with "C" as the prefix to the number and "01" for the first companion: "02" for the second companion and so on (i.e., C01 is the first companion. If the participant has a different companion at Visit 2, he/she will be assigned C02 as his/her number). This number will be used by the HSG Coordination Center to identifythe companion. This number should be entered on all CRF pages that require the companion number.

NOTE: A COMPANION CANNOT BE ENROLLED AS A PARTICIPANT.CONFIDENTIAL

PARTICIPANT/COMPANION LOG

Confidentiality of the participants' identification must remain <u>strict</u> throughout the course of the study. Responsibility for confidentiality rests with both the investigators and participants. Participants should consider carefully before disclosing their participation to anyone.

- Identifying information about a participant such as name, initials, or social security number must never be in the case report form (CRF) binder.
- The signed Consent Form must be kept separate from the CRF binder.
- We are providing you with a *<u>PREDICT-HD Confidential Participant Identification Code Log</u>* (see Appendix III) that should be kept in a locked secure location separate from the CRF binder. When participants are screened/baselined, you may write their initials along with the identification number on the PREDICT Confidential Participant Log. There is also a *<u>PREDICT-HD Confidential Companion Identification Code Log.</u>* The companion's name and number should be recorded and if the companion changes, the name and number for the new companion should be listed.

UNIQUE ID NUMBER

A 9-digit unique identification number will be assigned to each participant.

The number will be used to identify participants who are involved in more than one Huntington Study Group (HSG) research protocol without using personalidentifiers (e.g., name, initials). The Clinical Trials Coordination Center (CTCC)developed a system using a 9-digit unique identification number. This numberwill be computer-generated using 9 pieces of participant information: last name at birth, first name at birth, gender at birth, day of birth, month of birth, year of birth, city of birth, country of birth, and mother's maiden name. If a participant has participated in previous HSG CTCC studies and already has a unique ID number, this number will continue to be used for this study with thesubject's consent.

To obtain a CTCC unique ID or to look up the subject's unique ID, pleasego to the following web site: https:/www.ctcc.rochester.edu/uniqueid/.

SCREENING/PROJECTION LOG

- Used to determine projected timelines, the need for additional supplies, monitor schedules, and recruitment difficulties.
- Designed to capture information about all participants who sign the Informed Consent and are willing to be screened for PREDICT-HD eligibility.
- Reflects site predictions about the number and timing of future enrollments.
- Information provided is also used to describe recruitment efforts in reportsto the sponsor and IRB annual reports.
- **Fax the updated *Screening/Projection Log*** (see Appendix III) to the PREDICT-HD Data Control Clerk (Fax: 585-461-4594) at the CTCC on a biweekly basis until study enrollment is completed.
- In the case of a screening failure, update the log with the reason for the failure.
- At the end of the study, send a copy of the log to the CTCC with the final CRFs.

ENROLLMENT/PROJECTION REPORT (see Appendix III for sample)

- Generated from data entered on the *Screening/Projection Log*.
- Distributed on a regular basis to sites so all are able to see where theyrank in enrollment status relative to other sites.
- The Principal Investigator, Steering Committee, and monitors also receive this report.

APPENDIX III

Visit Window Schedule/Enrollment Verification Report
Sample of DNA Blood Tube Labels
Participant ID Label
Confidential Participant Identification Code Log
Confidential Companion Identification Code Log
Screening/Projection Log
Enrollment Projection Report

10/27/2003 12:47 *Clinical Trials Coordination Center*

PREDICT-HD

ENROLLMENT VERIFICATION / VISIT WINDOW

SITE: 001 UNIVERSITY OF ROCHESTER

ENROLLING INVESTIGATOR: 0345 GREAT DOC, MD

COORDINATOR: 0867 BEST COORD, RN

PARTICIPANT NUMBER: 0282

DATE OF BIRTH: 07/28/1951 GENDER: FEMALE

	START OF WINDOW	TARGET DATE	END OF WINDOW
VISIT			
Visit 1 (Baseline)		10/27/2003	
Visit 2	09/26/2004	10/26/2004	11/25/2004
Visit 3	09/26/2005	10/26/2005	11/25/2005
Visit 4	09/26/2006	10/26/2006	11/25/2006

PREDICT-HD SAMPLE OF DNA BLOOD TUBE LABELS

LABEL FOR CRF	LABEL FOR BLOOD TUBE	LABEL FOR BLOOD TUBE	LABEL FOR LAB REQUISITION	EXTRA LABEL FOR LAB REQUISITION
PREDICT-HD SITE NO._____ **PT ID NO.** 0101	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO. _____ BARCODE	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO._____ BARCODE
PREDICT-HD SITE NO._____ **PT ID NO.** 0102	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO. _____ BARCODE	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO._____ BARCODE
PREDICT-HD SITE NO._____ **PT ID NO.** **0103**	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO. _____ BARCODE	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO._____ BARCODE
PREDICT-HD SITE NO._____ **PT ID NO.** **0104**	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO._____ BARCODE

PREDICT-HD
PARTICIPANT ID LABEL (PTID)

(12)

All items must be completed.

PARTICIPANT NO. [ ][ ][ ][ ] SITE NO. [ ][ ][ ]

VISIT NO. [ ][ ]

DATE SAMPLE OBTAINED [ ][ ] MM [ ][ ] DD [ ][ ][ ][ ] YEAR

Directions:

- Affix label with participant identifier to this form.
- Make a copy of this page for retention with the site's CRFs.
- **Send this page to the Clinical Trials Coordination Center with Visit 1 (Screening/Baseline) CRFs.**

PLEASE AFFIX LABEL for CRF HERE

1. Was the extra label used? (0 = No, **1** = Yes) **1.** [ ]

If No, please attach extra barcode label to the ***DNA Blood Sample Laboratory Requisition.***

NOTE: Rember to complete the **DNA Sample Consent Form.**

PREDICT-HD
CONFIDENTIAL PARTICIPANT IDENTIFICATION CODE LOG

INVESTIGATOR:_____

ADDRESS: _____

_____

TELEPHONE/FAX: _____

SITE NO.: | | | |

This participant identification code list is a confidential record to be retained only at the investigational site to reveal the identity of any participant if needed. The list may not be destroyed before the Clinical Trials Coordination Center and/or Sponsor gives notice as to when the document is no longer required.

Participant No.	Date of Enrollment	Participant Initials	Participant's Full Name/Address/Phone Number	Date of Birth	Record No. (not mandatory)

At Close out: _____

Investigator Signature

Original: Investigator. Do not provide a copy to the Clinical Trials Coordination Center or Sponsor

PREDICT-HD
CONFIDENTIAL COMPANION IDENTIFICATION CODE LOG

INVESTIGATOR:_____

ADDRESS: _____

_____

TELEPHONE/FAX: _____

SITE NO.: | | | |

This companion identification code list is a confidential record to be retained only at the investigational site to reveal the identity of any companion if needed. The list may not be destroyed before the Clinical Trials Coordination Center and/or Sponsor gives notice as to when the document is no longer required.

Participant No.	Companion No.	Date of Enrollment	Participant Initials	Companion's Full Name/Address/Phone Number	Date of Birth	Record No. (not mandatory)

At Close out: _____

Investigator Signature Date

Original: Investigator. Do not provide a copy to the Clinical Trials Coordination Center or Sponsor

SCREENING/PROJECTION LOG
PREDICT-HD

Number 2 pencil NOT required. For optimum accuracy, please print capital letters and numbers carefully and avoid contact with the edges of the box. To make corrections put 2 lines through incorrect response, date and write correct response next to it. e.g. -> 1 2 3 4 5 A B C D E
Shade Circles like this --> ● Not like this -->
To make a correction fill in and circle the desired response e.g. ◉

Please list participants who have **signed a consent form** to participate in PREDICT-HD. At each reporting period use this sheet to add new participants and to update information for previously listed participants. Please indicate the referral source.

Site No. ___

ETHNIC CATEGORY
1 = Hispanic or Latino
2 = Not Hispanic or Latino
3 = Unknown or not reported

RACIAL CATEGORY
1 = American Indian/Alaskan Native
2 = Asian
3 = Native Hawaiian or other Pacific Islander
4 = Black or African American
5 = White
6 = More than one race
7 = Unknown or not reported

REFERRAL SOURCE
1 = PREDICT Site Personnel
2 = Advocacy Organization (HDSA, HSC, HDF)
3 = National HD Research Roster
4 = HSG Website
5 = HSG 1-800 #
6 = Family/Friend
7 = HD Conference/Support Group
8 = Genetic Counselor
9 = Other (specify)

SCREENING NUMBER	GENDER F	GENDER M	ETHNIC CATEGORY	RACIAL CATEGORY	PROJECTED ENROLLMENT DATE (MM/DD/YEAR)	REFERRAL SOURCE	ENROLLED? N	ENROLLED? Y	PARTICIPANT ID NUMBER (if applicable)
	○	○			/ /		○	○	
	○	○			/ /		○	○	
	○	○			/ /		○	○	
	○	○			/ /		○	○	
	○	○			/ /		○	○	
	○	○			/ /		○	○	
	○	○			/ /		○	○	
	○	○			/ /		○	○	
	○	○			/ /		○	○	
	○	○			/ /		○	○	

21848

Please FAX completed report ***bi-weekly*** to Data Control Clerk, Clinical Trials Coordination Center, (585) 461-4594

10/27/2003 17:00 *Clinical Trials Coordination Center*

PREDICT-HD

Enrollment / Projections Repor

t

EXAMPLE

SITE	NO IR B	TOTAL ENROLLED	PREVIOUS REPORT	ENROLLED IN PAST 14 DAYS	PROJ. WITHIN 15 DAYS	PROJ. WITHIN 30 DAYS	PROJ. WITHIN 60 DAYS	PROJ. > 60 DAYS	UNKNOWN DATE	TOTAL PROJ.	SCREEN FAILURE	DATE OF FIRST ENROLLMENT	WOMEN ENROLLED	MEN ENROLLED
UNIVERSITY OF IOWA (PAULSON MD)	0	30	29	1	0	1	0	0	2	3	0	09/26/2002	21	9
JOHNS HOPKINS UNIVERSITY (ROSENBLATTMD / ROSS MD PHD)	0	30	29	1	2	0	1	0	2	5	0	11/04/2002	18	12
EMORY UNIVERSITY SCHOOL OF MEDICINE (JONES PHD)	0	25	24	1	0	0	0	0	1	1	0	11/21/2002	14	11
UNIVERSITY OF BRITISH COLUMBIA (RAYMOND MD PHD)	0	25	25	1	1	0	0	0	1	2	0	09/12/2002	16	9
THE CENTRE FOR ADDICTION AND MENTAL HEALTH (GUTTMAN MD)	0	24	24	0	0	0	0	0	4	4	0	10/22/2002	12	12
UCLA MEDICAL CENTER (PERLMAN MD)	0	20	19	3	0	0	0	0	5	5	0	12/16/2002	16	4
UNIV OF WASHINGTON AND VA PUGET SOUND HEALTH CARE SYSTEM (SAMII MD)	0	19	19	0	0	0	0	0	1	1	0	11/07/2002	12	7
INDIANA UNIVERSITY SCHOOL OF MEDICINE (QUAID PHD)	0	18	18	0	0	0	0	0	4	4	0	12/06/2002	13	5
COLUMBIA-PRESBYTERIAN MEDICAL CENTER(MAZZONI MD PHD / MARDER MD)	0	12	12	0	1	0	1	0	2	4	0	01/29/2003	5	7
UNIVERSITY OF CALIFORNIA DAVIS (WHEELOCK MD)	0	12	12	0	0	0	0	0	1	1	0	12/19/2002	8	4
UNIVERSITY OF CALIFORNIA SAN FRANCISCO (GESCHWIND MD PHD)	0	12	12	0	0	0	0	0	1	1	0	01/14/2003	8	4
HEREDITARY NEUROLOGICAL DISEASE CENTRE (HNDC) (MALLONEE MD)	0	12	12	0	0	1	0	0	1	2	0	10/15/2002	9	3
WESTMEAD HOSPITAL (MCCUSKER MD)	0	5	4	1	2	0	0	0	14	16	0	08/06/2003	4	1
GRAYLANDS, SELBY-LEMNOS & SPECIAL CARE HEALTH SERVICES (PANEGYRES MB BS	0	3	3	0	1	0	0	0	1	2	0	08/20/2003	2	1
UNIVERSITY OF ALBERTA (MARTIN MD)	0	2	0	2	0	1	2	0	0	3	0	10/21/2003	2	0
UNIVERSITY OF MICHIGAN (LORINCZ MD PHD)	0	0	0	0	0	0	0	0	0	0	0		0	0
Total	0	327	319	12	10	5	4	0	75	94	0		205	122

SECTION IV

DATA ACQUISITION

APPENDIX IV

Data Acquisition Flow

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 systeminclude: 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 it produces a standards-based XML form as its output.

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

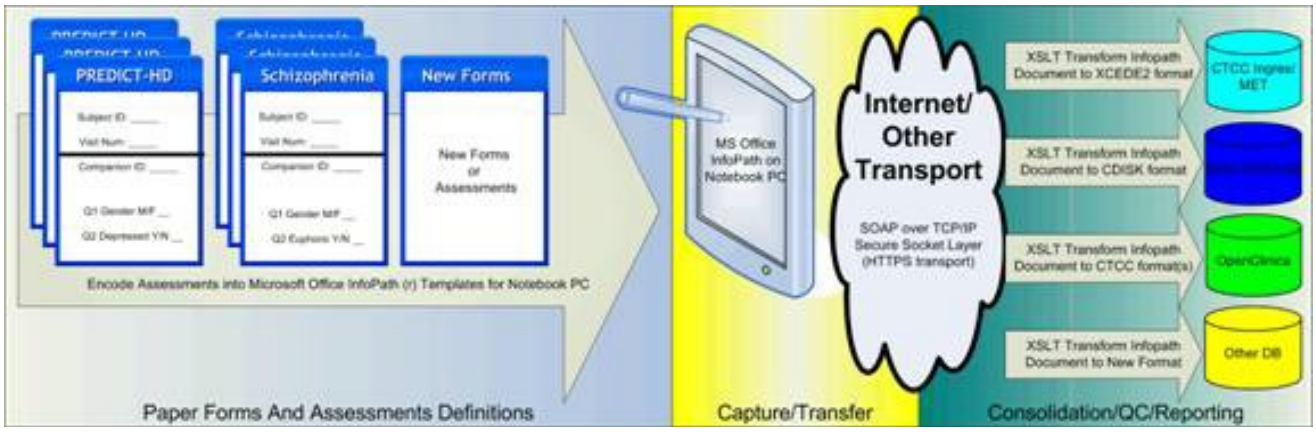
Predict HD assessments and forms will be entered directly on a tablet type Personal Computer (PC) using a writing stylus. Primary data transfer will occur via a secure internet connection to Simple Object Access Protocol (SOAP) WEB Services to the Clinical Trials Coordination Center at The University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

**Details outlining Electronic Data Capture and proper usage of notebook PC are forthcoming.*

Appendix IV

Data Acquisition Flow

DATA ACQUISITION FLOW



SECTION V

PSYCHIATRIC ASSESSMENTS

Symptom Checklist – 90 (SCL – 90)
Schedule of Compulsions, Obsessions and Pathological Impulses SCOPI)
Frontal Systems Behavior Scale (FrSBe)
Beck Depression Inventory-II (BDI - II)
Beck Hopelessness Scale (BHS)
Substance Use Form (SUF)
Haidt Scale (HAI)
Perceived Stress Scale (PSS)
UHDRS '99 – Part III

For instructions regarding the psychiatric battery, please refer to theAppendix Psychiatric Assessment section.

SECTION VI

COGNITIVE ASSESSMENTS

Symbol Digit Modalities Test (Symbol Digit)
Stroop Color Word Test (Stroop)
Trail Making Test (Trail Making) Smell
Identification Test (Smell ID) Hopkins
Verbal Learning Test-Revised
(Immediate and Delayed Recall)
Finger Tapping Task (Tapper)
Emotion Recognition Test (Emotions)
American National Adult Reading Test (ANART)
Verbal Fluency (Fluency)

For instructions regarding the Cognitive Testing Battery, please refer to the Cognitive Operations Manual.

SECTION VII

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

EXAMINATION GUIDELINES

FOR THE

MODIFIED UNIFIED HUNTINGTON'S DISEASE RATING SCALE '99

June 11, 1999

PRODUCED AND REVISED BY THE HUNTINGTONSTUDY GROUP

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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 ≤ 10° per second, which corresponds to about 2 seconds for moving an object from one shoulder to the other.

#2-3 SACCADE INITIATION AND VELOCITY - Saccade initiation should be tested over a 20° range, as for ocular pursuits. Saccade 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. Saccade 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 overa 10-second period, then continue as follows. Say *"Now lets 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 ofthe 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.

#11-12MAXIMAL 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 stepsin 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 learning 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 preventeither 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 thattaking 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 (≥ 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 ≥ 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.

II. COGNITIVE ASSESSMENT

General testing guidelines and instructions for administration and scoring are in the **PREDICT-HD Cognitive Operations Manual.**

III. BEHAVIORAL ASSESSMENT (#25-35)

Guidelines for administration of Behavioral Assessment and scoring are found in **Section V of the PREDICT-HD Operations Manual.**

IV. 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)

a. 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.

b. 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.

c. 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?"

d. 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.

e. 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.

f. 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*

g. *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.

h. 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?"*

i. 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 he/she 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 <u>is capable</u> of living at home, rather than in the equivalent of institutional care.

V. 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 of 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 theupper 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 forsubject.

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 canbe 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 great 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.

VI. 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 expectations (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* refer 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)*.

VII. CLINICAL SUMMARY (#80)

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

References:

a. 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.

SECTION VIII

MOTOR RATER'S MANUAL

TABLE OF CONTENTS

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 outcomevariable will be time to phenoconversion, judged to have occurredwhen the Motor Rater (MR) is 99% confident that the participanthas motor abnormalities that are unequivocal signs of HD (i.e., HDdiagnosis confidence level of 4 on item 17 of the UnifiedHuntington'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 knowledgein evaluating patients with HD, their experience in controlledclinical trials, and their skills in carrying out the UHDRSexamination. In operational terms, MRs should function as"UHDRS rating machines", while maintaining appropriate clinicalsensibilities with research participants and their families.

II. RESPONSIBILITIES OF THE MOTOR RATER 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 beused 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 inputof 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 MRto ensure availability at every visit.**

IV. 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 ofthe 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 InvestigatorPhone:
319-353-4551
Email: jane-paulsen@uiowa.edu

SECTION IX

REPORTABLE EVENTS

Instructions for Reportable Events
Reportable Events
Reportable Event Log Instructions
Notifications

Appendix IX

Incident Report
Reportable Event Log
Notifications Report

INSTRUCTIONS FOR REPORTABLE EVENTS

Reportable Events must be **telephoned** to the HSG Coordination Center within **three (3) working days** of discovery. Calls will be received 24 hours a day, 7 days a week.

During business hours Reportable Events are to be reported to **Elise Kayson, Project Coordinator, at (585) 275-4696 or Elaine Julian- Baros, Project Coordinator, at (585) 273-2879**. The answering machine on the HSG Coordination Center's mainline (585-275-7311) provides directions for reaching the Medical Monitor on-call when the office is closed.

Events must be reported only by either the Site Investigator or Coordinator. A sample of the ***Reportable Event Log*** is in Appendix IX.

The Site Investigator or Site Coordinator must have the following information available during the incident call:

- Caller's staff code
- Participant's ID number
- Type of Reportable Event
- Date of Reportable Event
- Details surrounding Reportable Event
- Last visit number and date

Once the event is called in to the HSG Coordination Center it will be entered into an on-line module and immediately distributed to the Site Investigator, Steering Committee and Principal Investigator.

An *Incident Report* (see Appendix IX) describing the event will be mailed to the site approximately one week after the call. This report should be kept with the participant's CRFs.

REPORTABLE EVENT LOG INSTRUCTIONS *

Instructions for the Study Sites

Reportable Event Definition

- The following events must be reported to the Clinical Trials Coordination Center within three (3) working days of discovery:
  1) new use of restricted medications (i.e., typical and atypical antipsychotics, phenothiazine-derivative antiemetic agents) –**complete Concomitant Medication Log**

2) new evaluation by a mental health professional
3) new onset depression - **complete Concomitant Medication Log if pharmacotherapy is required**
4) exacerbation of depression requiring either: change inpharmacotherapy or mental health visit
5) suicide attempt
6) hospitalization for serious (non-elective) medial issues (including childbirth)
7) any neurologic event (e.g., TBI, seizure, etc.)
8) premature withdrawal
9) death
10) suicide risk score
11) any psychiatric hospitalization
12) compromise of confidentiality
13) identification of a safety concern warranting referral for medicalevaluation
14) identification of a safety concern warranting referral to psychiatricevaluation

*** Refer to Amendment 4 for detailed reporting procedure.**

Site Management of Reportable Events

If a participant has a reportable event based on the suicide risk score the site is to discuss the score(s) with the participant, ask the participantwhy they feel the score(s) were elevated and ask if they (the participant) feels that they would benefit from a referral to a mental health care profession. If in the judgment of the site investigator or coordinator thereis a concern warranting a referral for a medical or psychiatric evaluation this should be documented in the participant's chart. The Events Monitoring Committee will closely review any reportable event that warrants referral for a medical or psychiatric evaluation.

Numbering Reportable Event

- Start with 01-05. If another page is required record as 06-10 and thenanother for 11-14.

Reportable Event

- Enter the corresponding number (1-14) to the event.

Onset Date/Resolution Date

- Enter Onset/Resolution Date. A complete date must be entered. If exact date is unknown, enter "01" or 15" and enter month and year.

Relationship to Study Participation
The subject and site investigator must enter the relationship assessmentusing one of the following terms:

- **Probable** = reasonable expected response pattern confirmed by otherfactors
- **Possible** = reasonable response but could be related to other factors
- **Unrelated** = sufficient evidence exists to indicate no relation
- **Unknown** = insufficient evidence to make a decision on the relationship

Disclosure of At-Risk Status

- If a disclosure about the at-risk status of a subject is revealed, a description of who disclosed the information and to whom must becompleted by the subject.

Effect of Disclosures

- The subject must rate how the disclosure affected them:1 = inconsequential
  2 = mildly disturbing
  3 = moderately disturbing4 = very disturbing

Submission of Form to CTCC

- This form must be copied and a copy submitted with each visit oroccurrence.
- The white NCR page should be submitted at the end of the study.

Responsibilities of the Event Monitoring Committee

An Event Monitoring Committee (EMC) has been established to address the concerns and risks of the PREDICT-HD population. The EMC will review blinded PREDICT data related to the safety and well being of this population and advise the Steering Committee about findings relevant tothe conduct of the trial and assist in training or other efforts related to human subject issues. The human subject protection issues addressed by the EMC remain the responsibility of the principal investigator, Steering Committee, IRBs and sponsor.

NOTIFICATIONS

A notification is any relevant clinical or data management (either subject or site specific) issue that may influence the interpretation of the study data.

- Examples of Notifications include: out of window visits, participation in another research study.
- Notifications must be reported to the project coordinator at the CTCCas well as documented at the site. Notifications Report (see AppendixIX) describing the event will be mailed to the site approximately one week after the call. This report should be kept with the participant's CRFs.

APPENDIX IX

Incident Report (sample)
Reportable Event Log (sample)
Notifications Report (sample)

Run Date: 31OCT2003 Clinical Trials Coordination Center

PREDICT INCIDENT REPORT

Reportable Events: Restricted Meds, Mental Health Visit, New Onset Depression,
Exacerbation of depression: Change in Pharmacotherapy/Mental health visit, Hospitalization
Neurological Event, Suicide Risk, Suicide Attempt, Withdrawal, Death

SITE: 001 University of Rochester
INVESTIGATOR: 0200 GOOD, MD
CALLED IN BY: 1072 SITE COORDINATOR, RN
SUBJECT NUMBER: 0201 ENROLLMENT DATE: 07/30/2003

THIS SUBJECT HAD A SUICIDE RISK IN PREDICT

The risk is based on UHDRS score

Date of SUICIDE RISK: 07/30/2003

COMMENTS:

PARTICIPANT ENDORSED UHDRS Q25B WITH A RATING OF 3. SITE INVESTIGATOR DOES NOT FEEL THAT THE PARTICIPANT IS AT RISK OF HARM TO SELF. PARTICIPANT DENIES ANY FEELINGS OF DEPRESSION OR SUICIDEDAL IDEATION AND DOES NOT FEEL A NEED FOR FOLLOW UP.

CTCC Staff Recording Information: 0749 ELISE KAYSON MS RNC

Call Date: 09/30/2003

PREDICT-HD

(24)

REPORTABLE EVENT LOG (RE)

Page ____ of ____

All items must be completed.

PARTICIPANT NO. | | | | | SITE NO. | | | |

INSTRUCTIONS: The following events must be reported to the Clinical Trials Coordination Center within three (3) working days of discovery. Enter the following number (1-10) in the column for Reportable Event Code.

1) new use of restricted medications (i.e., typical and atypical antipsychotics, phenothiazine-derivative antiemetic agents) - **complete Concomitant Medication Log**
2) seen by a mental health professional (new visit)
3) new onset depression - **complete Concomitant Medication Log if pharmacotherapy is required**
4) exacerbation of depression requiring either: change in pharmacotherapy or mental health visit
5) suicide attempt
6) hopitalization for any reason (including childbirth)
7) any neurologic event (e.g., TBI, Seizure, etc.)
8) premature withdrawal
9) death
10) suicide risk

Are there any Reportable Events (0 = No, 1 = Yes) ☐

	Reportable Event Code (1-10)	Onset Date MM/DD/YEAR	Resolution Date MM/DD/YEAR
__1.		/ /	/ /
__2.		/ /	/ /
__3.		/ /	/ /
__4.		/ /	/ /
__5.		/ /	/ /

	Reportable Event Code (1-10)	Onset Date MM/DD/YEAR	Resolution Date MM/DD/YEAR
__6.		/ /	/ /
__7.		/ /	/ /
__8.		/ /	/ /
__9.		/ /	/ /
__0.		/ /	/ /

Comments _____

_____

Site Investigator signature required: _____
Site Investigator's Signature

STAFF CODE

****SEND A COPY OF THIS LOG WITH EACH VISIT.****
****SEND THE WHITE NCR PAGE AT THE END OF THE STUDY.****

10/15/2005 12:07 Clinical Trials Coordination Center PREDICT-HD
NOTIFICTION REPORT

SITE: 001 UNIVERSITY OF ROCHESTER (GOOD, MD)
SITE STAFF: 0000 SITE COORDINTOR, RN
CTCC STAFF: 1985 CATHY COVERT
DATE OF NOTIFICATION / EVENT: 10/06/2003
PARTICIPANT SPECIFICS:
SUBJECT NUMBER: 01 SCREENING NUMBER:
DATE OF BIRTH: 12/15/1969 GENDER: Female
ETHNIC: Unknown or not reported RACE: White
DATE OF ENROLLMENT: 01/09/2004
FORM: INEX
VISIT: 01
TYPE OF CALL: Eligibility (E)
3
ACKNOWLEDGED
COMMENTS:
The observation note for the ANART task indicates that the participant's mother tongue is Finnish, but she speaks English at home. Inclusion criteria question 3 is answered as (1) English is primary language. English not spoken asthe first language is an issue for some of the cognitive testing for these subjects. Inclusion criteria are presently reviewed on a case by case basis.

SECTION X

LABORATORY SPECIMEN MANAGEMENT DNA SAMPLES

DNA Blood Sample Handling
Retention/Destruction of DNA Samples
Storage of DNA Samples
Shipment of DNA Samples

ANNUAL BLOOD SAMPLES
Blood Tube Handling
Storage of Samples
Shipment of DNA Samples
Blood Tube Shipping

CAG Genotyping
Blood Sample Handling
Shipment of Samples

Specimen Repository
Blood Tube Handling
Shipment of Samples

Cytokine and Cholesterol Project

Appendix X

Sample of DNA Blood Tube Labels DNA
Blood Sample Laboratory Requisition
Participant ID Label
DNA Sample Consent
Biomarker Sample Consent
Biomarker Sample Laboratory Requisition
Biomarker Blood Tube Label
Sample of Labels

LABORATORY SPECIMEN MANAGEMENT

A. DNA SAMPLES

- Laboratory analysis of DNA samples will be performed by Marcy MacDonald's Laboratory at Massachusetts General Hospital.
- Each site will be provided all the necessary materials to collect the required specimens.
- All laboratory supplies will be shipped to you from the Clinical Trials Coordination Center. Please contact Elaine Julian-Baros by completing and faxing in the PREDICT supply order form (see appendix IV) to (585) 461-3554. If you have any questions or concerns about supplies please contact Elaine Julian-Baros at (585) 273-2879.

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 1) <u>after</u> 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 <u>*Sample of DNA Blood Tube Labels*</u>, Appendix X) that corresponds to the participant ID number given to you at the enrollment call. The labels are designed in five sections. Place one barcode label on each tube collected. Place the remaining barcodes, one designated for the <u>*DNA Blood Sample Laboratory Requisition*</u> (see Appendix X) and one extra label, if unused, on the <u>*DNA Blood Sample Laboratory Requisition form*</u>. Put the label with the participant ID number on the CRF page marked <u>*Participant ID Label*</u> (see Appendix X).
- **ONLY THE SITE NUMBER SHOULD BE WRITTEN ON THE TUBES. NOOTHER IDENTIFYING INFORMATION SHOULD BE 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 *Blood Sample Consent* CRF page and check the appropriate boxes 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 tohave their DNA sample retained or destroyed. This information must beentered on the *Participant Disposition* CRF page.

Storage of DNA Samples

- DNA blood samples should be stored at -20°C or -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 DNA Samples

- **Frozen DNA 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 a50ml 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 *DNA Blood Sample Laboratory 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 and unusable or the barcode is unreadable when it arrives at the lab, the lab will request another DNA blood sample. You must call Elaine Julian-Baros at (585) 273-2879 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 roomtemperature. Ship those samples drawn on Wednesday – Friday on thefollowing 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 DNA blood specimens should be sent to the following address:

Ms. Lakshmi Srinidhi
Molecular Neurogenetics Unit
Center for Human Genetic Research
Massachusetts General Hospital
Richard B. Simches Research Center
5th Floor, Room 5300 – D2
185 Cambridge Street
Boston, MA 02114

Phone: (617) 726-5726
Fax: (617) 726-5736

B. 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 laboratories[1] 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 acquisitionand archiving across multiple sites must be addressed. We have used the protocols outlined below to minimize clinical site variations. All samples will besuitable 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 PHAROS 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 sitevariation. Note Heparin is suggested as the anticoagulant for plasma becauseit 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*. (Appendix 7A)

- 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** bloodsample. 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 areshipped 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 theCCS 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 protocol[2]. 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 CoriellLaboratory 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, NewhallK, 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.

C. 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 thequality 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.

D. 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 <u>each visit</u>.

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 genespreviously shown to modify timing or expression of disease features. For the purposes of genotyping, MGH will receive DNA from the cell line thatis 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 tope 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 thePREDICT Steering Committee.

E. 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/ehmokines 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.

F. 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.

APPENDIX X

Sample of Labels
DNA Blood Sample Laboratory Requisition
Participant ID Label
Blood Sample Consent (CRF) Blood
Sample Laboratory Requisition

PREDICT-HD SAMPLE OF DNA BLOOD TUBE LABELS

LABEL FOR CRF ↓	LABEL FOR BLOOD TUBE ↓	LABEL FOR BLOOD TUBE ↓	LABEL FOR LAB REQUISITION ↓	EXTRA LABEL FOR LAB REQUISITION ↓
PREDICT-HD SITE NO._____ PT ID NO. 0101	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO. _____ BARCODE	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO._____ BARCODE
PREDICT-HD SITE NO._____ PT ID NO. 0102	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO. _____ BARCODE	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO._____ BARCODE
PREDICT-HD SITE NO._____ PT ID NO. 0103	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO. _____ BARCODE	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO._____ BARCODE
PREDICT-HD SITE NO._____ PT ID NO. 0104	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO._____ BARCODE
PREDICT-HD SITE NO._____ PT ID NO. 0105	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO._____ BARCODE	PREDICT-HD SITE NO._____ BARCODE

PREDICT-HD

DNA BLOOD SAMPLE LABORATORY REQUISITION

SITE NO. | | | |

Instructions

- Affix two barcodes per participant on form.
- Send this form with blood samples.
- ***DO NOT RETAIN A COPY OF THIS PAGE.***

1. Date of Collection

1. | | | MM | | DD | | | | | YEAR

AFFIX BARCODE	AFFIX EXTRA BARCODE

2. Date of Collection

2. | | | MM | | DD | | | | | YEAR

AFFIX BARCODE	AFFIX EXTRA BARCODE

3. Date of Collection

3. | | | MM | | DD | | | | | YEAR

AFFIX BARCODE	AFFIX EXTRA BARCODE

PREDICT-HD
PARTICIPANT ID LABEL (PTID)

12

All items must be completed.

PARTICIPANT NO. [ ][ ][ ][ ]

SITE NO. [ ][ ][ ]

VISIT NO. [ ][ ]

DATE SAMPLE OBTAINED [ ][ ] MM [ ][ ] DD [ ][ ][ ][ ] YEAR

Directions:

- Affix label with participant identifier to this form.
- Make a copy of this page for retention with the site's CRFs.
- **Send this page to the Clinical Trials Coordination Center with Visit 1 (Screening/Baseline) CRFs.**

PLEASE AFFIX LABEL for CRF HERE

1. Was the extra label used? (0 = No, **1** = Yes) **1.** [ ]

If No, please attach extra barcode label to the ***DNA Blood Sample Laboratory Requisition.***

NOTE: Rember to complete the **DNA Sample Consent Form.**

PREDICT-HD
BLOOD SAMPLE CONSENT

10

All items must be completed.

PARTICIPANT NO. [ ][ ][ ][ ] SITE NO. [ ][ ][ ]

VISIT NO. [ ][ ] EVAL. DATE [ ][ ] MM [ ][ ] DD [ ][ ][ ][ ] YEAR

Consent (To be completed at time of Enrollment - Visit 1)

1. Has the participant given permission to the HSG to retain their blood sample for future HD-related research purposes? (0 = No, 1 = Yes) 1. [ ]

2. Has the participant given permission to the HSG to be contacted in the future for other HD-related research purposes? (0 = No, 1 = Yes) 2. [ ]

3. Date consent was signed: 3. [ ][ ] MM [ ][ ] DD [ ][ ][ ][ ] YEAR

PREDICT-HD
BLOOD SAMPLE LABORATORY REQUISITION

SITE NO. [ ][ ][ ]

Instructions:

- Place label provided on blood tube. Fill in site number, participant number, date and time of blood draw.
- Complete information as indicated below.
- Send the original form to Beal Lab, maintain a copy for your records and send a copy to the CTCC.

1a. Participant Number — 1a. [ ][ ][ ][ ]

1b. Date of Collection — 1b. [ ][ ] MM [ ][ ] DD [ ][ ][ ][ ] YEAR

1c. Time of Collection (use 24-hr clock) — 1c. [ ][ ] : [ ][ ] (24-hr clock)

1d. Storage Temperature (Celsius) — 1d. [ ][ ] (Celsius)

2a. Participant Number — 2a. [ ][ ][ ][ ]

2b. Date of Collection — 2b. [ ][ ] MM [ ][ ] DD [ ][ ][ ][ ] YEAR

2c. Time of Collection (use 24-hr clock) — 2c. [ ][ ] : [ ][ ] (24-hr clock)

2d. Storage Temperature (Celsius) — 2d. [ ][ ] (Celsius)

3a. Participant Number — 3a. [ ][ ][ ][ ]

3b. Date of Collection — 3b. [ ][ ] MM [ ][ ] DD [ ][ ][ ][ ] YEAR

3c. Time of Collection (use 24-hr clock) — 3c. [ ][ ] : [ ][ ] (24-hr clock)

3d. Storage Temperature (Celsius) — 3d. [ ][ ] (Celsius)

4a. Participant Number — 4a. [ ][ ][ ][ ]

4b. Date of Collection — 4b. [ ][ ] MM [ ][ ] DD [ ][ ][ ][ ] YEAR

4c. Time of Collection (use 24-hr clock) — 4c. [ ][ ] : [ ][ ] (24-hr clock)

4d. Storage Temperature (Celsius) — 4d. [ ][ ] (Celsius)

Modifications to this Operations Manual Section XI "MRI Protocol" are forthcoming and will incorporate transition to scanner changes as reflected in November 2007 grant.

Section XI

MRI PROTOCOL

MRI Protocol MRI
Scanner Settings
MRI Software
Scheduling
Special Requirements
Data Transfer
Questions

Appendix XI

Requirements for MRI Data Transfer
Checklist for Sending Data
MRI Form
MRI Transmittal Log

MRI PROTOCOL

All images are requested to be obtained on a 1.5 Tesla GE magnet usingthe 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 participantstravel 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.eduOR

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

APPENDIX XI

Requirements for MRI Data Transfer
Checklist for Sending Data
MRI Form (version 7/18/02)
MRI Form (version 6/17/04)
MRI Transmittal Logs (samples)

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 havehad 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 bebetween 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 serieswith 64 slices; on some scanners the number of slice may begreater 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

CHECKLIST FOR SENDING PREDICT HD MRI DATA TO THE UNIVERSITY OF IOWA

☐ Determine identifying characteristics of this scan
- SITEID – The 3 digit code that identifies your site, this number never changes (e.g., 001)
- SUBJECTID –The integer code that uniquely identifies the current subject (e.g., 0124)
- DATESTAMP-An 8 digit identifier for the date the scan was performed. This is created by concatenating the zero paddeddate numeric for year, month, and day the scan was performed.

Examples:

Date Scan performed	DATESTAMP
6th day of February 2004	20040206
January 19, 1999	19990119
October, 27, 1993	19931027

☐ Create prescribed directory structure for storing data. Noticethat there are no spaces in the directory names.
${SITEID}-PredictHD-${SUBJECTID}-${DATESTAMP}/3DSPGR
${SITEID}-PredictHD-${SUBJECTID}-${DATESTAMP}/PDT2
${SITEID}-PredictHD-${SUBJECTID}-${DATESTAMP}/SCOUT1
${SITEID}-PredictHD-${SUBJECTID}-${DATESTAMP}/SCOUT2

☐ Place the raw image data is in .MR or .dcm format into prescribed directories. All other file format will be rejected. Do not attempt to send jpeg, png, gif or any other file types.

☐ Confirm that each imaging modality has an appropriate numberof images to contain the entire brain.
- The ${SITEID}-PredictHD-${SUBJECTID}-${DATESTAMP}/3DSPGR should contain between 120 and128 image files. In almost all cases it will be exactly 124 image files.
- The ${SITEID}-PredictHD-${SUBJECTID}-${DATESTAMP}/PDT2 should contain at least 64 image files. Image files belonging to the “SCOUT” series should be put in ${SITEID}-PredictHD-${SUBJECTID}-${DATESTAMP}/SCOUT[123456789] directories.

☐ Create a compressed tar formatted file of the entire scan sequence directory to reduce the amount of data to be

☐ transferred and avoid many failures during the upload.

☐ The compressed tar formatted file should be named ${SITEID}-PredictHD-${SUBJECTID}-${DATESTAMP}.tar.gz.
Example command:

```
userid% tar –xzvf\
    ${SITEID}-PredictHD-${SUBJECTID}-${DATESTAMP}.tar.gz \
    ${SITEID}-PredictHD-${SUBJECTID}-${DATESTAMP}
```

☐ Send the compressed exam folder to the University of Iowa. All data is to be uploaded to a repository accessible only by your site. The upload host is completely isolated from the permanentstorage resources, and uploaded data will reside on this host forless than 48 hours.

Upload hostname: predict.psychiatry.uiowa.edu
Upload userid: site-${SITEID}
Upload password: Contact Leigh Beglinger for this information

- Example upload using secure copy:

```
userid% scp ${SITEID}-PredictHD-${SUBJECTID}-
${DATESTAMP}.tar.gz \
        predict.psychiatry.uiowa.edu:/secure/upload/sit
        e-
{SITEID}
```

- Example upload using secure ftp:

```
userid% sftp site-${SITEID}@predict.psychiatry.uiowa.edu
Connecting to predict.psychiatry.uiowa.edu
site-${SITEID}@predict.psychiatry.uiowa.edu's password >
sftp> put ${SITEID}-PredictHD-${SUBJECTID}-
${DATESTAMP}.tar.gzsftp>
quit
```

- Example upload using insecure ftp

```
userid% ftp predict.psychiatry.uiowa.edu
Connecting to
predict.psychiatry.uiowa.edu
predict.psychiatry.uiowa.edu's login > site-${SITEID}
predict.psychiatry.uiowa.edu's password >
ftp> put ${SITEID}-PredictHD-${SUBJECTID}-
${DATESTAMP}.tar.gzftp>
quit
```

OR

- If you need to physically mail us exams, please place the compressed tar files on CD-ROM and clearly label it as

  ${SITEID}-PredictHD-${SUBJECTID}-${DATESTAMP}. Mail the labeled CD-ROM to the following address:

  Leigh Beglinger, PhD
  University of Iowa
  Psychiatry Research
  1-321 Medical Education BuildingIowa
  City, IA 52242
  Work Phone: 319-335-8765

☐ A confirmation of successful upload will be emailed after the scan data has been moved to the permanent storage resourcesand verified for completeness. This notification will indicate whether there were any problems with the data that must be addressed by your site.

