Clinical Study Protocol

HDClarity: a multi-site cerebrospinal fluid collection initiative to facilitate therapeutic development for Huntington's disease

PROTOCOL NO.: UCL-CHDI-1

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PROTOCOL DATE AND VERSION: 19 December 2018 (Version No. 003)

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PROTOCOL APPROVAL SIGNATURES

This Clinical Study Protocol is approved by:

Signature: Date: 25 January 2019

Edward Wild, MA MB BChir PhD MRCP
Chief Investigator

Signature: ..... Date: .....25 January 2019

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

CHANGE LOG

Date	Description of change(s)	Name
2016-06-21	Addition of UK sites and update to CHDI study personnel	Elena Pak
2018-12-19	Compliance with EU General Data Protection Regulation (GDPR); removal of recruitment cap at 600 participants; change to huntingtin gene cytosine-adenine-guanine (CAG) expansion exclusion criteria for participant with manifest disease; relaxation of blood test exclusion criteria for minor abnormalities of no clinical significance; seeking permission to contact participants about future enrollment; addition of South American sites; and minor clarifications and corrections	Ed Wild

Site Principal Investigator Signature Page

Protocol Number:	UCL-CHDI-1
Protocol Title:	HDClarity: a multi-site cerebrospinal fluid collection initiative to facilitate therapeutic development for Huntington's disease
Protocol Date and Version:	19 December 2018, Version No. 003
Funding Source:	CHDI Foundation, Inc. (CHDI) c/o CHDI Management, Inc. 155 Village Boulevard Suite 200 Princeton, NJ 08540 Phone: +1 609 945 9600

By my signature below, I hereby attest that I have read and that I understand and will abide by all the conditions, instructions, and restrictions contained in the attached protocol.

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

Additionally, I will not initiate this study without approval of the appropriate Institutional Review Board (IRB)/Ethics Review Board (ERB). I understand that any changes in the protocol must be approved in writing by CHDI and the IRB/ERB before they can be implemented, except where necessary to eliminate hazards to participants.

_____ _____

Site Principal Investigator's Signature Date

_____

Site Principal Investigator Name (Print)

1. Synopsis

Name of the Funding Source: CHDI Foundation, Inc.	**Protocol No.:** UCL-CHDI-1
Study Title: HDClarity: a multi-site cerebrospinal fluid collection initiative to facilitate therapeutic development for Huntington's disease	
Short Study Title: HDClarity	
Planned Study Sites: Multiple sites in Europe, North America, South America, and Australasia.	
Number of Participants planned: participants across 6 clinical cohorts will be enrolled at multiple sites up to an estimated minimum of 1200 participants or until the study is terminated by either the Funding Source or Sponsor	
Chief Investigator: Dr. Edward Wild MRC Clinician Scientist, UCL Institute of Neurology; Honorary Consultant Neurologist, National Hospital for Neurology & Neurosurgery, Queen Square London WC1N 3BG, UK	
Study period: Ongoing from August 1, 2016 Date first participant enrolled: January 24, 2017 Estimated date last participant completed: the study is open to continuous recruitment up to an estimated minimum of 1200 participants	
Objectives: Primary: The primary objective of this study is to generate a high quality cerebrospinal fluid (CSF) sample collection for evaluation of biomarkers and pathways that will enable the development of novel treatments for Huntington's disease (HD). Secondary: • To generate a high quality plasma sample collection matching the CSF collections, which will also be used to evaluate biomarkers and pathways of relevance to HD research and development. • To collect phenotypic and clinical data for each participant.	
Study Design: This is an observational study. Within a single HDClarity enrollment, participants will attend two study visits, a Screening Visit, an Initial Sampling Visit, and may attend an optional third visit, an Optional Repeat Sampling Visit. During the Screening Visit, medical history, and clinical and phenotypic data will be obtained. Participants who meet the eligibility requirements of the study and are willing to continue in the study, will return for an Initial Sampling Visit. During that visit, biosamples will be collected following an overnight fast: blood will be obtained via venipuncture and CSF will be	

obtained via lumbar puncture. Some participants may be invited to return for an Optional Repeat Sampling Visit approximately 4-8 weeks later.

When participants have completed the Initial Sampling Visit, and Optional Repeat Sampling Visit, if relevant, their participation in HDClarity will be considered completed. However, participants may be invited to participate in the study multiple times, allowing at least 11 months between Screening Visits. They will complete a separate consent for any additional Screening and associated Sampling Visits and will be under no obligation to participate.

Participant cohorts are as follows and recruitment will be balanced across cohorts as far as possible. However, recruitment to the moderate and advanced manifest HD cohorts is expected to be approximately 50% of recruitment to other cohorts:

1. Healthy controls
2. Early Pre-manifest HD
3. Late Pre-manifest HD
4. Early Manifest HD
5. Moderate Manifest HD
6. Advanced Manifest HD

Diagnosis and main criteria for inclusion:

Healthy controls as well as Huntington's disease gene expansion carriers (HDGECs) will be enrolled. The latter will include five groups: early pre-manifest, late pre-manifest HD, early HD, moderate HD and advanced HD.