☐ The University of Iowa will relay the anonymized T1 data to the

NOTE:

ONLY AFTER AMENDMENT 3 **APPROVAL USE THIS FORM AND PLEASE SEND MRI DATA TO UNIVERSITY OF IOWA.**

PREDICT-HD

16

MRI

All items must be completed. Use **U** if information is **Unavailable**. Use **N** if information is **Not Applicable**.

PARTICIPANT NO. [ ][ ][ ][ ] SITE NO. [ ][ ][ ]

VISIT NO. [ ][ ]

1. Was MRI completed? (0 = No, 1 = Yes) 1. [ ]

If MRI not completed [0 = No], please explain under Comments (Question 4).

2. Date MRI completed: 2. [ ][ ] MM [ ][ ] DD [ ][ ][ ][ ] YEAR

3. Date MRI data sent to University of Washington 3. [ ][ ] MM [ ][ ] DD [ ][ ][ ][ ] YEAR

4. Comments:

_____

_____

_____

_____

PREDICT-HD
University of Iowa
MRI TRANSMITTAL LOG

Instructions: Please fax this log monthly to the attention of Cathy Covert at the Clinical Trials Coordination Center (fax: 585-461-4594).

Participant #	Visit #	Site #	Scan Date	Date of Receipt by UI	Date of Quality Check at UI	Need to be redone? Yes/No	Date of Site Contact	Date sent to UW	Date Log faxed to CTCC

Version 7/28/04

PREDICT-HD
University of Washington
MRI TRANSMITTAL LOG

Instructions: Please fax this log monthly to the attention of Cathy Covert at the Clinical Trials Coordination Center (fax: 585-461-4594).

Participant #	Visit #	Site #	Scan Date	Date of Receipt by UW	Date of Quality Check at UW	Need to be redone? Yes/No	Date of Site Contact	Date Log faxed to CTCC	Date data sent to UR

Version 7/28/04

SECTION XII

SOURCE DOCUMENTATION

Confidentiality of Source Documents
Instructions for Source
DocumentationInitial Visit Notes
Subsequent Visit Notes

SOURCE DOCUMENTATION

CONFIDENTIALITY OF SOURCE DOCUMENTS

It is the site's responsibility to ensure that every effort is made to maintain confidentiality of the source documents. Identifying information about a participant-such as name, initials, or social security number must never be found in a CRF binder.

INSTRUCTIONS FOR SOURCE DOCUMENTATION

Per FDA guidelines, source documents include the first record of any participant-related data, regardless of the medium used to record the data. These documents may include participant's medical records, progress notes, lab reports, computer data files and so on.

Sites are responsible for maintaining adequate source documents for this study. When CTCC-provided documents are used, sites must also keep visit summaries and participant correspondence notes. Participant charts must be made available to the monitor for review.

All CRFs are considered source documents except: *Concomitant Medication Log*, *Staff/Study Related Duties Log*, *Reportable Events Log*, *MRI Form*, *Participant Site Transfer Form*, *Medical History*, and *Signature Form*.

When an examination or assessment is recorded directly on the CRF, a note should be made in the source document that states, "Information was recorded directly on the CRF." The monitor will verify all CRF entries against the source documents.

The progress notes/source documentation/medical records should contain information about whatever has happened to the participant during the course of the study, especially if it is not captured on the CRF. Please keep your source documents either with your CRFs or in a participant folder, available at the time of the site-monitoring visit. The following are examples of the type of information that should be available for review:

Initial Visit Notes:

- Date of the visit
- Purpose of visit (e.g. screening/baseline for PREDICT-HD study)
- Past medical history, including pre-existing conditions or illnesses; activities completed at the visit including physical examination, verification that the participant meets inclusion/exclusion criteria, medication review, and labs completed for screening
- Date informed consent obtained

Subsequent Visit Notes:

- Date of each visit
- Participant ID
- Entries summarizing the study visit. These may be in narrative form or a checklist indicating that the participant was seen that day, activities for the study were performed, and stating if information was documented directlyon the CRF
- Entries for all concomitant medications and their start/stop dates, including new medications at each visit
- Entries for all Reportable Events (start/stop dates and treatments) andIncidents

Source documents should be kept either with the CRF or in a participant chart,so that they are available at the time of a site monitoring visit. Phone contactswith participants/CTCC/monitors should also be available for review.

SECTION XIII

MONITORING

Site Visits
Interim Monitoring Visit(s)
Clinical Site Close-Out Visit
Contents of Regulatory Binder

MONITORING

SITE VISITS

Periodic study monitoring visits will be conducted at the sites.

The Project Coordinator at the CTCC will work closely with the site monitors to provide consistent answers to investigators and coordinators regarding their protocol questions during monitoring visits.

After each monitoring visit, the study monitor produces a site progress report that is reviewed at the CTCC. The study monitor sends a follow-up letter to thesite reiterating any discussions that occurred at the monitoring visit and listingany action items.

INTERIM MONITORING VISIT(S)

At this visit, the motor rater, cognitive and psychiatric examiners, investigator, coordinator, and any other staff members involved in the study should be available (or easily reachable). During this visit, the following will be reviewed:

- Adequacy of study facilities
- Daily log of minimum/maximum temperatures reached for freezers and refrigerators
- Ensuring that the study staff has a good understanding of the protocol and proper procedures for the study and for CRF completion
- Regulatory binder, protocol, CRFs, reportable events, medical record (source) documentation, and informed consents (to assure that the inclusion/exclusion criteria have been properly met, that data forms are completed correctly, and the documentation adheres to the Good Clinical Practice (GCP) requirements)
- CRFs of currently enrolled participants will be reviewed for completeness and accuracy and compared to the source documentation
- Study correspondence, including correspondence between the site's investigator and the site's IRB, and between the site staff and the CTCC

CLINICAL SITE CLOSE-OUT VISIT

The monitor will perform a clinical site close-out visit when all site participants have completed the study. At the close-out visit, accountability for all study supplies will be reviewed. Monitors will also conduct a review of CRFs and logs for those participants not previously monitored. The site's regulatory

binder will be reviewed for all regulatory documents and correspondence pertaining to the study. Record retention requirements will also be discussed.

CONTENTS OF THE REGULATORY BINDER

The site must maintain a Regulatory Binder (also referred to as the study file). This binder will be reviewed at every monitoring visit and should therefore be kept up to date.

The Regulatory Binder should contain the following:

- Current CVs, Biographical Sketches, and licenses
- Other Support and Resource pages
- Protocol and Amendments (when applicable)
- Protocol Signature Form
- Participant Screening/Projection Log
- IRB communications
    - Approval letter(s) for protocol, consent form, ads, amendments
    - Approved consent form
    - Any approved ads
    - IRB Membership Inquiry Form
    - Correspondence to/from IRB
    - Letters, faxes, telephone contacts to or from CTCC, sponsor, and monitors
- General correspondence
- Study close-out letter to IRB
- Reportable Events
- Correspondence regarding RE forms
- Confidentiality Agreements
- Disclosure Agreements/Conflict of Interest Statement
- Monitoring Log
- Staff/Study Related Duties Log
- Notes to File
- Sample CRFs (should be kept either in the Operations Manual or Regulatory Binder)

SECTION XIV

UPDATES

(Please insert newsletters or general updates here)

SECTION XV

RETENTION OF STUDY PARTICIPANTS

Subsequent Visit Form
Confidential Visit Evaluation Form
Telephone Contact Form
Bi-Annual Retention Activity Record

RETENTION OF STUDY PARTICIPANTS

Throughout the PREDICT-HD study the focus will be on retention of study participants. Several retention tools have been created in an effortto facilitate the preservation of participant interest for the duration of the PREDICT-HD study period.

SUBSEQUENT VISIT FORM

Designed to assist the site coordinator in ensuring that the study participant has his/her next scheduled (retention and compliance) visit is the **Subsequent Visit Form** (see Appendix IV). This Case Report Formis to be completed at the end of each study visit and is to be submitted along with all visit case report forms to the Coordination Center.

CONFIDENTIAL VISIT EVALUATION FORM

During each clinic visit the participant will receive, from the site coordinator, the **Confidential Visit Evaluation Form** (see Appendix IV) and an envelope in which the participant is instructed to enclose the completed confidential form inside. This research form is specifically designed to facilitate a better understanding of the needs of the participant to continue their participation (retention) in the PREDICT study.

The Confidential Visit Evaluation Form surveys the participant for their opinion, as a research subject, in areas for improvement both at the sitelevel and at an overall view to the research study.

Once the participant completes the Confidential Visit Evaluation Form they will seal it in the supplied envelope and return it to the site coordinator at the end of each visit. The site coordinator will submit thissealed envelope containing the completed Confidential Visit Evaluation Form along with all the visit case report forms to the Coordination Center.

TELEPHONE CONTACT FORM

As frequency of contact is associated with retention of study participationit is important that contact be made with the participant by phone between each annual visit. Therefore, the study participant will be telephoned every 6 months between study visits. During these telephonecontacts the site coordinator will verify with the participant the date of

their next annual visit (schedule or reschedule if necessary). This telephone contact will also be used to capture any new contact information (change of phone number, address, etc). The **Telephone Contact Form** (see Appendix IV) will be completed during this call.

Once phone contact has been made, at each 6 month interval, the Telephone Contact Form must be mailed to the CTCC.

BI-ANNUAL RETENTION ACTIVITY RECORD

The **Bi-Annual Retention Activity Record** (see Appendix IV) is used to record retention activity between each visit. This retention record is to be faxed to the Coordination Center at (585) 451-3554 every 6 months.

IRB approved retention items may be sent out on a regular basis and tracked on the Bi-Annual Retention Activity Record. A key is provided on this record in tracking retention efforts. If a retention item not indicated in the key has been completed sites must indicate this in the comments section.

Additionally, each site **must** indicate on the Bi-Annual Retention Activity Record, whether or not, retention efforts will be conducted at the University of Iowa (distribution of retention items as consented by participant in Appendix F of informed consent).

SECTION XVI

AUSTRALIAN SITE PROCEDURES

Appendix XVI

Screening/Projection Log (electronic sample)
Manual Enrollment Form (electronic sample)
Notification Form (electronic sample)
Incident Form (electronic sample)

AUSTRALIAN SITE PROCEDURES

GENERAL INFORMATION FOR AUSTRALIAN SITES

General information such as Study Contacts, Office Closings and Study Personnel for all sites including Australian sites is located in Section I of this operations manual.

PROTOCOL ACTIVITIES

Protocol activities such as the Schedule of Activities, Protocol, Synopsis, and Amendments for all sites including Australian sites is located in Section II of this operations manual.

SCREENING/PROJECTION LOG

The PREDICT Screening/Projection Log (see sample log in Appendix XVI) is utilized to determine projected enrollment timelines, the need for additional supplies and is used to monitor anticipated and scheduled enrollments and monitor recruitment difficulties.

The Screening/Projection log was designed to capture information about all participants who may or may not have signed the Informed Consent and are willing to participate in PREDICT-HD if eligible. It reflects site predictions about the number and timing of future enrollments.

Information provided on this log is also used to describe recruitment efforts in reports to the sponsor and IRB annual reports.

PREDICT-HD SCREENING/PROJECTION LOG INSTRUCTIONS FORAUSTRALIAN SITES

Please follow the detailed instructions below for completion and submission of the PREDICT-HD Screening/Projection Log.

Site Number: Enter your 3-digit site number in the upper right hand corner.

Screening Number: The screening number is a two-digit number assigned by the site, beginning with 01, 02, 03 and so on. Sequentially assign a number for each potential participant.

Gender: Check “F” (Female) or “M” (Male).

Ethnic Category: Enter the appropriate number for the participant's ethnic category from the list provided. This response must be elicited from the participant.

Racial Category: Enter the appropriate number for the participant's racial category from the list provided. "Other" should be used to specify aborigines on the line provided. This response must be elicited from the participant.

Projected Enrollment Date: Enter the actual or anticipated date that the participant is scheduled to be seen for Screening/Baseline Visit 1 in **MM/DD/YEAR** format. If the visit is rescheduled, be sure to update the Log and **enter the new date followed by an asterisk (*)**. If the visit has not yet been scheduled, leave the space blank. Please be aware that blanks are talliedin the "Unknown date" column of the Enrollment Projections Report.

Referral Source: Enter the appropriate number that describes how the participant was referred to the study. If "other," specify on the line provided.

Enrolled: Check "Y" at the time the participant is enrolled or "N" at the time the participant is deemed ineligible or otherwise declines to enter the study. Leave blank prior to such a determination.

Participant ID Number: Enter the four-digit ID number assigned at the time the participant is enrolled. Leave blank if the participant declines to enter the study or is deemed ineligible.

Helpful Reminders When Filling Out the Screening Projection Log

1. **Do not re-assign screening numbers**. Once the number is given to a participant it will always belong to that participant even if he/she is deemed ineligible or chose to withdraw from the study prior to enrollment.

2. Do not re-enter an individual on a second line; for example, if screen number "05" is entered in row six, that person's information will alwaysremain in row six.

3. Once information is entered on the Log, it should not have to be changedunless the Projected Enrollment Date changes or a mistake was made. In such an event, **enter the new information followed by an asterisk (*)**. This will indicate to CTCC staff that this is a valid change.

4. Each time you submit the Screening/Projection Log, resend <u>all</u> pages regardless of whether or not any information has been updated or addedto a given page.

5. The Log is a cumulative running form. Therefore, it is not necessary to recopy the information from one sheet to a new sheet each time you submit it. Simply keep adding new participants to the Log over the weeks.

Timeline for Log Submission

Please Email the updated *Screening/Projection Log* to the PREDICT-HD Data Control Clerk (email address: Sue.Daigneault@ctcc.rochester.edu) at the CTCC on a **biweekly** basis until study enrollment is completed.

- In the case of a screening failure, update the log with the reason for the failure.
- At the end of the study, send a copy of the log to the CTCC with the final CRFs.

ENROLLMENT/PROJECTION REPORT (see Appendix XVI for sample)

- Generated from data entered on the *Screening/Projection Log*.
- Distributed on a regular basis to sites so all are able to see where theyrank in enrollment status relative to other sites.
- The Principal Investigator and Steering Committee also receive this report.

ENROLLMENT PROCEDURE FOR AUSTRALIAN SITESMANUAL

ENROLLMENT

The PREDICT-HD Manual Enrollment Form is designed to electronically notify the CTCC of a participant enrollment at your site. Upon receipt of your Manual Enrollment form the CTCC will enter all information into the enrollment module and an Enrollment Verification report will be sent electronically to the enrolling site. A participant officially enters the study when the site emails the completed Manual Enrollment Form to the Clinical Trials Coordination Center (CTCC).

PREDICT-HD participants will be enrolled after they have met all eligibility criteria. Australian sites will then assign the participant the **first number in the sequence of numbers** supplied by the Coordination Center. The assigned sequence of participant ID codes **must** be followed.

The Manual Enrollment Form (see sample in Appendix XVI) **must** be completed and returned **within 24 hours** of enrollment via email to Sue Daigneault at Sue.Daigneault@ctcc.rochester.edu.

Who may enroll a participant?

- Either the enrolling Site Investigator or the Site Coordinator (no othersite staff will be permitted to enroll participants).

When do I complete and return a Manual Enrollment Form?

- During the Screening/Baseline Visit (Visit 1) **after** all eligibility criteria are complete.
- Any questions regarding the participant's eligibility should be referred tothe Project Coordinator **prior** to placing the enrollment call.

PREDICT-HD MANUAL ENROLLMENT INSTRUCTIONS FOR AUSTRALIANSITES

Please follow the detailed instructions below for completion and submission of the PREDICT-HD Manual Enrollment Form.

1. Enter **all header information** (Caller Staff Code, Site Number and enrollment date (MM/DD/Year))

2. Enter **Y=Yes or N=No** if the participant signed the Informed Consent.

3. Enter **the date** that the participant signed the Informed Consentin MM/DD/Year.

4. HIPAA compliance does not apply to Australian sites. Please skip this question.

5. Enter **the screening number** of the participant. This screening number **must** match that entered on the screening/projection log.

6. Enter the **Screening/Baseline Visit date** in MM/DD/Year.

7. Enter the **participant's Date of Birth** in MM/DD/Year.

8. Check **Gender (one response only)**

9. Check **Ethnicity (one response only)**

10. Check **Racial Category (one response only)**

11. Check **Gene status (one response only)**

NOTE: You **must** enroll 7 gene positive participants before you can enroll a gene negative participant

12. Check **Y=Yes or N=No** (one response only) as to whether the participant has a **companion at visit 1.**

12a. If the response to question 12 is Y=Yes then you may skip question 12a. If the response to question 12 is N=No then you **must** answer question 12a with a response of Y=Yes or N=No as to whether you obtained a waiver. *If the participant does not have a companion with them at visit 1 aPREDICT-HD Notification **must** be completed and returned to the CTCC prior to this enrollment.*

13. Check **Y=Yes or N=No (one response only)** to whether the participant **met all other eligibility criteria.**

13a. If the response to question 13 is Y=Yes then you may skip question 13a. If the response to question 13 is N=No then you **must** answer question 13a with a response of Y=Yes or N=No as to whether you obtained a waiver. *If the participant does not meet all other eligibility criteria a PREDICT-HD Notification **must** be completed and returned to the CTCC prior to this enrollment.*

14. Enter the 4-digit assigned participant ID number. *These numbershave been provided to you by the CTCC.*

Submitting the Manual Enrollment Form

Once the PREDICT-HD Manual Enrollment Form has been completed please return it **immediately** via email to Sue Daigneault at Sue.Daigneault@ctcc.rochester.edu.

For any questions or concerns regarding the PREDICT-HD Manual Enrollment Form contact Sue Daigneault at Sue.Daigneault@ctcc.rochester.edu.

PARTICIPANT ID NUMBER ASSIGNMENT

Once a study participant meets all eligibility criteria the AU site will assign the participant his/her ID number. The Participant ID number sequence supplied by the Coordination Center **MUST** be followed when assigning participant numbers.

When the Coordination Center receives the Manual Enrollment Form it is entered and the Enrollment Module uses the date of enrollment to calculate the

participant's follow-up visit window schedule (the dates in which the participant should be seen by the study staff for a given visit). (See Appendix III for sample *Visit Window Schedule*.)

- Locate the Participant ID number on the set of labels and corresponding barcodes (*Sample of DNA Blood Tube Labels* - Appendix III). Enter this number in the space provided on the top of each CRF page. This number will be used by the HSG Coordination Center to identify the participant. The barcode labels contain a separate embedded number to be used by the lab for identifying the DNA blood samples. Peel off the Participant ID number and place it on the CRF page marked *Participant ID Label*.

NOTE: The participant ID numbers and barcodes are designed such that neither the HSG Coordination Center nor the DNA lab will individually be able to match the numbers to the participant by name.

An *Enrollment Verification Report* (see Appendix III for sample) listing the Participant ID and the visit window schedule will be emailed to the Site Coordinator following the receipt of the Manual Enrollment Form. Upon receiving the report, the coordinator should verify that the participant identifiers are correct and file the report in the participant's folder. If an erroris found, please notify the CTCC.

COMPANION ID NUMBER ASSIGNMENT

A Companion ID number for the study participant's companion will be assigned by the site staff. The companion number will begin with "C" as the prefix to the number and "01" for the first companion: "02" for the second companion and so on (i.e. C01 is the first companion. If the participant has a different companion at Visit 2, he/she will be assigned C02 as his/her number). This number will be used by the HSG Coordination Center to identify the companion. This number should be entered on all CRF pages that require the companion number.

NOTE: A COMPANION CANNOT BE ENROLLED AS A PARTICIPANT.CONFIDENTIAL

PARTICIPANT/COMPANION LOG

Confidentiality of the participants' identification must remain strict throughout the course of the study. Responsibility for confidentiality rests with both the investigators and participants. Participants should consider carefully before disclosing their participation to anyone.

- Identifying information about a participant such as name, initials, or social security number must never be in the case report form (CRF) binder.
- The signed Consent Form must be kept separate from the CRF binder.
- We are providing you with a *PREDICT-HD Confidential Participant Identification Code Log* (see Appendix III) that should be kept in a locked secure location separate from the CRF binder. When participants are screened/baselined, you may write their initials along with the identification number on the PREDICT Confidential Participant Log. There is also a *PREDICT-HD Confidential Companion Identification Code Log.* The companion name and number should be recorded and if the companion changes, the name and number for the new companion should be listed.

CASE REPORT FORM (CRF) INSTRUCTIONS

Case Report Form (CRF) instructions for all sites including Australian sites can be found in Section IV of this operations manual.

PSYCHIATRIC ASSESSMENTS

Psychiatric Assessments for all sites including Australian sites can be found in Section V of this operations manual.

COGNITIVE ASSESSMENTS

For instructions regarding the Cognitive Testing Battery, please refer to the Cognitive Operations Manual.

UNIFIED HUNTINGTON'S DISEASE RATING SCALE '99

Guidelines for the Modified Unified Huntington's Disease Rating Scale '99 forall sites including Australian sites can be found in Section VII of this operations manual.

MOTOR RATER'S MANUAL

Responsibilities of the Motor Rater, Precautions and Communications for all sites including Australian sites can be found in Section VIII of this operations manual.

NOTIFICATIONS AND REPORTABLE EVENTS

PREDICT-HD Notification Reporting Instructions for Australian Sites

NOTIFICATION REPORTING

- **Notification Definition:** The objective of the Notification process is to detail all noteworthy and relevant clinical or data management decisions that might influence the interpretation of the study data.

Instructions: When reporting an event (i.e., GCP guideline, site specific, eligibility, study procedure, protocol deviation) please complete the PREDICT-HD Notification Report as follows:

1. **Enter all header information** (Site Caller Staff Number, Site Number, Screening number, Subject number, CRF Name, Visit number and Date of Event)

2. **Enter comments:** It is very important that you supply the CTCC with clear detailed comments on this report for accurate coding.

DO NOT code, sub-code or list outcome. The CTCC will **code, sub-code** and list the **outcome** in-house.

Notification Report Sample…
Comment: Companion Waiver Participant's companion was unable to attend Visit 1 due to her work schedule. The wife will come within the month to complete the consent and fill out the questionnaires.

3. **Submitting Notification Report:** Once the PREDICT-HD Notification Report has been completed please return it **within 24hours** via email to Elaine Julian-Baros at Elaine.JulianBaros@ctcc.rochester.edu or fax to the attention of Elaine Julian-Baros at (585) 461-3554.

NOTE: If the Notification is for a "waiver" you must email this first to the CTCC before you can enroll the participant.

4. **Notification Report Acknowledgement:** The CTCC will send you electronically a completed Notification Report. Please keep this report with the participant's CRFs.

PREDICT-HD Incident Reporting Instructions for Australian Sites

INCIDENT REPORTING (Reportable Event)

❖ **Reportable Event Definition:** The objective of the Incident reporting process is to detail all the experiences that may influencethe safety of the participants in the study.

For a complete list of Reportable Events see Section IX Reportable Events of the PREDICT-HD Operations Manual.

Instructions: When reporting an incident (Reportable Event) please complete the PREDICT-HD Manual Incident Report asfollows:

1. **Enter all header information (Caller Staff Code, Site number, Subject number and Date of Incident)**

2. Check the box that corresponds to the event and enter the date ofthe event.

3. **Enter comments:** Please be detailed in your comments (i.e., BHS, BDI and UHDRS scores).

Incident Report Sample…

Comment: Participant had a total score on the BHS of 15, BDI was 20 and UHDRS Q25 a & b was 3. Participant has a hx of depression and has been on antidepressants and received therapy in the past. Participant is not currently on any medications. Depression is felt to be static. Risks were reviewed with participant and she was asked to follow up with her psychiatrist.

4. **Submitting the Incident Report:** Once the PREDICT-HD Incident Report has been completed please return it **within 24 hours** via email to Elaine Julian-Baros at Elaine.JulianBaros@ctcc.rochester.edu or fax to the attention of Elaine Julian-Baros at (585) 461-3554.

5. **Incident Report Acknowledgement:** The CTCC will send you electronically a completed Incident Report. Please keep this report with the participant's CRFs.

LABORATORY SPECIMEN MANAGEMENT

Management of laboratory specimens (DNA samples and annual blood samples)for all sites including Australian sites can be found in Section X of this operations manual.

MRI PROTOCOL

The MRI protocol for all sites including Australian sites can be found in Section XI of this operations manual.

SOURCE DOCUMENTATION

Information on source documentation for all sites including Australian sites can be found in Section XII of this operations manual.

MONITORING

Information on monitoring for all sites including Australian sites can be found in Section XIII in this operations manual.

UPDATES

All sites are to retain newsletters or general updates in Section XIV of this operations manual.

Appendix XVI

Screening/Projection Log (electronic sample)
Manual Enrollment Form (electronic sample)
Notification Form (electronic sample)
Incident Form (electronic sample)

SCREENING/PROJECTION LOG
PREDICT HD

Please record all potentially eligible Predict-HD participants and complete all information for each participant. At each reporting period use this sheet to add new participants and to update information for previously listed participants.

Site No _____

SCREENING NUMBER	GENDER F M	ETHNIC CATEGORY 1 = Hispanic or Latino 2 = Not Hispanic or Latino 3 = Unknown or not reported	RACIAL CATEGORY 1 = American Indian/Alaskan Native 2 = Asian 3 = Native Hawaiian or other Pacific Islander 4 = Black or African American 5 = White 6 = More than one race 7 = Unknown or not reported 8 = Other If 8 – please specify	PROJECTED ENROLLMENT DATE (MM/DD/YEAR)	**REFERRAL SOURCE** 1 = PREDICT Site Personnel 2 = Advocacy Organization (HDSA, HSC, HDF, AHDA) 3 = National HD Research Roster 4 = HSG Website 5 = HSG 1-800 # 6 = Family/Friend 7 = HD Conference/Support Group 8 = Genetic Counselor 9 = Other If 9 – please specify	ENROLLED N. Y	PARTICIPANT ID NUMBER (if applicable)
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Please COMPLETE report **bi-weekly** and e-mail to Sue Daigneault at sue.daigneault@ctcc.rochester.edu

PREDICT-HD

Manual Enrollment
Revised 4-14-03

CTCC Staff Code:_____ Site Number: _____

Caller Staff Code: _____ Enrollment Date:
_____/_____/____

Participant Screening Number (from enrollment projections log): _____

Date of Screening/Baseline Visit: (MM/DD/YEAR) _____

Participant's date of birth:_____/_____/_____

Gender (circle one): F = Female M = Male

Ethnicity (circle one):
1 = Hispanic or Latino
2 = Not Hispanic or Latino
3 = Unknown or not reported

Racial Category: (circle one)
1 = American Indian/Alaskan Native
2 = Asian
3 = Native Hawaiian or Pacific Islander
4 = Black or African American
5 = White
6 = More than one race
7 = Unknown or not reported

Has the participant signed the Informed Consent:
Y N

Date Informed Consent was signed:

_____/_____/_____
(mm/dd/yyyy)

If Informed Consent was signed on/after 04/14/2003 and site is a ***U.S. site***, did participant sign a **HIPAA-compliant Informed Consent** form?:

Y N

Note: Subjects cannot enroll <u>in U. S. sites</u> until a HIPAA-compliant Informed Consent is signed. Please call the project coordinator assigned to the study.

Is this person gene positive or gene negative?

Positive

Negative

Does this person have a companion at visit 01?

Y N

If no, did you obtain a waiver?

Y N

(if no, please contact the project coordinator to obtain waiver)

Does this participant meet all other eligibility criteria?

Y N

The Participant number for this person is ___ ___ ___ ___.

PREDICT-HD NOTIFICATION
REPORT
CLINICAL TRIALS COORDINATION CENTER

Date Report Received:

Site Caller Staff Number: CTCC Staff Number:

Site #	**Screening #**	**Subject #**	**CRF Name**	**Visit #**	**Date of Event**

Code: **Subcode**: **Outcome**

Code	**Subcode**	**Outcome**
DMI = Data Management Issue		**W** = Waived **A** = Acknowledged **D =** Disapproved
GCP = GCP Guidelines		
NCE = Noteworthy Clinical Event	***PREG*** *= Pregnancy*	
SSI = Site Specific Issue		
E =Eligibility	*Enter up to 3 question numbers from the Inclusion/Exclusion form, separated by a comma.*	
SP = Study Procedure	***LAB*** *=Lab* ***COG*** *= Cognitive* ***MRI*** *=MRI* ***MOT*** *= Motor Video* ***MV*** *= Missed Visit* ***CV*** *=Cognitive Video* *Multi:SV = Multiple Assessments/Split visit*	
PD = Protocol Deviation	***CNP:TR*** *= Companion not Present, Travel Requirements* ***CNP:W****= Companion not Present, Work Commitments* ***CNP:FSO****= Companion not Present, Family/Social Obligations* ***CNP:HI****= Companion not Present, Health Issues* ***CNP:MC****= Companion not Present, Subject wants tomaintain confidentiality* ***CNP:NIC*** *= Companion not Present, No identified companion* *CNP:OV = Companion not Present, Surveys completed outside study visit* ***DM*** *=Disallowed Medication* ***OWV*** *= Out of Window Visit*	
OTH = Other		

COMMENTS:

PREDICT-HD STUDY

Manual Incident Report

CTCC Staff Code: Site Number:

Caller Staff Code: Subject Number:

Date Reported:
(MM/DD/YY)

Is this event a new use of restricted medications? ☐ Y

Date of new use of restricted medications:
(MM/DD/YY)

Is this event a new evaluation by a mental health professional? ☐ Y

Date of new evaluation by a mental health professional:
(MM/DD/YY)

Is this event new onset depression? ☐ Y

Date of new onset depression:
(MM/DD/YY)

Is this event an exacerbation of depression requiring either:

a. change in pharmacotherapy? ☐ Y

Date of change in pharmacotherapy for depression:
(MM/DD/YY)

b. mental health professional visit? ☐ Y

Date of mental health professional visit for depression:
(MM/DD/YY)

Is this event a suicide attempt? ☐ Y

Date of suicide attempt:
(MM/DD/YY)

Is this event an inpatient hospitalization for a serious medical issue (including childbirth)? ☐ Y

Date of inpatient hospitalization:

(MM/DD/YY)

Is this event a neurological event? ☐ Y

Date of neurological event:

(MM/DD/YY)

Is the event a premature withdrawal? ☐ Y

Date of premature withdrawal:

(MM/DD/YY)

Last Visit Number:

Is this event a death? ☐ Y

Date of death:

(MM/DD/YY)

Is this event a suicide risk? ☐ Y

Date of suicide risk:

(MM/DD/YY)

Suicide risk reported in BHS? ☐ Y
Suicide risk reported in BDI? ☐ Y
Suicide risk reported in UHDRS? ☐ Y

Is this event a psychiatric hospitalization? ☐ Y

Date of psychiatric hospitalization:

(MM/DD/YY)

Is this event a compromise of confidentiality? ☐ Y

Date of compromise of confidentiality:

(MM/DD/YY)

Is this event an identification of a safety concern warranting referral for medical evaluation? ☐ Y

Date of safety concern warranting medical evaluation:

(MM/DD/YY)

Is this event an identification of a safety concern warranting referral for psychiatric evaluation? ☐ Y

Date of safety concern warranting referral for psychiatric evaluation: (MM/DD/YY)

Comments:

SECTION XVII

EUROPEAN SITE PROCEDURES

Appendix XVII

Screening/Projection Log (electronic sample)Manual Enrollment Form (electronic sample)Notification Form (electronic sample) Incident Form (electronic sample)

EUROPEAN SITE PROCEDURES

GENERAL INFORMATION FOR EUROPEAN SITES

General information such as Study Contacts, Office Closings and Study Personnel for all sites including European sites is located in Section I of this operations manual.

PROTOCOL ACTIVITIES

Protocol activities such as the Schedule of Activities, Protocol, Synopsis, and Amendments for all sites including European sites is located in Section II of this operations manual.

SCREENING/PROJECTION LOG

The PREDICT Screening/Projection Log (see sample log in Appendix XVI) is utilized to determine projected enrollment timelines, the need for additional supplies and is used to monitor anticipated and scheduled enrollments and monitor recruitment difficulties.

The Screening/Projection log was designed to capture information about all participants who may or may not have signed the Informed Consent and are willing to participate in PREDICT-HD if eligible. It reflects site predictions about the number and timing of future enrollments.

Information provided on this log is also used to describe recruitment efforts in reports to the sponsor and IRB annual reports.

PREDICT-HD SCREENING/PROJECTION LOG INSTRUCTIONS FOREUROPEAN SITES

Please follow the detailed instructions below for completion and submission of the PREDICT-HD Screening/Projection Log.

Site Number: Enter your 3-digit site number in the upper right hand corner.

Screening Number: The screening number is a two-digit number assigned by the site, beginning with 01, 02, 03 and so on. Sequentially assign a number for each potential participant.

Gender: Check “F” (Female) or “M” (Male).

Ethnic Category: Enter the appropriate number for the participant's ethnic category from the list provided. This response must be elicited from the participant.

Racial Category: Enter the appropriate number for the participant's racial category from the list provided. "Other" should be used to specify another category not listed on the line provided. This response must be elicited from the participant.

Projected Enrollment Date: Enter the actual or anticipated date that the participant is scheduled to be seen for Screening/Baseline Visit 1 in **MM/DD/YEAR** format. If the visit is rescheduled, be sure to update the Log and **enter the new date followed by an asterisk (*)**. If the visit has not yet been scheduled, leave the space blank. Please be aware that blanks are talliedin the "Unknown date" column of the Enrollment Projections Report.

Referral Source: Enter the appropriate number that describes how the participant was referred to the study. If "other," specify on the line provided.

Enrolled: Check "Y" at the time the participant is enrolled or "N" at the time the participant is deemed ineligible or otherwise declines to enter the study. Leave blank prior to such a determination.

Participant ID Number: Enter the four-digit ID number assigned at the time the participant is enrolled. Leave blank if the participant declines to enter the study or is deemed ineligible.

Helpful Reminders When Filling Out the Screening Projection Log

1. **Do not re-assign screening numbers**. Once the number is given to a participant it will always belong to that participant even if he/she is deemed ineligible or chose to withdraw from the study prior to enrollment.

2. Do not re-enter an individual on a second line; for example, if screen number "05" is entered in row six, that person's information will alwaysremain in row six.

3. Once information is entered on the Log, it should not have to be changedunless the Projected Enrollment Date changes or a mistake was made. In such an event, **enter the new information followed by an asterisk (*)**. This will indicate to CTCC staff that this is a valid change.

4. Each time you submit the Screening/Projection Log, resend <u>all</u> pages regardless of whether or not any information has been updated or addedto a given page.

5. The Log is a cumulative running form. Therefore, it is not necessary to recopy the information from one sheet to a new sheet each time you submit it. Simply keep adding new participants to the Log over the weeks.

Timeline for Log Submission

Please Email the updated *Screening/Projection Log* to the PREDICT-HD Data Control Clerk (email address: Sue.Daigneault@ctcc.rochester.edu) at the CTCC on a **biweekly** basis until study enrollment is completed.

- In the case of a screening failure, update the log with the reason for the failure.
- At the end of the study, send a copy of the log to the CTCC with the final CRFs.

ENROLLMENT/PROJECTION REPORT (see Appendix XVI for sample)

- Generated from data entered on the *Screening/Projection Log.*
- Distributed on a regular basis to sites so all are able to see where theyrank in enrollment status relative to other sites.
- The Principal Investigator and Steering Committee also receive this report.

ENROLLMENT PROCEDURE FOR EUROPEAN SITESMANUAL

ENROLLMENT

The PREDICT-HD Manual Enrollment Form is designed to electronically notify the CTCC of a participant enrollment at your site. Upon receipt of your Manual Enrollment form the CTCC will enter all information into the enrollment module and an Enrollment Verification report will be sent electronically to the enrolling site. A participant officially enters the study when the site emails the completed Manual Enrollment Form to the Clinical Trials Coordination Center (CTCC).

PREDICT-HD participants will be enrolled after they have met all eligibility criteria. European sites will then assign the participant the **first number in the sequence of numbers** supplied by the Coordination Center. The assigned sequence of participant ID codes **must** be followed.

The Manual Enrollment Form (see sample in Appendix XVI) **must** be completed and returned **within 24 hours** of enrollment via email to Sue Daigneault at Sue.Daigneault@ctcc.rochester.edu.

Who may enroll a participant?

- Either the enrolling Site Investigator or the Site Coordinator (no othersite staff will be permitted to enroll participants).

When do I complete and return a Manual Enrollment Form?

- During the Screening/Baseline Visit (Visit 1) **after** all eligibility criteria are complete.
- Any questions regarding the participant's eligibility should be referred tothe Project Coordinator **prior** to placing the enrollment call.

PREDICT-HD MANUAL ENROLLMENT INSTRUCTIONS FOR EUROPEANSITES

Please follow the detailed instructions below for completion and submission of the PREDICT-HD Manual Enrollment Form.

1. Enter **all header information** (Caller Staff Code, Site Number and enrollment date (MM/DD/Year))

2. Enter **Y=Yes or N=No** if the participant signed the Informed Consent.

3. Enter **the date** that the participant signed the Informed Consentin MM/DD/Year.

4. HIPAA compliance does not apply to European sites. Please skip this question.

5. Enter **the screening number** of the participant. This screening number **must** match that entered on the screening/projection log.

6. Enter the **Screening/Baseline Visit date** in MM/DD/Year.

7. Enter the **participant's Date of Birth** in MM/DD/Year.

8. Check **Gender (one response only)**

9. Check **Ethnicity (one response only)**

10. Check **Racial Category (one response only)**

11. Check **Gene status (one response only)**

NOTE: You **must** enroll 7 gene positive participants before you can enroll a gene negative participant

12. Check **Y=Yes or N=No** (one response only) as to whether the participant has a **companion at visit 1.**

12a. If the response to question 12 is Y=Yes then you may skip question 12a. If the response to question 12 is N=No then you **must** answer question 12a with a response of Y=Yes or N=No as to whether you obtained a waiver. *If the participant does not have a companion with them at visit 1 aPREDICT-HD Notification **must** be completed and returned to the CTCC prior to this enrollment.*

13. Check **Y=Yes or N=No (one response only)** to whether the participant **met all other eligibility criteria.**

13a. If the response to question 13 is Y=Yes then you may skip question 13a. If the response to question 13 is N=No then you **must** answer question 13a with a response of Y=Yes or N=No as to whether you obtained a waiver. *If the participant does not meet all other eligibility criteria a PREDICT-HD Notification **must** be completed and returned to the CTCC prior to this enrollment.*

14. Enter the 4-digit assigned participant ID number. *These numbershave been provided to you by the CTCC.*

Submitting the Manual Enrollment Form

Once the PREDICT-HD Manual Enrollment Form has been completed please return it **immediately** via email to Karen Rothenburgh at Karen.Rothenburgh@ctcc.rochester.edu.

For any questions or concerns regarding the PREDICT-HD Manual Enrollment Form contact Karen Rothenburgh at Karen.Rothenburgh@ctcc.rochester.edu

PARTICIPANT ID NUMBER ASSIGNMENT

Once a study participant meets all eligibility criteria the European site will assign the participant his/her ID number. The Participant ID number sequence supplied by the Coordination Center **MUST** be followed when assigning participant numbers.

When the Coordination Center receives the Manual Enrollment Form it is entered and the Enrollment Module uses the date of enrollment to calculate the participant's follow-up visit window schedule (the dates in which the

participant should be seen by the study staff for a given visit). (See Appendix III for sample *Visit Window Schedule*.)

- Locate the Participant ID number on the set of labels and corresponding barcodes (*Sample of DNA Blood Tube Labels* - Appendix III). Enter this number in the space provided on the top of each CRF page. This number will be used by the HSG Coordination Center to identify the participant. The barcode labels contain a separate embedded number to be used by the lab for identifying the DNA blood samples. Peel off the Participant ID number and place it on the CRF page marked *Participant ID Label*.

NOTE: The participant ID numbers and barcodes are designed such that neither the HSG Coordination Center nor the DNA lab will individually be able to match the numbers to the participant by name.

An *Enrollment Verification Report* (see Appendix III for sample) listing the Participant ID and the visit window schedule will be emailed to the Site Coordinator following the receipt of the Manual Enrollment Form. Upon receiving the report, the coordinator should verify that the participant identifiers are correct and file the report in the participant's folder. If an erroris found, please notify the CTCC.