Inclusion Criteria:

1. All eligible participants:
   a. Are 21-75 years of age, inclusive; and
   b. Are capable of providing informed consent or have a legal representative authorized to give consent on behalf of the participant; and
   c. Are capable of complying with study procedures, including fasting, blood sampling and lumbar puncture; and
   d. Are participating in the Enroll-HD study; and
   e. Will have had an Enroll-HD visit within two months of the Screening Visit.
2. For the **Healthy Control** group, participants eligible are persons who meet the following criteria:
   a. Have no known family history of HD; or
   b. Have known family history of HD but have been tested for the huntingtin gene CAG expansion and are not at genetic risk for HD (CAG < 36).
3. For the **Early Pre-manifest HD** group, participants eligible are persons who meet the following criteria:
   a. Do not have clinical diagnostic motor features of HD, defined as Unified Huntington's Disease Rating Scale (UHDRS) Diagnostic Confidence Score < 4; and
   b. Have CAG expansion ≥ 40; and
   c. Have burden of pathology score, computed as (CAG – 35.5) × age, < 250.
4. For the **Late Pre-manifest HD** group, participants eligible are persons who meet the following criteria:

a. Do not have clinical diagnostic motor features of HD, defined as Unified Huntington's Disease Rating Scale (UHDRS) Diagnostic Confidence Score < 4; and
b. Have CAG expansion ≥ 40; and
c. Have burden of pathology score, computed as (CAG – 35.5) x age, ≥ 250.

5. For **Early Manifest HD** group, participants eligible are persons who meet the following criteria:
   a. Have clinical diagnostic motor features of HD, defined as UHDRS Diagnostic Confidence Score = 4; and
   b. Have CAG expansion ≥ 40; and
   c. Have Stage I or Stage II HD, defined as UHDRS Total Functional Capacity (TFC) scores between 7 and 13 inclusive.
6. For **Moderate Manifest HD** group, participants eligible are persons who meet the following criteria:
   a. Have clinical diagnostic motor features of HD, defined as UHDRS Diagnostic Confidence Score = 4; and
   b. Have CAG expansion ≥ 40; and
   c. Have Stage III HD, defined as UHDRS TFC scores between 3 and 6, inclusive.
7. For **Advanced Manifest HD** group, participants eligible are persons who meet the following criteria:
   a. Have clinical diagnostic motor features of HD, defined as UHDRS Diagnostic Confidence Score = 4; and
   b. Have CAG expansion ≥ 40; and
   c. Have Stage IV HD, defined as UHDRS TFC scores between 0 and 2, inclusive.

Exclusion Criteria:

1. For all groups, participants are ineligible if they meet any of the following exclusion criteria:
   a. Use of investigational drugs or participation in a clinical drug trial within 30 days prior to Sampling Visit; or
   b. Current intoxication, drug or alcohol abuse or dependence; or
   c. If using any medications or nutraceuticals, the use of inappropriate (e.g., non-prescribed) or unstable dose within 30 days prior to Sampling Visit; or
   d. Significant medical, neurological or psychiatric co-morbidity likely, in the judgment of the Site Principal Investigator, to impair participant's ability to complete study procedures, or likely to reduce the utility of the samples and data for the study of HD; or
   e. Needle phobia, frequent headache, significant lower spinal deformity or major surgery; or
   f. Antiplatelet or anticoagulant therapy within the 14 days prior to Sampling Visit, including but not limited to: aspirin, clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban and apixaban; or
   g. Clotting or bruising disorder; or
   h. Screening blood test results more than 10% outside the lab's normal range for the following: white cell count, neutrophil count, lymphocyte count, hemoglobin (Hb), platelets, prothrombin time (PT) and activated partial thromboplastin time (APTT), or any combination of blood test results that the Site Principal Investigator deems to be of clinical significance; or

i. Screening blood test results for C-reactive protein (CRP)>2× upper limit of normal; or
j. Predictable non-compliance as assessed by Site Principal Investigator; or
k. Inability or unwillingness to undertake any of the study procedures; or
l. Exclusion during history or physical examination, final decision to be made by the Site Principal Investigator; including but not limited to:
   i. any reason to suspect abnormal bleeding tendency, e.g. easy bruising, petechial rash; or
   ii. any reason to suspect new focal neurological lesion, e.g. new headache, optic disc swelling, asymmetric focal long tract signs; or
   iii. any other reason that, in the clinical judgment of the Site Principal Investigator, it is felt that lumbar puncture performed per this protocol and associated manuals is unsafe without brain imaging.
m. Serious Adverse Event (SAE) related to study procedures during or following any previous HDClarity Sampling Visit (if applicable), or SAE related to any other lumbar puncture in the previous 12 months.

Sample Size:

The CSF and plasma samples collected in this study will be the basis of future biomarker analysis studies. Each of those studies will require a specific power calculation to determine how many samples to include in the analysis.

Only sites with access to in-patient facilities will likely be able to recruit volunteers with advanced HD, so those numbers will likely be smaller.

For some biomarkers, it may be important to understand the stability of the biomarker within participants over relatively short time periods (test-retest reliability). Thus, up to approximately 20% participants will be invited to return for an Optional Repeat Sampling Visit 4-8 weeks after their Initial Sampling Visit. Other biomarker discovery and analysis, e.g. analysis of disease progression, may require comparison of samples at longer intervals, and eligible participants may be invited to participate in the study multiple times, allowing at least 11 months between Screening Visits. No upper time limit or total number of enrollments will be imposed (e.g. a participant may enroll after 2 or 3 years or longer, or may enroll more than once, as long as valid informed consent is re-obtained and the study remains active).

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2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
APTT	Activated partial thromboplastin time
CAG	Cytosine-adenine-guanine codon whose count in the HTT gene determines the genetic diagnosis of HD
CRP	C-reactive protein
CSF	Cerebrospinal fluid
eCRF	electronic Case Report Form
ERB	Ethics Review Board
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
Hb	Hemoglobin
HD	Huntington's disease
HDGEC	Huntington's disease gene expansion carrier
HTT	huntingtin protein
ICH Guidelines	International Conference on Harmonisation Guidance for Industry
IRB	Institutional Review Board
KMO	kynurenine mono-oxygenase
KP	kynurenine pathway
PT	Prothrombin time
SAE	Serious Adverse Event
TFC	Total Functional Capacity
TMS	Total Motor Score
UHDRS	Unified Huntington's Disease Rating Scale

3. Roles & Responsibilities

3.1 Names, affiliations and roles of protocol contributors:

Bernhard Landwehrmeyer, MD PhD; CHDI Management and Ulm University Hospital; Funding Source Medical Consultant

Blair Leavitt, MD; The University of British Columbia, Centre for Molecular Medicine and Therapeutics; Site Principal Investigator

Jan Lewerenz, MD; Ulm University Hospital; Site Principal Investigator

Cristina Sampaio, MD PhD; CHDI Management; Funding Source Chief Clinical Officer

Edward Wild, MD; University College London, Institute of Neurology; Chief Investigator

3.1.1. Acknowledgement of Previous Contributors:

Beth Borowsky, PhD; previously CHDI Management; Funding Source Science Director - key contributor protocol up to VerNo002

Cheryl Fitzer-Attas, PhD, MBA; previously CHDI Management; Funding Source Vice President Clinical Research

3.2 Contact Information for the Study Sponsor

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3.3 CHDI contact information

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3.4 Medical Monitor contact information

The medical monitor can be contacted via email at hdclarity-mm@enroll-hd.org.

4. Introduction

4.1 Background and Rationale

Huntington's disease (HD) is an autosomal dominant genetic disease, which typically manifests beginning in adulthood in the form of movement symptoms, cognitive decline, and psychiatric changes (Roos, 2010). Currently the only approved treatment for HD is tetrabenazine, but several clinical trials are expected to launch in the next few years to explore novel therapeutic approaches to treating this disease. In preparation for such trials, biomarkers are needed to evaluate: (1) how well these novel therapeutics reach their intended target and have a biological effect (pharmacodynamic markers); (2) the effectiveness of these novel therapeutics at improving clinical signs and symptoms (efficacy biomarkers); and (3) the state of disease participants are in throughout the trial (disease progression biomarkers). Cerebrospinal fluid (CSF) is an ideal fluid compartment for assessing HD biomarkers, particularly pharmacodynamics markers, due to its proximity to the brain.

Several therapeutic approaches focused on lowering huntingtin protein (HTT) in the brain are currently pursued, and studies in animals suggest this is a promising approach (Kordasiewicz, 2012). However, one of the key tools needed to pursue such approaches in humans is the ability to demonstrate that the intervention did lower HTT levels in the brain. Fortunately, assays are being developed that can detect HTT in CSF. We propose to further the development and validation of CSF HTT assays by measuring HTT levels in CSF and plasma from those with manifest HD, premanifest HDGECs and healthy controls. The results of these studies will lead to the establishment of the best practices for measuring HTT in CSF before and after HTT lowering therapies. Furthermore, longitudinal data will help establish the value of mutant HTT in CSF as disease progression and as a prognostic or predictive marker.

Several CSF and plasma HD biomarker discovery programs have resulted in the generation of a “hot list” of proteins potentially differentially expressed in HD. While promising, this list needs to be replicated in a new sample set, potentially with more quantitative assays. We propose to use samples collected in the current study to further explore the potential of these and other proposed biomarkers to become validated HD CSF and plasma biomarkers.

For example, evidence from preclinical animal studies as well as post-mortem human brain studies suggests that the kynurenine pathway (KP) may be abnormally regulated in HD (Guidetti et al., 2004). To further investigate the potential dysregulation of the pathway, and inter-participant variability of the dysregulation, we propose to measure levels of some of the key KP metabolites.

4.2 Rationale for Current Study

With promising new therapeutic trials expected to begin in the next few years, exploration of potential biomarkers needs to be accelerated now. There is currently no high quality repository of CSF from well-characterized HDGECs spanning the disease spectrum. The current study will provide such a repository in order to expedite the research into biomarkers for HD.

4.2.1 Ethical Considerations

Institutional review board and ethics review board

Sites will be responsible for obtaining all appropriate approvals, supported by a CHDI-approved informed consent form. ERB and/or IRB approval will be sought for each site in each country as per their regulations prior to the start of the study activities at that site. For example, as relates to any UK participants or UK National Health Service (NHS) site, no study activities involving such UK participants or any such NHS site will occur until an application covering all proposed activities at any such NHS site or involving such UK participants, submitted via the Integrated Research Application System (IRAS), has been approved from an NHS Research Ethics Committee (REC).

Informed consent procedure

All participants must give informed consent prior to undertaking study procedures and these informed consents must be obtained by clinical site staff using approved processes. Signed consent forms will be maintained in a secure designated location at the site. Eligible participants may be invited to participate in the study multiple times, allowing at least 11 months between Screening Visits. They will complete a separate consent for any additional Screening and associated Sampling Visits and will be under no obligation to participate.

Participant safety

The procedures for performing lumbar punctures and venous blood draws have been designed to maximize participant safety.

Participant risk

Study-related risks are explained in the informed consent document. In particular, the following risks may be associated with lumbar puncture: pain; headache (approximately 5%), infection, bleeding and nerve root damage. Most headaches resolve spontaneously but occasionally a headache may be persistent; in rare cases this may necessitate treatment, which may include a second procedure (a blood patch), carried out in a clinical setting.

See Appendix A – Site Principal Investigator Obligations for additional information.

5. Study Objectives

The overall objective of this study is to generate a high quality CSF sample collection that can be used to identify and validate biomarkers for HD clinical development.