COMPANION ID NUMBER ASSIGNMENT

A Companion ID number for the study participant's companion will be assigned by the site staff. The companion number will begin with "C" as the prefix to the number and "01" for the first companion: "02" for the second companion and so on (i.e. C01 is the first companion. If the participant has a different companion at Visit 2, he/she will be assigned C02 as his/her number). This number will be used by the HSG Coordination Center to identify the companion. This number should be entered on all CRF pages that require the companion number.

NOTE: A COMPANION CANNOT BE ENROLLED AS A PARTICIPANT.CONFIDENTIAL

PARTICIPANT/COMPANION LOG

Confidentiality of the participants' identification must remain strict throughout the course of the study. Responsibility for confidentiality rests with both the investigators and participants. Participants should consider carefully before disclosing their participation to anyone.

- Identifying information about a participant such as name, initials, or social security number must never be in the case report form (CRF) binder.
- The signed Consent Form must be kept separate from the CRF binder.

- We are providing you with a *PREDICT-HD Confidential Participant Identification Code Log* (see Appendix III) that should be kept in a locked secure location separate from the CRF binder. When participants are screened/baselined, you may write their initials along with the identification number on the PREDICT Confidential Participant Log. There is also a *PREDICT-HD Confidential Companion Identification Code Log.* The companion name and number should be recorded and if the companion changes, the name and number for the new companion should be listed.

CASE REPORT FORM (CRF) INSTRUCTIONS

Case Report Form (CRF) instructions for all sites including European sites can be found in Section IV of this operations manual.

PSYCHIATRIC ASSESSMENTS

Psychiatric Assessments for all sites including European sites can be found in Section V of this operations manual.

COGNITIVE ASSESSMENTS

For instructions regarding the Cognitive Testing Battery, please refer to the Cognitive Operations Manual.

UNIFIED HUNTINGTON'S DISEASE RATING SCALE '99

Guidelines for the Modified Unified Huntington's Disease Rating Scale '99 for all sites including European sites can be found in Section VII of this operations manual.

MOTOR RATER'S MANUAL

Responsibilities of the Motor Rater, Precautions and Communications for all sites including European sites can be found in Section VIII of this operations manual.

NOTIFICATIONS AND REPORTABLE EVENTS

PREDICT-HD Notification Reportable Instructions for European Sites

NOTIFICATION REPORTING

- **Notification Definition:** The objective of the Notification process is to detail all noteworthy and relevant clinical or data management decisions that might influence the interpretation of the study data.

Instructions: When reporting an event (i.e., GCP guideline, site specific, eligibility, study procedure, protocol deviation) please complete the PREDICT-HD Notification Report as follows:

1. **Enter all header information** (Site Caller Staff Number, Site Number, Screening number, Subject number, CRF Name, Visit number and Date of Event)

2. **Enter comments:** It is very important that you supply the CTCC with clear detailed comments on this report for accurate coding.

DO NOT code, sub-code or list outcome. The CTCC will **code, sub-code** and list the **outcome** in-house.

Notification Report Sample… Comment: Companion Waiver Participant's companion was unable to attend Visit 1 due to her work schedule. The wife will come within the month to complete the consent and fill out the questionnaires.

3. **Submitting Notification Report:** Once the PREDICT-HD Notification Report has been completed please return it **within 24hours** via email to Elaine Julian-Baros at Elaine.JulianBaros@ctcc.rochester.edu or fax to the attention of Elaine Julian-Baros at (585) 461-3554.

NOTE: If the Notification is for a "waiver" you must email this first to the CTCC before you can enroll the participant.

4. **Notification Report Acknowledgement:** The CTCC will send you electronically a completed Notification Report. Please keep this report with the participant's CRFs.

PREDICT-HD Incident Reporting Instructions for European SitesINCIDENT

REPORTING (Reportable Event)

- **Reportable Event Definition:** The objective of the Incident reporting process is to detail all the experiences that may influencethe safety of the participants in the study.

For a complete list of Reportable Events see Section IX Reportable Events of the PREDICT-HD Operations Manual.

Instructions: When reporting an incident (Reportable Event) please complete the PREDICT-HD Manual Incident Report as follows:

1. **Enter all header information (Caller Staff Code, Site number, Subject number and Date of Incident)**

2. Check the box that corresponds to the event and enter the date ofthe event.

3. **Enter comments:** Please be detailed in your comments (i.e., BHS, BDI and UHDRS scores).

Incident Report Sample…

Comment: Participant had a total score on the BHS of 15, BDI was 20 and UHDRS Q25 a & b was 3. Participant has a hx of depression and has been on antidepressants and received therapy in the past. Participant is not currently on any medications. Depression is felt to be static. Risks were reviewed with participant and she was asked to follow up with her psychiatrist.

4. **Submitting the Incident Report:** Once the PREDICT-HD Incident Report has been completed please return it **within 24 hours** via email to Elaine Julian-Baros at Elaine.JulianBaros@ctcc.rochester.edu or fax to the attention of Elaine Julian-Baros at (585) 461-3554.

5. **Incident Report Acknowledgement:** The CTCC will send you electronically a completed Incident Report. Please keep this report with the participant's CRFs.

LABORATORY SPECIMEN MANAGEMENT

Management of laboratory specimens (DNA samples and annual blood samples)for all sites including European sites can be found in Section X of this operations manual.

MRI PROTOCOL

The MRI protocol for all sites including European sites can be found in Section XI of this operations manual.

SOURCE DOCUMENTATION

Information on source documentation for all sites including European sites can be found in Section XII of this operations manual.

MONITORING

Information on monitoring for all sites including European sites can be found in Section XIII in this operations manual.

UPDATES

All sites are to retain newsletters or general updates in Section XIV of this operations manual.

Appendix XVII

Screening/Projection Log (electronic sample)
Manual Enrollment Form (electronic sample)
Notification Form (electronic sample)
Incident Form (electronic sample)

SCREENING/PROJECTION LOG
PREDICT HD

Please record all potentially eligible Predict-HD participants and complete all information for each participant. At each reporting period use this sheet to add new participants and to update information for previously listed participants.

Site No. _____

SCREENING NUMBER	GENDER F M	ETHNIC CATEGORY 1 = Hispanic or Latino 2 = Not Hispanic or Latino 3 = Unknown or not reported	RACIAL CATEGORY 1 = American Indian/Alaskan Native 2 = Asian 3 = Native Hawaiian or other Pacific Islander 4 = Black or African American 5 = White 6 = More than one race 7 = Unknown or not reported 8 = Other If 8 – please specify	PROJECTED ENROLLMENT DATE (MM/DD/YEAR)	**REFERRAL SOURCE** 1 = PREDICT Site Personnel 2 = Advocacy Organization (HDSA, HSC, HDF, AHDA) 3 = National HD Research Roster 4 = HSG Website 5 = HSG 1-800 # 6 = Family/Friend 7 = HD Conference/Support Group 8 = Genetic Counselor 9 = Other If 9 – please specify	ENROLLED N. Y	PARTICIPANT ID NUMBER (if applicable)
	☐ ☐					☐ ☐	
	☐ ☐					☐ ☐	
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	☐ ☐					☐ ☐	

Please COMPLETE report **bi-weekly** and e-mail to Sue Daigneault at sue.daigneault@ctcc.rochester.edu

PREDICT-HD

Manual Enrollment
Revised 4-14-03

CTCC Staff Code:_____ Site Number: _____

Caller Staff Code: _____ Enrollment Date:
_____/_____/____

Participant Screening Number (from enrollment projections log): _____

Date of Screening/Baseline Visit: (MM/DD/YEAR) _____

Participant's date of birth:_____/_____/_____

Gender (circle one): F = Female M = Male

Ethnicity (circle one):
1 = Hispanic or Latino
2 = Not Hispanic or Latino
3 = Unknown or not reported

Racial Category: (circle one)
1 = American Indian/Alaskan Native
2 = Asian
3 = Native Hawaiian or Pacific Islander
4 = Black or African American
5 = White
6 = More than one race
7 = Unknown or not reported

Has the participant signed the Informed Consent:
Y N

Date Informed Consent was signed:

_____/_____/_____
(mm/dd/yyyy)

If Informed Consent was signed on/after 04/14/2003 and site is a ***U.S. site***, did participant sign a **HIPAA-compliant Informed Consent** form?:
Y N

Note: Subjects cannot enroll <u>in U. S. sites</u> until a HIPAA-compliant Informed Consent is signed. Please call the project coordinator assigned to the study.

Is this person gene positive or gene negative?

Positive

Negative

Does this person have a companion at visit 01?

Y N

If no, did you obtain a waiver?

Y N

(if no, please contact the project coordinator to obtain waiver)

Does this participant meet all other eligibility criteria?

Y N

The Participant number for this person is ___ ___ ___ ___.

PREDICT-HD
NOTIFICATION REPORT
CLINICAL TRIALS COORDINATION CENTER

Date Report Received:

Site Caller Staff Number: CTCC Staff Number:

Site #	**Screening #**	**Subject #**	**CRF Name**	**Visit #**	**Date of Event**

Code: **Subcode**: **Outcome**

Code	Subcode	Outcome
DMI = Data Management Issue		**W** = Waived **A** = Acknowledged **D =** Disapproved
GCP = GCP Guidelines		
NCE = Noteworthy Clinical Event		
SSI = Site Specific Issue	***PREG*** *= Pregnancy*	
E =Eligibility	*Enter up to 3 question numbers from the Inclusion/Exclusion form, separated by a comma.*	
SP = Study Procedure	***LAB*** *=Lab* ***COG*** *= Cognitive* ***MRI*** *=MRI* ***MOT*** *= Motor Video* ***MV*** *= Missed Visit* ***CV*** *=Cognitive Video* *MULTI:SV = Multiple Assessments/Split visit*	
PD = Protocol Deviation	***CNP:TR*** *= Companion not Present, Travel Requirements* ***CNP:W****= Companion not Present, Work Commitments* ***CNP:FSO****= Companion not Present, Family/Social Obligations* ***CNP:HI****= Companion not Present, Health Issues* ***CNP:MC****= Companion not Present, Subject wants tomaintain confidentiality* ***CNP:NIC*** *= Companion not Present, No identified companion* *CNP:OV = Companion not Present, Surveys completed outside study visit* ***DM*** *=Disallowed Medication* ***OWV*** *= Out of Window Visit*	
OTH = Other		

COMMENTS:

PREDICT-HD STUDY

Manual Incident Report

CTCC Staff Code: Site Number:

Caller Staff Code: Subject Number:

Date Reported:
(MM/DD/YY)

Is this event a new use of restricted medications? ☐ Y

Date of new use of restricted medications:
(MM/DD/YY)

Is this event a new evaluation by a mental health professional? ☐ Y

Date of new evaluation by a mental health professional:
(MM/DD/YY)

Is this event new onset depression? ☐ Y

Date of new onset depression:
(MM/DD/YY)

Is this event an exacerbation of depression requiring either:

a. change in pharmacotherapy? ☐ Y

Date of change in pharmacotherapy for depression:
(MM/DD/YY)

b. mental health professional visit? ☐ Y

Date of mental health professional visit for depression:
(MM/DD/YY)

Is this event a suicide attempt? ☐ Y

Date of suicide attempt:
(MM/DD/YY)

Is this event an inpatient hospitalization for a serious

medical issue (including childbirth)? ☐ Y

Date of inpatient hospitalization:

(MM/DD/YY)

Is this event a neurological event? ☐ Y

Date of neurological event:

(MM/DD/YY)

Is the event a premature withdrawal? ☐ Y

Date of premature withdrawal:

(MM/DD/YY)

Last Visit Number:

Is this event a death? ☐ Y

Date of death:

(MM/DD/YY)

Is this event a suicide risk? ☐ Y

Date of suicide risk:

(MM/DD/YY)

Suicide risk reported in BHS? ☐ Y
Suicide risk reported in BDI? ☐ Y
Suicide risk reported in UHDRS? ☐ Y

Is this event a psychiatric hospitalization? ☐ Y

Date of psychiatric hospitalization:

(MM/DD/YY)

Is this event a compromise of confidentiality? ☐ Y

Date of compromise of confidentiality:

(MM/DD/YY)

Is this event an identification of a safety concern warranting referral for medical evaluation? ☐ Y

Date of safety concern warranting medical evaluation:

(MM/DD/YY)

Is this event an identification of a safety concern warranting referral for psychiatric evaluation? ☐ Y

Date of safety concern warranting referral for psychiatric evaluation:
(MM/DD/YY)

Comments:

SECTION XIV

UPDATES

Predict Visit Schedule
UHDRS Motor Assessment
Examples from UHDRS training video
Brain Bank
Newsletters

University of Iowa
Predict Visit Schedule

Day before visit date		Coordinator prepares consent form, information sheet, MRI checklist,DPA form Coordinator, sets up relevant computer programs and ensures adequatesample tubes, equipment, questionnaires etc.
08:30	Subject arrival	Subject arrives at centre, greeted by Coordinator 1. Offered refreshment 2. Discussion of study, suitability for MRI, subject given copy of information sheet 3. Informed consent taken 4. Pseudonymisation procedure carried out 5. Consent form photocopied and copy given to subject; scanned andelectronic copy saved 6. Data Protection Act form signed 7. MRI checklist filled out (first half, contraindications)
09:00	Cognitive testing	Coordinator takes subject 1. Cognitive assessment
11:00	Clinical Neuropsychiatric	Coordinator takes subject 1. Clinical and neuropsychiatric assessment 2. Self-administered questionnaires
12:00	Lunch	Coordinator treats participant and companion to lunch
12:45	Biosamples	Coordinator and nurse take subject 1. Blood samples and vitals taken
13:15	MRI	Coordinator escorts subject to scanner 1. MRI checklist completed (second half, removal of all metal objects) 2. Subject scanned 3. Staff member escorts subject back to the centre
14:00	Motor	Motor rater takes subject 1. Quantified motor assessment
14:30	Subject departure	Coordinator takes leave of subject 1. Ensures subject is satisfied and all questions answered 2. Subject informed when to expect phone call regarding next visit 3. Travel expenses collected from subject 4. Subject escorted to building exit and received reimbursement forparking costs
14.45		Coordinator 1. Receives signatures from Site Investigator 2. Photo copies and processes forms to be sent to data managementcenters 3. Orders MRI from lab to have transferred. 4. Prepares and sends thank you letter to participant

UHDRS MOTOR ASSESSMENT

Item	Instruction	Video recording	Score	Subscores
Gait	Observe the participant walking approximately 9 meters (10 yards) as briskly as they can, then turning and returning to the starting point.	Handheld	0 = normal gait, narrow base 1 = wide base and/or slow 2 = wide base and walks with difficulty 3 = walks only with assistance 4 = cannot attempt	Single score
Tandem gait	The participant 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.	Handheld	0 = normal for 10 steps 1 = 1 to 3 deviations from straight line 2 = More than 3 deviations 3 = cannot complete 4 = cannot attempt	Single score
Retropulsion test	The participant's response to a sudden posterior displacement produced by a pull on the shoulder while the participant 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 participant 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 participant's shoulders, the examiner should instruct the participant to stand up straight and not lean forward. The examiner should instruct the participant to take a step backward to avoid falling. Examiners must catch subjects who begin to fall.	Tripod (whole body)	0 = normal 1 = recovers spontaneously 2 = would fall if not caught 3 = tends to fall spontaneously 4 = cannot stand	Single score

Item	Instruction	Video recording	Score	Subscores
Tongue protrusion	Ask participant to open their mouth wide while you inspect it using a torch. Then ask participant to protrude their tongue well beyond their front teeth while keeping their mouth wide open and to keep it out as long as it takes you (as the examiner) to count aloud from 1 to 10. Participants should be made aware that they are not allowed to prevent their tongue from slipping back into the mouth by biting on it.	Tripod (face)	0 = can hold tongue fully protruded for 10 sec 1 = cannot keep fully protruded for 10 sec 2 = cannot keep fully protruded for 5 sec 3 = cannot fully protrude tongue 4 = cannot protrude tongue beyond lips	Single score
Ocular pursuit	Should be assessed over a range of approximately 20° with a slowly moving target taking about 2 seconds to move from one shoulder to the other.	Tripod (face)	0 = complete (normal) 1 = jerky movement 2 = interrupted pursuits/full range 3 = incomplete range 4 = cannot pursue	Horizontal and vertical
Saccade initiation	Should be tested over a 20° range, as for ocular pursuits. Saccade 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. If any head movements are made, subject should be prompted to keep head still.	Tripod (face)	0 = normal 1 = increased latency only 2 = suppressible blinks or head movements to initiate 3 = unsuppressible head movements	Horizontal and vertical
Saccade velocity	Should be tested at a larger range of approximately 30° so as to be able to detect incomplete range.	Tripod (face)	0 = normal 1 = mild slowing 2 = moderate slowing 3 = severely slow, full range 4 = incomplete range	Horizontal and vertical
Rigidity	Rigidity is judged on passive movement of the arms with the participant relaxed in the sitting position.	Tripod (upper body)	0 = absent 1 = slight or present only with activation 2 = mild to moderate 3 = severe, full range of motion 4 = severe with limited range	Left and right

Item	Instruction	Video recording	Score	Subscores
Finger taps	Participant taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately. Count the full-size taps made over 5 seconds.	Tripod (upper body)	0 = normal (≥15 in 5 sec.) 1 = mild slowing, reduction in amplitude (11-14 in 5 sec.) 2 = moderately impaired (7-10 in 5 sec.) 3 = severely impaired (3-6 in 5 sec.) 4 = can barely perform task (0-2 in 5 sec.)	Left and right
Pronate/supinate	Requires the participant 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. The participant should do this task as quickly as possible over a five-second interval. The task is graded according to the degree of slowing and irregularity.	Tripod (upper body)	0 = normal 1 = mild slowing and/or irregular 2 = moderate slowing and irregular 3 = severe slowing and irregular 4 = cannot perform	Left and right

Item	Instruction	Video recording	Score	Subscores
Luria	Fist-hand-palm sequencing - Say 'Can you do this?' Examiner puts hand into fist on flat surface and sequences as follow: fist, side, flat (do not repeat this out loud). Watch to make sure that participant can mimic each step. When participant is able to join you then say 'Very good, now keep going, I am going to stop. Rest hand and start timing participant's sequences. A sequence is considered correct only if it is unaided by examiner and in the correct order. If participant is unable to complete any sequences over a 10-second period, then continue as follows. Say 'Now lets try it again. Put your hands like this. FIST; SIDE; FLAT'. Watch to make sure the participant can mimic each step. Using the verbal labels, begin the sequences again and ask the participant to 'Do as I do, Fist, Side, Flat' (repeat this as you continue). Continue to perform Luria 3-step. When participant is able to join you say 'Very good, now keep going, I am going to stop'. Rest hand and start timing participant'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.	Tripod (upper body)	0 = ≥4 in 10 sec, no cue 1 = <4 in 10 sec, no cue 2 = ≥4 in 10 sec with cues 3 = <4 in 10 sec with cues 4 = cannot perform	Dominant hand only
Bradykinesia	Observe the participant 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.	(recorded throughout)	0 = normal 1 = minimally slow (?normal) 2 = mildly but clearly slow 3 = moderately slow, some hesitation 4 = markedly slow, long delays in initiation	Single score

Item	Instruction	Video recording	Score	Subscores
Maximal dystonia	Maximal dystonia is defined here as a tendency toward a posture, posturing along an axis. Observe the participant during the examination; i.e., no particular manoeuvres are required to elicit these features. Maximal dystonia are typically observed during demanding motor tasks such as tandem gait. When rating dystonia facial dystonia (blepharospasm, jaw opening and closing) should be included in your assessment of the truncal region.	(recorded throughout)	0 = absent 1 = slight/intermittent 2 = mild/common or moderate/intermittent 3 = moderate/common 4 = marked/prolonged	Trunk, Right upper limb, Left upper limb, Right lower limb, Left lower limb
Maximal chorea	Maximal chorea is defined here as movement, not posture. Observe the participant during the examination; i.e., no particular manoeuvres are required to elicit these features. Maximal chorea is typically observed during demanding motor tasks such as tandem gait.	(recorded throughout)	0 = absent 1 = slight/intermittent 2 = mild/common or moderate/intermittent 3 = moderate/common 4 = marked/prolonged	Face, Buccal/oral/lingual, Trunk, Right upper limb, Left upper limb, Right lower limb, Left lower limb
Dysarthria	Observe speech throughout encounter	(recorded throughout)	0 = normal 1 = unclear, no need to repeat 2 = must repeat to be understood 3 = mostly incomprehensible 4 = anarthria	Single score

EXAMPLES FROM THE NEW TEACHING VIDEO FOR UHDRS MOTOR EXAMINATION:

Figure 1. Ocular pursuit and Saccade initiation and velocity

Figure 2. Luria Test

Figure 3. Gait analysis

Figure 4. Chorea observation

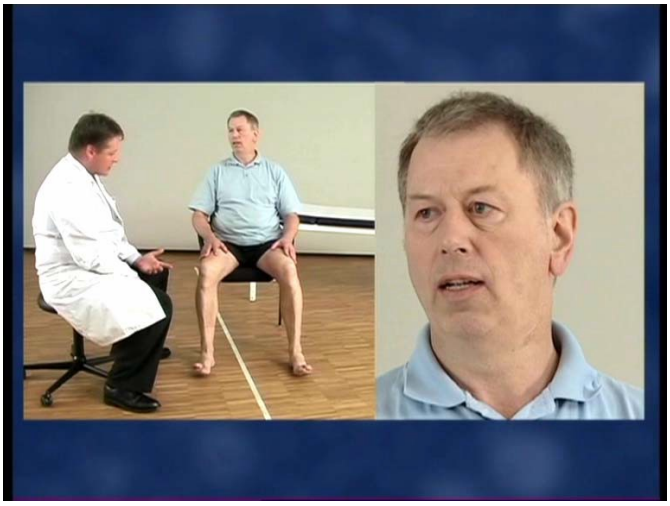
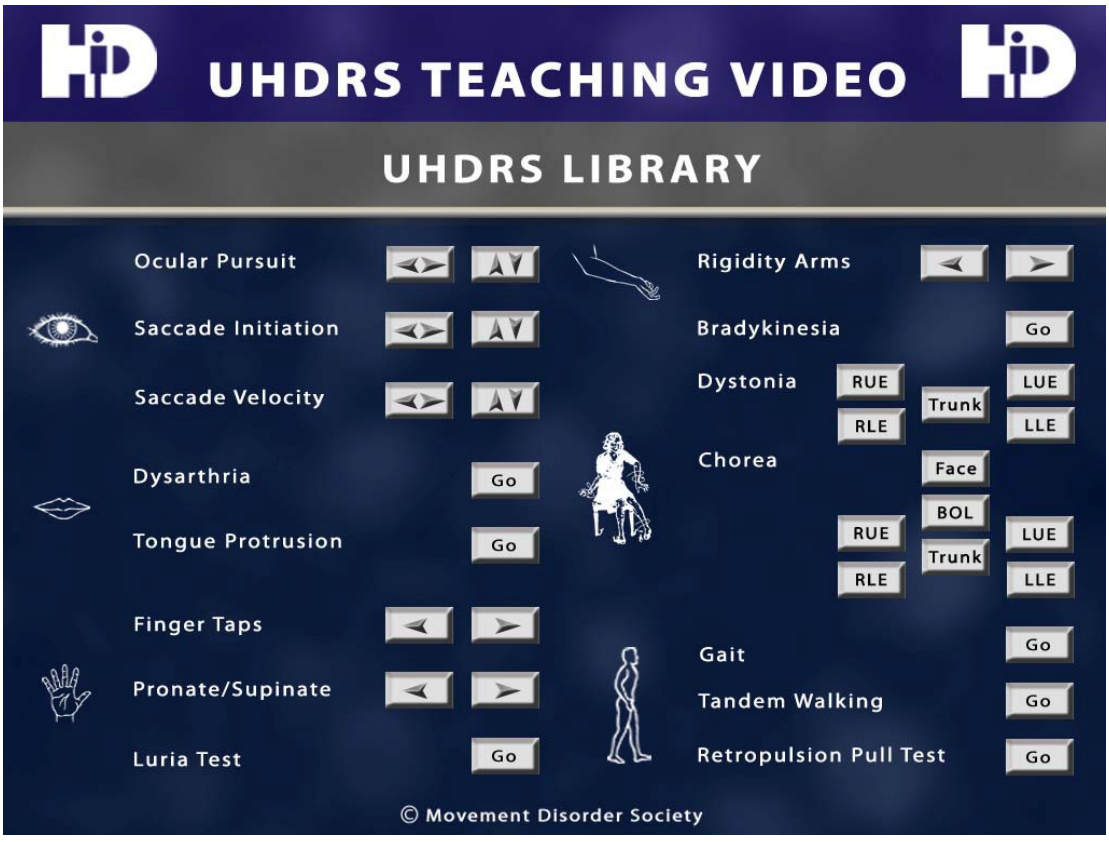
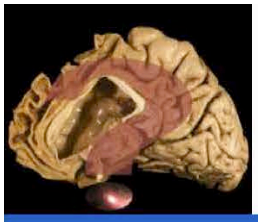


Figure 5. WEB Menu for easy access to the sample video clips of all sub items of the UHDRSteaching video.



BRAIN BANK



New York Brain Bank at Columbia University

Alzheimer Disease Research Center
Taub Institute

About Us

FAQ

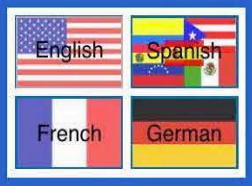
Tissue Donation

Tissue Request

Shipping Information

Our Staff

External Advisors



The **New York Brain Bank** (NYBB) at Columbia University was established to collect postmortem human brains to meet the needs of neuroscientists investigating specific psychiatric and neurological disorders.

The tasks of the NYBB include:

- Collection and processing of human postmortem brain samples for research.
- Neuropathological evaluation and diagnosis.
- Storage and computerized inventory of brain samples.
- Distribution of brain samples to investigating clinicians and scientists.

The study of human postmortem brain tissue has unveiled structural and biochemical changes that are contributing to the development of drugs. For example, studies using postmortem human brains have led to the development of genetic tests, identification of neurotransmitters essential to Parkinson disease treatment and cytoskeletal abnormalities in Alzheimer disease.

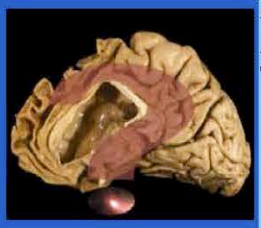
To study the brains of patients with disorders of the central nervous system, brains from individuals without neurological or psychiatric disorders are necessary for comparison. All individuals are encouraged to donate their brains to science with authorization to remove it as soon as possible after death. The identity of each donor will remain strictly confidential.

NYBB will disburse tissue samples to investigating clinicians or scientists, whose research has been approved by their Institutional Review Board (IRB).

Should you have any questions please contact us at:

NYBB / Taub Institute
Children's Hospital of New York-Presbyterian, Room T-8
3959 Broadway
New York, NY 10032
Telephone: 1-212-305-2299
Fax: 1-212-342-0083
E-mail: nybb@columbia.edu

Last updated 5/21/2003



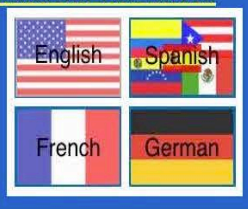
New York Brain Bank at Columbia University
Alzheimer Disease Research Center
Taub Institute

About Us

FAQ

Many neurodegenerative disorders are unique to human beings. Therefore, brains from other species are of limited value for research. Thus, human brain donation is crucial. Furthermore, the definite diagnosis of neurodegenerative diseases depends on a postmortem examination of the brain (i.e. brain autopsy).

Tissue Donation
Tissue Request
Shipping Information
Our Staff
External Advisors



Brain autopsy is a type of surgical procedure done after death, which does not disfigure and does not interfere with funeral plans.

Some neurodegenerative disorders, including subtypes of Alzheimer or Parkinson disease and Huntington disease, are related to gene dysfunction. Brain autopsy may help to identify the genetic dysfunction causing the disease.

Postmortem brains from individuals without neurological or neuropsychiatric disorders are important for research to determine the differences between functional and dysfunctional brains. To facilitate this research, the Taub Institute at Columbia University established the NYBB. The NYBB is the link between the family, caregiver, donor, clinician and basic scientist.

Donating your brain will greatly contribute to the progress towards understanding why and how these diseases occur, and how they can be prevented or treated.

To learn more about brain donation, please contact a research coordinator, or visit the site of the Taub Institute.

Last updated 12/6/2003

Instructions for Shipping Fresh Brains to the NYBB – Taub

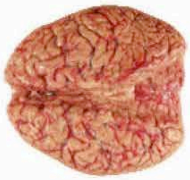
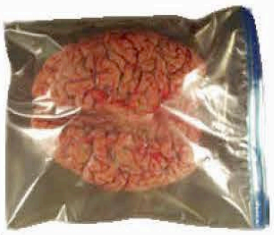
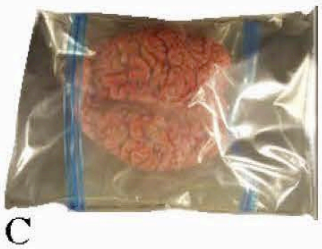
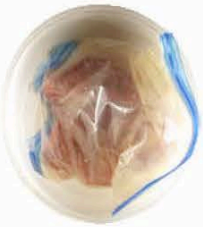
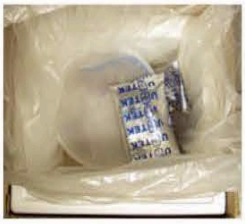
http://nybb.hs.columbia.edu – nybb@columbia.edu

These instructions outline the procedures of packing a fresh brain for shipment to the NYBB. Upon request, we provide packing material. For further assistance call 212-305-2299.

1. Recommended items to pack a fresh brain:

<table>
<tr><td>Two clean, dry ziploc plastic bags
(about 22.0 x 30.0 cm)
  </td><td>Plastic bucket with a tightly fitting lid
(about 4.0 liters)
  </td></tr>
<tr><td>Large plastic
bag (about 40.0 x 50.0 cm)</td><td>Envelope for documents</td></tr>
<tr><td>Thermosafe polyfoam container
(about 38.0 x 33.0 x 31.0 cm)
  </td><td>Two refrigerant packs
about (17.0 x 10.0 cm)
  </td></tr>
<tr><td colspan="2">Wet ice (about 1.0 kg)</td></tr>
</table>

2. Packing procedure:

Put the fresh brain in the first ziploc bag (A).  **A**	Ziploc first bag (B).  **B**
Place bag (B) in second bag and ziploc it (C).  **C**	Place 0.5 kg of wet ice into the bucket and transfer the double-bagged brain onto the ice (D).  **D**
Cover double-bagged brain with wet ice (E) and tightly fit the lid on the bucket.  **E**	Put big plastic bag into the polyfoam container and place wet ice (about 0.3 kg) into the bag (F).  **F**
Transfer sealed bucket into plastic bag of the container, onto the ice and add refrigerant packs (G).  **G**	Close plastic bag (H), put polyfoam lid in place, add documents and close cardboard box.  **H**
Please provide information pertaining to the donor of the specimen and the time intervals between the steps of obtaining and packing the brain. Please refer to the information sheet, which may be downloaded from our Internet site. (http://www.nybb.hs.columbia.edu)	
We use "*Sterling Courier Systems*" as they are familiar with our operations. For pickup call: **1-888-633-6666** and indicate that you would like to send tissue samples to: **"NYBB - Taub"**.	

NEWSLETTERS
VOLUME 1

PREDICT-HD

Volume 1 **October 2002**

PARTICIPANT ENROLLMENT

Congratulations to Joji Deolongon and Lynn Raymond from UBC for enrolling the **first** PREDICT participant on September 12, 2002.

As of October 18, 2002 the enrollment status is:

- 10 participants enrolled

Special thanks to **UBC**, **Iowa HNDC** and **Rochester** for enrolling participants.

EXPECTATIONS (N=625)

Just a reminder of our timelines and enrollment expectations for PREDICT.

DATE	EXPECTATION	TOTAL
12/01/02	7 participants / site	7/site
03/01/03	7 participants / site	14/site
06/01/03	7 participants / site	21/site
09/01/03	7 participants / site	28/site

SITE STATUS

Six additional sites have met all the Critical Activities Checklist requirements to begin enrollment: **Baylor, Indiana, Johns Hopkins, Kansas, Toronto, and Washington**. Ready to ROLL!

SCREENING PROJECTION LOGS (Oops!)

Please disregard the directions on the Screeing Projection Log asking a consent be signed prior to completion. **Once you have IRB approval** and participants with an **actual scheduled appointment**, then complete this log and send it to the CTCC.

RECRUITMENT

A PREDICT Recruitment Committee chaired by Elizabeth Penziner (Iowa) was formed to help sites with their recruitment efforts. Members of the committee include: Michelle Fox, Elaine Julian-Baros, Elise Kayson, Martha Nance, Jane Paulsen, Kim Quaid, Greg Suter, and Andrea Zanko. We have set up a mentorship program where each member is a resource to 2-3 PREDICT sites. Your mentor is noted on the attached list and will be in contact with you throughout the study for issues related to recruitment, enrollment, and retention. Please feel free to contact your mentor, or Elizabeth Penziner directly, if you have questions about the issues indicated above.

INSIDE THIS ISSUE

STUDY INITIATION REQUIREMENTS

IRB Approval

Please contact your IRB to encourage them to move your submission through the system. Once you receive IRB approval fax your IRB approval

letter and approved consent forms to E. Julian-Baros at (585)461-3554.

Subcontracts

Keep an eye on your contract. It can get lost for months in your grants office. Call your grants office to determine the status of your contract.

Cognitive Training Certification

Prior to study initiation you must send a pilot video to Shannon Johnson (Indiana) and have completed a formal training course.

Many thanks to Shannon Johnson and Julie Stout for all the hours they have put into making sure the cognitive portion of PREDICT is successful!

Motor Rater Training

If you did not attend the Toronto 2001 Orientation meeting you must review the video from that meeting and complete the training test. You will not be able to begin enrollment until that occurs.

PREDICT STUDY TIPS

Predict Companions – Who Can they be?

1) A Companion cannot be a participant in PREDICT-HD.
2) A Companion can be used for more than one participant.
3) If you have questions about companions, please contact Elise Kayson.

CRF Transmittal Log

- Check all tasks completed
- Send log to CTCC only
- All pages indicated as "pink" are "yellow".
  - Motor Video Tape Form
  - Cognitive Video Tape Form
  - Cognitive Assessment Summary

MRI

- Identify MRI with Participant ID and Site #.
- No other identification
- Confirmation of receipt will be sent to sites from the University of Washington

Full address for shipment of MRIs:
Elizabeth Aylward
University of Washington
Department of Radiology
Box 357115
Seattle WA 98195 USA
Work Phone: 206-221-6610
Fax Number: 206-543-3495
E-mail: eaylward@u.washington.edu
Misc: Fed-Ex shipments send to 1959 NE Pacific Street

Motor Video Tape

- Identify tape with Participant ID and Site #
- No other identification
- Send to Jane Paulsen at Iowa
- Confirmation of receipt will be sent to sites.

Teleform® Surveys

We are piloting select surveys in a teleform® format. Please remember the following tips:

- No sharpie® pens
- Use ballpoint pen or pencil
- Do not fold or staple surveys

Smell Identification Test

- Send **original** booklets to Indiana, not a copy.

Life Experiences Scale (54)

- Q#5 "Death of close family member"
  No deaths = No circles filled

Companion Surveys

- Site must obtain consent in person first before forms can be completed.

Cognitive Materials and Blood Sample Shipments

At this time costs for shipping cognitive materials and blood supplies will be absorbed by the site. We are working on ways to supplement the sites for shipment costs.

PERSONNEL CHANGES

Any change in personnel for PREDICT must be communicated to Elaine Julian-Baros as soon as it occurs. A Change in Staff Form must be completed and faxed to (585)461-3554. If a site requests a change for the Site Investigator or Motor Rater, a letter and CV must be emailed to Jane Paulsen and Elise Kayson for approval by the Steering Committee. If an Investigator is new to the HSG, an HSG Credentials packet needs to be completed and be approved through the HSG Credentials Committee.

CONTACT PERSONS FOR THE PREDICT STUDY

Protocol Issues

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PREDICT-HD

Volume 2 **MAY 2003**

PREDICT COORDINATOR AND INVESTIGATOR CONFERENCE CALLS

The PREDICT Coordinator Conference Call was held on Thursday, February 6, 2003. Attendance was strong and participants were enthusiastic about the progress of our study. Current and planned changes in the Inclusion/Exclusion Criteria were reviewed along with issues regarding companion availability and waivers. The purpose of this call was to allow study sites the opportunity to voice their recruitment concerns and share personal experiences. Discussions ensued regarding how best to involve people in this study. Problem areas for many sites include scheduling personnel and the burden of travel for participants.

The PREDICT Investigator Conference Call was held on Tuesday, March 11, 2003. This conference call informed investigators of the recruitment numbers and ideas were generated to plan activities that enhance enrollment at the sites.

The fine efforts of all the sites are well recognized. Many initiatives are underway to address the feedback received at these conference calls. For instance, the promotion and marketing of the PREDICT study has been targeted to local and national meetings involving HD Communities. Comparisons between Phillips, GE and Siemans scanners are underway to address the compatibility of varying scanner types available at each study site. Travel guidelines are in place and have been distributed to study coordinators.

PREDICT TRAINING MEETING

The PREDICT Training Meeting will take place on Saturday, May 17, 2003 in Key Biscayne, Florida. In addition to a general overview of PREDICT, special attention will be given to recruitment, enrollment and retention issues. Shannon Johnson will conduct Cognitive Training for new raters at the meeting. Note: Please notify Shannon Johnson throughout the PREDICT study for any new and/or additional cognitive rater from your site who requires training.

FUTURE TRAINING MEETINGS

The HSG Annual Meeting will be held on November 13-16, 2003 in Atlanta, GA.

INSIDE THIS ISSUE

PARTICIPANT ENROLLMENT

As of April 22, 2003 we have **149** participants enrolled in PREDICT-HD. YAHOO!
Kudos to the following high recruiting sites:

- The Centre for Addiction and Mental Health
- University of Iowa
- Johns Hopkins University
- University of British Columbia
- University of Washington
- University of Rochester
- Emory University

And a special thanks to all sites for your determined efforts in the success of PREDICT-HD.

THANK YOU !

RECRUITMENT

With over 150 subjects recruited for PREDICT, we would like to **thank everyone involved** for their commitment to making this study work.

Over the past 8 months, we have learned a lot about the recruitment process and are in a great position to meet our participation goals. We have met challenges head-on, exchanging ideas to develop solutions, including:

- Centralizing travel services and guidelines
- Training additional personnel as cognitive raters
- Adjusting protocol when needed to accommodate unique circumstances

Please continue to share your learning and your needs with the recruitment committee and we will help you however we can. We are available to make presentations in your communities and otherwise reach out to participants in your state.

Members of the committee include: Michelle Fox, Elaine Julian-Baros, Elise Kayson, Martha Nance, Jane Paulsen, Kim Quaid, Julie Stout, Greg Suter, and Andrea Zanko. Please feel free to contact Elizabeth Penziner directly throughout the study for issues related to recruitment, enrollment, and retention.

ENROLLMENT EXPECTATIONS (N=500)

New timelines and enrollment expectations for PREDICT:

Established Sites:

DATE	EXPECTATION	TOTAL
06/01/03	~1 participant / week	~20/site
09/01/03	2 participants / month	~25/site

New Sites :

DATE	EXPECTATION	TOTAL
06/01/03	~1 participant / week	~8/site
09/01/03	~1 participant / week	~20/site

SITE STATUS

PREDICT now has **25** participating sites.

As you know, sites are eligible to enroll participants when all regulatory components (IRB approval, subcontract, and both cognitive and motor rater training)are in place.

Currently, 20 sites have all necessary components in place to enroll participants

NEW SITES

WELCOME !

Five new sites will soon join PREDICT !

- **Westmead Hospital, Sydney, Australia**
- **University of Melbourne, Melboune, Australia**
- **The Mount Medical Centre, Perth, Australia**
- **University of Medicine and Dentistry, New Jersey**
- **Univeristy of Alberta, Edmonton, Ontario**

NEED MORE STAFF?

Additional staff may help sites in their effort to successfully meet recruitment goals for PREDICT. When the need for an additional PREDICT staff person arises at your site, please notify Elise Kayson, Elizabeth Penziner or Elaine Julian-Baros to assist in the process of credentialing, certifying and training them.

HIPAA REQUIREMENTS

Please contact your IRB to encourage them to move your HIPAA submission through the system. Once you receive HIPAA IRB approval fax your IRB approval letter and approved HIPAA stand-alone authorization or revised consent form

including HIPAA language to E. Julian-Baros at (585) 461-3554.

PREDICT STUDY MANAGEMENT TIPS

Ensuring accurate completion and submission of CRFs is key in decreasing data queries. This next section will be included in every PREDICT newsletter and will offer you extra guidance in decreasing "do-over" time.

Screening Projection Logs

Please do not re-assign screening numbers. The screening projection log is a running log of screened subjects. The Screening Projection Logs help the coordination center anticipate enrollments for PREDICT. If you have any questions please don't hesitate to contact Elaine Julian-Baros at (585) 273-2879.