CSF and blood samples will be collected from select sites throughout the world using a standardized protocol. Careful collection of clinical and phenotypic data on each donor will enable us to appropriately select subsets of samples for each set of experimental assays.

5.1 Primary Objective

The primary objective of this study is to generate a high quality CSF sample collection for evaluation of biomarkers and pathways that will enable the development of novel treatments for HD.

5.2 Secondary Objective(s)

The secondary objectives of this study are:

- To generate a high quality plasma sample collection matching the CSF collections, which will also be used to evaluate biomarkers and pathways of relevance to HD research and development.
- To collect phenotypic and clinical data for each participant.

6. Study Design

6.1 Overall Study Design

This is a Phase 0 observational study.

Recruitment: Participants will be recruited at multiple sites in Europe, North America, South America and Australasia from among participants in the Enroll-HD study who will have had an Enroll-HD study visit within two months of the Screening Visit.

Study Visits: Within a single HDClarity enrollment, participants will attend two study visits: a **Screening Visit** and an **Initial Sampling Visit**. During the **Screening Visit**, which may coincide with an Enroll-HD visit, medical history, clinical and phenotypic data (including a screening blood sample) will be obtained. These data will determine participant eligibility for participation in the study and will be used in the analysis of biomarker data. Participants meeting the eligibility requirements of the study and willing to continue in the study, will return for an **Initial Sampling Visit** within 30 days of the Screening Visit. During that visit, biosamples will be collected following an overnight fast: blood will be obtained via venepuncture and CSF will be obtained via lumbar puncture. Participants will be contacted by telephone approximately 24-72 hours after the Sampling Visit. Some participants may be invited to return for an **Optional Repeat Sampling Visit** 4-8 weeks following the **Initial Sampling Visit**.

Eligible participants may be invited to participate in the study multiple times, allowing at least 11 months between Screening Visits. Participants are under no obligation to take part in additional HDClarity visits and will only be eligible to do so if they did not experience any Serious Adverse Events (SAEs) related to study procedures during or following previous HDClarity Sampling Visits, if applicable, or SAE related to any other lumbar puncture in the previous 12 months. No upper time limit or total number of enrollments will be imposed (e.g. a participant may enroll after 2 or 3 years or longer, or may enroll more than once, as long as valid informed consent is re-obtained and the study remains active).

Enroll-HD visits will provide the clinical data for this study. Where possible, routine, planned Enroll-HD visits will be used to plan recruitment into HDClarity. However, where such scheduling may jeopardise a potential participant's inclusion in HDClarity, assessments equivalent to an Enroll-HD Core visit may be performed at the Screening Visit, after prior approval by the Chief Investigator.

Biosample Preparation: Samples will be processed and stored as described in Sections 10.1, 10.2 and 10.3 until ready for analysis.

Laboratory analyses: Samples will be shipped to laboratories, as directed by CHDI, for multiple HD research investigations.

Statistical analysis: For each set of laboratory analyses conducted, a statistical analysis plan will be finalized before samples are sent to the laboratory conducting the studies.

7. Study Population

Six participant cohorts will be included in the study and recruitment will be balanced across cohorts as far as possible. However, recruitment to the moderate and advanced manifest HD cohorts is expected to be approximately 50% of recruitment to other cohorts:

1. Healthy controls
2. Early Pre-manifest HD
3. Late Pre-manifest HD
4. Early Manifest HD
5. Moderate Manifest HD
6. Advanced Manifest HD

7.1 Diagnosis and Main Selection Criteria

Both male and female participants, aged between 21 and 75 years, inclusive, will be enrolled in the study. Eligible participants include healthy controls, people who are in the early pre-manifest and late pre-manifest stage of HD, and people diagnosed with early HD, moderate HD or advanced HD.

7.1.1 Inclusion Criteria

1. **All eligible participants**:
   a. Are 21-75 years of age, inclusive; and
   b. Are capable of providing informed consent or have a legal representative authorized to give consent on behalf of the participant; and
   c. Are capable of complying with study procedures, including fasting, blood sampling and lumbar puncture; and
   d. Are participating in the Enroll-HD study; and
   e. Will have had an Enroll-HD visit within two months of the Screening Visit.
2. For the **Healthy Control** group, participants eligible are persons who meet the following criteria:
   a. Have no known family history of HD; or
   b. Have known family history of HD but have been tested for the huntingtin gene CAG expansion and are not at genetic risk for HD (CAG < 36).
3. For the **Early Pre-manifest HD** group, participants eligible are persons who meet the following criteria:
   a. Do not have clinical diagnostic motor features of HD, defined as Unified Huntington's Disease Rating Scale (UHDRS) Diagnostic Confidence Score < 4; and
   b. Have CAG expansion ≥ 40; and
   c. Have burden of pathology score, computed as (CAG – 35.5) × age, < 250.
4. For the **Late Pre-manifest HD** group, participants eligible are persons who meet the following criteria:

   a. Do not have clinical diagnostic motor features of HD, defined as Unified Huntington's Disease Rating Scale (UHDRS) Diagnostic Confidence Score < 4; and
   b. Have CAG expansion ≥ 40; and
   c. Have burden of pathology score, computed as (CAG – 35.5) x age, ≥ 250.
5. For **Early Manifest HD** group, participants eligible are persons who meet the following criteria:
   a. Have clinical diagnostic motor features of HD, defined as UHDRS Diagnostic Confidence Score = 4; and
   b. Have CAG expansion ≥ 40; and
   c. Have Stage I or Stage II HD, defined as UHDRS Total Functional Capacity (TFC) scores between 7 and 13 inclusive.
6. For **Moderate Manifest HD** group, participants eligible are persons who meet the following criteria:
   a. Have clinical diagnostic motor features of HD, defined as UHDRS Diagnostic Confidence Score = 4; and
   b. Have CAG expansion ≥ 40; and
   c. Have Stage III HD, defined as UHDRS TFC scores between 3 and 6, inclusive.
7. For **Advanced Manifest HD** group, participants eligible are persons who meet the following criteria:
   a. Have clinical diagnostic motor features of HD, defined as UHDRS Diagnostic Confidence Score = 4; and
   b. Have CAG expansion ≥ 40; and
   c. Have Stage IV HD, defined as UHDRS TFC scores between 0 and 2, inclusive.

7.1.2 Exclusion Criteria

1. For all groups, participants are ineligible if they meet any of the following exclusion criteria:
   a. Use of investigational drugs or participation in a clinical drug trial within 30 days prior to Sampling Visit; or
   b. Current intoxication, drug or alcohol abuse or dependence; or
   c. If using any medications or nutraceuticals, the use of inappropriate (e.g., non-prescribed) or unstable dose within 30 days prior to the Sampling Visit; or
   d. Significant medical, neurological or psychiatric co-morbidity likely, in the judgment of the Site Principal Investigator, to impair participant's ability to complete study procedures, or likely to reduce the utility of the samples and data for the study of HD; or
   e. Needle phobia, frequent headache, significant lower spinal deformity or major surgery; or
   f. Antiplatelet or anticoagulant therapy within 14 days prior to Sampling Visit, including but not limited to: aspirin, clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban and apixaban; or
   g. Clotting or bruising disorder; or

h. Screening blood test results more than 10% outside the lab's normal range for the following: white cell count, neutrophil count, lymphocyte count, hemoglobin (Hb), platelets, Prothrombin time (PT) and activated partial thromboplastin time (APTT), or any combination of blood test results that the Site Principal Investigator deems to be of clinical significance; or

i. Screening blood test results for C-reactive protein (CRP) >2× upper limit of normal; or

j. Predictable non-compliance as assessed by the Site Principal Investigator; or

k. Inability or unwillingness to undertake any of the study procedures; or

l. Exclusion during history or physical examination, final decision to be made by the Site Principal Investigator; including but not limited to:

   i any reason to suspect abnormal bleeding tendency, e.g. easy bruising, petechial rash; or

   ii any reason to suspect new focal neurological lesion, e.g. new headache, optic disc swelling, asymmetric focal long tract signs; or

   iii any other reason that, in the clinical judgment of the Site Principal Investigator, it is felt that lumbar puncture performed per this protocol and associated manuals is unsafe without brain imaging.

m. Serious Adverse Event (SAE) related to study procedures during or following any previous HDClarity Sampling Visit (if applicable), or SAE related to any other lumbar puncture in the previous 12 months.

7.2 Criteria for Termination of the Study

The Chief Investigator may terminate this study prematurely as follows: (a) on an immediate basis for any reason reasonably related to the health or safety of the participants and (b) upon 90 days written notice to CHDI for any other reason. CHDI may terminate this study prematurely for any reason. The Sponsor and Institutional Review Board(s) (IRBs)/Ethics Review Board(s) (ERBs) must be informed promptly.

If the study is prematurely terminated or suspended for any reason, the Site Principal Investigator/institution should promptly inform the study participants and should assure appropriate follow-up for them.

8. Study Procedures

Within a single HDClarity enrollment, participants will attend two study visits, a Screening Visit, an Initial Sampling Visit, and may attend an optional third visit, an Optional Repeat Sampling Visit. When participants have completed the Initial Sampling Visit, and Optional Repeat Sampling Visit, if relevant, their participation in HDClarity will be considered completed. However, participants may be invited to participate in the study multiple times, allowing at least 11 months between Screening Visits and will complete a separate consent for any additional visits.

Visit Number	1	2	3
Visit Type	Screening	Initial Sampling	Optional Repeat Sampling[4]
Days	-30 to -1	Day 0	Day 28 - 56
Study Procedure			
Informed Consent	X	X[3]	X[3]
Inclusion/Exclusion Criteria review	X	X	X
Demographics update	X		
Confirm Enroll-HD core assessments completed within last two months [1]	X		
Brief Physical Exam	X	X	X
Medical History update	X	X	X
Prior/Concomitant Medication update	X	X	X
Standard Neurological Examination	X	X	X
Total Motor Score (TMS)		X	X
Vital Signs (BP, pulse, body temp)		X	X
Safety Laboratory Assessments	X		
Adverse Events (AE)		X	X
Final Eligibility Check		X	X
Lumbar CSF Collection		X	X
Venous Blood Draw[2]		X	X
CSF and Blood Sample Processing		X	X
CSF QC Processing		X	X
Telephone Follow-Up within 1-3 days (concomitant medication and AEs)		X	X

[1] If not, check CI permission in place and complete Enroll-HD core assessments (listed at section 8.1.1)
[2]Obtain venous blood sample immediately after CSF collection is complete
[3]Confirm and record continued consent
[4] For selected participants only

8.1 Description of Study Assessments

Participants will attend two study visits, a Screening Visit and an Initial Sampling Visit, and may attend an optional third visit, an Optional Repeat Sampling Visit. The Screening and Initial Sampling Visits should be no more than 30 days apart. The Screening Visit may occur with an Enroll-HD visit. The Optional Repeat Sampling Visit will occur within 4-8 weeks of the Initial Sampling Visit.