General CRF TIPS

- The first subject visit is a combined screening/baseline visit, therefore the enrollment date and the baseline (visit 01) date on the CRFs should match.
- **Blanks** should not be used unless specified. Use **'N'** if not applicable.
- When using **'N'** for CRF questions that are 'not applicable'- the response boxes must be filled (**NN**), beginning in the leftmost box or enter **'N'** in the leftmost box and draw a line through any remaining boxes. **'NA'** should not be used.
- For CRFs that read Evaluator-Participant (like the SCL-90 and Leyton) please complete the blanks for header information in **"C_ _"** with the Companion ID Number. If the Participant did not enroll with a companion for the first visit please complete the blanks for header information in **"C_ _"** with **"NN"**.
- Number fields must be **right** justified, i.e., blanks are not allowed, use leading zeros when necessary.
- If the participant does not have a companion please do not send in blank companion forms. Please keep those forms at your site.

CRF Transmittal Log

- Check all tasks completed
- Send log to CTCC only
- All pages indicated as "pink" are "yellow" (oops, sorry:).
  - Motor Video Tape Form
  - Cognitive Video Tape Form
  - Cognitive Assessment Summary

Medical History (CRF 04)

- Check the **'None'** box if the subject has no medical condition applicable to the specific category. No entries should be written on the lines.
- Leave the **'None'** box blank if the subject has a medical condition applicable to the specific category. Enter one condition per line.
- Question 8b- If subject is single, the number of times married is **'N'** (not applicable).
- Question 13c- If subject did not have a head injury, the number of injuries resulting in unconsciousness is **'N'** filled, **'NN'** (not applicable).
- Question 31b- If subject does not wear dentures, dentures fit properly? is **'N'** (not applicable).
- Question 36b- If subject has not attempted suicide, number of suicide attempts? is **'N'** (not applicable).
- Question 45c – This is a three character field, please remember to zero fill the first box if the repeat length is less than 100.

UHDRS (CRF 08)

- Questions 78/79 – For rater's assessment of subject since last visit, the response should be **'4'** (never seen before) for the first visit.
- Question 85a- For patient's clinical disposition- institutionalized, since the last visit, the response should be **'N'** (not

applicable) for the first visit. It should **not** be left blank.

Motor Assessment Video Consent (CRF 14)

- The top (white) original should always be sent to CTCC. Iowa gets one copy with the videotape, site keeps one copy.
- Question 4a- The response should be **'NN'** for years to store tape when question 4b has a '1' response (indefinite). It should **not** be left blank.

Signature Form (CRF 22)

- Question 1 response should be **'1'** (within visit window) for Visit 01. It should **not** be left blank or marked 'N' (not applicable).
- Question 2a-2e responses should be **'0' or '1'** (yes or no) not **'N'** (not applicable). This includes Visit 01.

Reportable Events (CRF 24)

- The use of "U" or "N" is unacceptable on this form. If a date is unknown use an arbitrary date of the 1st or 15th of the month.

Substance Use Form (CRF 50)

- Questions 14a, 14b response for 'Other Drugs' should be **'0, 1, or 2'** (times used in lifetime/past six months) just like all previous questions. It should **not** be left blank or marked as **'N'** (not applicable).
- The response key should be used for **both** the left and right columns. Questions 1b-14b responses for times used drugs in past six months should be **'0'** (never used) when responses for questions 1a-14a are **'0'** (never used in lifetime). Should **not** be **'N'** (not applicable) or left blank.

Cognitive Assessment Video (CRF 74)

- The top **white** original should **always** be sent to CTCC. Indiana gets one copy with the videotape, site keeps one copy.
- This form should be completed for **every** subject.
- If a subject is not going to be videotaped then Question 1a should be '0' (no) and the rest of the form should be blank. The site is to send a copy to coordination center **only**.
- Question 4a- The response should be **'NN'** for years to store tape when question 4b has a **'1'** response (indefinite). It should not be left blank.

ETHNIC/RACIAL CATEGORIES

Based on the latest census reports, NIH has developed new categories of reporting Ethnicity and Race. You will see these new categories on the Enrollment Projection Log (version 8/21/02) and the Medical History CRF (Form). Please use the following definitions when discussing Ethnicity and Race with your participants.

Ethnic Categories:

Hispanic or Latino: A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term, "Spanish origin," can be used in addition to "Hispanic or Latino".

Not Hispanic or Latino

Racial Categories

American Indian or Alaska Native: A person having origins in any of the original peoples of North, Central, or South America and maintains tribal affiliation or community.

Asian: A person having origins in any of the original peoples of the Far East, Southern Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.

Black or African American: A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or Other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White: A person having origins in any of the original peoples of Europe, North Africa, or the Middle East.

Ethnic/racial subpopulations. In addition to the OMB ethnic and racial categories, NIH uses the following definition for ethnic/racial subpopulations:

Subpopulations. Each ethnic/racial group contains subpopulations that are delimited by geographic origins, national origins, and/or cultural differences. It is recognized that there are different ways of defining and reporting racial and ethnic subpopulation data. The subpopulation to which an individual is assigned depends on self-reporting of specific origins and/or cultural heritage. Attention to subpopulations also applies to individuals who self identify with more than one ethnicity or race. These ethnic/racial combinations may have biomedical, behavioral, and/or social-cultural implications related to the scientific question under study. (http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm).

Eligibility for Mental Retardation and Special Education

Please use the following expanded guidelines when completing the **Inclusion/Exclusion** CRF 02. The purpose of these criteria is to exclude only those participants that have documented mental retardation or a documented severe learning disability. Answer the question on the CRF in the same location, but use the following guidelines to help you answer the question.

Exclusion Criteria #13:
Has the participant been diagnosed with *mental retardation* (MR)?

Include if:

- There is no documentation of MR and the participant is able to understand the consent process and presents with sufficient intelligence to complete cognitive testing.

Exclude if:

- An educational or psychological report documenting formal testing of intellectual functioning indicates an overall IQ below 70.
- There is no documentation of MR, but the person is clearly not of sufficient intelligence to complete the consent process and cognitive testing.

Exclusion Criteria #14:
Was the participant always in Special Education classes?

Include if:

- The individual was in Special Education due to low IQ, but was not diagnosed with mental retardation. (i.e., IQ above 70).
- The person was in Special Education due to behavioral problems.
- A mild learning problem was the reason for Special Education and the time spent in these classes did not comprise a majority of the individual's education.

Exclude if:

- There is formal documentation (e.g., psychometric report) of a history of severe learning disability.

Exclusion Criteria #15:
Does the participant have a history of Special Education for reading or math? Specifically, Special Education was related to learning problems, NOT ONLY behavioral problems.

Use the same guidelines as stated for #14. Please keep in mind that the answer will be the same for items #14 and #15.

If at any time there are questions, concerns or uncertainties of eligibility we urge you to contact the Coordination Center for clarification.

Supply order forms

A PREDICT supply order form can be found in Appendix IV of your Operations Manual (please

make copies). Sites have been fully cooperative making special consideration in allowance for shipping and delivery time. This has been greatly appreciated. **Thank you!**

PERSONNEL CHANGES

Any change in personnel for PREDICT must be communicated to Elaine Julian-Baros as soon as it occurs. A Change in Staff Form must be completed and faxed to (585)461-3554. If a site requests a change for the Site Investigator or Motor Rater, a letter and CV must be emailed to Jane Paulsen and Elise Kayson for approval by the Steering Committee. If an Investigator is new to the HSG, an HSG Credentials packet needs to be completed and be approved through the HSG Credentials Committee.

PREDICT CONTACT PERSONS

Protocol Issues

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Psychiatric Testing Issues

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MRI Issues

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PREDICT-HD

Volume 3 **November 2003**

HSG ANNUAL MEETING

The HSG Annual Meeting will be held starting Thursday November 13 through Sunday, November 16, 2003, in Atlanta, Georgia at the Four Seasons Hotel.

The PREDICT sessions are to be held on Thursday, November 13, 2003 and Friday, November 14, 2003. General Protocol and cognitive updates will be presented along with focus on recruitment, enrollment and retention.

Thursday, November 13, 2003 is the PREDICT mandatory session for all to attend, and Friday, November 14, 2003 is the PREDICT Motor Rater Training session.

Shannon Johnson will conduct Cognitive Training for visits 1 and 2 on Friday, November 14, 2003 and Saturday, November 15, 2003. These training sessions will run all day by appointment only made through Shannon Johnson.

Reservations for attending the HSG Annual Meeting were to be made by Wednesday, October 1, 2003. For questions or concerns regarding your reservations please contact Becky Dean at the Coordination Center at (585) 275-0554.

We're looking forward to seeing everyone in Atlanta!

INSIDE THIS ISSUE

PARTICIPANT ENROLLMENT

As of November 3, 2003, we have **334** participants enrolled in PREDICT-HD.

With the addition of the Australian sites, PREDICT is now **26** participating sites strong.

High Kudos to the top recruiting sites! These sites have enrolled 20 or more subjects to date and they are:

- John Hopkins
- University of Iowa
- The Centre for Addiction and Mental Health
- University of British Columbia
- Emory University

Additional kudos to those sites having enrolled 15 or more subject to date and they are:

- University of Washington
- Indiana University
- UCLA Medical Center

And a special thanks to all sites for your determined efforts in the success of PREDICT-HD.

THANK YOU !

RECRUITMENT

The Recruitment Committee was established to provide support to PREDICT-HD sites that express a need for assistance, in order to increase enrollment for these sites. Since the establishment of the committee, our team has attempted to identify and connect with HD communities around the country. Through presentations on HD research, the PREDICT-HD recruitment team is able to effectively inform HD communities about current research efforts and the importance of our project. Members of the committee have traveled to many different locations to promote the study at annual meetings, research forums, and local support groups. Cities visited by the team to give presentations include *Phoenix, San Diego, St. Louis, Kansas City, Houston, Milwaukee, Oklahoma City, Charlotte, Baltimore,* and *Omaha.* Of course, participants are needed from all areas, not just metropolitan areas, and some less well-known locations visited by the team include *Davis, CA; Hutchinson, KS; Piscataway, NJ; Eden Prairie, MN; Northbrook, IL; Grand Island, NE; Key Biscayne, FL;* and *Storm Lake, IA.*

Each of these trips provided an opportunity for us to develop new relationships within the HD community. In doing so, we have been able to generate a number of subject referrals for regional PREDICT-HD sites. We meet and talk with families and their health care professionals. We discuss the latest HD research efforts and the variety of ways that families contribute. Presentations that are planned for the months ahead include *Springfield, Indianapolis, Tucson, Chicago, and Denver.* As you can see, we've been hard at work to seek the attention of research participants from coast-to-coast. Just the same, many regions remain "untapped", since many people may not be aware of the financial support that is available to assist interested participants in covering travel costs. It is critical that we continue efforts to promote the study, and your support will make this possible. Please contact the recruitment committee to request a presentation in or near, your community. Talk with each other to learn about how community presentations have boosted enrollment and established new-found partnerships with families and professionals. We also want to know about other HD events in your state, as most event planners are glad to help promote the study, with or without a formal presentation. We welcome any thoughts and suggestions; tell us what works best in your community, and allow us to support the outstanding effort already taking place at each site!

ENROLLMENT EXPECTATIONS (N=500)

The PREDICT-HD study has enrolled over 320 participants! We are very excited about the enrollment progress since the last newsletter. We would like to thank everyone involved for all of your hard work and dedication to PREDICT! Our target goal remains a minimum of 500 research participants. The PREDICT Steering Committee has reviewed enrollment progress to make decisions regarding the most efficient use of study resources. NIH funding regulations require that our study sample be recruited according to the grant proposal (i.e., 25 participants per site). At this point some sites have enrolled many more than 25 participants and some sites have not yet enrolled 10. We will need to make up for the lower number of enrollees at some sites, to assure that the total goal will be reached. Please contact Jane Paulsen as soon as possible with your total site projections. The Steering Committee has decided that a minimum number of 12 participants will be needed for a site to continue in the Predict longitudinal study.

PREDICT-HD AMENDMENT 2

PREDICT-HD Amendment 2 was circulated to all site investigators and coordinators electronically on August 26, 2003 followed by distribution of hard copies via FedEx ground shortly thereafter.

Amendment 2 changes include eligibility for required CAG length based on standard clinical practice, at-home completion of the companion

surveys, year 2 cognitive changes and additional sites.

Site are strongly advised to read the amendment carefully to become familiar with the changes.

Prior to IRB submission of amendment 2, sites please remember to forward your consent form changes to Elaine Julian-Baros at the Coordination Center for review and approval. If an IRB has additional suggested changes please review these with the Coordination Center prior to incorporating. Once sites receive IRB approval, fax the IRB approval letter and approved consent forms to Elaine Julian-Baros at (585) 461-3554.

Also, please send the original signed and dated Amendment 2 Signature Page to the attention of Elaine Julian-Baros at the Coordination Center and retain a copy at the site.

NOTE: Changes to visit 2 cannot be implemented without IRB approval of Amendment 2.

For any questions or concerns regarding Amendment 2 submission or any regulatory issue feel free to contact Elaine Julian-Baros at (585) 273-2879 or email ElaineJulianBaros@ctcc.rochester.edu.

YEAR 2 CASE REPORT FORMS (CRFs)

Case Report Forms (CRF) for year 2 were designed to capture amendment 2 changes. These new CRFs have been recently distributed to all sites. The quantity of packets shipped to each site was based on survey responses taken several weeks prior to the shipment.

It is important for sites to keep in mind that these new CRFs reflect PREDICT amendment 2 and can be completed and submitted to the Coordination Center only **after IRB approval has been granted on Amendment 2.**

The year 2 CRFs consist of two separate shrink-wrapped packets.

The **first shrink-wrapped packet** contains new CRFs for visit 2. This packet will be for those subjects who are **currently enrolled**. Sites will replace previous CRF versions with current versions. The following forms were included in this packet:

- PREDICT-HD Schedule of CRF Completion and Study Activities, pages 1 and 2 (version 7/30/03)
- PREDICT-HD Visit 2 checklist (12 mo. ± 1 month) (version 7/30/03)
- PREDICT-HD CRF Transmittal Log Visit 2 (12 mo. ± 1 month) (version 7/30/03)
- PREDICT-HD Cognitive Assessment Summary Sheet-Visit 2 form, pages 1 and 2 (68) (version 7/30/03)
- PREDICT-HD Participant HD History (HDHX) (Form 78), page 1 (version 7/30/03) (for visits 2, 3 and 4)

The **second shrink-wrapped packet** contains CRFs for visits 1, 2, 3 and 4. This packet will be for your remaining **unused binders** (for upcoming enrollments). Sites will replace previous CRF versions with current versions. The following forms are included in this packet:

- PREDICT-HD Schedule of CRF Completion and Study Activities, pages 1 and 2 (version 7/30/03)
- PREDICT-HD Visit 1 Screening/Baseline checklist (version 7/30/03)
- PREDICT-HD CRF Transmittal Log Visit 1 Screening/Baseline (version 7/30/03)
- PREDICT-HD Visit 2 checklist (12 mo. ± 1 month) (version 7/30/03)
- PREDICT-HD CRF Transmittal Log Visit 2 (12 mo. ± 1 month) (version 7/30/03)
- PREDICT-HD Cognitive Assessment Summary Sheet-Visit 2 Form, pages 1 and 2 (68) (version 7/30/03)
- PREDICT-HD Inclusion/Exclusion Criteria (INEXB) (Form 76), pages 1 and 2 (version 7/30/03)
- PREDICT-HD Participant HD History (HDHX) (Form 78), page 1 (version 7/30/03) (for visits 2, 3 and 4)

It is understandable that the shipment of year 2 CRF supply may not have reflected the sites demand at the time of their delivery, as it is possible that sites could have enrolled additional subjects since the collection of the survey responses. In those cases, sites are asked to be patient, do not destroy any CRF, but notify Elaine Julian-Baros via phone at (585) 273-2879 or via email at Elaine.JulianBaros@ctcc.rochester.edu and instruction for exchange or return of forms will be given.

PAYMENT SCHEDULE

Sites received notice from the University of Iowa that the payment schedule will now be aligned with the grant funding dates. Payments are based on a full visit set of subject Case Report Forms completed and received at the Coordination Center.

The Payment Schedule will be as follows:

CRFs Received at CTCC	Payment Month
By November 19, 2003	December 1, 2003
By February 18, 2004	March 1, 2004
By May 19, 2004	June 1, 2004
By August 18, 2004	September 1, 2004

PREDICT DATA MANAGEMENT TIPS

OR

"HOW TO AVOID A QUERY"

Ensuring accurate completion and submission of CRFs is key in decreasing data queries. This next section will be included in every PREDICT newsletter and will offer you extra guidance in decreasing "do-over" time.

Screening Projection Logs

The Coordination Center has been receiving screening projection logs from sites on schedule but with no updated information. So, please remember to update your screening log prior to faxing it in to the Coordination Center. Also, **do not** re-assign screening numbers or enter duplicate information on another line. The screening projection log is a running log of screened subjects.

The Screening Projection Logs help the coordination center anticipate enrollments for PREDICT. If you have any questions please don't hesitate to contact Elaine Julian-Baros at (585) 273-2879.

BDI and BHS (scanned forms)

The completed BDI and BHS forms are electronically scanned once they are received at the Coordination Center. Because these completed forms are scanned with specialized computer software they MUST be accurately completed at the site.

- **USE BLACK INK ONLY**
- **WRITE LEGIBLY**
- Subject Identification Number NOT subject name is entered in the Header (even though the form asks for name) on page 1 of the form.
- ENTER HEADER INFORMATION ON THE LINE PROVIDED. (The scanner software will not pick up (scan) header information written outside the lines provided.)
- Please complete **ALL** header information including; 4- digit **Identification Number** (not subject name), **Date of Birth**, **Sex**, and **Date** (date of testing).
- Information must be completed in the shaded portion of the Page 2 grid. Please fill in the 'bubbles' for **Date of Birth**, **Date of Testing, Sex** and **ID Number**. DO NOT COMPLETE LAST NAME/FIRST NAME PORTION.
- Send the original BDI and BHS to the Coordination Center and retain copies at the site in the subject binder.

Cognitive Assessment Video (CRF 74)

Sites are still unclear on the submission of the Cognitive Assessment Video CRF (CRF 74). **Please read and follow the instructions below for ALL PREDICT-HD subjects.**

Complete this form for every subject at each visit.

Subjects who ARE video taped:

- The top **white original** is sent to **CTCC**. **Indiana** gets **one copy** with the videotape, and the **site** keeps **one copy**.

Subjects who ARE NOT video taped:

- The top **white original** is sent to **CTCC** and the **site retains the remaining copies**. (Indiana does NOT get a copy of the CRF)
- Question 1a- If a subject is not going to be videotaped then Question 1a should be '0' (no) and the rest of the form should be blank.

Signature Form (CRF 22)

- If any assessments are not completed at the scheduled visit, they **MUST** be listed in the comments section of the Signature Form. If these missed assessments are not listed in the comments section the CTCC assumes the CRFs are missing and the sites will get queried.
- Sites should also notify the project coordinator about any missed assessments.
- Question 1 response should be **'1'** (within visit window) for Visit 01. It should **not** be left blank or marked 'N' (not applicable).
- Question 2a-2e responses should be **'0' if there have been any staff changes or '1' if the site staff have remained the same. 'N'** (not applicable) is not an acceptable response. This includes Visit 01.

Identifying the Companion on CRFs

- The first companion participating in PREDICT-HD for every subject is identified as **companion 01** or "**C01**". On any given visit if a subject returns with a different companion other than the person initially consented, that companion would be identified by the site as companion 02 or "**C02**".

- For CRFs that read Evaluator-Participant (like the SCL-90 and Leyton) please complete the blanks for header information in **"C_ _"** with the Companion ID Number. If the Participant did not enroll with a companion for the first visit please complete the blanks for header information in **"C_ _"** with **"NN"**.

MRI Data Submissions

MRI scans are to be completed at Visit 1 and Visit 3 no more than one month before or after the neuropsychological testing is completed. If the participant is not scanned within this time frame, the site MUST notify the Coordination Center.

Upon completion of subject's MRI sites MUST:

1) Transfer data via FTP to Elizabeth Aylward at the University of Washington
2) Retain a copy of the MRI scan (CD, tape, etc) at the site and
3) Complete the MRI CRF (16) found in the subject binder and send top original page to the Coordination Center.

Please refer to the back of this newsletter for helpful hints on sending PREDICT-HD data to the University of Washington.

Supply order forms

A PREDICT supply order form can be found in Appendix IV of your Operations Manual (please make copies). Please remember that supply orders

are filled in sets of **3** participants only, at any one time.

Sites continue to be fully cooperative, making special consideration in allowance for shipping and delivery time. This has been greatly appreciated. **Thank you!**

PERSONNEL CHANGES

Any change in personnel for PREDICT must be communicated to Elaine Julian-Baros as soon as it occurs. A Change in Staff Form must be completed and faxed to (585)461-3554. If a site requests a change for the Site Investigator or Motor Rater, a letter and CV must be emailed to Jane Paulsen and Elise Kayson for approval by the Steering Committee. If an Investigator is new to the HSG, an HSG Credentials packet needs to be completed and be approved through the HSG Credentials Committee.

PREDICT CONTACT PERSONS

Protocol Issues

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Regulatory Document Issues

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Data Management Issues

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Cognitive Testing Issues

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MRI Issues

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MRI Transfer Issues

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Finance Issues (site payments/subcontracts)

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Travel Guidelines (by site or subject) and Reimbursements

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Email: Elaine.JulianBaros@ctcc.rochester.edu

PREDICT HD

TO: PREDICT Site Investigator and Coordinators

FROM: Elizabeth Aylward, Jane Paulsen and PREDICT Steering Committee

DATE: November 1, 2003

SUBJECT: PREDICT HD Site MRI Data Transfer

This memo contains helpful information for your site, which will facilitate standard MRI acquisition processes, and accurate, efficient transfer of MRI data to the MR Imaging Laboratory at the University of Washington. Thus far, much of the MRI data acquisition and transfer has gone smoothly. However, we have identified a few more common problems that can introduce compromises in the data quality and/or substantially deviate from the procedures that need to be followed to ensure timely processing by the MRI lab. To improve on our process, we providing a summary of the issues that sometimes arise, and their remedies, along with a checklist that you can incorporate both at the imaging facility and in your site's data transfer process. Please contact Dr. Elizabeth Aylward (contact information below) if you have questions or need clarification.

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 requires 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 separate folder identified by Site ID and Predict HD subject ID number. For example a transferred exam would be sent in a folder titled 023-Predict HD 123. 023 is the Site ID # and 123 is the Predict subject ID number . 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 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. Usually sites send 1 to 3 series: always the 3D SPGR, and sometimes one or two "scout" series. You do not need to send the scout series, but if you do, please label them in individual folders.

- Data from the 3D SPGR series must include the entire brain. We have received incomplete structural image datasets. Missing data files have occurred both with CD transfer and with ftp. It is very simple and straightforward to check each dataset for completeness prior to sending the images.

- 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 is the best protection of confidentiality for the participant.

- 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 most the lack of conformity occurs in the NEX parameter.

Checklist for sending Predict HD MRI data to the University of Washington

- ❑ Confirm that raw image data is in MR or .dcm format, not .pgn or .jpeg
- ❑ Confirm that 3D SPGR structural exam contains an anatomical series of the whole brain. One slice is represented by a line of data that looks like this:

  1.2.840.113619.2.1.1.27034430554.1012.1054822439.759.dcm

  There should be 124 of these (sometimes 120-128, depending on the scanner).
- ❑ Ensure that entire 3D SPGR structural image is placed in a folder titled 3DSPGR.
- ❑ Additional slices may belong to the "scout" series, and can be omitted or can be put into folders that are identified as such.
- ❑ Place all subfolders (you should have one with the 3DSPGR, and optionally one or two with "scout" images) inside a folder titled with the Site # and Subject ID #. For example: "023-Predict HD 123" for subject 123 from site 023
- ❑ Compress the main folder using .tar or .tar.gz
  The command to .tar is: tar cvf name-of-exam.tar
  The command to .tar.gz is: tar cvzf name-of-exam.tar.gz
  For example: tar cvzf Predict_43.tar.gz
  .tar makes files small and .tar.gz makes them really small; these files are much easier to ftp, thus avoiding failure during upload
- ❑ ftp the compressed exam folder to the University of Washington. Once they have received the scan, have been able to open it and start to process it, they will send the site an email notification that the image data have been received. This notification will also indicate whether there were any problems with the data that must be addressed by the site.
- ❑ Addresses for sending image data:

  The ftp address is: ftp://obtuse.chdd.washington.edu
  The login is anonymous and there is no password. You will not be able to see other exams in this folder due to security precautions.

  If you need to mail us exams, the address is:
  Elizabeth Aylward, PhD
  Dept. of Radiology, Univ of Washington
  1959 NE Pacific St.
  AA-010 Health Science Bldg Box 357115
  Seattle, Washington 98195

PREDICT-HD

Volume 5 **October 2004**

INSIDE THIS ISSUE

UPCOMING EVENT

HSG 12TH ANNUAL MEETING

The HSG 12th Annual Meeting will be held November 4-7, 2004 in St. Louis, Missouri at the Ritz-Carlton Hotel. The PREDICT-HD Training Meeting will take place on Friday, November 5, 2004, PREDICT cognitive training sessions held on Saturday, November 6, 2004 and PHAROS & PREDICT UHDRS video training held on Saturday, November 6, 2004.

We're looking forward to seeing everyone there!

ENROLLMENT STATUS

As of October 22, 2004 we have **533** subjects enrolled.

We have **9** sites leading the way with **25** subjects or more enrolled to date. Those sites are:

- Johns Hopkins, Baltimore, MD
- University of Iowa, Iowa City, IA
- University of British Columbia, Vancouver, BC
- St. George's Health Service, Melbourne, Australia
- Westmead, Sydney, Australia
- Emory University, Atlanta, GA
- The Centre for Addiction and Mental Health, Markham Ontario, Canada
- UCLA, Los Angeles, CA
- University of Washington, Seattle WA

Sites having enrolled **20-24** subjects to date are:

- Indiana University, Indianapolis, IN
- Hereditary Neurological Disease Centre, Wichita, KS

…AND THANKS TO ALL SITES FOR YOUR CONTINUED RECRUITMENT EFFORTS!

Please continue to update your screening projection logs and fax them in to the Coordination Center every two weeks.

RECRUITMENT/RETENTION

By Elizabeth Penziner

It will be exciting to reunite at the HSG/PREDICT-HD training meeting in St. Louis next month. As most of you know, we have developed a new monthly Retention Report to help coordinators identify "out of window" participant research visits for their site. We will work together to help

participants and coordinators achieve long-term participation. We intend to discuss the procedures for completing yearly retention activities in greater detail at the St. Louis meeting.

Activities completed **at each visit**:

Subsequent Visit Information Form

- Assists scheduling for subsequent study visit.
- Included in CRF submission packet.

Confidential Visit Evaluation

- Seal evaluation envelope and include in CRF submission packet.

Retention Contact Sheet

- Determines participant preferences for retention contact.
- Indicates if annual activity will be conducted locally by the site or by the centralized mail team.
- Mailed to Iowa after each research visit.

Bi-Annual Retention Record

- Records retention efforts during visits.
- Photocopy included in CRF submission packet.

Activities completed **at mid-year**:

Bi-Annual Retention Record

- Records retention efforts between visits.
- Faxed to CTCC
- Newsletters and other items will be distributed to sites regularly.
- If an activity is not complete but another retention effort has been put forth, please indicate this in the comments section.

Telephone Contact Form

- Verifies next visit date; captures changes in contact information.
- Original mailed to CTCC upon completion or within the month if submitting other CRFs.

Important Retention Update:

Missed Visits

- Participant visits are considered "out-of-window" if the visit is +/- 30 days of the target visit date.
- Participant visits are considered "missed" if the visit is 11 months past the target visit date.
- For "missed" Year 2 visits, if the participant returns for the Year 3 visit, **the WASI-Vocabulary and Matrix Reasoning (and N-Back if time allows) from the Year 2 cognitive assessments should be administered at this visit.** The Year 2 Signature Form and the Year 2 Cognitive Assessment Summary Form should be included with the Year 3 CRF submission packet.
- Participants having "Missed Visits" should be encouraged periodically by the site to return throughout the longitudinal study.

Thank you for your help with PREDICT's retention plan.

THE CORNERSTONE

When I took over as the coordinator for the PREDICT study at Johns Hopkins University, for almost two months I had the opportunity to watch my predecessor working with the CRFs. By the time I became solely responsible for the CRFs, I already had a fair idea as to what I would do differently to save me some time. I was pleasantly surprised when I read the cornerstone article by Rachel Conybeare in the June 2004 issue of the newsletter; she echoed a lot of my own thoughts about timeliness.

Over the next few months, I made it a point to complete the CRFs, including reportable events, the very same day, even if it is 4:45 pm and it is almost time to go home. There is usually more than enough time for completing the CRFs while the study participants are completing their end of it, especially if the participants are right there in front

of you in your office. This also gives me the opportunity to interact with the study participants, get to know them better, and make them more comfortable. It surprised me initially to see how emotional participants become when answering some of those questionnaires. I even make sure I have a short note in the chart for every reportable event, counter-signed by the investigator, just in case it comes up for discussion at a later date. I spend a little extra time making sure I don't repeat mistakes that have been pointed out in previous queries. Believe me, it saves me a lot of time not having to answer queries later.

At the very end, I would like to mention that the staff over at Rochester has been very cooperative and prompt every time I have sent them an email or given them a call. That help in and of itself has made this transition easier and more bearable.

-Abhijit Agarwal

Being the "Cornerstone" to the PREDICT project, it's necessary to have a smooth administrative transaction plan in place when staff changes occur.

Please send your administrative tips, suggestions or positive management anecdotes for publication in the next site newsletter to Elaine Julian-Baros at Elaine.JulianBaros@ctcc.rochester.edu.

PAYMENT SCHEDULE

Sites received notice from the University of Iowa that the payment schedule will now be aligned with the grant funding dates. Payments are based on **a full visit set of subject Case Report Forms** completed and received at the Coordination Center. In addition, Cognitive Assessment Summary Forms and data should be sent to Shannon Johnson at Indiana University and motor videotapes should be sent to the University of Iowa at that time.
The Payment Schedule will be as follows:

CRFs Received at CTCC **Payment Month**

By November 17, 2004……..December 1, 2004
By February 16, 2005……March 1, 2005
By May18, 2005……..June 1, 2005

AMENDMENT 3 CASE REPORT FORMS

Amendment 3 Case Report Forms were distributed to sites on October 5, 2004.

Important Amendment 3 Case Report Form Summary:

- Life Experiences Scale (updated form)
- Subsequent Visit Information Form (new)
- Telephone Contact Form (new)
- SCOPI-P and SCOPI-C (replaces the Leyton)
- Reportable Event Log (new)
- Bi-Annual Retention Activity Record (new)
- Cognitive Assessment Summary Sheet – Visit 3 (new)

Sites were instructed to complete page 3 of the Amendment 3 CRF cover letter and fax to Elaine Julian-Baros as confirmation of receipt of these materials.

ADDENDUM TO AMENDMENT 3

Addendum to Ammendment 3 was distributed to sites on August 24, 2004.

IRB approval of this addendum allows sites to begin the new MRI transfer process at which sites transfer MRI data to Iowa and then Iowa will extrapolate the additional MRI data and then forward the original MRI data on to University of Washington.

Also, with IRB approval sites may implement the Confidential Visit Evaluation Form (new form distributed with amendment 3 CRFs).

Once sites receive IRB approval they must fax IRB approval letters to Elaine Julian-Baros at (585) 461-3554.

Please feel free to speak with Elaine Julian-Baros during the HSG annual meeting with any questions and/or concerns regarding forms submission, regulatory issues, etc.

NEW MRI TRANSFER PROCESS

The Coordination Center will notify the University of Iowa and the University of Washington of a site's IRB approval of addendum to amendment 3.

Leigh Beglinger from the University of Iowa will then be in touch with the designated MRI contact person. She will supply the contact person with a password for electronic transport of MRI data.

Leigh Beglinger is available for questions and /or concerns regarding the new MRI data transfer process at (319) 335-8765 or email leigh-beglinger@uiowa.edu .

DATA MANAGEMENT

Notification Reporting

A notification is any relevant clinical or data management (either subject or site specific) issue that may influence the interpretation of the study data.

Be sure to notify the Project Coordinator for all notifications. If you are not sure that it is reportable contact Elaine Julian-Baros at the Coordination Center.

Please remember at each visit a notification must be generated on companions…

- Not present (and reason)
- Not identified (and reason)
- Not present, surveys completed outside study visit (and reason)
- Change in companion

Also remember a notification must be generated when there are issues related to any combination of assessments not conducted on scheduled visit day (giving details including name(s) of assessments and date(s) assessments completed). This is referred to as a Multiple Assessment Split Visit.

REPORTABLE EVENT LOGS

Once your site has Amendment 3 IRB approval, transfer all open events from the original Reportable Event Log to the revised Amendment 3 Reportable Event Log. Complete as many of the fields as possible. Record a U in the appropriate field if not collected on the original Log.

Corresponding open events from the original Log should have a line drawn through the entries and date and initial the strike through just as you would any data change.

The original Log should now include only events that are "closed", meaning they have both a start and stop date. Submit the original Log to CTCC. Record all new events on the revised Amendment 3 Reportable Event Log. A copy of the new Log should be sent to CTCC with the other CRF s submitted at each visit.

COGNITIVE ASSESSMENT FORMS

Submission of Cognitive Assessment Video Form

Please read and follow the instructions below for ALL PREDICT-HD subjects.

Complete the Cognitive Assessment Video Form for every subject at each visit.

Subjects who ARE video taped:

- The top **white original** is sent to **CTCC**. **Indiana** gets **one copy** with the videotape, and the **site** keeps **one copy**.

Subjects who ARE NOT video taped:

- The top **white original** is sent to **CTCC** and the **site retains the remaining copies**. (Indiana does NOT get a copy of the CRF)

- Question 1a- If a subject is not going to be videotaped then Question 1a should be '0' (no) and the rest of the form should be blank.

Submission of Cognitive Assessment Summary Form

For Visits One and Three, the top two pages (**white and yellow**) are sent to **Indiana**, and the **site** keeps **one (pink) copy.**

For Visit Two, because the form was printed on 2-part NCR paper instead of 3-part, please send the original (white) page to Indiana and keep the yellow copy at the site. If any revisions to the form are made in Indiana, you will receive a fax corrected copy. This should be retained with your yellow copy.

PERSONNEL CHANGES

Any change in personnel for PREDICT must be communicated to Elaine Julian-Baros as soon as it occurs. A Change in Staff Form must be completed and faxed to (585) 461-3554. If a site requests a change for the Site Investigator or Motor Rater, a letter and CV must be emailed to Jane Paulsen and Elise Kayson for approval by the Steering Committee. If an Investigator is new to the HSG, an HSG Credentials packet needs to be completed and approved through the HSG Credentials Committee.

HOLIDAY CLOSINGS

The Coordination Center will be closed for the upcoming holidays.

- 12 PM EST on Wednesday, November 24
- All day on Thursday and Friday, November 25-26
- All day Friday, December 24
- All day Friday, December 31

PREDICT CONTACT PERSONS

Protocol and Regulatory Document Issues

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Protocol Issues

Elise Kayson
Phone: (585) 275-4696
Email: Elise.Kayson@ctcc.rochester.edu

Data Management Issues

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Cognitive Testing Issues

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Psychiatric Testing Issues

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MRI Issues

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MRI Transfer Issues

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Finance Issues (site payments/subcontracts)

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Travel Guidelines (by site or subject), Reimbursements and Motor Videos

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PREDICT-HD

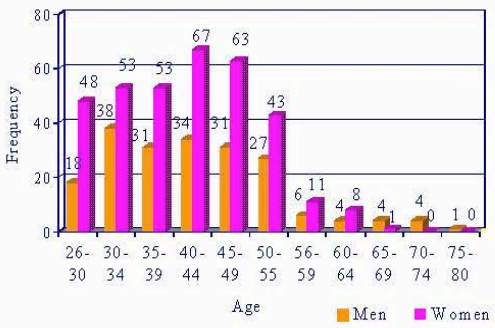
Volume 6 February 2005

INSIDE THIS ISSUE

ENROLLMENT STATUS

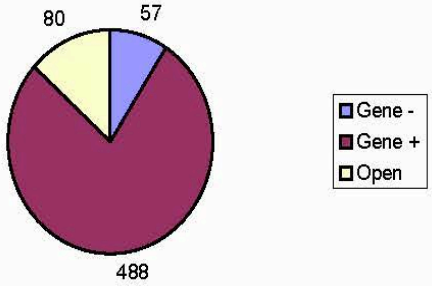
As of February 14, 2005, **545** subjects have been enrolled in PREDICT-HD.
The graph below demonstrates the age and gender distribution of the current enrolled PREDICT-HD population.

Age and Gender Distribution



The pie chart below demonstrates the total population enrolled (gene – vs. gene +) and remaining to be enrolled in PREDICT-HD.

PREDICT Enrollment Target = 625



SITE ENROLLMENT ACTIVITY

We have **9** sites leading the way with **25** subjects or more enrolled to date. Those sites include:

- Johns Hopkins, Baltimore, MD
- University of Iowa, Iowa City, IA
- University of British Columbia, Vancouver, BC
- St. George's Health Service, Melbourne, Australia
- Westmead, Sydney, Australia
- Emory University, Atlanta, GA
- The Centre for Addiction and Mental Health, Markham Ontario, Canada
- UCLA, Los Angeles, CA
- University of Washington, Seattle WA

Sites who have enrolled **20-24** subjects to date include:

- Indiana University, Indianapolis, IN
- Hereditary Neurological Disease Centre, Wichita, KS

THANKS TO ALL SITES FOR YOUR CONTINUED RECRUITMENT EFFORTS.

Please continue to update your screening projection logs and fax them in to the Coordination Center every two weeks.

RECRUITMENT/RETENTION

By Elizabeth Penziner

As a result of your collaboration at the HSG PREDICT meeting in St. Louis, we have launched the New Year with a head start on participant retention. Your patience through this process has been sincerely appreciated. Monthly reports are showing gradual improvement thanks to your on-going commitment to our study participants. PREDICT coordinators are clearly a mark above the rest!

Some reminders for your reference:

Missed visits

- Participant visits are considered "out-of-window" if the visit is +/- 30 days outside of the target visit date.
- Participant visits are considered "missed" if the visit is 11 months past the target visit date.
- For "missed" Year 2 visits, if the participant returns for the Year 3 visit, **the WASI-Vocabulary and Matrix Reasoning (and N-Back if time allows) from the Year 2 cognitive assessments should be administered at this visit.** The Year 2 Signature Form and the Year 2 Cognitive Assessment Summary Form should be included with the Year 3 CRF submission packet.
- Participants having "Missed Visits" should be encouraged periodically by the site to return throughout the longitudinal study.

Appendix F

- If participants prefer that their local site conduct retention activity please email stacie-vik@uiowa.edu with subject # only and specify: "local retention".
- If Iowa completes retention activity, send a copy of the signed *Appendix F* and the *participant contact sheet* using the pre-addressed reply envelopes distributed to sites in December.

In an effort to facilitate the sites with a guide to the retention activity process please see the PREDICT Rention Activity Table found on the last page of this newsletter.

Ideas to help track lost participants

- Directory assistance is likely to store changes to participant telephone numbers.
- Free Internet directories (www.whitepages.com) may track residential changes.
- Letters mailed to a participant's last address may return to sender with updated information maintained by the postal service.
- Participants may inquire about, or become involved in upcoming clinical trial initiatives; consider this an opportunity to ask about returning for PREDICT visit.

Thank you.
Elizabeth Penziner
elizabeth-penziner@uiowa.edu
(319) 353-4292

THE CORNERSTONE

By Melinda Kavanaugh

I became a PREDICT coordinator last year, and for the first time found myself coordinating research here at Washington University. Prior to that point, and currently, I am the Social Worker for our HDSA Center of Excellence. While being a "newbie' coordinator has certainly had its share of interesting, educational moments (so, what is a CRF??), carrying the dual job of coordinator and social worker has been the most educational.

One of the things we do here is pre-symptomatic testing, and one of my jobs is to coordinate the pre-symptomatic testing protocol; making appointments, counseling those testing and being present when results are given.

Being a part of the process from the first testing inquiry, to the date of testing and after has provided me with the tremendous opportunity to get to know these people and their families – often speaking to them multiple times before they actually test. I always let them know ahead of time that research opportunities exist and that we will discuss it at length later should they meet eligibility criteria. From this vantage point, I see people move from getting a positive result and committing their personal involvement to "fight back", to doing everything they can to avoid taking part in research.

At first it really surprised me when people I knew who were so excited at the prospect of testing were now not returning my calls. When I did speak to them, it was never quite the right time. They had job issues, they were moving, or just did not have the time to participate. I thought maybe I was not doing it "right"; maybe I was not approaching them in the best possible way.

Thinking about it has made me step back and realize how truly difficult it can be to digest the result, then act on it. Taking part in PREDICT means acknowledging their gene status, and no matter how hard we as research professionals try to be there for them, these individuals may just not be ready to accept their results.

Now when folks receive positive results, I make sure they have the basic information about research opportunities to take with them. I make sure we talk, but not right away. Even if it seems as though they want to know everything – it is just too much at the time, and may be overload to where they don't want to discuss it in the future. I let them know I will follow-up with them after they have had some time to digest the test result. I always leave them with my direct line, so that they can call me at any time. On many occasions it has taken several tries before I reach them, often chatting about other issues before they are ready to discuss research.

While some are ready, others never seem to be. I always tell them if they take part in PREDICT great, if not, I assure them that our site PREDICT staff is here for them when they are ready to participate.

Please send your administrative tips, suggestions or positive management anecdotes for publication in the next site newsletter to Elaine Julian-Baros at Elaine.JulianBaros@ctcc.rochester.edu.

PAYMENT SCHEDULE

Payments are based on **a complete visit set of subject Case Report Forms** and received at the Coordination Center. In addition, Cognitive Assessment Summary Forms and data should be sent to Shannon Johnson at Indiana University and motor videotapes should be sent to the University of Iowa at that time.
The 2005 Payment Schedule will be as follows:

CRFs Received at CTCC	Payment Month
By February 16, 2005	March 1, 2005
By May18, 2005	June 1, 2005
By August 17, 2005	September 1, 2005

COGNITIVE TRAINING

A training meeting for new Cognitive Examiners will take place at Indiana University during the week of April 18th. If you expect any changes in the Cognitive Examiner position at your site, please contact Petra Theiner-Schumacher (ptheiner@indiana.edu or 812-855-2963) as soon as possible. It is important that we plan accordingly as the next cognitive training is scheduled for October 2005 at HSG.

MRI UPGRADES

MRI Software/Hardware Changes

If a site has an MRI software upgrade or change in scanner, they should contact Dr. Elizabeth Aylward at University of Washington **BEFORE** the upgrade or change. Sites should scan 5 people (these can be participants or any other volunteer) before and after the upgrade so that comparisons on volumetric measurement can be made.

For questions or concerns regarding MRI upgrades or changes in scanner please contact Elizabeth Aylward at (206) 221-6610 or email at eaylward@u.washington.edu or Kate Field at kfield@u.washington.edu .

DNA SAMPLES

Please **be certain** to label DNA yellow top tubes appropriately.

EXAMPLE:

DATA MANAGEMENT

CONFIDENTIAL EVALUATION FORM

Sites MUST complete the header information on the Confidential Evaluation Form before presenting it to the subject. A few of these forms have been received by the Coordination Center without visit number, site number and/or visit date information.

TELEPHONE CONTACT

Please **DO NOT** complete and submit the Telephone Contact form **UNLESS** you have IRB approval for Amendment 3 **AND** the subject has signed the consent form containing the amendment 3 changes.

If you have already submitted this form prior to IRB approval the Coordination Center will be returning it to the site.

SCREENING/BASELINE CONFIRMATION

Email distributed on **December 20, 2004** to all sites requested completion and submission of the PREDICT Screening/Baseline Confirmation Case Report Forms on all screened subjects not enrolled.

PREDICT Screening/Baseline Confirmation forms on screened subjects not enrolled will give us a complete assessment of why potentially eligible participants did not enroll in PREDICT.

For any questions or concerns please contact Elaine Julian-Baros at elaine.julianbaros@ctcc.rochester.edu .

SUBSTANCE USE FORM

Sites should be reviewing the Substance Use Form before the conclusion of each visit to be certain that the response key was used. The response key codes are as follows:
0=never used
1=1-10 times
2=more than 10
The participant should NOT be entering the number of times the substance was used.

BRAR

When completing the BRAR (Bi-Annual Retention Activity Record) note the following:

- At least ONE activity from each category (1, 2 and 3) must be entered in the corresponding category visit period box.
- Once one or more activity codes are entered in any category all remaining category boxes should be blank. For example: if only 2 activities are entered in category #1 then 3 boxes will remain blank.

- If retention activities are being conducted by Iowa please indicate this by entering "**8**" in a category #2 box.
- Include a photocopy of the BRAR in your CRF submission packet for each visit and fax copy to CTCC at mid-year.

REPORTABLE EVENT LOGS

IMPORTANT REMINDER…

Once your site has Amendment 3 IRB approval, **transfer** all open events from the original Reportable Event Log to the revised Amendment 3 Reportable Event Log. Complete as many of the fields as possible. Record a U in the appropriate field if not collected on the original Log.

Corresponding open events from the original Log should have a line drawn through the entries and date and initial the strike through just as you would any data change.

The original Log should now include only events that are "closed", meaning they have both a start and stop date. Submit the original Log to CTCC. Record all new events on the revised Amendment 3 Reportable Event Log. A copy of the new Log should be sent to CTCC with the other CRF s submitted at each visit.

If you are unsure of this process please contact Elaine Julian-Baros at 585-273-2879 or Cathy Covert at 585-275-7161.

ALL REPORTABLE EVENTS ARE TO BE CALLED IN AND REPORTABLE EVENT LOG FAXED TO THE COORDINATION CENTER WITHIN 24 HOURS OF SITE'S AWARENESS.

HOLIDAY CLOSINGS

The Coordination Center will be closed for the upcoming holidays.

- **All Day Friday, March 11, 2005**
- **All Day Monday, May 30, 2005**

PREDICT CONTACT PERSONS

Protocol and Regulatory Document Issues

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Data Management Issues

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Recruitment Issues and Retention Issues

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Cognitive Testing Issues

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Psychiatric Testing Issues

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MRI Issues

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MRI Transfer Issues

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Travel Guidelines (by site or subject), Reimbursements and Motor Videos

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Email: Elaine.JulianBaros@ctcc.rochester.edu

PREDICT Retention Activity Table

Retention Activity Table		
*Completed **at each visit***	*Completed **at mid-year***	**Process**
Bi-Annual Retention Record	Bi-Annual Retention Record	Include photocopy in CRF submission packet at each visit (and fax copy to CTCC at mid-year)
Retention Contact Sheet		Mail to Iowa after each research visit with copy of signed Appendix F
Subsequent Visit Information Form		Include in CRF submission packet
Confidential Visit Evaluation		Include sealed envelope in CRF submission packet
	Telephone Contact Form	Mail original to CTCC upon completion or within month if submitting other CRFs

Please make every effort to submit your case report forms to CTCC within one week following the research visit. Timely submission of forms is essential to monitor retention, process site payment, and promote data analysis. We are thankful for your support. Suggestions and comments are welcome and encouraged so please don't hesitate to contact us with your ideas. We look forward another successful year and exciting research developments in 2005!

Best Wishes,
Elizabeth Penziner

elizabeth-penziner@uiowa.edu
(319) 353-4292

PREDICT-HD

Volume 7 October 2005

WELCOME EUROPEAN SITES

Please welcome the following seven PREDICT-HD European sites!

University of ULM
Ulm, Germany (site 175)

Hospital Ramón y Cajal
Madrid, Spain (site 176)

National Hospital for Neurology and Neurosurgery, London UK (site 177)

University of Cambridge
Cambridge Centre for Brain Repair
Cambridge, UK (site 178)

Cardiff University
Cardiff, Wales (site 179)

NHS Grampian
Clinical Genetics Centre
Aberdeen, Scotland (site 180)

University of Manchester
Manchester, UK (site 181)

Orientation for the PREDICT-HD European sites occurred in London, England on April 27-29, 2005. The first European enrollment is anticipated for October 2005 and the European sites will have an independant recruitment goal.
We are all very excited to have these European sites join PREDICT-HD.

WELCOME!

INSIDE THIS ISSUE

ENROLLMENT STATUS

As of October 3, 2005, **634** subjects have been enrolled in PREDICT-HD. Although we are at our original accrual goal sites can continue enrolling until January 2006. Sites are **strongly encouraged to list all projected enrollments on your screening projection logs**.

SITE ENROLLMENT ACTIVITY

We have **9** sites leading the way with **25** subjects or more enrolled to date. Those sites include:

- University of Iowa, Iowa City, IA
- Johns Hopkins, Baltimore, MD
- University of British Columbia, Vancouver, BC
- St. George's Health Service, Melbourne, Australia
- Emory University, Atlanta, GA

- Westmead, Sydney, Australia
- The Centre for Addiction and Mental Health, Markham Ontario, Canada
- University of Washinton, Seattle, WA
- UCLA, Los Angeles, CA

6 Sites who have enrolled **20-24** subjects to date include:

- Massachusetts General Hospital, Charlestown, MA
- Hereditary Neurological Disease Centre, Wichita, KS
- University of Calgary, Calgary, Canada
- Indiana University, Indianapolis, IN
- University of California San Francisco, San Francisco, CA
- Columbia University Medical Center, New York, NY

THANKS TO ALL SITES FOR YOUR CONTINUED RECRUITMENT EFFORTS.

HSG 13th ANNUAL MEETING

The HSG 13th Annual Meeting will be held October 20-22, 2005 at the Hyatt Regency Philadelphia at Penn's Landing, Philadelphia, Pennsylvania. Please save the dates. We're looking forward to seeing all PREDICT personnel there.

THE CORNERSTONE

This issue features words from Kimberly Bastic, coordinator at the University of Iowa.

As a new coordinator I'd like to extend my gratitude and appreciation to everyone involved in the PREDICT-HD study. I have been impressed with the organization that surrounds this study. I've also learned that having close participant contact can at times be disheartening. Hearing the personal stories and struggles that PREDICT participants experience as well as in some cases, seeing them decline before my eyes can be difficult. However, I've realized that it benefits my participants to remain positive and remember that we are conducting a unique study in order to answer very important questions about HD.

As a coordinator, it is easy to get frustrated with all the paper work and we may have a hard time remembering when to send in which log, but when you look at the big picture and see how this data will benefit HD research, suddenly the paperwork seems worth it. We're all experiencing similar situations, so as we progress each year, feel free to communicate with other PREDICT personnel such as site personnel, other site coordinators, recruitment and retention personnel or the Coordination Center. It is always better to ask questions, even if you have asked them before. Most importantly, keep up the good work and be proud of what you do.

Study tips I have learned and would like to share:

- Allow the participant time to ask questions about HD research. Getting research updates can be one of the most beneficial parts of their visit. It's their chance to be around experts and talk to people who really understand.
- Have someone on the PREDICT team other than the cognitive rater reiterate that PREDICT tasks are meant to be difficult. As we are all aware, these tasks can be stressful for people who are not showings signs of HD, let alone those who are showing signs. To ease the participant's stress and anxiety, it may be beneficial for more than one person to express that the tests are meant to be difficult and that the participant shouldn't get down on themselves.
- Revisit old potential participant lists for possible enrollments. Some people on your list may have turned 26 since you last contacted them or may be in a better position personally to enroll if invited to participate again. Remember it is not a burden to ask participants to participate in a research study. Our work has long-term promise for them and we should offer them the opportunity to make a difference in HD research.

Respectfully,
Kimberly Bastic
University of Iowa, PREDICT Site Coordinator

Please send your administrative tips, suggestions or positive management anecdotes for publication in the next site newsletter "Cornerstone" to Elaine Julian-Baros at Elaine.JulianBaros@ctcc.rochester.edu.

PAYMENT SCHEDULE

Payments are based on **a complete visit set of subject Case Report Forms** received at the Coordination Center. In addition, Cognitive Assessment Summary Forms and data should be sent to Shannon Johnson at Indiana University and motor videotapes should be sent to the University of Iowa.
The 2005 Payment Schedule will be as follows:

PREDICT Payment Schedule 2005

CRFs Received at CTCC	Payment Month
By November 16, 2005…….	December 1, 2005

MRI Reminder:
Full payment of a site visit includes completion of MRI.
Please contact:

1) Ellen Samuel and Leigh Beglinger **if you are concerned about missing/incorrectly acquired MRI scans that may result in withheld payments**
AND
2) Elaine Julian-Baros or Cathy Covert **for a notification to be generated.**

COGNITIVE

Reminder: Annual Cognitive Videotapes

Please help us in our efforts to keep the Predict Cognitive data reliable by completing your annual videotapes and sending them to Indiana University in a timely manner.

Below are a few things to keep in mind:

1. We require one videotape per battery per year for every certified cognitive examiner. That is, each cognitive examiner must send one videotape for each battery that is active at your site; currently, this means nearly all sites will need to send two videotapes annually (i.e., one for the full battery, Visit 1/3; one for the brief battery, Visit 2/4) per examiner.

2. In order to keep your cognitive examiner certification current, we must receive a required videotape within one year of the previous videotape. If we don't receive the videotapes, an examiner may need additional training or re-certification. If circumstances make this annual videotaping difficult, please contact Shannon Johnson or Petra Schumacher at Indiana University so that they can help to troubleshoot and provide alternatives (such as training at an HSG or other training meeting) if necessary to keep your certification and skills current.

3. Complete the videotape as early as possible in each new study year (i.e., the study year begins on the date of the initial enrollment at your site).

4. Back-up examiners are also required to send videotapes if the site plans to maintain their cognitive examiner status. If it is not possible for the back-up examiner to complete the videotape with a study participant, a pilot subject may be used.

5. Every examiner must be videotaped annually. If an examiner is added to your site or the examiner changes, the new cognitive examiner must be videotaped as well.

6. Any and all videotape formats are acceptable.

MRI ISSUES

Amendment and addendum to amendment #3 contained 2 important MRI protocol changes: 1) the added sequence to the MRI protocol and 2) the new transfer process from the site to Iowa.
If you have any questions about these changes or any other MRI concerns please feel free to contact

Ellen Samuel (ellen-samuel@uiowa.edu; 319-353-4537) or Dr. Leigh Beglinger (leigh-beglinger@uiowa.edu; 319-335-8765).

ANNUAL BLOOD SAMPLES

On Friday, May 13, 2005 email was distributed to all sites regarding the annual blood sample shipments. This email requested that sites NOT ship annual samples to ESA Inc. until further notice. Please continue to retain all PREDICT annual blood samples at your site until further notice. A new repository location is currently under discussion. Once an agreement is made regarding the new location of the repository, the Coordination Center will notify all sites. Again we apologize for any inconvenience this may have caused.

If you have any concerns please contact Elaine Julian-Baros at (585) 273-2879 or email Elaine.JulianBaros@ctcc.rochester.edu

DATA MANAGEMENT

CONCOMITANT MEDICATION LOG (CRF 06)

We review data on interim logs rather than waiting until the final log is submitted. To avoid queries, please be sure to complete all information for each medication listed. Also, please be sure to submit a photocopy of the Log at every visit even when there are no changes or additions to the previous log submitted.

Leave the 'None' box blank (un-checked) on interim logs. You will not get a query on an interim log if the 'None' box is un-checked and no medications are listed. You will get a query on an interim log if the 'None' box is checked and medications are listed.
When you submit the final log (Original), please enter a check mark in the 'None' box if no medications are listed.

At the Screening/Baseline Visit, list all current medications and those taken during the preceding **30 days** (the preceding **6 months** for neuroleptic drugs). Number the Page 1 rows 01-10, Page 2 rows 11-20, and so on.

Complete the information in every column for each medication listed. Blanks will be queried, if information is unknown, record a "U". For dates, record "U" if the exact day is unknown and enter a valid month and year.

You will not get a query on an interim log if the response in the 'ongoing' column is blank and no 'stop date' is recorded for the medication listed in that row.
You will get a query on an interim log if the response in the 'ongoing' column is (1) yes and a 'stop date' is recorded for the medication listed in that row.
When you submit the final log, please record (1-yes) in the 'ongoing' column and "N's" in the 'stop date' if the subject is still taking that medication at the end of the study. Blanks will be queried.

Please record the reason subject is taking each medication listed ("indication") and record (0- no) in the 'therapy for RE' column if the medication in that row has not been prescribed for a Reportable Event (RE). Blanks will be queried.

If a medication is listed and related to a reportable event (therapy for RE is 1-yes) the event should be listed on the subject's Reportable Event Log.

At follow-up visits, update the subject's Original log from the Screening/Baseline Visit. Please do not start a new log! List new medications and update previously listed ones if the dosage has changed or the medication has since been discontinued. Please date and initial any **changes** you make to previously submitted rows. Please also date and initial any **additions** to 'blank' columns in previously submitted rows. Please submit a photocopy of the updated Original log along with the other forms for that visit.

Please refer to the Concomitant Medication Log section in the Predict-HD CRF Binder for further instructions.

REPORTABLE EVENT LOG (CRF 24)

This CRF should be submitted for all subjects who enrolled prior to Predict-HD Protocol Amendment 3. Please submit the Original Log along with the CRFs for the follow-up visit when the subject signs the Amendment 3 ICF.

Please record a response for "Are there any Reportable Events?" (0=no, 1=yes).
You will get a query if the Reportable Event Box is 'blank', whether or not events are listed.
You will get a query if the Reportable Event Box is marked (0-no) and events are listed.
You will get a query if the Reportable Event Box is marked (1-yes) and no events are listed.

Number the Page 1 rows 01-05, Page 2 rows 06-10, and so on.

Complete dates must be entered. You will get a query for an invalid date (day=U), an event 'onset' date that is prior to the subject's randomization date, or an event 'onset' date that does not match the date on the Incident Report for that RE.

Please refer to Predict Site Newsletter Volume 6 (February 2005) for instructions for transferring 'open' (un-resolved) events to the Amendment 3 Reportable Event Log (CRF 86).

The site investigator must sign the Reportable Event Log and record his/her Staff Code when the final (Original) log is submitted.

AMENDMENT 3, REPORTABLE EVENT LOG (CRF 86)

CRF 86 is the RE log to be used when the subject signs the Amendment 3 ICF. Please submit a photocopy of the Log along with the CRFs for the visit

On interim logs, if there are no events listed and you do not record a response for "Are there any Reportable Events?" (0=no, 1=yes), you will not get a query.

Please refer to the previous section and Reportable Event Log section in the Predict-HD CRF Binder for further instructions.

SUICIDE RISK ASSESSMENT (CRF 64)

The Site Investigator's signature and the sign-off date are required. The investigator needs to sign-off to ensure that the subject was counseled about an elevated score(s) as the investigator is the person ultimately responsible that the discussion occurs.

HOLIDAY CLOSINGS

The Coordination Center will be closed for the upcoming U.S. holidays.

- **Thanksgiving Holiday**
  - **Beginning 12noon (EST) November 23, 2005**
  - **All Day Thursday, November 24, 2005 and All Day Friday November 25, 2005**
- **Christmas Holiday**
  - **All day Monday, December 26, 2005**
- **New Year's**
  - **All Day Monday, January 2, 2006**

PREDICT CONTACT PERSONS

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Data Management Issues

Cathy Covert
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Recruitment Issues and Retention Issues

Elizabeth Penziner
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Cognitive Testing Issues

Shannon Johnson
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Psychiatric Testing Issues

Kevin Duff
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Email: kevin-duff@uiowa.edu

MRI Issues

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MRI Transfer Issues

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Finance Issues (site payments/subcontracts)

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Travel Guidelines (by site or subject), Reimbursements and Motor Videos

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PREDICT-HD

Volume 8 **March 2006**

HSG 13th ANNUAL MEETING

Two hundred and forty HSG members were in attendance for the HSG 13th Annual Meeting held October 20-22, 2005 at the Hyatt Regency Philadelphia at Penn's Landing, Philadelphia, Pennsylvania.

During this annual meeting, members attended individual HSG meeting sessions as well as gathering for the grand Meeting of All HSG Attendees.

PREDICT-HD sessions included the Investigator, Coordinator and Cognitive Rater meeting held on Thursday, October 20, 2005. During this session, Jane Paulsen, PREDICT PI addressed the group with study updates, findings and "Where We Go From Here". Announced during this presentation was the continuation of PREDICT into the extension of four visits to seven and the continuation of recruitment.
At the conclusion of this meeting gift bags, thermal mugs and study other study materials were distributed to coordinators in appreciation of sites' dedication and effort.

The PREDICT Cognitive Training Sessions with trainers from Indiana Univeristy, Shannon Johnson, Petra Schumacher, and Andrea Solomon were held from Thursday, October 20, 2006 through Saturday, October 22, 2006, several new PREDICT cognitive personnel were successfully certifed.

The Coordinators' Reception drew a very positive response this year. A big 'Thank You' should be extended to all PREDICT coordinators for joining the reception and sharing your thoughts.

And special thanks go to Carolyn Gray, Vicki Hunt, Elise Kayson, Carol Moskowitz, Elke Rost-Ruffner, and Terry Tempkin who led an exciting new theme for this meeting, "Project Management". This meeting sparked a lot of brainstorming and lively interaction from site coordinators in the audience. I'm certain people who attended would agree…Who ever said learning can't be fun?

A meeting such as this aimed at organization and management can definitely facilitate time and effort towards recruitment and retention.

INSIDE THIS ISSUE

ENROLLMENT STATUS

PREDICT-HD is looking to enroll a total of 900 subjects. As of March 1, 2006, a total of **728** subjects have been enrolled in PREDICT-HD!

Sites are **strongly encouraged** to list all projected enrollments on your screening projection logs **AND** communicate the gene status of each of your projected enrollments either on your log or in an email to Karen Rothenburgh at Karen.Rothenburgh@ctcc.rochester.edu

SITE ENROLLMENT ACTIVITY

We have **12** sites leading the way with **25** subjects or more enrolled to date. Those sites include:

- St. George's Health Service, Melbourne, Australia
- University of Iowa, Iowa City, IA
- Johns Hopkins, Baltimore, MD
- University of British Columbia, Vancouver, BC
- Westmead, Sydney, Australia
- Emory University, Atlanta, GA
- University of Washinton, Seattle, WA
- The Centre for Addiction and Mental Health, Markham Ontario, Canada
- Hereditary Neurological Disease Centre, Wichita, KS
- UCLA, Los Angeles, CA
- Indiana University, Indianapolis, IN
- University of California San Francisco, San Francisco, CA

4 Sites who have enrolled **20-24** subjects to date include:

- Massachusetts General Hospital, Charlestown, MA
- University of Calgary, Calgary, Canada
- Graylands, Selby-Lemnos & Special Care Health Service, Perth Australia
- Columbia University Medical Center, New York, NY

We'd also like to recognize the Univeristy of Ulm for their contribution of **15** subjects enrolled since November 4, 2005.

THANKS TO ALL SITES FOR YOUR CONTINUED RECRUITMENT EFFORTS.

RECRUITMENT AND RETENTION

The PREDICT-HD team was pleased to announce during the HSG meeting this past year that PREDICT-HD received a superior review from the National Institutes of Health and was renewed at 100% for three years. We are excited to have the opportunity to continue to advance this important research project, and are grateful to have 32 outstanding sites to make this study a success.

Recently, the PREDICT-HD steering committee approved the addition of 100 gene negative participants to provide control data. All sites have the option to enroll additional control participants until the necessary sample size is achieved. By enrolling new participants before the summer, we will optimize to the likelihood of obtaining repeat visit measures, which is critical to the goals of PREDICT. If you are interested in enrolling additional participants but do not have an identified subject pool, the R&R team may refer gene negative individuals from their database to your site. If your site is not interested in enrolling more participants, please let the R&R team know so that participants may be referred to another near-by location.

Sites are encouraged to continue to enroll gene positive until otherwise announced. We also remind you to verify the gene status of each individual on enrollment projection logs. This will assist in establishing when enrollment will close.

The recruitment and retention team will be working hard to assist sites in order to engage participants throughout the study extension. Retention site presentations will be offered to express our thanks and to invite participants to learn about the preliminary data findings. The R&R team looks forward to collaborating with sites to make these visits rewarding for both participants and site personnel.

We thank you for your hard work and continued efforts in recruiting and accommodating participants at your site!

Stacie Vik & Elizabeth Penziner

THE CORNERSTONE

This issue features words from Jenny Naji coordinator at the Cardiff University in Wales.

Let me start by saying that I feel really privileged to be working in such an important and sensitive area of research. As we all know, Huntington's disease (HD) has no cure and only limited treatments so it is very positive for people to have the opportunity to take part in research that could potentially improve quality of life for themselves and others.

Prior to joining the Cardiff University as a Research Fellow in January 2004, I completed a PhD in visual psychophysics (looking at how our perceptions change when we make an eye and/or head movement!) so I was working in a very different area. I have therefore been on a steep learning curve finding out everything I can about HD over the past 2 years.

As part of my post, I work as a cognitive rater for the All Wales HD Service, which includes the Cardiff HD Management team (for those affected with HD) and the Presymptomatic Genetics Testing Clinic (for those at risk of HD). I also coordinate clinical networks for HD (the UKHD Network, UK language coordinator for the Euro-HD Network: www.euro-hd.net), am the site coordinator and cognitive rater for the Amarin (E-EPA) trial and PREDICT -HD and am also a Research Fellow in the School of Biosciences at Cardiff University, so I am kept pretty busy!

I began my involvement with PREDICT-HD in April 2005 when I went to London for the initial coordinator and cognitive rater training. Being involved in such a large and well-coordinated study is an exciting first for me, even though there are many things to remember. A nursing colleague, Ruth Glew, recruits our participants for PREDICT-HD from the Presymptomatic Genetics Testing Clinic. We find this works really well as Ruth has often been there for the participant throughout the testing procedure and giving of results.

We saw our first participant for the study last fortnight and I spent all day with him taking him to each assessment, performing the cognitive exam and making sure that he was happy and refreshed throughout the day. It made me realise what a big commitment PREDICT-HD participants are making by joining the study. They often have to take a day off work, which may prompt difficult questions if the employer is unaware of their gene status and maybe have to confront their gene status when they don't normally have to think about it. Because of this I ensure that everything runs smoothly and aim to make the day as fun as possible for them.

Jenny Naji
Brain Repair Group
Cardiff University
U.K.

Please send your administrative tips, suggestions or positive management anecdotes for publication in the next site newsletter "Cornerstone" to Elaine Julian-Baros at Elaine.JulianBaros@ctcc.rochester.edu.

PAYMENT SCHEDULE

Payments are based on **a complete visit set of subject Case Report Forms** received at the Coordination Center. In addition, Cognitive Assessment Summary Forms and data should be sent to Shannon Johnson at Indiana University and motor videotapes should be sent to the University of Iowa.
The 2006 Payment Schedule will be as follows:

PREDICT Payment Schedule 2006

CRFs Received at CTCC	Payment Month
By February 15, 2006	March 1, 2006
By May 18, 2006	June 1, 2006
By August 18, 2006	September 1, 2006
By November 17, 2006	December 1, 2006

COGNITIVE

Administering Tests and Providing Performance Feedback to Participants

It is a noteworthy achievement that in the coming year many of our participants will be volunteering for a fifth year in the PREDICT-HD research study. As the study progresses and some members of the participant cohort begin to develop signs of HD, we must all give careful consideration to how this affects the experiences of our participant, such as their comfort with our procedures and their enjoyment of the visit. Please be in close contact with the study team about your experiences with participants so that we are familiar with the situations that you encounter. We have many suggestions and can work together to develop solutions to deal with whatever situations arise.

Regarding the cognitive assessment, for example, if a participant had a difficult experience in their previous visit, you should contact the Predict Cognitive Team at Indiana University in advance of their next visit to discuss strategies for the participant's upcoming visit. Also, if you experience difficulty or have questions about any test during a PREDICT visit, please remember that our cognitive team is always available to assist you 24 hours a day at (812) 327-6779, or at 1-866-697-0005 from 8-5pm EST.

Below are some tips to help you provide appropriate feedback to participants:

1. First and foremost, always try to be aware of the participant's level of comfort and respond to signs of frustration or anxiety.
    - Offer support and encouragement along with periodic breaks when necessary.
    - Explain that certain tasks are designed to be more difficult than others. Encourage him/her to try his/her best and not to give up too quickly.
    - Do not give specific feedback regarding the accuracy of responses. Instead, for example, if a participant is concerned about performance, note that many participants find that particular task difficult.
    - If a participant appears overwhelmed or expresses significant frustration during a task, please keep in mind that discontinuing the task is an option. Allow the participant to become relaxed and comfortable before moving on to the next test.
    - In the rare event that a participant experiences difficulty with multiple tests, please call the cognitive team to discuss how to proceed with data collection during the remainder of the visit.

2. If a participant voices concerns about possible signs of HD, ask the participant about his/her specific concerns. Some participants may have questions about the typical progression of HD and what they can do to maintain their current level of functioning.
    - Rely on the research team to help address any concerns. If in doubt about how to answer specific questions, you should feel free to contact the study team.
    - Remember that performance on PREDICT cognitive and psychiatric tasks should not be interpreted on an individual basis.
    - If possible, concerns and questions should be addressed before the participant leaves the study visit.
    - If needed, provide a clinic referral to address specific questions and concerns.

3. If concerns about individual tests arise (i.e. The Haidt scale), take time to explain the purpose of the measure after completing it.
    - The cognitive team can provide additional explanations or scripted language at your request.

We thank you for your commitment to providing participants with the most rewarding visit by offering feedback and encouragement. We welcome your thoughts and comments regarding the PREDICT visit, and we will continue to integrate your input into PREDICT study procedures and protocol. Thank you!

~R&R Committee and Cognitive Team

PREDICT-HD Cognitive Team

(812) 327-6779 or 1-866-697-0005
24 hours a day 8am-5pm EST

Cognitive Reminder: Accurate recording of the start, stop, and break times of the Cognitive Assessment is important!

To assist us in gathering accurate data about the duration of all Cognitive Assessment batteries, we ask that you keep the following rules in mind when recording timing data:

1. Use the standard 24-hour clock when recording the start and stop time of the battery and the mandatory break on the Cognitive Assessment Summary Sheet.
2. Always double check all recorded times before submitting the CAS form to Indiana. Consider these questions: Is the stop time after the start time? Are the break times somewhere in between? If I calculate the difference between the start and stop time, and then subtract the duration of all of the breaks, is this an accurate measure of how long it took the participant to complete the assessment?
3. Include information about the start and stop times of any additional breaks on the Observation Form. Make sure this information is recorded clearly and accurately.
4. Make a note on the Observation Form if any tasks were administered out of order.

MRI ISSUES

On Tuesday, January 3, 2006 sites received an email from Ellen Samuel regarding the upcoming individualized scan reports. Since that January 3rd email, sites have received their initial reports. These reports include information on how many scan have been received at the University of Iowa (since addendum to amendment #3) as well as PREDICT parameters. Sites may expect to receive these reports a few times per year (exact frequency not yet determined).

If you have any questions concerns please feel free to contact Ellen Samuel (predictmrcoordinator@psychiatry.uiowa.edu; 319-353-4537) or Dr. Leigh Beglinger (leigh-beglinger@uiowa.edu; 319-335-8765).

ANNUAL BLOOD SAMPLES

Please continue to store the PREDICT annual blood samples at your site until further notice.

Thank you.

If you have any concerns please contact Elaine Julian-Baros at (585) 273-2879 or email Elaine.JulianBaros@ctcc.rochester.edu

DATA MANAGEMENT

PREDICT-HD NOTIFICATIONS

A *notification* is any relevant clinical or data management (either subject or site specific) issue that may influence the interpretation of the study.

As out-of-window visits and missed visits influence the interpretation of the study these are considered reportable.

Please be aware that out-of-window visits and missed visits are closely tracked not only at the CTCC but also by the University of Iowa retention group (Stacie Vik and Elizabeth Penziner).

All notifications are to be reported to Elaine Julian-Baros at Elaine.JulianBaros@ctcc.rochester.edu or (585) 273-2879 as well as documented at the site.

HOLIDAY CLOSINGS

The Coordination Center will be closed for the upcoming U.S. holidays.

- **Memorial Day**
  - **All day Monday, May 29, 2006**
- **4th of July**
  - **All day Monday, July 3, 2006**
  - **All day Tuesday, July 4, 2006**

PREDICT CONTACT PERSONS

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Regulatory Documents and Supply Orders

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Data Management Issues

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Travel Guidelines (by site or subject), Reimbursements and Motor Videos

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Phone: (319) 353-4212
Email: Kimberly-bastic@uiowa.edu

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Associate Project Coordinator
Clinical Trials Coordination Center
1351 Mt. Hope Avenue, Suite 223
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INSIDE THIS ISSUE...

Predict-HD Enrollment Goal

Our enrollment as of November 2, 2006 is 929. We currently have exceeded the enrollment goal for our gene positive population however have fallen short of our goal to enroll 175 gene negatives.

On September 15, 2006 sites received an email requesting additional enrollments of gene negative participants. In this email a strategy was outlined to guarantee that this goal would be accomplished. The strategy presented to PREDICT participating sites was that only those gene positive individuals entered on the projection log by September 30, 2006 could be enrolled, even if they anticipated enrollment after September 30, 2006. If gene status is not listed on your log you will be requested by the Coordination Center to identify the participant's gene status.

PREDICT gene negative recruitment is emphasized at this point in time and will continue until further notice. The current enrollment of gene negative participants is 155 therefore we are asking that sites focus strongly on enrollment of the gene negative population and place all projections on your logs promptly in order to assist with determining our enrollment closure date.

As we come closer in reaching this accrual goal for PREDICT-HD we ask that sites continue the balance of recruitment and retention efforts as you have done so well throughout this study.

Thank you.

For Recruitment and Retention questions/concerns please feel free to contact Elizabeth Penziner at (319) 353-4292 or elizabeth-penziner@uiowa.edu and Stacie Vik at (319) 353-3716 or stacie-vik@uiowa.edu.

Site Enrollment Activities

As of November 2, 2006 a total of **929** subjects have been enrolled in PREDICT-HD!

We have **4** sites enrolling **greater than 50 subjects** to date. Those sites include:

- University of Iowa, Iowa City, IA
- University of British Columbia, Vancouver, BC
- St. George's Health Service, Melbourne, Australia
- Johns Hopkins, Baltimore, MD

Sites enrolling between **25-50 subjects** to date include:

- Hereditary Neurological Disease Centre, Wichita, KS
- Emory University, Atlanta, GA
- Westmead Hospital, Sydney, Australia
- University of Washington, Seattle, WA
- University of Ulm, Ulm, Germany
- The Centre for Addiction and Mental Health, Ontario, Canada
- UCLA, Los Angeles, CA
- University of California SF, San Francisco, CA
- Massachusetts General Hospital, Charlestown, MA
- Indiana University, Indianapolis, IN
- Graylands, Selby-Lemnos & Special Care Health Services, Perth, Australia
- University of Manchester, United Kingdom

Sites enrolling between **20-24 subjects** to date include:

- University of Calgary, Canada
- National Hospital for Neurology and Neurosurgery, United Kingdom
- Columbia University, New York, NY
- Cambridge Centre for Brain Repair, United Kingdom
- Clinical Genetics Centre Aberdeen, United Kingdom
- University of California Davis, Sacramento, CA
- University of Rochester, Rochester, NY

Thanks to all sites for continued efforts in both enrollment and retention efforts!

HSG 14th Annual Meeting

"The Gateway to the West"

St. Louis Missouri is the setting for this year's HSG 14th Annual Meeting. The meeting will be held from November 8-11, 2006 at the Ritz Carlton.

We're looking forward to seeing everyone!

Invitations for this meeting have been sent to all via email and include travel and lodging details. Thank you for your prompt responses to this invitation.

There will be several new PREDICT Site Coordinators as well as our European Site Personnel attending for the first time, so please feel free to stop and chat with members from the Recruitment and Retention Committee and the Coordination Center. And The Coordinator's Reception on Friday, November 10th is a great place to mingle, meet colleagues and share knowledge.

See you in St. Louis!

Motor Videos

Motor Videos must contain the following information:

- **Site Number**
- **Subject Number**

All motor videos are to be sent to:
Ann Dudler
The University of Iowa
Psychiatry Research
1-309A MEB
Iowa City, IA 52242

Sites will receive an email to confirm receipt.

Travel Reimbursement

Travel reimbursement requests must be approved by Ann Dudler at the University of Iowa prior to travel arrangements being made. *Please contact Elizabeth Penziner or Stacie Vik (see contact information on page 6) at the University of Iowa for approval.*

All travel expenses, excluding airfare, must be paid by subcontractor site or individual.

Request travel reimbursement by e-mail to: ann-dudler@uiowa.edu

Prior Approval for reimbursement to individuals (research participants or staff) must include the following:

- Staff or Participant Name
- Staff or Participant Address
- Destination
- Dates of Travel

Please Itemize estimated expenses.

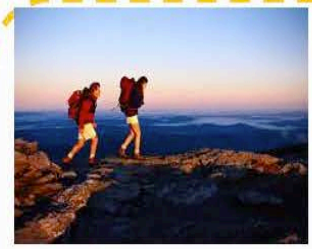
Note: It is extremely helpful if you let the participant know before their visit what type of receipts they need to provide in order to received reimbursement.

Hotel costs must not exceed the federal travel directory of reasonable cost.

See www.uiowa.edu/~fustd/travel for federal guidelines for domestic/international travel.

Reimbursement Documentation
An itemized invoice from your institution should be sent to:
Ann Dudler
The University of Iowa
Psychiatry Research
1-309A MEB
Iowa City, IA 52242
Phone: (319) 353-4542
Fax: (319) 353-4438

Predict Companion Participation



Got companions?

Maintaining companions' enthusiasm in returning for Predict visits can be challenging. As site researchers, you have likely provided companions with the scientific rationale for needing their yearly input. For example, companions provide valuable information about the daily functioning of the participant that cannot be observed in a standard research visit. You may have appealed to the companion's own sense of curiosity and self-education. For example, companions can use their involvement with Predict to stay on the "cutting edge" of HD developments. You may even have pointed to the study's eligibility criteria requiring participants to have companions to participate in the study.

Preliminary results from the behavioral assessments of this longitudinal observational trial can offer additional reasons that companions stick with Predict. With the assistance of our PREDICT statistician, Doug Langbehn, Ph.D. at the University of Iowa , preliminary findings suggest that several markers of disease progression are associated with companion ratings on several of the psychiatric assessments. These include:

Companion ratings of participants on the FrSBe (a measure of apathy, disinhibition, and executive dysfunction) were related to motor exam scores on the UHDRS.

Companion ratings of change across two visits on the FrSBe were related to changes in motor functioning across two visits.

Companion ratings on the Behavioral Assessment of the UHDRS (which assesses the frequency and severity of a range of psychiatric symptoms) were also related to changes in motor functioning across two visits.

Participants' performances on several cognitive measures that assess executive functioning and psychomotor speed (e.g., Stroop Interference trial, Symbol Digit Modalities Test, verbal fluency) were related to companions' ratings on the FrSBe.

Striatal volumes on MRI (size of the caudate and putamen) were related to companion ratings on our new measure of obsessions and compulsions (SCOPI).

Using current age and CAG repeat length, a participant's probability of onset within the next 5 years was related to their companions' ratings on the FrSBe.

Although these findings need to be replicated with the entire Predict sample once enrollment is complete, they provide some initial indications that the companions are identifying some subtle behavioral manifestations that are linked to other markers of disease progression in HD. These findings are not only supportive of the goals of Predict, but also can be used to demonstrate that companions are making a difference in this scientific endeavor. Indirectly, these findings also suggest that a participant's companion should not switch between Predict visits. The variability introduced by changing companions has the potential to obscure the current relationships between companions' ratings of behavior and other markers of disease progression. Lastly, although site personnel might use the general message that "companions are making a difference in detecting the earliest markers of disease progression in HD" to inspire companions, the communication of any of the specific relationships mentioned above should be avoided.

Concomitant Medication

At each visit, review the subject concomitant medication list. Please end date those medications which have stopped or have had changes in frequency or dosage and enter all new concomitant medication the subject reports.

To avoid queries, please be sure to complete all information (columns) for each medication listed. List all medications in BRAND name, be certain that the spelling of the medication name is accurate and be certain that all columns are completed. For dates, record "U" if the exact day is unknown and enter a valid month and year.

Please record the reason the subject is taking each medication listed ("indication") and record "0"-no in the 'therapy for RE' column if the medication in that row has not been prescribed for a Reportable Event.

All BLANKS will be queried.

Completion of the PREDICT Concomitant Medication Log is much more than dotting your "I's" and crossing your "T's".

Why is this CRF so important to the PREDICT study? Medications reported for PREDICT participants are coded and categorized for the researcher to analyze what, if any, significance these drugs have on the health and well-being of the at-risk HD population.

For questions or concerns in completion of the PREDICT Concomitant Medication Log please contact Cathy Covert, PREDICT Information Analyst, at (585) 275-7161 or cathy.covert@ctcc.rochester.edu.