Eligible participants may be invited to participate in the study multiple times, allowing at least 11 months between Screening Visits. No upper time limit or total number of enrollments will be imposed (e.g. a participant may enroll after 2 or 3 years or longer, or may enroll more than once, as long as valid informed consent is re-obtained and the study remains active).

Information regarding occurrence of adverse events (AEs) and Serious Adverse Events (SAEs) will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study procedures will be recorded on the electronic case report form (eCRF).

8.1.1 Screening Visit

- The study will be described in detail to prospective participants and informed consent obtained.
- Confirm that Enroll-HD study core assessments have been performed within the last two months. If not, confirm that approval is in place from the CI and perform the Enroll-HD core assessments during the Screening Visit according to the procedures in the Enroll-HD Protocol and study materials. The Enroll-HD core assessments currently include:
    - Height and weight measurement
    - UHDRS motor assessment, diagnostic confidence score, total functional capacity and Independence Scale.
    - Short Problem behaviours assessment (PBA-S)
    - Symbol-digit modality test
    - Stroop word reading
    - Stroop color naming
    - Categorical verbal fluency
- Medical history update since the last Enroll-HD study visit, including medication history and co-morbidities, is obtained.
- Demographic information update since the last Enroll-HD study visit.
- A standard neurological examination is performed as below, as well as a brief general physical examination. Evidence of possible bleeding tendency such as bruises or petechial rash should be noted.
    - Cranial nerves
        - visual acuity
        - visual fields to confrontation
        - fundoscopy (including appearance of discs and presence / absence of venous pulsations)
        - smooth pursuit and saccadic eye movements
        - facial sensation
        - jaw power
        - facial symmetry and power

        - bedside auditory acuity
        - palatal elevation
        - pharyngeal sensation
        - cough
        - Sternocleidomastoid muscle and trapezius power
    - Upper and lower limbs
        - Tone
        - Proximal and distal power
        - Reflexes (-, +/-, +, ++, +++)
        - Pinprick sensation
        - Plantar responses
        - Coordination
- Up to 15 ml of venous blood is drawn according to local clinical standards and procedures, and routine blood tests performed by a local accredited clinical laboratory:
    - Full blood count
    - Clotting profiles: PT and APTT
    - CRP

If the blood count or clotting profiles are outside normal range, or if CRP is greater than 2× the upper limits of normal the participant will not be booked for an Initial Sampling Visit. The Site Principal Investigator will act on any abnormalities according to clinical judgment.

If participants do not fulfill all inclusion criteria, they may be rescheduled to repeat some or all of the screening assessments above with the prior approval of the Chief Investigator.

If these assessments confirm all the eligibility requirements are met for the study, a date will be given via a telephone call for the Initial Sampling Visit.

8.1.2 Initial Sampling Visit

- The Initial Sampling Visit is scheduled in such a way to allow for the lumbar puncture to be performed between 8:00 and 10:30 am local time. All participants will be asked to fast from midnight the night before their appointment, but are permitted to drink water freely. Compliance with instructions to fast is recorded.
- If participant has not complied with pre-sampling instructions such as fasting or medications, or if the Site Principal Investigator deems the sampling procedure unsafe, unwise or unlikely to produce satisfactory samples, the participant should be sent home, and the sampling rescheduled at the discretion of the Site Principal Investigator.
- Participant continued consent to participate and eligibility are confirmed and recorded.
- The results of the routine laboratory examination are reviewed and recorded.
- Medical and concomitant medication history is updated.
- Measurement of vital signs.

- Any changes to medical history and medication are noted.
- The neurological examination and brief physical exam are repeated for safety.
- The Total Motor Score (TMS) of the UHDRS is performed.
- Lumbar CSF Collection is performed. (See Section 9.1 for complete instructions)
- Venous blood sampling is performed immediately after CSF collection is complete. (See Section 9.2 for complete instructions)
- AE recording
- Process CSF, Serum and Plasma samples per Sections 10.1, 10.2 and 10.3, respectively
- Perform sample quality control (QC) per Section 12.
- Store samples per Section 11.

8.1.2.1 Participant Discharge

Participants are observed for potential complications as per routine clinical practice and discharged once appropriate. Record any AEs.

Participant is discharged by nurses with instructions for over the counter pain medication and hydration in the event of headache.

8.1.3 Follow-up Telephone Call

Contact participant 24 to 72 hours following Initial Sampling Visit to collect any AE and/or concomitant medication data.

8.1.4 Optional Repeat Sampling Visit

- This visit is optional. Participant continued consent to participate and eligibility are confirmed and recorded.
- This visit should be scheduled 4 - 8 weeks following the Initial Sampling Visit.
- The Optional Repeat Sampling Visit is scheduled in such a way to allow for the lumbar puncture to be performed between 8:00 and 10:30 am local time. Participants performing this Optional Repeat Sampling Visit will be asked to fast from midnight the night before their appointment, but are permitted to drink water freely. Compliance with instructions to fast is recorded. If the participant did not fast, they will be sent home, and the procedure rescheduled.
- The results of the routine laboratory examination are reviewed and recorded.
- Measurement of vital signs
- Any changes to medical history and medication are noted.
- The neurological examination and brief physical exam are repeated for safety.
- The TMS of the UHDRS is repeated.
- Lumbar CSF Collection is performed. (See Section 9.1 for complete instructions)
- Venous blood sampling is performed immediately after CSF collection is complete. (See Section 9.2 for complete instructions)

- AE recording
- Process CSF, Serum and Plasma samples per Sections 10.1, 10.2 and 10.3, respectively
- Perform sample QC per Section 12.
- Store samples per Section 11.

8.1.4.1 Participant Discharge

Participants are observed for potential complications as per routine clinical practice and discharged once appropriate. Record any AEs.