Recruitment and Retention

Yearly Visits are Key to PREDICT's Success

The success of the PREDICT-HD research study relies on the longitudinal data collected annually from enrolled participants. We understand that there are situations and times where a participant may have difficulties returning for a given year; however, we must all strive to keep these instances to a minimum to help ensure the strength of the study and longitudinal data. Thanks to the organization, accommodation and prompt scheduling by coordinators at our study sites the following are the overall retention rates:

Year 2: 90.4%

Year 3: 85.4%

Year 4: 76.%

Important Retention Reminders:

Missed Visits

- Participant visits are considered "missed" if the visit is 11 months past the target visit date.
- Participants having a "missed visit" should be encouraged periodically by the site to return throughout the longitudinal study.
- If a participant is a "missed visit" and they return for the subsequent year, please remember that there are additional tests that need to be obtained during the visit.

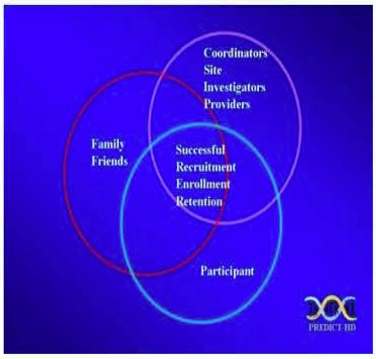
If a participant is "missing" and you are having a difficult time locating him or her, this does not constitute withdrawing the individual. Periodic attempts at locating the person should continue. Your persistence and patience is appreciated!

Important Withdrawal Reminders:

Withdrawals:

Participants should only be withdrawn after discussing the situation and details with the retention contact, Stacie Vik at the University of Iowa. Withdrawals are determined on a case-by-case basis under consultation with Jane Paulsen. Sites **MUST** contact Stacie Vik at (319) 353-3716 or email at stacie-vik@uiowa.edu in cases of potential withdrawals.

Please remember that your mid-year contact with participants helps maintain open communication and up-to-date contact information. These valuable efforts are critical to minimizing missed visits and withdrawals. We thank you for supporting the study's retention plan.



Data Clarification Worksheets (Queries)

The frequency of Data Clarification Worksheet distribution from the Coordination Center has increased to approximately every four weeks. Therefore sites should make every effort to respond to those queries between distributions to avoid a 'snowball effect'. Sites with large numbers of outstanding queries will be requested by the Coordination Center to conference to discuss query issues and help resolve as quickly as possible.

For questions or concerns regarding data clarifications please contact Cathy Covert, PREDICT-HD Information Analyst at (585) 275-7161 or cathy.covert@ctcc.rochester.edu.

Predict-HD Amendment #4

Amendment 4 was sent to sites for IRB submission on 07/25/2006 and reflected changes in administrative staff, increased number of sites to 31, changes to Appendix A-E, Research design and methods, MRI methodology, Visit 4 cognitive battery, consent changes in reporting MRI incidental abnormalities and new procedure in reporting Reportable Events.

Although all changes reflected in amendment 4 deserve an equal share in importance, the new procedure in reporting Reportable Events warrants review.

This new tiered level reporting process is being implemented to continue tracking of important safety concerns in an expedited manor by utilizing a priority reporting level of PREDICT reportable events while maintaining the integrity of the data base.

Reportable Events that require both a telephone call within 3 days of notification to the Coordination Center and entered on the Reportable Event Log will be considered Level 1.

Reportable Events that require entry on the Reportable Event Log only (not telephoned to the Coordination Center) will be considered Level 2.

Reporting Levels are as follows:

Level 1 Reportable Events

- Suicide attempt
- Hospitalization for serious (non-elective) medical issues (including childbirth)
- Any psychiatric hospitalization
- Premature withdrawal
- Death
- Identification of any safety concern warranting referral for a medical evaluation
- Identification of any safety concern warranting referral for a psychiatric evaluation
- Participation in an HD investigational drug research study

Level 2 Reportable Events

- New use of restricted meds
- New evaluation by a mental health professional
- New onset depression
- Compromise of confidentiality
- Exacerbation of depression requiring either change in pharmacotherapy or mental health visit
- Suicide risk score
- Any neurological event

It may be helpful to **post this new reporting process** somewhere in sight for ease in referencing so that unnecessary calls are not made.

If you have any questions or concerns regarding reportable events please contact Elaine Julian-Baros at (585) 273-2879 or elaine.julianbaros@ctcc.rochester.edu

The rationale behind this new reporting process...less burden for the site coordinator.

Cognitive

Staff updates Noelle Carlozzi, Ph.D., recently joined the Cognitive Assessment Laboratory at Indiana University replacing Shannon Johnson's responsibilities as Shannon has moved on to an assistant professorship at Dalhousie University in Halifax, Nova Scotia. Noelle comes from New York and recently finished her training in clinical neuropsychology in Oklahoma and South Carolina. She oversees the day to day operations of the cognitive data team and works closely with the Predict scientific team on data analysis and dissemination of findings. She is joined by Sarah Queller, Ph.D., a research scientist in the laboratory who now devotes a portion of her time to working with the Predict scientific team. New research assistants include many new college graduates: Shelley Swain (University of Colorado at Boulder), Jennifer Richards (University of South Florida), and Adolfo Rio Blanco (University of California at Berkeley). Two of our long time research assistants have moved on. Petra Schumacher is now a student in nursing school, and Amanda Wolfe began a graduate program at Boston University in Law and Public Policy. We wish them well and welcome these new additions to the Cognitive Team at Indiana.

What's in store for the Predict Cognitive Assessment? We are currently in the process of analyzing cross-sectional and longitudinal data to determine the sensitivity of specific tests in the pre-diagnosis period of HD. Please watch for preliminary results at the HSG meeting in November. Thanks to our sites, cognitive examiners, and participants for all of your efforts in producing this high quality data. Data analyses are revealing a clear picture of the subtle changes that develop in the pre-diagnosis period of HD. These are the exact data we need to design a sensitive, and SHORTER test battery for use in clinical trials during the pre-diagnosis period of HD. We are aware that the battery takes a lot of time and energy on the part of examiners and participants and we appreciate both your efforts and patience. We are currently conducting the analyses needed to determine an abbreviated battery, but we must continue to wait for sufficient longitudinal data to make final decisions. In the meantime, we continue to make minor improvements in the software and instructions with suggestions from our cognitive examiners.

We appreciate your detailed comments and your observations regarding tasks that participants struggle with as some members of the cohort progress. We encourage you to continue providing us with this invaluable information. Please remember, if a participant had a difficult experience in their previous visit, we'd like for you to contact the Predict Cognitive Team at Indiana University to help prepare for their next visit. We can make recommendations about shortening the test session, even dropping certain tests from the battery, to reduce the strain of the cognitive assessment. And, if you experience difficulty or have questions about any test during a Predict visit, please remember that our cognitive team is available to assist you at 1-866-697-0005 or (812) 855-2963.

Thanks for all of your hard work and we look forward to seeing many of you at HSG next month!

Holiday Closings

The Coordination Center will be closed in observance of the upcoming holidays:

- **12:00 PM EST on Wednesday, November 22, 2006**
- **ALL DAY on Thursday and Friday, November 23-24, 2006**
- **ALL DAY on Monday, December 25, 2006**
- **ALL DAY on Monday, January 2, 2007**

PREDICT-HD CONTACT PERSONS

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Cognitive Testing Issues

Noelle Carlozzi

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MRI Issues

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MRI Transfer Issues

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avel Guidelines (by site or bject), Reimbursements and otor Videos

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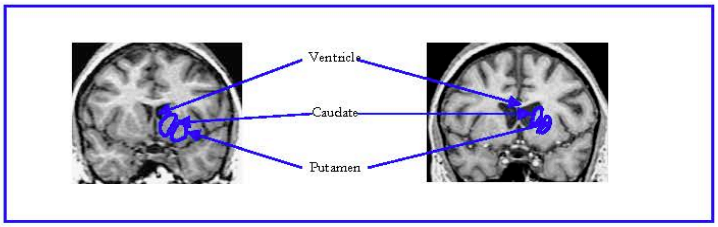
PREDICT-HD SITE NEWSLETTER
VOLUME 10
AUGUST 2007

INSIDE THIS ISSUE...

PREDICT-HD MRI Component

PREDICT-HD Investigators, Motor Raters, Coordinators and Cognitive Raters,

PREDICT-HD participants are asked to have a MRI scan every other year. This involves a 30-minute session in a MRI scanner, which is painless, requires no injections, and involves no radioactivity. Although some people find the experience a bit claustrophobic, most of our participants have had no difficulty completing their scans. We are using the scans to track brain changes that occur during the presymptomatic stages of HD, using two major approaches. The first focus is on the striatum—made up of two structures deep in the brain, called the caudate and putamen. These are gray-matter structures, meaning that they contain the cell bodies of the neurons, the type of nervous system cells that send and receive messages. The striatum is involved in the control of a number of different functions, including mood regulation, motor control, and certain cognitive abilities. We measure the volume of the striatum on the MRI scans, either by hand-tracing around the structures using computer software that allows us to visualize the structures in every slice of the MRI, or by allowing the computer to automatically "segment" the structures from other regions of the brain. We are currently studying which of these methods gives the most accurate and reproducible measurements. A second focus of the MRI study involves looking at regions of the brain other than the striatum—particularly the cortex, which is the gray matter on the surface of the brain. Computerized automatic segmentation programs are used to measure the volume of gray matter in specific regions of the cortex. Measurements of the striatum and cortex are then examined to determine at what stage of the presymptomatic period each of the structures begins to change, the amount of change over time in individual participants, the ability of structural change to predict when HD symptoms will start to be observed, and the association between structural volumes and specific HD symptoms.



Brain scan of a 40-year-old woman prior to the onset of HD (left), and the same woman at age 50, after HD diagnosis (right). The ventricles (in Black), which are filled with fluid, become enlarged as the size of the caudate and putamen decreases.

Results from the PREDICT-HD MRI study, so far, show that the striatum are smaller in presymptomatic participants than in control subjects who do not carry the HD gene and that they get progressively smaller as an individual approaches onset of the disease. For people who are far from onset (at least 15 years from diagnosis, as estimated by their CAG repeat length and age), the rate of shrinkage does not appear to be significantly faster than for control subjects. It is not until individuals get closer to onset that the rate of shrinkage increases. Once the rate of shrinkage increases from the normal, however, it remains fairly constant throughout the course of the disease.

~Elizabeth Aylward, MD
PREDICT Co-Principal Investigator

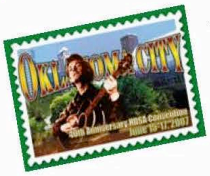
The quality of MRIs and site compliancy with the MRI protocol in the last year has been outstanding! I'd like to thank all the sites for their continued hard work and persistence with regards to consenting participants for MRIs and in sending those MRIs to Iowa for cataloging and analyzing.

To date we have received 1,521 total MRIs at Iowa from all sites (over 100 of which are from year 5 visits), with another 60 that have been completed and are en route.

Andrew Juhl, University of Iowa

HDSA Meeting 2007

The Huntington's Disease Society of America (HDSA) celebrates 40 years at the 22nd Annual Convention held on June 15-17, 2007 at the Cox Convention Center in Oklahoma City, Oklahoma. Over 600 people in attendance! Professionals, HD families and friends from across the country came together to inspire each other in the fight against HD. Speakers for this annual convention included several familiar PREDICT personnel including Jane Paulsen, Ph.D. presenting **Basic HD Gene** and **Managing Challenging Symptoms**; Kimberly Quaid, Ph.D. presenting **Understanding the HD Gene/ Genetic Testing Issues** and **Family Planning Options**; Martha Nance, M.D. presenting **Treatment Options for JHD** and **Understanding & Managing Psychiatric Symptoms** and **Understanding the Differences Between JHD and HD**; Kevin Duff, Ph.D. presenting **HD 101**, **New HD** and **Managing Cognitive and Behavioral Symptoms**; Vicki Wheelock, M.D. presenting **Review of Medications to Treat Chorea**, **Complementary and Alternative Therapies**, **Evidence Based Treatment of HD** and **Medications for Movement**; Peter Como, Ph.D. presenting **Understanding the Progression of HD** and **Medications for Behavior**; Amy Chesire, LCSW-R, MSG presenting **Sharing Session for New to HD/At Risk**; Cheryl Erwin, J.D., Ph.D. presenting **Genetic Discrimination** and **Privacy Protection** and Marcy MacDonald, Ph.D. presenting **HD Research Today**. These were critical topics for all in attendance and it was enlightening to witness valuable information shared by both speaker and participants during the sessions.



The 3rd Annual PREDICT-HD Study Participant Luncheon. For the third straight year, the PREDICT-HD study hosted a luncheon for currently enrolled PREDICT participants, their companions and study researchers. Over 60 people attended this exclusive gathering and were eager to hear about the preliminary research study updates and findings.

Dr. Jane Paulsen, PREDICT's principal investigator, extended her sincere thanks to everyone for their dedication to this important research study and offered attendees an opportunity to ask questions in an open forum. Dr. Kevin Duff, University of Iowa, provided brief updates on the psychiatric components and measures that are currently used to gather information during study visits. In many cases, the psychiatric changes are some of the first symptoms to appear in persons with HD and are proving to be an important biomarker to focus attention for in the pre-symptomatic cohort. Dr. Noelle Carlozzi, from Indiana University's cognitive team, was excited to announce the future reduction of the cognitive test battery. With longitudinal data now beginning to be analyzed, the team has been able to determine what tests are sensitive to measuring changes in cognition over time; thus discarding the other tests that are not as sensitive. For future yearly visits, the team anticipates that the computer and paper and pencil tests will take only half as much time to complete. Dr. Elizabeth Alyward, University of Washington in Seattle, displayed fascinating images of MRI scans which displayed examples of brain changes that can be seen across the study population as a whole.

Manuscripts and journal articles are currently being written so that the PREDICT-HD research team can share more specific preliminary findings with our dedicated participants as well as with HD researchers and scientists around the world. In the meantime, Dr. Paulsen and her research team will continue to travel the world throughout the year to update all of you about PREDICT; they hope to see you at the next meeting!

PREDICT Assistant Project Coordinator

Kay Meyers Assistant Project Coordinator!

Kay Meyers
University of Rochester
Clinical Trials Coordination Center
1351 Mt. Hope Avenue, Suite 223
Rochester, NY 14620
Phone: 585-275-3507
Fax: 585-461-3554
Email: kay.meyers@ctcc.rochester.edu

Please feel free to contact Kay with your PREDICT questions and concerns.

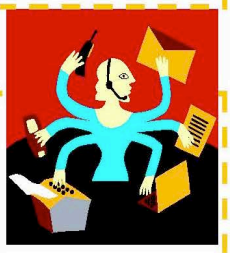
Please welcome the Clinical Trials Coordination Center's new PREDICT Assistant Project Coordinator, Kay Meyers!

Kay has her BS degree in Biology from the University of Rochester and prior to joining the CTCC worked as a Grant Developer at the University of Rochester in the department of Emergency Medicine. There she identified and assisted with grant opportunities in the areas of disaster medicine and emergency preparedness and utilizing the expertise within the Medical Center and the University. She also is a former Biomedical Information Specialist for a global pharmaceutical company where she conducted biomedical and competitive research in support of marketed and developmental products.

Kay keeps very busy with her hobbies and interests which include riding her horses and flower gardening. Kay is a Dog Obedience Instructor, and is an owner of 2 German Shepherds that compete in obedience, protection and tracking competitions. She also volunteers as an Emergency Medical Technician with a local ambulance corps.

Kay's Assistant Project Coordinator responsibilities are collecting and tracking of regulatory documents, preparation of materials for grant and other funding application, assisting in the development of consent forms, data collection tools and writing of operations manuals and liaison with physicians and site coordinators.

Data Management



Reportable Event Logs...

For Data Management purposes please follow these guidelines for Reportable Event Log completion:

Once your site has approval for amendment #4 you **MUST** transfer **ALL** entries from Predict Reportable Event Log amendment # 3 **(version 6/17/04 Amend #3)** onto the new amendment #4 Reportable Event Log **(version 2/16/06 Amend #4)**.

After you transfer all entries to Predict Reportable Event Log (amendment #4), please have your site investigator sign Predict Reportable Event Log (**amendment # 3)** and submit the original form to the Coordination Center.

Please re-enter all events, ongoing and resolved, that you reported on Amendment # 3 Log on the current Amendment # 4 Reportable Event Log. If you did not report any events on Amendment # 3 Log, after your site investigator signs the form, you must still submit the original to the Coordination Center.

For questions and concerns regarding forms completion please feel free to contact Cathy Covert, PREDICT Information Analyst at cathy.covert@ctcc.rochester.edu.

PREDICT Payment Schedule 2007

Payments are based on **a full visit set of subject Case Report Forms** completed and received at the Coordination Center.

The Payment Schedule will be as follows:

CRFs Received at CTCC	Payment Month
By August 15, 2007	September 1, 2007
By November 14, 2007	December 1, 2007

For questions and concerns regarding payment please contact Christine Anderson at the University of Iowa at christine-m-anderson@uiowa.edu

Friendly Reminders...

Travel Reimbursement Changes for PREDICT Participants and Staff:

Mileage Reimbursement: Beginning February 1st, 2007, mileage will be reimbursed at a rate of $.485 per mile (1.6 kilometers).

Airline Reservations: As of February 1st, 2007, Predict-HD participants and staff* can make airline reservations through **Winebrenner Red Carpet Travel** in association with The University of Iowa. Confidentiality waivers have been signed by the travel representatives to ensure that patient confidentiality is enforced. Please contact Kim or Jill at **866-236-1424** and mention that this is travel for the PREDICT-HD study. Tickets will be billed direct to The University of Iowa. Do not contact Short's Travel.

*Traveling for PREDICT business must be approved by the University of Iowa

Motor Videos:

Important notice: Sites that are not currently using MiniDV video cameras will be receiving replacement video cameras in the next few weeks.

Preparing the Motor Video

- Before filming, make sure the camera is in the correct orientation.
- If possible, record videos in NTSC (National Television System Committee) format, the analog television system used in the US, and Canada. If NTSC format is not available, please include the format on the label (i.e. PAL, PAL60).
- Multiple participants can be recorded on the same tape.
- Each **tape or segment** must begin by identifying the participant with the following information: 1) Site Number, 2) Participant Number, 3) Visit Number and 4) Date of Visit.

Helpful Hints: Some sites show the top of the completed CRF, some use a white board, others print an identifying form, and some simply write the information on a small piece of paper that the participant holds before the camera.

- Review tapes before sending to insure video quality. Make sure that the participant is clearly visible throughout the entire exam.
- Rewind tapes before sending.

If sending videos on CDs or DVDs, please send as a data file in MPEG format. Separate participants into individual files if possible.

Sending the Motor Videos

- Each **tape or disk** must be clearly labeled with the following information in the order the participants appear on the tape:
  1) Site Number
  2) Participant Number(s)
  3) Visit Number(s)
  4) Date of Visit(s)

- Motor videos should be sent in protective packaging.
- Motor videos should be sent to:

  Ann Dudler
  University of Iowa
  Psychiatry Research
  1-309A MEB
  Iowa City, IA 52242

PREDICT Enrollment

As of July 9, 2007 a total of 979 subjects have been enrolled in PREDICT-HD!

Sites enrolling between 20-29 subjects to date include:

The Centre for Addiction and Mental Health (CA)
Indiana University (US)
UCLA, Los Angeles (US)
University of California SF (US)
National Hospital for Neurology and Neurosurgery(EU)
Cambridge Centre for Brain Repair (EU)
Cardiff University (EU)
Massachusetts General Hospital (US)
University of Calgary (CA)
Graylands, Selby-Lemnos (AU)
Clinical Genetics Centre (EU)
University of Manchester (EU)
Columbia-Presbyterian (US)
Washington University (US)
University of Rochester (US)
University California Davis (US)

Sites enrolling between 30-59 subjects to date include:

Hereditary Neurological Disease Centre (US)
Emory University (US)
Westmead Hospital (AU)
University of Washington (US)
University of Ulm (EU)

Sites enrolling 60 or more subjects to date include:

University of Iowa (US)
St. George's Health Service (AU)
University of British Columbia (CA)
Johns Hopkins (US)

PREDICT HSG Recent Publications & Presentations 2007

1. Carlozzi, N.E., Stout, J.C., Queller, S., Solomon, A. C., Duff, K., Beglinger, L., Langbehn, D., and Paulsen, J.S. Assessment of intellectual functioning in pre-diagnostic Huntington's disease. Poster session presented at the 35th Annual International Neuropsychological Society meeting, Portland, Oregon, February 7-10, 2007.
2. Duff, K.D., Paulsen, J.S., Beglinger, L.J., Langbehn, D.R., Stout, J.C., and the PREDICT-HD Investigators of the Huntington Study Group. Psychiatric symptoms in pre-clinical Huntington's disease: The Predict-HD study. Biological Psychiatry, in press. Available on line May 3, 2007.
3. Langbehn, D.R., Paulsen, J.S. and the Huntington Study Group. Predictors of diagnosis in Huntington's disease. Neurology. 68(20):1710-7, 2007 May 15.
4. Solomon, A.C., Stout, J.C., Johnson, S.A., Langbehn, D.R., Brandt, J., Brandt, J., Aylward, E.H., Julian-Baros, E., Ross, C.A., Beglinger, L., Hayden, M., Kayson, E., Duff, K., Guttman, M., Nance, M., Oakes, D., Kieburtz, K., Shoulsen, I., Penziner, M.A., Paulsen, J.S., and the Predict-HD Investigators of the Huntington's Study Group (2006). Verbal episodic memory declines prior to diagnosis in Huntington's disease. Neuropsychologia. 45(8):1767-76, 2007 Apr 9.
5. Stout., J.C., Queller, S., Langbehn, D.R., Johnson, S.A., Carlozzi, N.E., Miura, T.K., Solomon, A. C., Cruce, C.B., Beglinger, L., Duff, K., Aylward, E.H., and Paulsen, J.S. Detecting cognitive changes in pre-diagnosis HD in the Predict-HD study. Poster session presented at the 35th Annual International Neuropsychological Society meeting, Portland, Oregon, February 7-10, 2007.
6. Stout, J. C., Queller, S., Langbehn, D. A., Johnson, S. A., Carlozzi, N. E., Duff, K., Beglinger, L., and Paulsen, J. S. Two-Year longitudinal sensitivity of cognitive measures in pre-diagnosis Huntington's disease in the Predict-HD cohort. Poster session presented at the 18th Annual Meeting of the American Neuropsychiatric Association, Tuscan, Arizona, February 17-20, 2007.

The Cornerstone: IRB Submission

In 1974 U.S. Congress passed the National Research Act and by 1979 the Belmont Report was published giving us informed consent and Institutional Review Board oversight. All institutions are held responsible for being compliant with regulations in their research activities involving human subjects. To uphold these regulations all sites including the Clinical Trials Coordination Center work with an Investigations Review Board (IRB) or Investigational Ethics Committee (IEC) in the review and approval process of clinical research. Thus IRBs and/or IECs serve from an ethical standpoint overseeing that the protection of human subjects is respected.

The steps to IRB/IEC approval are at times exasperating but nonetheless completely necessary.

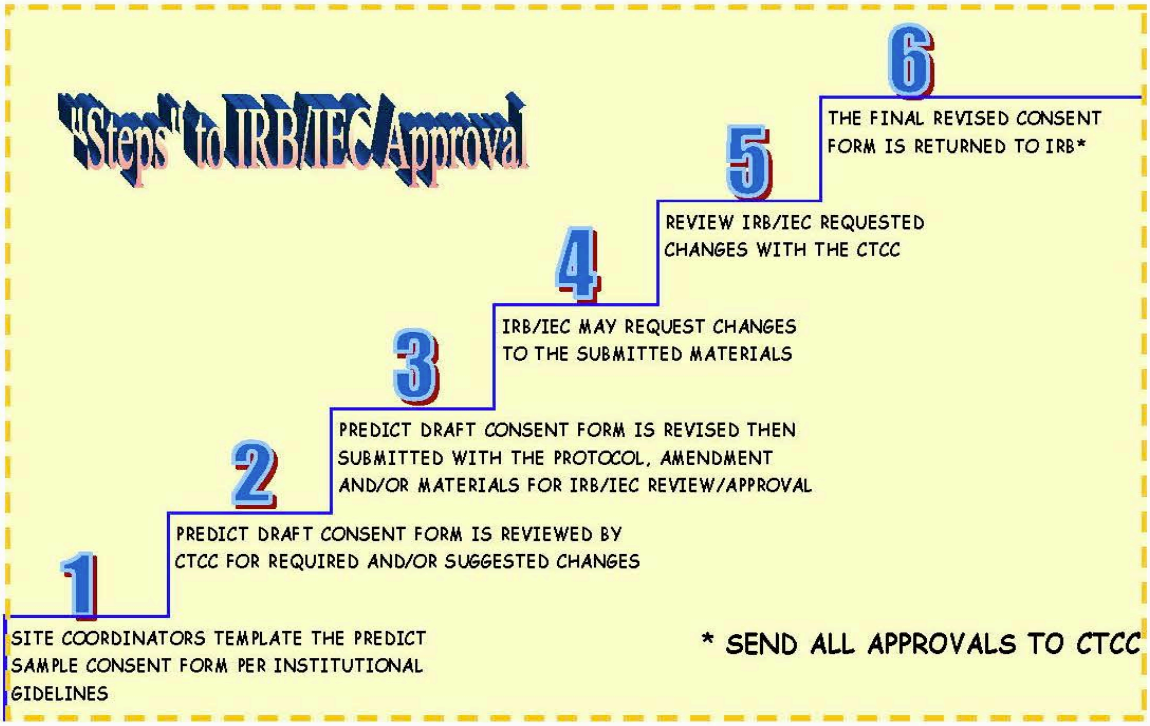
You can see why each one of us are responsible for what is placed in each PREDICT-HD informed consent and why the "Steps" to IRB/IEC Approval are many. Here at the Coordination Center from the initial informed consent to every modification we too submit to our IRB for review and approval. Once approved we then distribute the approved version to each PREDICT-HD site. As the Coordination Center has agreed with the IRB to distribute the approved informed consent, we are then responsible for all site versions to properly reflect the approved distributed version. The Coordination Center understands the uniqueness of each institution and will make every reasonable effort while reviewing each institutions informed consent version.

It's the Coordination Center's intention to move review along as quickly as possible. Follow-up from the site level with your IRB/IEC is extremely helpful and important to decrease any delay in approval. It could mean the difference in a higher recruitment and retention rate.

For questions or concerns regarding IRB submissions please contact Kay Meyers or Elaine Julian-Baros at the Clinical Trials Coordination Center.

International Conference on Harmonization (ICH)

1.31 Institutional Review Board (IRB): An independent body constituted of medical, scientific, and nonscientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.



Holiday Closings

The Coordination Center will be closed in observance of the upcoming holidays:

ALL DAY on Monday, September 3, 2007

12 noon (EST) on Wednesday, November 21, 2007

All Day Thursday and Friday, November 22-23, 2007

12 noon (EST) on Monday, December 24, 2007

All Day Tuesday, December 25, 2007

12 noon (EST) Monday, December 31, 2007

All day Tuesday, January 1, 2008

PREDICT-HD CONTACT PERSONS

Protocol Issues, Regulatory Documents and Supply Orders

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Data Management Issues

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Recruitment and Retention Issues

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Email: ncarlozzi@indiana.edu

Julie Stout
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Email: jcstout@indiana.edu

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Email: leigh-beglinger@uiowa.edu

Andrew Juhl
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Fax: (319) 353-3003
Email: andrew-juhl@uiowa.edu

Finance Issues (site payments/subcontracts)

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Email: christine-m-anderson@uiowa.edu

Brenda McAreavy
Phone: (319) 353-4236
Email: brenda-mcareavy@uiowa.edu

Travel Guidelines (by site or subject), Reimbursements and Motor Videos

Ann Dudler
Phone: (319) 353-4542
Email: ann-dudler@uiowa.edu

Please send correspondence about newsletter content to:

Elaine Julian-Baros,CCRC
Associate Project Coordinator
Clinical Trials Coordination Center
1351 Mt. Hope Avenue, Suite 223
Rochester, NY 14620
Phone: (585) 273-2879
Fax: (585) 461-3554

Email:Elaine.JulianBaros@ctcc.rochester.edu

The PREDICT-HD Study
Amendments to renewal grant
2004-2008

The PREDICT-HD study was funded 2001-2004 although the budget was significantly reduced by NIH and cut to a 3-year grant. The High Q Foundation supported the project and agreed to continue to do so for this renewal if we expanded the research to a more worldwide study. This renewal was funded by NIH and HighQ from 2004-2008.

AMENDMENT 4 TO PREDICT-HD:

1. CHDI, Inc. requested we set up sites in Europe and agreed to provide support for this increase in demand. Renewal was submitted with 38 sites; 10 were designated back-up sites.
2. Kevin Biglan replaced Karl Kieburtz on the Steering Committee. Bernhardt Landwehrmeyer joined the Steering Committee to facilitate establishment of European sites.
3. An additional longitudinal MRI scan was added to visit 5.
4. The cognitive battery for visit 4 was added.
5. Shifter was removed from the cognitive battery due to copyright concerns.
6. The consent form requested that audiotapes of the cognitive assessment and videotapes of motor assessments could be shared to HSG members to assist with reliability of scoring.

AMENDMENT 5:

1. A submission to NIH for 5-year grant renewal was submitted in 2007.
2. The cognitive battery was re-evaluated and shortened for all visits. 13 tasks were removed from the battery and/or altered to reduce time and participant burden.
3. Additional acquisition of blood and urine were added to the protocol, along with the additional of lymphoblastoid cell lines, for future research.
4. An additional quality of life survey was added to the battery.
5. A 9-digit unique identifier was added to each participant to track across studies.

It is worth noting that shortly after amendment 5 was released, the 2.0 version of the study was funded and efforts were made to roll out the 2.0 study. This meant that many of the sites involved in the study shifted efforts to submit the 2.0 study to their respective IRBs as opposed to the amendment 5 version. Since changes found in Amendment 5 were incorporated into the 2.0 study, some sites never received IRB-approvals for Amendment 5 changes.

Updated **Schedule of Activities** provided to all sites.

	Visit 1 month 0	**TC 6mos**	**Visit 2 month 12**	**TC 18 mos**	**Visit 3 month 24**	**TC 30 mos**	**Visit 4 month 36**	**TC 42 mos**	**Visit 5 month 48**	**TC 54 mos**	**Visit 6 month 60**	**TC 66 mos**	**Visit 7 month 72**
Informed consent	x		x		x		x		x		x		x
Eligibility criteria	x												
Medical history	x												
General physical exam and Neuro exam	x												
Participant HD History			x		x		x		x		x		x
UHDRS '99	x		x		x		x		x		x		x
Concomitant Medication Review	x		x		x		x		x		x		x
Reportable Event Review	x		x		x		x		x		x		x
Participant Entry Number	x												
Blood draw for CAG analysis	x												
Blood draw for biomarkers	x		x		x		x		x		x		x
Cognitive tests	x		x		x		x		x		x		x
Cognitive[1] & Motor[2] Videotaping	x		x		x		x		x		x		x
MRI	x				x				x				x
Psychiatric ratings	x		x		x		x		x		x		x
Telephone Contact													

Neurobiological Predictors of Huntington's Disease (PREDICT-HD) version 2.0

PREDICT-HD 2.0

8-12 RO1 NS 040068

An international 30-site observational study of over 1000 persons at-risk for HD to characterize the natural history of the pre-manifest period, to develop tools for clinical trials, and to identify markers that will make it possible to test putative neuroprotective therapies that could delay or prevent diagnosis.

Study PI and Chair:

Jane S. Paulsen
The University of Iowa

Executive Committee: An Executive Committee has been added to facilitate communication between study implementation and sponsors. The Executive Committee consists of Marg Sutherland of NINDS, Robi Blumenstein of CHDI, Inc., Mark Guttman of The Centre for Addiction and Mental Health, Michael Hayden of the University of British Columbia, and the PI, Jane Paulsen.

Steering Committee:

The Steering Committee has been revised and consists of the Executive Committee members and a rotating membership of 7 individuals derived from the Chairs of the Scientific and Core Sections of the PREDICT-HD Team Roster*.

Supported by:

The National Institute of Neurological Disorders and Stroke (NINDS) NS40068 and the CHDI Foundation

TABLE OF CONTENTS

CLINICAL SITES PARTICIPATING IN THE STUDY

Site Name	*Site Investigator*
Baylor College of Medicine, Houston, Texas	J. Jankovic, W. Ondo
Cambridge Centre for Brain Repair, Cambridge, UK	R. Barker
Cardiff University, Cardiff, Wales	A. Rosser
Clinical Genetics Centre, Aberdeen, Scotland, UK	S. Simpson
Colorado Neurological Institute, Denver, Colorado	R. Kumar
Columbia University Medical Center, New York City, New York	P. Mazzoni
Emory University School of Medicine, Atlanta, Georgia	R. Jones
Graylands Hospital, Selby-Lemnos & Special Health Care Services, Perth, Australia	P. Panegyres
Harvard University / Massachusetts General Hospital, Boston, Massachusetts	D. Rosas
Hereditary Neurological Disease Center, Wichita, Kansas	W. Mallonee
Hospital Ram'on y Cajal, Madrid, Spain	J. Garcia De Yebenes
Indiana University School of Medicine, Indianapolis, Indiana	K. Quaid
Johns Hopkins University, Baltimore, Maryland	A. Rosenblatt, C. Ross
Manchester University, Manchester, UK	D. Craufurd
National Hospital for Neurology and Neurosurgery, London, UK	T. Warner, S. Kloppel
Royal Melbourne Hospital and St. George's Health Service, Melbourne Australia	P. Chua / E. Chiu, D. Ames
University of Alberta, Edmonton, Alberta, Canada	W. Martin
University British Columbia, Vancouver, British Columbia, Canada	L. Raymond
University of Calgary, Calgary, Alberta, Canada	O. Suchowersky, S. Furtado
University of California Davis, Davis California	V. Wheelock
University of California Los Angeles Medical Center, Los Angeles, California	S. Perlman
University of California San Francisco, San Francisco, California	M. Geschwind
University of Iowa, Iowa City, Iowa	K. Duff
University of Minnesota; Hennepin County Medical Center, Minneapolis, Minnesota	M. Nance
University of Rochester, Rochester, New York	P. Como
University of Toronto/Centre for Addiction & Mental Health, Markham, Ontario, Canada	M. Guttman
University of ULM, Ulm, Germany	B. Landwehrmeyer, S. Trautman
University of Washington and VA Puget Sound Health Care System, Seattle, Washington	A. Samii
Washington University, St. Louis, Missouri	J. Perlmutter
Westmead Hospital, Westmead, Australia	E. McCusker

LEADERSHIP STUDY TEAM ROSTER

Scientific Sections

Scientific Section	*Chair*	*Location*
Biomarkers	Blair Leavitt (retired 2009) Coriell Biorepository Tatiana Foroud, NINDS Biosend	University of British Columbia Cornell University Indiana University
Brain Donation and Pathology	Carol Moscowitz and Jean Paul Vonsattel	Columbia University
Cognitive	Julie Stout (retired 2009) Holly Westerfeld Tamara Hershey Deborah Harrington Leigh Beglinger, Kevin Duff, Megan Smith	Monash University Brown University Washington University, St. Louis UCSD University of Iowa
Functional	Leigh Beglinger, Nancy Downing, and Janet Williams	University of Iowa
Genetics	Marcy MacDonald and Jim Gusella	Harvard University
Motor	Kevin Biglan	University of Rochester
Psychiatric	Kevin Duff and Eric Epping	University of Iowa
Imaging	Hans Johnson	University of Iowa
➢ General	Ron Pierson	University of Iowa
➢ Striatal Analysis-	Elizabeth Aylward	University of Washington
➢ Shape Analysis-	Chris Ross and Michael Miller	Johns Hopkins University
➢ Surface Analysis-	Peg Nopoulos (retired 2010)	University of Iowa
➢ DTI	Vincent Magnotta	University of Iowa
➢ fMRI	Steve Rao	Cleveland Clinic

Core Administrative Sections

Core	*Chair*	*Location*
Recruitment-Retention	Martha Nance Sean Thompson	Hennepin County, MN University of Iowa
Statistics	Doug Langbehn (retired 2009) James Mills Jeffrey Long	University of Iowa University of Iowa University of Iowa
Ethics	Cheryl Erwin Kimberly Quaid Janet Williams	University of Texas Indiana University University of Iowa

Information Technology	Hans Johnson Jeremy Bockholt	University of Iowa University of Iowa
Administrative	Christine Werling Stacie Vik	University of Iowa University of Iowa
	Elise Kayson Elaine Julian Baros	University of Rochester University of Rochester
Financial	Steve Blanchard Phil Danzer Kelsey Montross	University of Iowa University of Iowa University of Iowa

PRÉCIS

TITLE: The PREDICT-HD Study v. 2.0

OBJECTIVES: The ultimate goal of the PREDICT-HD study is to define the neurobiology of Huntington disease (HD) and to develop tools to allow clinical trials of potential dis- ease-modifying therapies before at-risk individuals have diagnosable symptoms of the disease. By identifying disease state markers that are useful during the premanifest period, PREDICT-HD will make it possible to test putative neuroprotective therapies that could delay or prevent the onset of disease.

DESIGN: The longitudinal study uses MRI, blood and urine samples, and comprehensive assessments of cognitive, motor, functional and psychiatric outcomes to characterize the premanifest syndrome in HD, to document the rate of change of these variables during the years leading up to and following a clinical diagnosis of HD, and to investigate the relationship among neurobiologic factors, clinical diagnosis and CAG repeat length. Assessment tools are refined in an iterative fashion until each measure is reliable and valid and ready for clinical trials.

PARTICIPANTS: To date, over 800 at-risk participants who have an expanded CAG mutation and over 200 at risk persons with normal CAG repeat length have been enrolled in the study. One thousand at risk participants who had previously undergone genetic testing for HD will remain active in the ongoing study. To date, 98 participants have prospectively undergone HD diagnosis.

RESEARCH SETTINGS/SITES: Thirty total sites are currently active: 16 USA, 4 Canadian, 3 Australian, 7 European sites. Genetic testing rates vary significantly worldwide. For in- stance, estimated prevalence of predictive genetic testing among those at familial risk in the US is 5%, Canada=15%, Australia=20% and Europe=25%. The generalizability of our study findings is enhanced by recruiting from countries with varying rates and potentially differing factors that influence the testing decision. We anticipate that about 30 sites will remain active in the next 5 years of the study, although specific sites may vary to assure that each site maintains 25 active research participants at all times to assure that samples are ready for transition to clinical trials.

TIMELINE: All subjects will be examined annually. Criteria for traditional motor disease diagnosis will be considered at each visit as well as comprehensive cognitive, neuro- psychiatric, functional and motor assessments, and lifestyle and opinion surveys. Our rationale for annual assessments is to establish a time interval that provides a balance between the disease development rate and the need to rapidly test experimental com- pounds. Blood and urine are collected annually whereas MRI evaluations will occur every two years due to extra cost. All participants are asked to make a brain donation should an untimely death occur. Minor modifications will be made to items involved in scale development for clinical trials on an ongoing basis.

1. STUDY OBJECTIVES

The ultimate goal of the PREDICT-HD study is to define the neurobiology of Huntington's dis- ease (HD) sufficiently to allow clinical trials of potential disease-modifying therapies before at- risk individuals have diagnosable symptoms of the disease. By identifying disease state markers that are useful during the premanifest period, PREDICT-HD will make it possible to test putative neuroprotective therapies that could delay or prevent the onset of disease. Specific aims (and example hypotheses) are:

1. To refine the prediction of disease diagnosis (motor conversion) using longitudinal measures of plasma, imaging, cognitive performances, motor ratings, psychiatric and functional measures.

   Hypothesis: HD diagnosis will be better predicted by adding longitudinal change to the baseline measures of striatal and white matter volumes, tone-paced and speeded tapping score, tower moves, stroop interference and motor score.

2. To improve markers of disease progression that become abnormal prior to the clinical diag- nosis and to characterize their natural history. A subset of the PREDICT-HD cohort will test whether leading candidate therapeutic compounds impact the identified markers.

   Hypothesis: Predictive models for HD diagnosis will be further improved (resulting in greater power and lower clinical trial sample size) by adding additional, sensitive measures to the PREDICT-HD exam (e.g., behavioral: companion frontal rating, cognitive: Maze test score, imaging: DTI fractional anisotropy, plasma marker: 8OHDG).

   Hypothesis: Comparisons of change rates across time will suggest measures best suited to clinical trials by large effect sizes and low variability.

3. To establish the validity and reliability of disease measures identified in Specific Aims 1 and 2. The power and sensitivity of future multi-site trials and studies depend on accurate measures of marker validity.

   Hypothesis: HD diagnosis will be better predicted by UHDRS total motor score following new standardized reliability training and by the tapping task under modified more challeng- ing, conditions. Psychiatric and functional ratings will be improved with item response anal- yses and dynamic piloting of item edits to establish the most psychometrically sound items for clinical trials.