Participant is discharged by nurses with instructions for over the counter pain medication and hydration in the event of headache.

8.1.5 Follow-up Telephone Call 2

Contact participant 24 to 72 hours following Optional Repeat Sampling Visit to collect any AE and/or concomitant medication data.

9. Sample Collection Procedures

9.1 Lumbar CSF Collection

1. Ensure that all equipment is on hand and that ice is available for CSF collection and transportation of samples to the lab.
2. Ensure availability and settings of centrifuges for appropriate temperatures and timely processing of CSF and blood samples.
3. Pre-cool CSF collection tubes on ice.
4. Prepare a sterile field containing all equipment needed, label tubes.
5. Place participant into lateral decubitus position with pillow between knees.
6. Identify L4/5 or L3/4 space using surface markings.
7. Disinfect skin using pre-filled sponge.
8. It is highly recommended that adequate lidocaine is used to reduce the discomfort of this lumbar puncture procedure. If, after noting allergies or sensitivities to lidocaine and discussing the risks and benefits of local anaesthesia, it is decided to forgo this step, it should be noted in the electronic case report form (eCRF). Inject up to 5ml of 2% lidocaine for local anaesthesia. Use the 25g needle and inject lidocaine to raise a skin wheal. Then inject lidocaine more deeply.
9. Obtain CSF using the supplied spinal needle. If the participant is thin, do not insert the deep infiltration needle all the way. Use only about 2/3 of its length (to prevent entering the subarachnoid space with anything other than the pencil-point spinal needle).
10. If CSF cannot be obtained, up to three needles may be used. An alternative design of spinal needle supplied by the site may be used if, after at least one attempt with the supplied needle, it is felt this will increase the chance of success.
11. An adjacent space may be used (with further lidocaine, max. total 10 ml, if needed).

12. If necessary, CSF space may be located by sitting participant up, but once CSF is seen, it is recommended to have participant lie back in lateral decubitus position for 30 seconds before collection begins. Document positions of participant during puncture and collection in the eCRF.
13. Document the space used for lumbar puncture, the number of attempts and volume of lidocaine used in the eCRF.
14. Omit pressure measurement for all participants (because spinal manometers are not polypropylene).
15. CSF is collected in 50ml tubes placed on ice in the Styrofoam cup.
16. Collect the first 1 ml of CSF into the supplied tube labelled 'CSF'. If the first 1 ml (approx. 15 drops) is not macroscopically bloody, continue sampling CSF in the same tube up to 15-20 ml, as allowed locally, keeping the tube in the ice cup. If the first 1 ml is macroscopically bloody, stop collecting CSF by reinserting the stylet partially, discard the tube, and collect a second 1 ml in a new pre-cooled 'CSF' tube, and examine it visually for blood contamination. If it is free of blood, continue collecting CSF up to 14-19 ml. If the second separately collected ml of CSF is also macroscopically bloody, discard the tube, and continue to collect 13-18 ml of CSF in a third pre-cooled 'CSF' tube. Stop collecting CSF when sampling time exceeds 20 minutes. Document these details in the eCRF.
17. Place cap on tube and leave on crushed ice until further processing.
18. Reinsert the stylet before withdrawing the needle.
19. Cover the puncture site with sterile dressing.
20. Record time of CSF collection.
21. At the discretion of the Site Principal Investigator, participants may be instructed to lie flat for up to one hour.
22. Transport samples immediately to laboratory for processing.

9.2 Venous Blood Collection

Venous blood is drawn immediately after CSF collection is complete, recording the time. Up to 50 ml of blood will be collected as described in the HDClarity Laboratory Manual.

If venepuncture with vacuum tubes proves challenging, a needle and syringe may be used and the blood transferred immediately into the vacuum tubes, observing safety precautions.

10. Sample Processing Procedures

10.1 CSF Sample Processing

CSF samples must be processed according to the procedures specified in the HDClarity Laboratory Manual.

10.2 Serum Sample Processing

Serum samples must be processed according to the procedures specified in the HDClarity Laboratory Manual.

10.3 Plasma Sample Processing

Plasma samples must be processed according to the procedures specified in the HDClarity Laboratory Manual.

11. Sample storage and shipment

Storage and shipment of the samples must be handled according to the procedures specified in the HDClarity Laboratory Manual.

12. Sample Quality Control

Quality control will be performed on all samples according to the procedures specified in the HDClarity Laboratory Manual and/or at a central laboratory.

13. Medical Monitoring

The Medical Monitor should be contacted directly to report medical concerns or questions regarding safety. The medical monitor can be contacted via email at hdclarity-mm@enroll-hd.org.

14. Adverse Event Reporting and Documentation

14.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence during a clinical investigation and that does not necessarily have a causal relationship with study treatments or procedures. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of study procedures.

The Site Principal Investigator will probe, via discussion with the participant, for the occurrence of AEs during each participant visit, after the Screening Visit, and record the information in the site's source documents. AEs will be recorded in the participant eCRF. AEs will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study procedures if applicable, or if unrelated, the cause.

14.1.1 AE Severity Grading

The severity of an AE will be graded on a 5-point scale (Common Terminology Criteria for Adverse Events v3.0 (CTCAE; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm) defined as follows:

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening or disabling AE
Grade 5	Death related to AE

14.1.2 AE Relationship to study procedures

The relationship of an AE to the study procedures will be evaluated according to the following guidelines:

Probable: This category applies to AEs which are considered with a high degree of certainty to be related to the study procedure. An AE may be considered probably related to the study procedure if:

1. It follows a reasonable temporal sequence from administration of the study procedure;
2. It cannot be reasonably explained by the known characteristics of the participant's clinical state, or by environmental or toxic factors;
3. It follows a known pattern of response to the study procedure;

Possible: This category applies to those AEs in which the connection with the study procedure appears unlikely but cannot be ruled out with certainty. An AE may be considered as possibly related if it has at least two of the following:

1. It follows a reasonable temporal sequence from the study procedure
2. It may readily have been produced by the participant's clinical state, or by environmental or toxic factors;
3. It follows a known response pattern to the study procedure.