2. BACKGROUND

Huntington disease is an autosomal dominant illness of the brain known to be due to a trinucleo- tide expansion of CAG in the 5'-translated region of the IT-15 gene on the short arm of chromo- some 4 (4p16.3) affecting the huntingtin protein. A recent evidence-based review found no symptomatic or disease-modifying treatment recommendations for clinical practice. A clinical diagnosis of HD is based on the presence of unequivocal motor signs, although more subtle motor signs, neuropsychological deficits, psychiatric problems, neurophysiological alterations, and brain changes often precede the formal diagnosis. Ideally, disease-modifying treatments should target at-risk individuals at or before the earliest stages of neural degeneration, before functional decline. Proving the efficacy of these treatments requires the ability to detect and

track reliably these or other subtle changes in a clinically healthy individual. To this end, a better understanding of the evolution from the presymptomatic state to the clinical diagnosis is critical.

PREDICT-HD is an international 30-site observational study of persons at-risk for Huntington's disease (HD) funded from 2001 to 2008. PREDICT-HD capitalizes on two unique aspects of HD among neurodegenerative disorders—the ability to know in advance exactly who will develop the disease, and the knowledge that all affected individuals have the same root cause (a CAG repeat expansion in the huntingtin gene). The PREDICT-HD project has fulfilled all aims from its initial submissions and has become part of a world-wide effort to provide treatments for HD— both symptomatic and presymptomatic ("premanifest"). The PREDICT-HD cohort and database have become international resources and offer an unprecedented opportunity to examine the pathophysiology and neurobiology of early HD. The continuation of this project will capitalize on the impact of this resource and test new and refined hypotheses to advance clinical trials in HD and related diseases.

Obstacles to Preventive Trials Today. Despite the progress made, there remain several gaps in our ability to use these measures to launch preventive trials in HD. (1) Although we have identi- fied cognitive, motor, sensory, physiological, and neuroimaging markers of premanifest HD, these measures are far from proven as acceptable valid outcomes in clinical trials. The most critical step is eventual validation against a well-defined (non-surrogate) clinical endpoint. Prior to that, further test-retest and inter-rater reliabilities, multi-site feasibility, and direct comparisons for redundancy are needed for each marker. In addition, there remains a paucity of biological markers. (2) Further longitudinal study is now critical to determine accurately the natural rate of change of the markers we have identified in this population; markers cannot be used in a clinical trial without first completing this task. (3) We have found that the functional capacity measures used in symptomatic patients are not useful in the presymptomatic population, because of a ceiling effect. In addition, we believe that the clinical reliability of the UHDRS research tool can be improved, with consequent reduction in sample sizes for future clinical trials. (4) Recruitment for a large-scale preventive clinical trial outside of PREDICT-HD would require at least two years. Maintaining this cohort will greatly facilitate the transition into clinical trials in the pre-symptomatic population, and ensure a wealth of baseline historical data on subjects entering the trial. (5) A critical review of current compounds suggests that no treatment is yet ready for effi- cacy trials in this sample. We are fortunate to work closely with CHDI, Inc., however, who ex- pect to have 1-3 compounds requiring phase II trials within the grant renewal period. Finally, (6) HD research is over-reliant on clinical trial designs and methodologies that are insufficient to track the highly variable and insidious decline we observe in brain disease. Testbeds for im- provement are lacking and much is needed to continue to improve the experimental therapeu- tics of neurodegeneration.

Products of PREDICT Continuation. Completion of this project will facilitate preventive therapeu- tic trials at or before clinical diagnosis of HD. At least 6 products will contribute to this: (1) We will better characterize the early longitudinal course of functional, cognitive, motor, and psychiat- ric change in the period encompassing 10-20 years before to 0-3 years after the traditional point of clinical diagnosis. (2) We will extend our identification and characterization of candidate bio- logical, and neuroimaging markers that have potential as useful biomarkers and possibly as sur- rogate endpoints in clinical trials. Markers identified in PREDICT-HD could be used to reduce dramatically the number of subjects needed in future clinical trials, and/or to stratify subjects for selection in studies. (3) We will refine and better standardize the measurement of neurological and functional impairment in the earliest stages of HD development, including the point oftradi-

tional clinical diagnosis. (4) We will provide a cohort from which sub samples may volunteer for early (phase I and II) trials of candidate therapies and be poised for Phase III trials when need- ed. (5) We will examine available compounds for safety and tolerability, and then for impact on newly developed disease state markers in this presymptomatic cohort. (6) Our innovations in infrastructure and worldwide collaboration will continue to serve as a model and catalyst for clin- ical trials in other neurodegenerative diseases.

3. STUDY DESIGN

The longitudinal study uses MRI, blood and urine samples, and comprehensive assessment of cognitive, motor, and psychiatric outcomes to characterize the premanifest syndrome in HD, to document the rate of change of these variables during the years leading up to and following a clinical diagnosis of HD, and to investigate the relationship among neurobiologic factors, clinical diagnosis, functional outcomes, and CAG repeat length.

Research Settings/Sites**:** The sites were selected for their pool of potential subjects, ongoing relationship with a predictive testing center, methodological capability, prior experience in HD collaborative research, availability of specific research components (MRI, Neuropsychologists), and geography. Thirty total sites are currently active: 16 USA, 4 Canadian, 3 Australian, 7 Euro- pean sites. Genetic testing rates vary significantly worldwide. For instance, estimated preva- lence of predictive genetic testing among those at familial risk in the US is 5%, Canada=15%, Australia=20% and Europe=25%. The generalizability of our study findings are enhanced by recruiting from countries with varying rates and potentially differing factors that influence the testing decision. Sites unable to maintain a minimum of 25 Pre-HD participants will be replaced by sites who demonstrate a consistently high number of new enrollments to assure that the PREDICT-HD study can be efficiently transitioned to a clinical trial for premanifest HD. In situa- tions where a site requires replacement, every effort will be made to transfer all currently en- rolled participants to the most appropriate sites.

Timeline**:** All subjects will be examined annually. Criteria for traditional motor disease diagnosis will be considered at each visit while comprehensive cognitive, neuropsychiatric, motor, and neuroimaging assessments will characterize disease progression. Our rationale for annual as- sessments is to establish a time interval that provides a balance between the disease develop- ment rate and the need to rapidly test experimental compounds. An annual test interval seems best suited for now. MRI evaluations will occur every two years due to extra cost.

4. CHARACTERISTICS, SELECTION AND ENROLLMENT OF PARTICIPANTS

Participants: To date, over 800 at-risk participants who have an expanded CAG mutation and over 200 at risk persons with normal CAG repeat length have been enrolled in the study. One thousand at risk participants who had previously undergone genetic testing for HD will remain active in the ongoing study. To date, 98 participants have prospectively undergone HD diagno- sis. A primary change includes a modification to the study inclusion/exclusion criteria to further refine measures and terminology within the field of HD research. CAG repeat length windows were adjusted based on new description of “intermediate allele length” and were updated to make the study more inclusive of these individuals.

Gender: Both males and females are included in and being recruited for this study.

Race/Ethnicity: No restrictions on race or ethnicity exist within the study. Past HD research has shown an underlying low prevalence of the disease in non-Caucasian populations, although no racial predispositions are known to exist and the disease is found in populations worldwide.

Drop-out rates and potential bias to date. Our original design and power calculations had antici- pated a 10 % dropout rate. To date, we estimate annual follow-up loss at 8.5%. The rate is un- certain because of subjects who are currently more than one month past scheduled follow-up but not explicitly withdrawn or clearly lost. As of April 2007, of 996 subjects enrolled, 81 had withdrawn or were at least 11 months past scheduled follow-up. Another 83 were 2 to 11 months late. Exponential survival modeling of these data provides annual loss estimates of 5% and 10% respectively. Similar "2-11 month late" data from April 2006 shows that 70% of such subjects were eventually lost; leading to our final estimate of 8.5% loss.

Within the context of these relatively low rates, we have investigated potential biases due to fol- low-up loss. Using multivariate Cox survival models, stratified by investigation site, we find drop- out to be most strongly predicted by younger age (hazard ratio = 1.51 per decade, p = .004) and education (hazard ratio = 1.16 per year less education, p = .006). In the same multivariate anal- ysis, neither gender nor gene-expansion status predict study loss. Nonetheless, ongoing, proac- tive vigilance will be critical to assuring that this continues. Additionally, we will embark upon efforts to emphasize communication with, and understanding of, the younger and less educated of our cohort.

Enrollment Projections: We assume a continued loss rate of 8.5% per year with a continued 5% diagnosis rate per year. Once a diagnosis of HD is given we plan continuation in PREDICT-HD for at least two years to assure adequate observation of decline markers. This information will be invaluable in designing future peri-diagnostic clinical trials. To maintain our cohort at its ap- proximate present size, we will continue enrolling 80 gene-expanded subjects and 20 gene negative controls each year. With 30 sites this enrollment goal translates to 3- 4 partici- pants/year/site. Given that our enrollments in PREDICT-HD have gone well, this ongoing projec- tion should not be difficult for our study sites. We predict that a total of 115 new cases would be diagnosed during the follow-up period resulting in a total of 222 prospectively diagnosed HD participants.

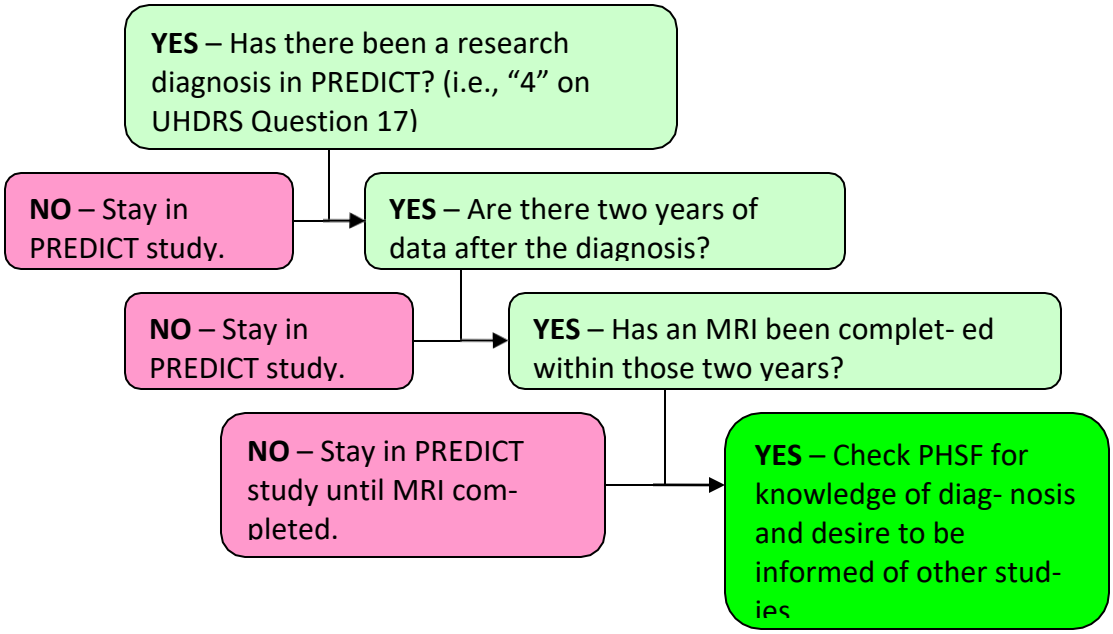
Participant inclusion criteria are as follows: a) Completed predictive testing with CAG length >= 36 for expansion group or CAG < 36 for comparison group (this enrollment strategy will include a few rare persons in the clinically described "intermediate allele length" which are of increasing scientific interest but should not significantly impact our conversion rate); b) Men and women ages 18 or older; c) Commitment to complete annual evaluations for five years; d) Commitment of an informant to enhance retention. Exclusion criteria are as follows: a) evidence of unstable medical or psychiatric illness (including substance abuse); b) History of severe learning disabil- ity, mental retardation, or other CNS disease or event (e.g., seizures, head trauma); c) Current treatment with anti-psychotic medications, including the traditional neuroleptics such as haloperidol as well as the atypical antipsychotics risperidone, clozapine, quetiapine and olanzapine; d) Treatment with phenothiazine-derivative antiemetic medications such as pro- chlorperazine, metoclopramide, promethazine and Inapsine greater than 3 times per month; e) Pacemaker or metallic implants.

Retention: To establish a retention protocol, we conducted a thorough review of the literature (27 retention studies reviewed) and talked by telephone with the coordinators of other multi-site longitudinal studies. The following practices were cited as most successful (in ascending order): 1) frequent contact with participants; 2) incentives for participation (small gifts and logo- identified items increasing group identification); 3) reimbursement of all costs (child care, trans- portation, meals, time); 4) staff (training, communication, encouragement to develop a relation-

ship and offer time to listen); 5) offering feedback on research; 6) inviting participation with a companion; and 7) demonstration of giving back to the community and helping others. Based upon these findings we developed a retention protocol. Briefly, all study staff undergo formal training in retention practices. Frequent contact has been integrated into the study design in- cluding a 6-month telephone call. Data analyses shows that participants who were contacted at more frequent intervals and given newsletters and other study items showed better study reten- tion than participants contacted less often and not enrolled in retention practices. Because of this finding the new protocol will invite each participant to release contact information to the PI so that they may receive periodic updates about the study and its impact on our understanding of HD. All participants will be offered a newsletter with specific updates on the study as well as its findings and will be invited to participate in regional study events and WEB chat rooms (all confidential and password-protected). We have also initiated some retention activities directed at site personnel. We initiated a staff newsletter, a quarterly "Webinar" to review findings, and a site support plan that includes centralizing as much work as possible.

Participant Withdrawal: As some participants did not want feedback on their disease status through their involvement in PREDICT, individuals who are deemed by investigators to have a diagnosis of manifest disease but have requested that they NOT discuss diagnosis will continue to be followed in PREDICT. In addition, individuals who do meet criteria for withdrawal from PREDICT, yet want to continue to be followed may enroll in COHORT or REGISTRY, which are observational studies for all HD participants, whether or not they are diagnosed. A CRF (named the 'Participant HD Status Form', or PHSF) has been developed to ask each participant (a) whether they consider themselves to have manifest HD; (b) whether they have been given a diagnosis of HD since the previous visit; and (c) whether they want to be informed of all studies for which they meet entrance criteria. Participants enrolled in PREDICT-HD will be evaluated at each visit using the PHSF. The figure below reflects the proposed decision analysis to determine if a participant is eligible for study withdrawal. If a participant receives a score of 4 (motor abnormalities that are unequivocal signs of HD (≥99% confidence)) on question #17 (diagnostic confidence) of the Unified Huntington Disease Rating Scale (UHDRS) at the current visit then the investigator will determine whether the participant has acquired enough post-diagnosis data to warrant withdrawal consideration. If the participant has been seen for two research visits since receiving a diagnostic confidence of 4 and also has received an MRI since the diagnosis was obtained, then the investigator will examine the participant's responses to question #1 ("I am aware that I have received a clinical diagnosis of HD") on the PHSF. If the participant an- swered "yes" to having received a clinical diagnosis of HD then they will be given the option of withdrawing from PREDICT and participating in studies for individual's with manifest HD. Individuals that do not want to withdraw from PREDICT may continue to be followed in the study. Since many alternative studies are available on all phases of HD from pre-diagnosis through diagnosis and beyond, we believe allowing individuals who have been diagnosed as having a motor diagnosis of HD the opportunity to withdraw from PREDICT and enroll in more appropriate studies for individuals with manifest HD is most ethical and appropriate.

PREDICT Withdrawal Decision Tree



5. CLINICAL AND LABORATORY EVALUATIONS

PREDICT-HD v 2.0 Schedule of Activities

	Visit 1 month 0	TC 6mos	Visit 2 month 12	TC 18 mos	Visit 3 month 24	TC 30 mos	Visit 4 month 36	TC 42 mos	Visit 5 month 48	TC 54 mos
Informed consent	x		x		x		x		x	
Eligibility criteria	x									
Medical history	x									
General physical and Neuro exam	x									
Participant HD History			x		x		x		x	
UHDRS Motor Exam	x		x		x		x		x	
Concomitant Medication Review	x		x		x		x		x	
Reportable Event Re-view	x		x		x		x		x	
PREDICT Entry Number	x									
Unique ID number	x									
Blood draw for DNA analysis and repository	x									
Blood draw for bi-omarker analysis and repository	x		x		x		x		x	
Cognitive tests	x		x		x		x		x	
Behavioral Ratings	x		x		x		x		x	
Opinion Surveys	x		x		x		x		x	
Videotaping	x		x		x		x		x	
MRI	x				x				x	
Telephone Contact		□		□		□		□		□

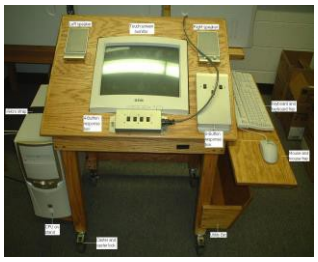
Activities in red font are only acquired at the first visit for each participant and DO NOT require REPEAT- ING with participants who were enrolled in PREDICT-HD version 1.0. Annual updates to these items may be required.

UHDRS Motor Exam and Disease Diagnosis Definition. The Motor section of the UHDRS has 15 individual items measuring eye movements, speech, motor coordination, rigidity, dystonia, chorea and gait/balance. Training has previously focused on the UHDRS diagnostic confidence level. The diagnostic confidence level is a scale from 0 (normal) to 4 (unequivocal signs of HD, >=99% confidence) operationally defined as “the unequivocal presence of an otherwise unexplained

extrapyramidal movement disorder in a subject at risk for HD". In the upcoming project period we will focus our training on the UHDRS motor assessment using professionally vide- otaped standardized examinations of a western European population that more closely reflects the PREDICT-HD cohort, and mirrors the motor assessment in PREDICT-HD. The European HD Network (EHDN), funded by the CHDI foundation, has recently compiled professionally filmed teaching videos of the UHDRS motor section incorporating over 100 exams at various stages of HD which is being validated and edited into a training tape and a "UHDRS-Library", with three examples of each possible score for each item on the motor exam. .All motor raters will be required to complete annual training on the UHDRS motor assessment, either in person or on-line. Training will entail completing the instructional video and reviewing examples of mo- tor scores followed by performing a full-length motor UHDRS assessment on 3 individuals in the UHDRS library. Inter-rater reliability will be calculated based on these assessments. All individ- uals will be required to meet specific standards. Individuals will be provided feedback on their scores and training will continue until standards are met. All motor exams will be standardized and videotaped. All tapes will be reviewed by a member of the motor team. Should the vide- otape reviewer disagree with a rating given the tape will be reviewed at a consensus meeting attended by no fewer than 3 expert motor raters. A consensus meeting can also be requested by the statistician or the PI should an outlier be discovered in the motor rating. The motor team will review and assign all motor ratings on a consensus basis.

Cognitive Methodology. To determine whether we can detect progression over intervals shorter than two years, we will shift from biennial to annual cognitive assessments.

Top: system for cog- nitive data acquisition to replace Bottom older system



Enhancement of Sensitivity. We are actively engaged in collaborations and studies, funded separately from PREDICT-HD, which will identify additional sensitive cognitive tests that may be phased into the PRE- DICT-HD cognitive battery once they have shown cross-sectional sen- sitivity. All PREDICT-HD sites will be ready to add cognitive tests at any time. Efforts will be made by the Scientific Section Chairs to coor- dinate the changes so that sites can make variations in an efficient manner. Cognitive changes that involve a modification not considered "significant" will be expected to be approved by the IRB in an expedited manner whereas major changes will require full board IRB review. Site assistants will assist and track all protocol changes.

Increased Efficiency and Feasibility. We will be upgrading from the current outdated Predict-HD computer hardware, which consists of a desktop pc on a large wooden stand, to a laptop based system. Prior to this conversion we will complete a validation process on the soft- ware and hardware to determine comparability between the old and new systems. This upgrade is a necessity as the older hardware is near end of life and similar models are no longer available.

We are also planning to implement a streamlined data collection and electronic routing of the paper/pencil tasks from the cognitive battery. This will involve either 1) scanning paper cognitive assessment records followed by electronic transfer of the digitized documents to the cognitive assessment team or 2) implementation of computerized versions of the Predict-HD cognitive

tasks that have been traditionally administered via paper and pencil. This change will only be implemented after establishing comparable performance on the computerized and paper/pencil versions of the tasks. **Cognitive Assessment Protocol: Core Cognitive Battery**

a. The following tests will be completed in the visit 1 battery.

First visit Tasks
1. Trailmaking Test (parts A & B; Trails)
2. Stroop Color Word Interference Task (Stroop)
3. Symbol Digit Modalities Test (SDMT)
4. Smell Identification Test (UPSIT; 20 items only; Smell)
5. Emotion Recognition Task-Static version (Emostatic)
6. Simple/Dual Reaction Test (Chooser Block 2 & 4)
7. Finger Tapping Task (nondominant hand speeded tapping, alternating thumb paced tapping (Tapper)
8. Buttons Task (Blocks 1, 2 & 3)
9. Hopkins Verbal Learning Test-Revised (HVLT-immediate and delayed)
10. American National Adult Reading Test (ANART)

b. The following tests will be completed in the battery at **all follow up visits.**

Follow up visit Tasks
1. Trailmaking Test (parts A & B; Trails)
2. Stroop Color Word Interference Task (Stroop)
3. Symbol Digit Modalities Test (SDMT))
4. Smell Identification Test (UPSIT; 20 items only; Smell)
5. Emotion Recognition Task-Static version (Emostatic)
6. Simple/Dual Reaction Test (Chooser Block 2 & 4)
7. Finger Tapping Task (nondominant hand speeded tapping & - alternating thumb paced tapping (Tapper)
8. Buttons Task (Blocks 1, 2 & 3)

c. The following tasks will no longer be administered at any visit.

Task
Benton Faces Recognition Task (Faces)
Controlled Oral Word Association (Verbal Fluency)
Serial Task (Serial)
Blocks 1, 3 and 4 from the Finger Tapping Task (Tapper)
20 items from the Smell Identification Test/UPSIT (Smell)
Tower Task (3- and 4-disk versions; Tower)
Emotion Recognition Task-Dynamic version (Emodynamic)
Letter-Number Sequencing from the WAIS-III (Letter-Number)
Continuous Dimension Category Learning Task (Implicit Version; Categories)
WASI Vocabulary (Vocab)
WASI Matrix Reasoning (Matrix)
1-back task (N-Back Task)
CogState

Psychiatric Assessment. Initial findings indicate that it will be important to track psychiatric functioning as this cohort progresses towards HD diagnosis. Findings to date suggest that companion ratings provide valuable information about functioning as premanifest individuals get closer to clinical disease diagnosis and all psychiatric assessments will be completed by both

participant and companion. The new proposed battery, which will be completed in less than two hours is described below. The **Frontal Systems Behavior Scale** (FrSBe) (Grace and Malloy 2001) rates participants on "frontal" behaviors, such as interest in activities, planning and executive functions, and disinhitibion. Discrepancies between participant and companion ratings could suggest decreased insight/awareness in premanifest HD individuals. The **Symptom Checklist 90- Revised** (SCL-90-R) (Derogatis, 1975) is a brief, multidimensional self-report instrument designed to evaluate a broad range of psychological problems such as depression, anxiety and obsessive-compulsive behaviors. Ratings will be given by both participant and companion for reasons stated above. The **Substance Use Form** (SUF) requires self-reports of the frequency of taking any of a checklist of nonprescription drugs and alcohol. **The Columbia Suicide Severity Rating Scale** is a structured interview of suicidal ideation and intent.

Quality Control. All PREDICT-HD site investigators and examiners will receive training in the administration and scoring of these psychiatric measures in person and online as needed.
Three levels of quality control will be exercised with the psychiatric forms. First, examiners will inspect all forms before sending them to the University of Rochester's CTCC. Second, the CCTC also inspects psychiatric forms for valid entries and generates site queries over irregulari- ties. Finally, individual and total scores are checked by the statistical team upon receipt from the CTCC. All psychiatric interviews will be videotaped and mailed. All psychiatric interviews will be reviewed by the psychiatric team. Should a member of the team consider a rating not consistent with training by experts, a consensus meeting will take place. Ratings will be established by consensus of not less than 3 experts in the psychiatric team and feedback will be given to the site(s).

Functional Assessment. The current measures of functional capacity in PREDICT-HD and other HD studies appear insensitive in premanifest samples due to ceiling effects. Since governmental regulatory agencies (e.g., Food and Drug Administration) have indicated that adequate functional measures are necessary endpoints for clinical trials in diseases like HD, we propose to further examine new potential measures of functional capacity as well as Patient-Reported Outcomes, such as quality of life. Additionally, each participant will complete the **World Health Organization Disability Assessment Scale (WHODAS)** since it is the recommended measure for functional capacity in worldwide neuropsychiatric disorders. PREDICT-HD was also supportive of additional research in functional assessment and facilitated additional research in Work Function (funded under a separate grant) as well as Quality of Life in several research projects funded under separate funding mechanisms

Opinion Surveys. Survey completion will emphasize two primary goals: 1) to invite input from participants about future clinical trials in pre-HD; and 2) to invite input about stigmatization and discrimination experiences, including but not limited to the ethical, legal and social implications of discrimination, funded separately through the National Human Genome Research Institute. The Opinion surveys will take approximately one hour to complete.

MRI Methodology. MRI scans will be obtained every other year. The standard protocol for this study includes a sagittal localizing series (2D spin echo), an axial 3D volumetric spoiled gradient echo series with a 1.0x1.0x1.5mm resolution, and dual echo sequence with both a PD and T2 in the same acquisition window using a fast spin-echo sequence (1.0x1.0x3.0mm). (We have reported no difficulty with data from different scanners)

Transition to Scanner Changes. A recent survey of PREDICT-HD sites indicates that 24 sites currently have the ability to collect data on 3T scanners. Since an average institutional scanner lasts 7 to 10 years, we anticipate that all scanners will be replaced within the next 5- year continuation period, generally by 3T scanners. The resultant need to define a new scan- ning sequence is also an opportunity to capitalize on the increased signal to noise ratio that affords higher resolution scans and shorter scan times on 3T scanners. The proposed 3T scan protocol will collect isotropic voxels 1mm for the T1 weighted scan and 1x1x1.25 mm voxels for the T2 weighted scan. We are also proposing to add a diffusion tensor

imaging study to evaluate white matter changes. To prepare for the unavoidable effects of equipment change, a balanced strategy is defined that maintains the longitudinal integrity of the existing cohort by continuing use of the current 1.5T scan protocol and also provides a comprehensive transition path to 3T scanning.

At enrollment (baseline) visits:

- If a 3.0T scanner is available to the site, then the participant should be scanned in a 3.0T scanner for their baseline visit, and continue to be scanned on a 3.0T scanner for the remainder of the time that they are in the study.
- If no 3.0T scanner is available to the site, then the participant should be scanned in a 1.5T scanner.

During return visits:

- If exactly zero (0) sets of validated 1.5T multimodal scans exist for the participant, then the participant should be scanned in a 3.0T scanner (at sites where one is available).
- If exactly one (1) set of validated 1.5T multimodal scans exist for the participant, then the participant should be scanned in a 1.5T scanner.
- If two or more (2+) sets of validated 1.5T multimodal scans exist for the participant, then the participant should be scanned in a 3.0T scanner (at sites where one is availa- ble).

In addition, site assistants and site coordinators will be able read a report of each participant's past scan history to help them identify the correct scanner strength to use for upcoming visits. This information can be found in an easy-to-read report on the HDNI website

(http://www.hdni.org/gridsphere) and is available to both the site assistants and the site coor- dinators. Specific parameters for each scanner—dependent on manufacture and magnet strength—will also be available upon request to site assistants and site coordinators. All spe- cific scan parameters will be communicated to each site individually and programmed into available scanners when possible. Every effort will be made to communicate directly with ra- diology staff and technicians to establish protocols.

Tracking and Quality Control. As scans are received via a web based transfer, they are logged into an online scan tracking system. Acquisition parameters are automatically checked and catalogued and conformance information is relayed to the retention committee for inse r- tion into site feedback reports available through the PREDICT-HD web portal. If acquisition parameters are incorrect or the scan is compromised, this information is communicated to the site via a personal phone call and a decision is made to either reacquire or use the compro- mised scan. Next a standards compliant (HIPPA, NIH, HSG) de-identification occurs to pre- pare each scan for transfer to external collaborators for data analyses.

MRI Processing. The processing methods using BRAINS have been developed with an un- derstanding of the challenges inherent in a multisite study with scanners of different manufac- turers (the current PREDICT-HD study) and field strengths (MIND Clinical Imaging Consorti- um) as well as the difficulties due to software and hardware upgrades, scanner replacement, and scanning protocol. By addition and optimization of various Iowa AutoWorkup modules we will continue to create the best processing methods, ensuring that these ongoing challenges introduce minimal variance into the research data.

Other than possible geometric distortions, the primary differences we address are the effec- tive resolution of the acquired scans and variations in intensity, inhomogeneity and tissue con- trast. The best results so far have been to make the scans most similar prior to tissue classif i- cation. When comparing scans with different resolution, the higher resolution scans are re- sampled in raw space into the lower sample resolution. Inhomogeneity correction is performed on the raw image, with an appropriate brain mask to limit the introduction of non-brain arti- facts. Finally, careful intensity normalization and/or histogram equalization ensures that the tissue-type intensity profiles are similar. It is important to realize that, while the methods r e- move much cross-site variance, the primary strength of these centralized methods is our abil- ity to use data from any protocol or scanner without having to lose longitudinal continuity.
Therefore, for subjects transferring from one imaging protocol to another, we will have stand- ard Phase 1 as well as higher-quality Phase 2 longitudinal data. Data can be pooled from both phases, with additional measures available during statistical analysis to control for any re- maining systematic differences.

Measures evaluated: Quantification of a brain scan runs the gamut from global to regional to surface measures. All measures are of volume, expressed as cc's: Intracranial volume, sepa- rated into cerebrum and cerebellum. Total brain tissue is segmented into gray matter (exclud- ing striatum), white matter, and cerebral spinal fluid (CSF). Within the cerebrum, tissue is segmented into cortical gray matter (excludes the striatum), cerebral white matter and ventric- ular CSF. Regional cerebral measures include frontal, temporal, parietal, and occipital lobes, each segmented into gray and white matter volume. Measured sub-cortical structures include thalamus, putamen, and caudate. FreeSurfer measures the cortex by parcellating each hemi- sphere into 34 separate regions as defined by Desikan . Each region is quantified by gray matter volume, surface area (in cm^2) and cortical depth (in mm^3).

Plasma and Urine Samples:

1. Specimen Repository (blood and urine collection)

Plasma marker collection, analyses and storage was part of the initial grant and is not new to the project. The method of sample attainment has been updated to improve sample quality for more sophisticated analyses, such as metabolomics, proteomics lipidomics, and mass spec- troscopy. Blood and urine samples (approximately 30 ml of blood and 50 ml of urine) will be ob- tained from all consenting PREDICT participants at all participating sites annually. For blood collection, 2 purple tops, 2 green tops and 1 red top will be collected at each visit. Urine collec- tion involves 1 falcon tube and 1 red top. As initially planned and executed, the PREDICT-HD samples will be stored and made available for testing new biomarkers as they are hypothesized. For instance, the samples will be evaluated to measure the DNA injury markers (such as 8- hydroxy-2' deoxyguanosine (8-OH2'dG)) and the RNA injury markers (such as 8- hydroxyguanosine (8OHrG)). The samples will be labeled with the Subject ID number, site number, date and visit number and sent to the Coriell Institute for Medical Research. Sub- jects will be asked whether their samples can be kept indefinitely for future research. HD re- searchers who have had their research reviewed by an Institutional Review Board (IRB) will be able to request coded plasma samples following approval from the principal investigator (PI) and the PREDICT-HD Steering Committee. Samples will be identified by a barcode label includ- ing the PREDICT-HD ID code, PREDICT-HD Site ID number, visit number, and the date of sample acquisition

2. Lymphoblastoid cell line repository

The initial study allowed DNA collection and genotyping. Subsequent research has identified additional genetic polymorphisms that add knowledge into the underlying biologic mecha- nisms of the disease as well as to variations in clinical phenotype and age of disease diag- nosis. The following procedure and language is added to the Research Design and Methods section to allow establishment of lymphoblastoid cell lines at the initial or first follow-up visit following new protocol approval, for storage and future research. All PREDICT subjects will continue to have blood specimens 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 other polymor- phisms 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. The research lab of Dr. Marcy MacDonald at Massa- chusetts General Hospital, Harvard University will be receiving the blood samples which will be processed into plasma, lymphocytes and lymphoblastoid cell lines for the PREDICT study. HD researchers who have had their research reviewed by an Institutional Review Board (IRB) will be able to request coded lymphoblastoid cell lines and/or coded lympho- blastoid cell line DNA from Dr. MacDonald following approval from the PI and the PREDICT- HD Steering Committee. Samples will be identified only by the PREDICT-HD ID code. The following process will be utilized for the collection and processing for the cell line and obtain- ing DNA for genotyping at the CAG or for other authenticated genetic polymorphisms:

- Two yellow top tubes of blood (10 ml ea) will be collected and shipped (at room temperature on the same day of collection) by overnight courier with the subject number, site number, date and visit number for identification purposes.

- Dr. MacDonald (or her staff) will process the blood samples to produce plasma, lymphocytes, and a lymphoblastoid cell line and will store these for future HD re- search.
- For each lymphoblastoid cell line, Dr. MacDonald will produce lymphoblastoid cell line DNA.
- Routine quality control studies will be conducted to estimate the quality and integ- rity of the DNA.
- All activities will be documented by Dr. MacDonald.
- Consistent with the previous 7 years of study, genotyping for the HD CAG repeat will be performed at the Genomics facility (Molecular Neurogenetics Unit, Massa- chusetts 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.

3. Brain Donation

All participants will be invited to donate their brain to research should an untimely death occur. The New York Brain Bank at Columbia University will receive all donations and the brain bank will analyze and store all samples. Researchers who have had their research reviewed by an Institutional Review Board (IRB) can request brain samples from Dr. Jean Paul Vonsattel with approval from the PREDICT-HD PI and Steering Committee. All pheno- type, plasma, and genetic data can be combined and made available to the researchers using the repositories.

Integrity, confidentiality and security of laboratory data and information systems.

DNA Data. The samples will be reviewed, scanned and logged into an Excel database unique for the PREDICT study. The database used for PREDICT is on an 'isolated' PC computer that has double password protection, and which is not networked. Back-ups are kept in Dr. MacDonald's office, which is locked at all times. The results are read into the Excel database and checked for accuracy by Dr. MacDonald. The results are stored in a locked room and except for the PREDICT-HD identification code are not labeled in any other way. The results from each subject will be sent to the University of Iowa where the results will be added to the clinical data to create a single dataset for analysis.

Plasma Samples. The PREDICT Sample Repository for markers of DNA and RNA damage will be held at the Coriell Institute for Medical Research who is responsible for receiv- ing and cataloging all biological specimens. Researchers who have had their research re- viewed by an Institutional Review Board (IRB) will have the ability to request any phenotyp- ic information that has been collected in the study. If a request is made for phenotypic in- formation with specimens in the repository, the PREDICT-HD subject identification number will be used to link samples. The correlated information will be compiled and then will be sent to the requesting researcher. All requests will be handled through the PREDICT HD Steering Committee with the University of Iowa.

Brain Samples. The NYBB will conduct some analyses and make it available for PREDICT researchers. Additional brain tissue will be stored at the NYBB for use by other research- ers. Researchers who have had their research reviewed by an Institutional Review Board (IRB) will have the ability to request any phenotypic information that has been collected in

the study. If a request is made for phenotypic information with specimens in the repository, the PREDICT-HD subject identification number will be used to link samples. All research requests will be reviewed by Dr. Vonsattel and the PREDICT PI and Steering Committee.

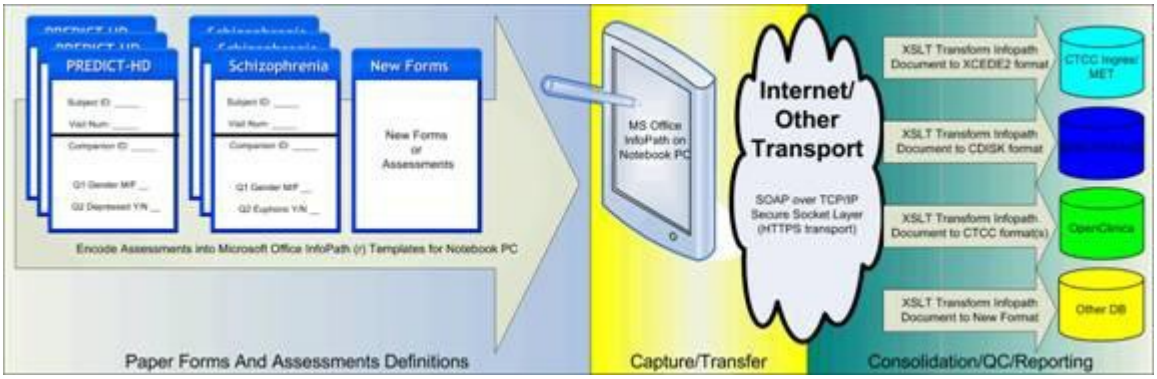
Regular data transfers will take place between the University of Iowa, MGH, NYBB and the Coriell Institute for Medical Research to confirm that all expected samples have been received, catalogued, and stored appropriately.

Protections Against Breach of Confidentiality

The Repositories have several provisions in place to maintain integrity, confidentiality, and security of its data and information systems. Neither MGH, the NYBB, nor Coriell have any subject's confidential information, and both facilities have security policies in place to as- sure that all data are protected from unauthorized access, and maintain audit trails, backup procedures and error checking to assure accuracy and protection of its data.

Tracking, Quality Control, and Biomarker Exploration. Upon receipt, all samples are cata- loged, archived and qualified according to acquisition and storage criteria received from the site and rated by the sample recipient. A master spread sheet is updated weekly and provided to the PI, which Iowa (Paulsen) edits for accuracy quarterly.

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 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 include: 1) Forms can be com- pleted on a notebook or desktop personal computer (PC) 2) In the event of a network outage, forms are saved locally and can be later be retransmitted; 3) Microsoft InfoPath can support multiple languages and produces a standards-based XML form as it's output. Sites will be pro- vided two notebook PC's running Microsoft Windows. Site managers/users will require approxi- mately 2-3 hours of training on form completion and another 2-3 hours on the proper notebook PC use.

Predict HD assessments and forms will be entered directly on a tablet-type 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 for the PREDICT HD data repository. A second transfer will occur to a secure SOAP web service at the University of Iowa for archival purposes in standard XML formatted docu- ments on a secure file server.

Data integrity and security is inherent in the EDCS system. The current protocols for subject de-identification through the use of a participant/site number ID will continue. Additional electronic security occurs via: (1) User/Password Security on the PC; 2) Se- cure Socket Layer (SSL) encryption using a public certificate for data links; 3) Physical security of the file and WEB service servers; 4) authentication of all users though cen- trally controlled LDAP/Active Directory. Data integrity is achieved by eliminating single points of failure, error checking, and maintaining redundant copies of the source files, and through periodic backups of file systems and database servers. Safety features in- clude: Multiple notebook PC's at each site; 2) saved copies of the original documents at both the originating PC and at the SOAP server; 3) daily backups of the SOAP server documents to magnetic tape; 3) file check-summing using a Cyclical Redundancy Check (CRC) algorithm before electronic transmission and are sent using HTTPS Se- cure Sockets Layer (128-bit) encrypted TCP/IP transport to maintain data integrity. Fur- ther, form templates only allow valid answers to assessment questions and provide in- stantaneous feedback on common errors (i.e. incomplete form, out of range answers).

Biomarker data will be conveyed electronically in password-protected files from the labs directly to the University of Iowa study coordination center. All data is identified by ran- domly assigned study identifiers only. MRI scans are conveyed in password-protected files directly from each site to the University of Iowa Imaging Center.

6. DATA MANAGEMENT AND STATISTICAL CONSIDERATIONS

Data Management: The PREDICT-HD data is currently stored and maintained in an In- gres database, and data collection and query processes are paper-based. In 2009, we plan to transform the current database into an Oracle-based system that uses electronic data capture (EDC) for collection and cleaning. The PREDICT-HD database will be cre- ated and built using CTCC's Oracle-based eRT Clinical Data Management System in accordance with Standard Operating Procedures and standard methodologies for test- ing, validation, and user acceptance of the production database. The eRT system is compliant with 21 CFR Part 11. CTCC Data Management staff have already used this software to create 18 study databases, 12 using electronic data capture. The Clinical Trials Coordination Center at the University of Rochester (CTCC) provides interactive Internet-based training for site personnel requiring additional training and assistance.

CTCC has trained and certified over 200 site personnel. Many of the HSG site staff have already been trained and are accessing this system through other HSG studies. To review data, site staff will enter a web address provided by CTCC into the browser and will connect to the collaborative workspace (eResearch Community) that resides on secured servers at the CTCC. The system uses HTTPS Secure Sockets Layer (128-bit) encryption algorithms to protect the security and confidentiality of data across the Inter- net. Utilizing a unique user ID and password combination supplied by the CTCC (pro- vided only upon successful completion of research application training), the investiga-

tive site staff will gain access to the collaborative workspace where they can receive messages, review electronic documents, post questions, obtain help through frequently asked questions and gain access to the electronic data capture application and their own site-/subject-specific data. Our new electronic and WEB-based system will reduce the need for later queries, which are inevitably more demanding of resources and less accurate.

Once data are entered into the web-based form and saved, they are immediately stored in the central study database where they are accessible for review by CTCC staff. Addi- tional edit checks for inconsistencies and errors are performed overnight and, if neces- sary, queries are automatically generated. Should questions arise during CTCC staff review, the electronic data capture application allows staff to flag a query for the data in question. All queries are maintained in the system and accessible to site personnel. The software also keeps a full audit trail of the query: the original value, the corrected value, the reason for change, the date and time of the change, and the ID of the person who made the change. As eCRF-recorded data are received, narrative text of ad- verse/reportable events and concomitant medications will be periodically coded using established coding methodologies. This cycle of electronic data capture, review, query identification/resolution and database correction occurs repeatedly over the course of the study. Once the last visits are completed, the database will have few, if any, remain- ing queries or corrections pending, allowing very rapid database closure.

Data will be securely transferred from the data management system to the analysis sys- tem at the UR Biostatistics Department by unloading the relational Oracle database to a SAS format. Any errors found in analytic manipulations will be forwarded for clarification by the data management staff. The HSG Coordination Center merges the eCRF data- bases with the neuropsychology electronic databases. An integrated database is sent bi-annually to the University of Iowa, where additional quality control mechanisms are conducted and additional data is merged with imaging, plasma and DNA databases. In particular, the PI and Predict-HD statistician, inspect the data and decide whether it is ready for statistical analysis. Prior to finalization of the database, a detailed and final analysis plan is prepared that incorporates any adjustments or amendments made to the original protocol. Once the CTCC determines, in conjunction with the Study PI, that all queries have been resolved and the database has been deemed “clean”, the data- base is officially locked. All permissions to make changes (append, delete, modify or update) are removed at that time.

The HSG CTCC has several provisions in place to maintain integrity, confidentiality, and security of subject information. All hard copies of the PREDICT-HD data are kept in locked, fire-retardant secure cabinets, and the office containing the cabinets is locked at all times. All personnel who work with the data have signed confidentiality agreements. Both the CTCC and the DBCB maintain the most up-to-date computer hardware and software to support data collection, analysis, biostatistical research and consulting. The CTCC and HSG Biostatics Department are physically and geographically separate.
Both groups have comprehensive security plans and procedures.

Study Identification and Assignment of Unique ID for HD Research

Upon enrollment in the study, each participant is assigned a study code that is randomly gener- ated by the CTCC. In addition, during the first follow up visit of the study renewal, subjects will be asked to have an ID number assigned to them to enable the HSG and the worldwide HD re- search network to track individual subjects across multiple HD studies without storing any per- sonally identifiable information. The protected system uses an algorithm of nine data element inputs (last name at birth, first name at birth, gender at birth, day, month and year of birth, city and country of birth, and mother's maiden name), and produces an electronic "fingerprint" out- put. The system stores only the "fingerprint" and clears the individual's inputted data elements from memory. The subject is then assigned a nine-digit Unique ID Number, which is associated to their electronic "fingerprint."

Once a subject signs the informed consent form, s/he will be directed to a secure website where s/he or the Site Coordinator will enter the nine data elements. The Unique ID Number will be provided to the subject. The Site Coordinator will record this number on the subject's de- mographics electronic case report form (eCRF). If a subject has participated in previous HSG studies and already has an existing Unique ID Number, this number will be used for this study. If a subject forgets his/her Unique ID Number, s/he can return to the secure website, but the same nine data elements must be entered again to receive the same Unique ID Number.

These nine data elements were chosen as the least likely to change for an individual thus mini- mizing the likelihood of multiple numbers for an individual. The CTCC uses the NIST/NSA (Na- tional Institute of Standards and Technology/ National Security Agency) designed hash function known as SHA512 because there is no known way to reverse or 'decrypt' the nine data ele- ments, and it is a completely one-way function. The system then stores only the fingerprint and clears the individual's responses from memory. The user is then assigned a number, which is associated with the user's fingerprint. Users never have access to the fingerprint resulting in a further level of protection. All system components are protected behind a Cisco firewall device and the individual's responses are protected by a 128-bit secure socket layer encryption to their point of entry.

Power Analyses*:* We approximate statistical power using the Cox Proportional Hazard sample size formula of Hsieh and Lavori (Hsieh and Lavori 2000). Key assumptions are the eventual accumulation of 115 new diagnoses during the follow-up period and 222 diagnoses throughout the life of the project. The power is expressed as detectable hazard ratio per between-subject standard deviation (SD) of the predictor variable. To date, many of our survival analyses have been based on a log-logistic model rather than some form of proportional hazards model, and we will also use this model in the future if it continues to give better goodness-of-fit. The log- logistic model yields risks in terms of constant failure odds ratios rather than hazard ratios. For relatively low incidence rates, these statistics approximate each other, and we have verified via simulation that the proportional hazard-based formula still yields accurate power approxima- tions.

For measures newly instituted or revised at the beginning of the renewal period we will have 80% power with a 5% type I error rate to detect a hazard ratio of 1.30 per between-subject SD of a prognostic variable. We will detect a hazard ratio of 1.43 per SD with 90% power and a 1% type I rate. Most predictors identified to date have correlations with CAG-based diagnosis prob- ability between .3 and .4. Assuming a correlation of .35, after control for CAG-based diagnostic

probability we will have power to detect hazard ratios of approximately 1.32 (80% power, 5% type I) and 1.47 per SD (90% power, 1% type I).

For measures that are essentially unchanged since the beginning of the study, pooling renewal data with information collected by the end of the current project period will yield 80% power, 5% type I error to detect a hazard ratio of 1.21 and 90% power, 1% type I error, to detect a 1.30 hazard ratio per SD. These rates increase, respectively, to 1.22 and 1.32 after control for CAG- based diagnostic probability.

Strictly, the above hazard (or approximate odds) ratios assume a correctly specified model. However, nonlinear survival models with and without a covariate will generally not both be cor- rectly specified (Hsieh and Lavori 2000). Nonetheless, our simulations suggest that these esti- mates are accurate for the *apparent* hazard ratio under a broad range of moderate misspecifica- tion—a conclusion consistent with White's asymptotic properties for maximum likelihood estima- tors under misspecification (White 1982).

Longitudinal Analyses*:* For measures with moderate reliability or better, relatively small sam- ples suffice to detect longitudinal change with progression towards HD diagnosis. However, judgment of the potential utility of a measure as a longitudinal marker and, possibly, a treatment surrogate requires much more than a demonstration of statistical significance. Instead, a key criterion is the precision with which the natural rate of change is determined. Assume that, in a future study, the impact of a preventive treatment on a marker's rate of change is to be studied. (We emphasize again that this is a necessary but far from sufficient step in demonstrating sur- rogacy.) Typically, the hypothesized treatment impact will only be a fraction of the untreated change rate. In order to plan the size of such a study with any confidence, one needs a fairly precise estimate of the natural rate of change, relative to measurement uncertainty.

We illustrate the above principle using our knowledge to-date regarding change in self-paced tapping, which has one of the strongest longitudinal effects observed so far in "mid" and "near" prognostic groups. We consider a standard longitudinal linear model with compound symmetry assumed for the within-subject residuals. It is well-known that, in addition to subject number, the power to detect between-group differences in a within-subject temporal effect depends upon (1) the number and variance of repeated observation times and (2) the ratio (effect size) of within- subject change relative to within-subject standard deviation (measurement error or instability) (Liu and Liang 1997; Diggle, Heagerty et al. 2002). Based on our current data, we estimate this change ratio to be 0.488 (annually) with standard estimation error 0.079 in the "near" group. The estimate is 0.230 with standard error 0.073 in the "mid" prognosis group. Designing a trial to look for a treatment impact of 25% on these longitudinal rates, we find that the assumed treat- ment effect-size is 0.122 (= 0.488*0.25) in the "near" group with 95% confidence interval (0.083, 0.161). For a 3-year study with equal allocation to treatment and placebo groups, repeated measures every 6 months, 80% power at 5% type I error, these estimates translate to samples sizes of 151 per group with 95% confidence interval of 86 to 325, nearly a four-fold factor of un- certainty. The situation is more dramatic for the "mid" group, where the assumed treatment ef- fect size would be .057 per year with 95% confidence interval (.021, .093). The corresponding sample size is 681 per group with confidence interval of 257 to 4,900. The need for an alterna- tive treatment marker is perhaps greatest for this middle group—too far from clinical illness to use diagnosis as an endpoint. Despite identification of measures such as the above, which show significant longitudinal change in this group, we cannot yet estimate the change precisely

enough to know whether these measures are realistic candidates for further study with this type of trial.

Based on projected future enrollment and dropout rates, we estimate, by simulation, that the standard error of annual longitudinal change will be approximately 0.026 within-subject standard deviations for annual measures that are new or substantially revised at the beginning of the re- newal period. This standard error will be notably smaller, approximately 0.011 in each of the gene-expanded prognostic groups, for annual measures that continue unchanged. For meas- urements previously performed every two years that will now be annual (such as the tapping task), standard errors will be approximately .0125 if minor modifications do not prevent pooling of previous and future data. The resultant sample size confidence intervals for the hypothetical trial described above are in the table below. Decisions regarding such future trials would clearly be much better informed.

	95% sample size conf. interval per group in "Near" subjects	95% sample size conf. interval per group in "Mid" subjects
Conf. interval based on cur- rent Predict data	(86, 325)	(257, 4900)
New annual measure with renewal	(123, 188)	(456, 1125)
Continued annual measure from previous	(139, 166)	(570, 830)
Previous biennial measure, annual with renewal	(137, 168)	(556, 854)

Statistical analysis: A central feature of our cohort is its division into various prognostic groups: Non-gene-expanded controls, gene-expanded subjects who have not yet received a clinical diagnosis of HD, and gene-expanded subjects who have received such a diagnosis dur- ing their prior longitudinal follow-up in PREDICT-HD. The "pre-diagnosed", gene-expanded group can be further divided on the basis of CAG and age-derived prognosis. (In the future we may revise these subset definitions to incorporate additional prognostic markers already estab- lished and described in the above progress report.) The prognostic groups are naturally ordered in a way that provides immediate insight into early HD development. Our statistical analyses will continue to use these groupings and take advantage of this natural ordering. When analyses are limited to CAG-expanded, non-diagnosed participants, we may alternatively treat CAG-age based probability of diagnosis as a continuous linear predictor.

Key a priori measurements or data reduction methods (e.g., partial least squares for metabo- lomic screening) were described in earlier, corresponding parts of the Methods. We generically refer to such measures as candidate *markers* or *predictors*. Prediction of future manifest HD by such candidate markers. will be assessed via semi-parametric (Cox proportional hazards) and parametric survival analysis as appropriate and deemed reasonable by goodness-of-fit analyses (Harrell 2001), bearing in mind that models of the entire survival function (and not just propor- tional hazards) are needed for many future applications. We adjust for inter-rater variation among neurologists in declaring manifest HD diagnosis by incorporating random 'frailty' effects (Therneau and Grambsch 2000; Kalbfleisch and Prentice 2002) or stratification adjustments (Kalbfleisch and Prentice 2002) for each rater in all models. As described elsewhere, reduction of this variation, which may be a limiting factor in much early-HD research, is another major goal of the renewal. Our success in this goal will be judged primarily by reduction of rater-specific frailty effects in the above analyses. Parametric models gain attraction because of difficulties estimating survival function in Cox models that incorporate these adjustments.

Measurable longitudinal change in candidate markers, including differences between CAG- expanded prognostic groups and controls, will be assessed using repeated-measure "mixed" models (Verbeke and Molenberghs 2000) (including generalized linear models (Diggle, Heager- ty et al. 2002), where appropriate). Longitudinal significance will be studied via interactions in- volving time-by-gene status (to study overall CAG-expansion effects) and time-by-prognostic group (to study potential differences in the rates of change among those recently clinically diag- nosed and those in various pre-diagnosed strata.) The subjects are, of course, treated as a ran- dom effect. The potential confounding role of raters and site-specific equipment, such as MRI machines, will also be explored by treating these as additional candidate random effects. Re- peated-measure covariance structures will be chosen from plausible candidates by the AIC sta- tistic (Akaike 1974).

We will assess the combined utility or redundancy of separate predictors by including them joint- ly as predictors in survival and mixed models. We will adjust all such models for key, potentially confounding background covariates such as age, gender, estimated premorbid intelligence, and other factors that will vary, depending on the outcome under study. (For example, the role of musical and typing training in neuropsychological testing was described earlier.) As documented throughout this application, we have already established and successfully used each of the above analysis methods during the current renewal.

We will calibrate our final multivariate models to estimate the degree of over-fitting introduced by screening and selection among candidate HD predictors. For all regression models, shrinkage coefficients will be estimated by Efron's optimism bootstrap (Efron 1983; Efron and Tibshirani 1993), as described in particular by Harrell (Harrell 2001), care being taken to bootstrap the en- tire candidate predictor screening process. For longitudinal models, resampling will occur at the level of individuals' observation blocks. For survival models, predictive accuracy will be further calibrated by applying Efron's .632 bootstrap estimator to cumulative discriminant prediction of diagnosis and by Harrell's bootstrap for comparing quantiles of the estimated survival function to stratified Kaplan-Meier estimates from the entire sample (Harrell 2001). Our variable selection process is a complex procedure. We will attempt to automate the essential features of this pro- cess, but if necessary, will perform the bootstrap repetitions in real time (at least 100). We will only undertake this effort for final, published models. If needed, calibration of regression coeffi- cients in intermediate results will be estimated by the chi-square penalty approximation of van Houwelingen and le Cessie (Van Houwelingen and Le Cessie 1990), penalizing for the number of variables screened rather than selected.

If subjects are entered into phase II trials and receive active treatment, they will either be re- moved from the "naturalistic" analyses described above or, if treatment effects appear minimal, the above analyses will be adjusted for attempted treatment. Of course, any such trial will entail a separate specific statistical analysis plan beyond the scope of the present application.

Analytical data will be screened for outliers, including possible data errors prior to analyses. Published analyses will always be subject to further outlier and influence analysis using graph- ical plots and residual statistics appropriate to the method (e.g., subject-specific approximate likelihood displacement (Pettitt and Bin Daud 1989)).

We will continue to study interrelationships among candidate predictors and putative markers of HD progression via standard cross-sectional methods. Use of these methods, such as correla- tion and simple linear regression, were illustrated throughout the progress report. Serious viola-

tions of modeling or inferential assumptions will either be corrected by variable transformation (e.g., as we already employ for tapping variability), introduction of more flexible assumptions (e.g. regression splines or weighted least squares), or nonparametric or exact inferential ana- logs of the intended analysis when available and practical.

We will continue to assess the predictability of study dropout using survival analysis methods as described in "Dropout rates and potential bias". If dropout and its predictability become substan- tial (i.e., "missing-at-random" [MAR], but not completely at random), we will augment our anal- yses by multiple imputation to correct the bias potentially induced (Molenberghs and Kenward 2007). Further, if faced with suspicion of notable nonignorable missing data, we will conduct sensitivity analyses, for example, as proposed by Verbeke and Molenberghs for mixed models (Verbeke and Molenberghs 2000).

7. DATA SHARING POLICY

Background: The PREDICT-HD group seeks to promote the development of valuable discoveries and inventions beneficial to the public health based upon use of the PRE- DICT-HD repositories of valuable materials and data. Since the PREDICT-HD group has made a substantial long-term contribution in establishing and maintaining the data, we request that the contribution of the investigators and participants be appropriately acknowledged in each project. To date we have shared the data with the PREDICT-HD investigators, coordinators, and participants via publications, newsletters and quarterly presentations. In addition, we have released raw data sets to eight imaging research groups in 6 different countries. We have released DNA and blood samples to 3 research groups interested in genetic modifiers and biomarkers of HD. Clinical data has been re- leased to five cognitive groups, one analytic group, and one psychiatric group. The ma- jority of these data releases were to researchers who are not part of PREDICT-HD. We now seek to encourage many new collaborative relationships. The primary goal of PREDICT-HD data sharing is to maximize knowledge and make a difference for per- sons, families, friends and health professionals associated with HD.

Rationale: The PREDICT-HD Data Sharing Policy is designed to be consistent with the NIH Data Sharing Policy that states "Data should be made as widely and freely availa- ble as possible while safeguarding the privacy of participants and protecting confidential and proprietary data." (Final NIH Statement on Sharing Research Data February 26, 2003) The clinically, genetically, and biologically well characterized cohort provides a rare and valuable scientific resource directed and maintained at the University of Iowa under the leadership of JS Paulsen, Principal Investigator, and funded by the NIH and CHDI. We have a responsibility to the public in general, and to the scientific community in particular to encourage as rapid scientific progress as possible using the resources obtained from PREDICT-HD. In order to take full advantage of such rich data and max- imize their research value, it is important that samples and data collected with public funds be made available to the largest possible number of qualified investigators in a timely manner. Sensitivity for the confidentiality and privacy of these participants and their families will remain chief in the ongoing development and refinement of the PRE- DICT-HD Data Sharing Policy.

Data Sharing Proposal: Data sharing will be accomplished through one of five methods described below. Methods 1, 3, and 5 are currently available. Methods 2 and 4 will be developed over the renewal period.

1) Publication and Presentation: Data sharing will continue to be accomplished through peer-reviewed publishing in accordance with the PREDICT-HD Publication Policy that was developed with the commencement of PREDICT-HD and revised in January of 2004 and May of 2008. To date PREDICT-HD has generated numerous publications and presentations. Data sharing of all citations will be listed on the PREDICT WEB site for efficient review by all interested parties. Publications that are not copyright-protected will be placed on the WEB site for easy viewing and downloading. When publications are protected by copyright laws, summary data will be presented on the WEB site in de- scriptive and tabular forms with links to the copyright-protected sites so interested par- ties can proceed with full acquisition of papers when possible. Once published, both raw data and analytic databases are archived to allow other researchers to analyze the ex- act data sets.

2) WEB Data Sharing Pages will be updated every six months for presentation on the PREDICT-HD site so that all interested persons can review participant activities and study progress. Shared data will be in compliance of the consent provisions, non- disclosure policies, and safeguards that are in place to protect confidentiality of our par- ticipants. Only summary data will be presented in tabular and descriptive forms to pro- tect the privacy of our participants. This strategy will help inform the lay and professional communities of the available data and study progress while maintaining the confidential- ity of the data. Presentation of data will not involve any identifiable information such as site-, geographic-, or CAG-specific data. Data will be presented at local, regional, na- tional and international meetings and conventions of the lay and professional communi- ties to generate interest in findings and stimulate new hypothesis testing.

3) Investigator-Initiated Data Requests will be submitted to the PI and the Data Access Committee (DAC) of PREDICT-HD. An abridged data dictionary of potentially available information will be available as well as an explanation of data that is available in limited form due to privacy concerns. All core PREDICT-HD data will be de-identified in ac- cordance with the HIPPA Privacy Rule (Complete Privacy, Security, and Enforcement Regulation Text [45 CFR Parts 160 and 164] before being made available under this policy. In addition all subject IDs will be randomized with each data extraction for shar- ing. Since sensitivity of and access to phenotypic and genotypic data is a dynamic pro- cess we will limit data released to variables that reduce identification disclosure or at- tribute disclosure. Other sensitive variables such as drug use and disease status could cause harm to an individual if they were revealed so probability of disclosure will be used as a proxy for data sensitivity and the PI and the DAC will consider whether shar- ing of sensitive data is worthwhile for any particular study and for what purpose. As rec- ommended in the NIA/BSR Workshop for Behavioral and Social Studies that Collect Genetic Data document (4-14-06) access to age, site, and geography data will be re-stricted. Site, rater, and MRI machine specific information cannot be shared since identi-

ty is possible with these specific factors. The combination of gender, age, and CAG length is too specific to release since demographic and genetic information in this rela- tively small and rare cohort could allow identification of participants. To allow data shar- ing while maintaining a high level of privacy protection, we will use data summary tech- niques for age (rounding to nearest 5-year brackets) and CAG repeat length (grouping by formula estimates into control, far, mid, near, or at diagnosis for HD). The Data Shar- ing Application will be available on the WEB site and from the PI. All investigators and institutions seeking data from PREDICT-HD will be expected to meet data security measures (such as physical security, information technology security, and user training) and will be asked to submit a data access request, including a Data Use Certification (DUC), that is co-signed by the investigator and the designated Institutional Official(s).
When more specific age or CAG information is arguably needed for a proposed analy- sis, multiple versions of the data will be created, each with random noise added. For example, we would provide 5 sets of age and CAG length, but with a normal random number added to the age and CAG length in each data set. Each of these data sets will be merged separately to the rest of the data and the analysis will be repeated five times. There are valid ways to average out the results of the analysis, closely related to tech- niques used for multiple imputation with missing data. It can be shown that little infor- mation is lost if the standard deviation of the added noise is reasonably small and this is done over five data sets. The techniques for averaging everything together do increase the probability that external users would have to find a qualified statistician to assist in the analyses.

4) NIH WEB Access: dbGaP. The ultimate goal of Data Sharing for PREDICT-HD will be to have data on the NIH WEB site entitled the **d**ata**b**ase of **G**enotype **a**nd **P**henotype (**db GaP**). The method used by PREDICT-HD over the past 7 years (#3 above) will be useful in helping us set up and maintain the PREDICT-HD data on db GaP. The Data Access Committee established above will be active in designing db GaP for PREDICT. The initial timeline will be established on an annual basis by the DAC each year of the renewal. Year one goals will consist of the development of the data dictionary, infra- structure and IT functions necessary to transfer our data to the NIH WEBsite. The data obtained and archived by the end of our first grant period will be used for site and policy development (August 31, 2004). By the end of the first year of the renewal, data will be placed on Web site with the ability to download datasets for analyses. A data dictionary will be included as well as how to contact consultants from each scientific section and study core from PREDICT-HD. Development of this project will begin in Fall of 2008 and a revised annual timeline will be developed and established in the Fall of 2009. The overview site for dbGaP is http://www.ncbi.nlm.nih.gov/entrez/query/Gap/gap_tmpl/about.html. The actual data site for dbGaP is http://www.ncbi.nlm.nih.gov/sites/entrez?Db=gap. A fully function- ing db GaP will be available by the close of the grant renewal.

5) PREDICT-HD Data Enclave. Prior to completion of db GaP, there may remain que- ries that would absolutely require more specific data, such as those that require the con- trol of site or rater-specific variability. Collaborative analyses with the PREDICT-HD sta- tistical team will be available (time and resources permitting). Otherwise, a fourth possi-

bility for data sharing will be available---Centralization of data sharing services, or a Da- ta Enclave. The PREDICT-HD study will allow for a “safe room” or centralized data analyses when externally shared data is not possible, due to privacy concerns. Current- ly, investigators are welcome to come to the University of Iowa where controlled, secure environments can be established to eligible researchers to perform analyses using data resources associated with the PREDICT-HD project. A data enclave typically involves non-linked, independent computers available with statistical packages for analyses in a room where data is provided on CDs. The only data removed from the room involves group and summary statistics.

8. EVENT MONITORING AND ETHICAL OVERSIGHT

PREDICT-HD is among the first studies to prospectively and systematically follow large samples of currently healthy unaffected individuals at risk for developing HD. The sub- ject populations who are ‘at-risk’ or premanifest are poorly understood. The concerns and risks they face, as study participants, have not been prospectively and systemati- cally examined. Thus learning to understand these concerns and risks with the goal of minimizing them in this and future studies is an important research opportunity. The PREDICT-HD has an Ethics Committee, chaired by experts in bioethics, IRB admin- istration and conduct, and law. One charge of the Ethics Committee is to provide over- sight of the ethical conduct of the study and assist with IRB preparations and approvals. In addition, the Ethics Committee will participate in the Event Monitoring Committee (EMC) of the Huntington Study Group, who reviews study data, advises the steering committee about findings relevant to the conduct of the trial, and assists in training re- lated to human subjects issues. Although the human subject protection issues ad- dressed by the Ethics Committee and the EMC remain the responsibility of the principal investigator and steering committee of PREDICT-HD, as well as the IRBs and sponsors, the special vulnerabilities of these subject populations are generally outside of the expe- rience of all of these groups. Therefore, the establishment of a study-specific committee can help insure that all possible issues receive consideration and scrutiny, when appro- priate. Among the most important issues of concern to date are: (1) the need for main- taining an extraordinary level of confidentiality in the setting of perceived risks of genetic discrimination, (2) the need to preserve subject control and autonomy of personal ge- netic and clinical information, (3) the need to understand the stresses that these unique- ly vulnerable subjects undergo, so as to best balance research aims with concerns for the well-being of the participants, and, (4) the need to deal responsibly with the complex medical and research issues that can arise as subjects develop symptoms consistent with HD or other serious health problems. These concerns have become a component of the data acquisition and are coded as “events” to be reported for monitoring. These “events”, developed by the PI, Steering Committee, and Ethics Committee are tracked and discussed in real time. For instance, when a site reports an “event” an email is dis- tributed to the Ethics Committee, the PI, and the Event Monitoring Committee of the HSG. The Ethics Committee of PREDICT-HD has primary responsibility to determine whether the event reported requires immediate attention and/or action. All events are discussed at monthly review meetings of the EMC.

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SCHEDULE OF CRF COMPLETIONS

SCHEDULE of eCRF & CRF COMPLETIONS (PARTICIPANTS)			Screening/ Baseline	Initial 2.0 Visit		
			Month 0	Month 0	6 Month intervals	12 Month annual visit
Form/Activity	**Participant Administration**	**Paper or Computer**	**Baseline 201 (new enrollee)**	**Year 20x (Roll Over)**	**T1-14**	**Year 202-215**
Consents						
Informed Consent/Record of Consent	all	Paper	X	X		X
Inclusion/Screening						
Inclusion/Exclusion (INEXB)	all	C	X			
Participant HD History (HDHX)	gene positive only	C		X		X
Participant HD Status	gene positive only	C		X		X
Enrollment						
Enrollment Form	all	C	X			
PREDICT-HD Participant ID Code (from DMC)	all	N/A	X			
CTCC Unique ID Number	all	C	X	X		
CTCC Unique ID Questions	all	Paper	X	X		
Demographics						
Medical History/Demographics	all	C	X			
Cognitive						
CAS Baseline	all	C	X			
CAS Follow Up	all	C		X		X
HVLT-R (imaging sites only)	all	Paper	X	X		X
ANART/NART	all	Paper	X			
Symbol Digit Modalities Test	all	Paper	X	X		X
Stroop Color Word Test	all	Paper	X	X		X
Smell Identification Test	all	Paper	X	X		X
(UPSIT; 20 items only)						
Speeded Finger Tapping Task	all	C	X	X		X
Paced Finger Tapping Task	all	C	X	X		X
Trails A & B	all	Paper	X	X		X
Video	N/A	N/A	X			
(one per examiner per year for certification)						
Functional						
UHDRS Functional	all	C	X	X		X
WHODAS II	all	C	X	X		X
CONTINUES…						

SCHEDULE of eCRF & CRF COMPLETIONS (PARTICIPANTS)			Screening/ Baseline	Initial 2.0 Visit		
			Month 0	Month 0	6 Month intervals	12 Month annual visit
Form/Activity	**Participant Administration**	**Paper or Computer**	**Baseline 201 (new enrollee)**	**Year 20x (Roll Over)**	**T1-14**	**Year 202-215**
Motor						
UHDRS'99 (I Motor Exam)	all	C	X	X		X
Surveys						
Confidential Visit Evaluation	all	Paper	X	X		X
Behavioral						
Symptom Checklist-90 (SCL-90)	all	C	X	X		X
Frontal Systems Behavioral Scale Revised (FRSBE)	all	C	X	X		X
Beck Depression Inventory (BDI-II)	all	C	X	X		X
Columbia Suicide Severity Rating Scale--Baseline/Initial (C-SSRS_B)	all	C	X	X		
Columbia Suicide Severity Rating Scale--Since Last Visit (C-SSRS_F)	all	C				X
Environmental Survey Part 1: Family Hx	all	C	X	X		
Environmental Survey Part 2: Substance Use	all	C	X	X		
Environmental Survey Part 3: Residence	all	C	X	X		
Environmental Survey Part 2: Substance Use (FOLLOW UP)	all	C				X
Problem Behaviours Assessment- Short Form (PBA-s)	all	C	X	X		X
Logs						
2.0 Participant Enrollment Log	all	Paper	X	X		
Screening Log [2]	N/A	C	X			
Medical Events Log	all	C				X
Social Events Log	all	C	X	X		X
Study Staff/Study Related Duties Log [2]	N/A	C				
Concomitant Medication Log (CMED)	all	C	X	X		X
Family Participation Log (FAM)	all	C	X	X		X
Reportable Event Log (RE)	all	C	X	X		X
Biospecimens						
Blood Draw for DNA and RNA	all	N/A	X	X		X
Blood Draw for Biomarkers	all	N/A	X	X		X
Urine	all	N/A	X	X		X
Lumbar Puncture (Cerebral Spinal Fluid)	all	N/A	X	X		X
Saliva sample (as needed)	all	N/A	X	X		X
Biomarker Laboratory Requisition	all	Paper	X	X		X
DNA Blood Sample Laboratory Requisition	all	Paper	X	X		X

CONTINUES…

SCHEDULE of eCRF & CRF COMPLETIONS (PARTICIPANTS)			Screening/ Baseline	Initial 2.0 Visit		
			Month 0	Month 0	6 Month intervals	12 Month annual visit
Form/Activity	**Participant Administration**	**Paper or Computer**	**Baseline 201 (new enrollee)**	**Year 20x (Roll Over)**	**T1-14**	**Year 202-215**
Imaging						
MRI scan (imaging sites only)	all	N/A	X	X		X
MRI Record Form	all	C	X	X		X
Other Forms						
Telephone Contact Form (TC)	all	C			X	
Manual Incident Report (Level 1 REs only)	all	Paper	X	X		X
Biannual Retention Activity Record (BRAR)	all	C	X	X	X	X
Participant Disposition (DISP) [3]	as needed	C				
Participant Site Transfer Form (STF) [4]	as needed	C				
Autopsy/Mortality Form (AP) [5]	as needed	C				
Vitals	all	C	X	X		X
Brain Donation Packet	all	Paper	X	X		X
Centralized Retention Contact Form	all	Paper	X	X		X
Transmittal Log Baseline	N/A	Paper	X			
Transmittal Log Initial	N/A	Paper		X		
Transmittal Log Follow-up	N/A	Paper				X
Payment Information Forms	all	Paper	X			
Signature Form (SIG) – Notifications (also with 3 or 5)	all	C	X	X		X

COMPANION SCHEDULE OF ACTIVITIES

SCHEDULE of eCRF & CRF COMPLETIONS (COMPANIONS)		Screening/ Baseline	Initial 2.0 Visit		
		Month 0	Month 0	6 Month intervals	12 Month annual visit
Participant	**Paper or Computer**	**Baseline 201 (new enrollee)**	**Year 20x (Roll Over)**	**T1-14**	**Year**
Informed Consent/Record of Consent	Paper	X	X		X
Enrollment					
Companion Enrollment Log	Paper	X	X		
CTCC Unique ID Number	C	X	X		
CTCC Unique ID Questions	Paper	X	X		
Demographics					
Demographics	C	X	X		
Functional *NOTE forms are subject to change					
WHODAS II - Companion	C	X	X		X
Behavioral *NOTE forms are subject to change					
Symptom Checklist-90 – Companion (SCL-90-C)	C	X	X		X
Frontal Systems Behavioral Scale Revised – Companion (FRSBE_C)	C	X	X		X
Environmental Survey Part 2_Companion Baseline/Initial	C	X	X		
Environmental Survey Part 2_Companion Follow-up	C				X
Centralized Contact (Retention) Form in Packet	Paper	X	X		X
Other Forms					
Payment Information Forms	Paper	X	X		

The PREDICT-HD Study v. 2.0
2009-2014
(ancillary studies through 2017)

2.0 STUDY:

The initial 2.0 study was released September 1, 2008. A major change in the protocol was how the data would be collected. Although computerized tests were collected during the 1.0 study, the collection occurred on large, bulky, non-portable, plywood-encased machines. In addition, other than the computerized cognitive tasks, all data was collected via paper-based forms. In the 2.0 study, tablets were implemented to provide an easier, portable way of collecting data.

Another significant change for the study occurred with MRI scanners. Sites that had access to 3T scanners were asked to utilize them for brain scanning data collection. Sites that did not have access to a 3T were asked to continue collecting on 1.5T scanners until the site was able to access a 3T scanner in their geographic area that was feasible and convenient for enrolled participants. The rationale behind this was that an average institutional scanner lasts 7-10 years. It was anticipated that institutions with 1.5T scanners would replace them within 5 years. Given hardware and software updates, as well as additional acquisition sequences added throughout the study, image analyses using the shared PREDICT-HD data requires careful attention to the details provided.

The third primary change in the 2.0 PREDICT-HD study was the organizational structure. The study had grown considerably and additional methods of communication and good practices for "team science" were required to maintain efficiency and maximize progress. Operations manuals were separated into separate manuals for Cognitive, MRI, Psychiatric, Motor, Functional, Patient-Reported Outcomes, Biomarkers and Administration.

A summary of PREDICT 2.0 Amendments over the course of the 5-year study are provided below.

PREDICT 2.0 AMENDMENT 1:

Amendment 1 updated the specific aims of the study to the renewed NIH grant and updated the administrative oversight procedures. Significant changes to data/sample collection are as follows:

1. The federal Health Insurance Portability and Accountability Act (HIPPA) was integrated into all materials and special attention was devoted to confidentiality practices throughout the research. The Ethics Committee addressed HIPPA in the context of data sharing for a rare disease. A Confidentiality Certificate from the Department of Health and Human Services (DHHS) in the US was obtained and shared widely to prevent disclosure of research information.
2. Administrative oversight was re-organized for PREDICT 2.0. An Executive Committee was developed for the grant renewal submission to facilitate communication between study sponsors, the PI and study leadership. A number of changes were occurring in the HD scientific community with the now very active involvement of CHDI (previously HighQ, who supported PREDICT 1.0). Some members of the Steering Committee retired from PREDICT-HD to develop additional HSG and EHDN studies. Outgoing members included David Oakes, Doug Langbehn, and Julie Stout. Brown University under the leadership of Holly Westerfeld took on the responsibility for quality control and assurance of all neuropsychological standardization and double-scoring. Tamara Hershey (WUSL) and Deborah Harrington (UCSD), both senior cognitive scientists took responsibility for further cognitive task development, data analyses, and refinement of measures for preventive trials as clinical outcome assessments reflecting the cognitive decline in HD. James Mills stepped in a chief Biostatistician.

Brain Donation was added to the protocol. Efforts to maximize successful cell line development were incorporated and a Genome Wide Association Study was funded for n=1223 PREDICT-HD participants through another funded NIH grant led by MacDonald and Gusella. The following specialty groups met weekly: imaging, cognition, clinical (motor, psychiatric, functional, QOL) and staff were assigned to track wet biomarkers (with overnight fasting integrated), DNA, and retention.

3. The new organizational structure utilized a Steering Committee designed to be a rotating set of active PREDICT-HD researchers each identified to represent an administrative component of the research and/or the scientific specialties of the grant.
4. The cognitive battery was provided for all visits in Standard Operating Procedure (SOP) formats and many tests were retired. Hardware and software advances resulted in required re-programming of all computerized tests.
5. Sites with low enrollment numbers (n=2) were retired to assure valid and reliable assessments and annual certification of all raters.
6. The Columbia Suicide Severity Rating Scale (CSSRS) was added to replace our Suicide Risk algorithm for adverse events that we had constructed based on the literature and investigator expertise with HD.
7. Preliminary findings and advances initiated through the Huntington Study Group in the US and the European Huntington Disease Network suggested which measures were considered best for the ongoing PREDICT research. The following measures were removed: Perceived Stress Scale, Haidt Disgust Scale, Schedule of Compulsions and Obsessions Inventory, Beck Depression Inventory, Beck Hopelessness Scale, and the UHDRS Behavioral Section.
8. The World Health Organization Disability Assessment Scale (WHODAS) was added to the existing measures of UHDRS functional capacity (TFC, FAS and IS) to determine whether more subtle decline could be detected. The rationale is that government regulatory agencies required accurate measures of functionality as endpoints for clinical trials models and we hoped to develop preventive clinical trials for prodromal HD. Additionally, items from the UHDRS functional scales were removed if they were endorsed in over 95% of prodromal participants. The FAS and IS were deleted and the TFC was reduced to the first two items that were demonstrated as lost as a person with prodromal HD advanced through the study. A decision was made to impute the complete TFC adding full value to the items for living arrangement (i.e., placement in a nursing home), feeding and caring for oneself.
9. Opinion surveys were added to increase participant engagement in study design and implementation.
10. Additional Plasma (up to 30ml) and Urine (50ml) was collected.

PREDICT 2.0 AMENDMENT 2:

Items changed regarding data/samples are the following:

1. Computer errors were frequent with the new computerized assessments (Buttons and Chooser) so order of assessment was altered to make an attempt to improve computer operations.
2. DNA was collected at every visit until a viable Lymphoblastoid cell line was obtained.
3. Jeffrey Long was recruited to lead the Biostatistics section and additional statisticians were added to increase dissemination of research findings.
4. Sites with low enrollment numbers (n=4) were retired to assure valid and reliable assessments and annual certification of all raters.
5. Motor video recording was discontinued, and quantitative motor assessment was established at select sites under the leadership of Ralf Reilman.
6. Cerebral Spinal Fuid (CSF) sample collection and two additional whole blood Pax tubes for RNA analyses were added to the biospecimen protocol using Michael J. Fox PPMI PD Biomarkers

protocols for collection and standard operating procedures.

PREDICT 2.0 AMENDMENT 3:

The primary modification was to clarify that the Behavioral Section of the UHDRS was removed and replaced with the Problem Behavior Assessment, revised by the EHDN. This revised behavioral interview added a third dimension to each item that asked each person what the "worst" expression of a problem behavior was. The previous UHDRS Behavioral Scale was adapted from the Neuropsychiatric Inventory and required the "frequency" and "severity" of each behavioral problem discussed.

PREDICT 2.0 AMENDMENT 4:

This amendment marks a significant change in data/samples. The modifications are listed below:

1. The Emostatic, Chooser and Buttons cognitive science tests were all removed due to computer programming limitations and the longitudinal hypothesis-testing for all of these items became impossible on the newer portable computers. Though new attempts were made to correct these issues, it was determined that the data from PREDICT 1.0 would be used for hypothesis testing only. There are very limited longitudinal data available for these tasks since they were discontinued very early in PREDICT 2.0.
2. The HVLT to be given at select imaging sites only due to an ancillary grant proposal that was to examine imaging and learning/memory in HD.
3. DNA samples were collected via saliva instead of blood. This allows for collection at home.
4. Beck Depression Inventory II was reinserted into the protocol to have a quantitative measure of depressed mood.
5. Problem Behaviours Assessment short form (PBA-s) was added to the protocol per Amendment 3.
6. The Substance Use form was analyzed and deemed to have questionable validity secondary to a brief review of the data. Efforts were made to improve assessment of recreational substances and alcohol. It was widely acknowledged that self-report of substance use is often of questionable validity secondary to legal and social consequences.
7. The Frontal System Behavioral Scale (FrSBe) and the Symptom Checklist 90-R were reduced from 28 to 23 items and 90 to 28. The rationale was that data analysis revealed clear differences between items showing sensitivity in the pre-HD population versus those items that were not. Permission was obtained to reduce the measures to only the relevant items by the publishers of both of these scales.
8. An Enviromental and Family History questionnaire was piloted in PREDICT to facilitate comparisons with another study, PHAROS, of persons at-risk with unknown genetic outcomes. The new measure was developed to collect substance abouse, residential locations, occupation(s), religious affiliation, etc. over the participants lifetime. Participant burden was high and it was agreed to determine whether the benefit from the data was sufficient for the burden.
9. A Cerebral Spinal Fluid protocol was added for sites who could integrate this data collection.
10. Two additional whole-blood PaxGene tubes were collected for RNA analyses.

PREDICT 2.0 AMENDMENT 5:

The following items were modified in this amendment:

1. The HVLT implemented at select imaging sites was removed. The rationale was that the ancillary grant was not awarded and participant burden was reduced to support funded research only.
2. The Environmental and Family History questionnaire was discontinued due to the burden

placed on the participant and that the form was not capturing the necessary data in order to allow for quality data analyses.

3. The Substance Use form was reinserted into the protocol to allow a measure of self-reported alcohol and recreational drug usage, despite data suggesting poor reliability and validity. Each investigator should decide for him- and her-self how to best utilize these data.

PREDICT 2.0 AMENDMENT 6:

The HD field developed a newer method to identify HD participants across studies and all sites were asked to use the HDID unique identifier in the remaining of the PREDICT study.