Unrelated: This category applies to those AEs which are judged to be clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and do not meet the criteria for study procedure relationship listed under possible or probable.

14.2 Serious Adverse Events

A Serious Adverse Event (SAE) is defined as any AE that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect
- any other serious medical occurrence

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the participant or require intervention to prevent one of the outcomes listed.

An AE is considered to be life-threatening if, in the view of the Site Principal Investigator, the participant was at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more serious form, might have caused death.

Serious Adverse Events will be documented from the point of enrollment until the participant is exited from the study. If a participant enrolls multiple times, AEs and SAEs will be documented from the point of each new consent until the final study visit for that enrollment.

Information recorded and reported shall include:

- A description of the event
- the date of event onset

- The relatedness of the event to the procedure
- The expectedness of the event
- The outcome of the event
- The date the event was first noticed by, or reported to the Site Principal Investigator

All ongoing Serious Adverse Events will be followed-up until the last study visit and post study follow-up is described in Section 14.4 below.

14.2.1 Serious Adverse Event Reporting

SAEs (as defined in Section 15.2) must be reported to the designated Medical Monitor immediately, and also to the Sponsor by email, and in no case later than within 24-hours of awareness of the event.

All SAEs that occur (whether or not related to study procedures) will be documented. The collection period for all SAEs will begin from the Initial Sampling Visit and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local IRB/ERB, the Site Principal Investigator will report SAEs to the IRB/ERB.

14.3 Reporting incidents

An incident in a research study is:

- Something that should not have happened OR
- Something that should have happened but didn't which, in either case, significantly affects any of the following:
  - the rights and wellbeing of the study participant,
  - the scientific value of the study,
- the compliance of the study with all applicable legal rules or ethics guidance including, as applicable, the Data Protection Act, the General Data Protection Regulation, and the Human Tissue Act, or
  - the reputation of the Sponsor.

This includes a requirement to report all serious breaches of protocol or GCP (if applicable).

All incidents must be reported through the appropriate host site incidents reporting system. For any host site where no United Kingdom National Health Service Trust is involved, the incident should be reported by completing the “Incident Report Form” that may be found at http://www.ucl.ac.uk/jro/postapproval.

14.4 Post-study Follow-up of Adverse Events

Any AE, including clinically significant physical examination findings and SAEs, must be followed until the event resolves, the condition stabilizes, the event is otherwise

explained, or the participant is lost to follow up. If resolved, a resolution date should be documented on the eCRF and in the source documents. The Site Principal Investigator is responsible for ensuring that follow up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals as is medically indicated.

15. Statistical Methodology

15.1 Determination of Sample Size

The CSF and plasma samples collected in this study will be the basis for future biomarker analysis studies. Each of those studies will require a specific power calculation to determine how many samples to include in the analysis. However, the open-ended nature of biomarker discovery and validation and the purpose of HDClarity as a biorepository favours placing no upper limit on the number of participants that may be enrolled.

While most of the biomarker development focus is on earlier stages of the disease, it may also be important to assess some biomarkers at more advanced stages. Only sites with access to in-patient facilities will likely be able to recruit this cohort.

For some biomarkers, it may be important to understand the stability of the biomarker within participants over relatively short time periods. Thus, up to approximately 20% participants will be invited to return for an Optional Repeat Sampling Visit 4-8 weeks after their Initial Sampling Visit. Other biomarker discovery and analysis, e.g. analysis of disease progression, may require comparison of samples at longer intervals, and eligible participants may be invited to participate in the study multiple times, allowing at least 11 months between Screening Visits.

16. Study Management

16.1 Roles and responsibilities

Except where dictated by convention, statute or GCP, the roles and responsibilities of all parties involved in the study will be set forth in study site agreements or other contracts or subcontracts agreed by the parties concerned.

16.2 Ethics and Regulatory Considerations

This study will be conducted according to Good Clinical Practice (GCP), 21 CFR Part 50, (Protection of Human Subjects), 21 CFR Part 56 (Institutional Review Boards), International Conference on Harmonisation Guidance for Industry (ICH guidelines), E6 Good Clinical Practice: Consolidated Guidance, the Nuremberg Code, and the Declaration of Helsinki.

Sites will be responsible for obtaining all appropriate approvals from IRBs/ERBs, supported by a CHDI-approved informed consent form. ERB and/or IRB approval will be sought for each site in each country as per their regulations prior to the start of study activities at that site.

16.2.1 Audits and Inspections

CHDI, regulatory authority, Sponsor or IRB/ERB may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of such an audit or regulatory inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements. Site Principal Investigators should contact the Chief Investigator and CHDI immediately if contacted by a regulatory agency about an inspection at their site.

16.2.2 Ethics Committee Approval

This protocol and any amendments will be submitted to a properly constituted IRB/ERB, in accordance with the ICH guidelines, the applicable European Directives and local legal requirements, for approval of the study. Approval must be obtained in writing before the first participant can be recruited.

16.3 Insurance

University College London, the Sponsor, holds insurance against claims from participants for harm caused by their participation in this study. Participants may be able to claim compensation if they can prove that the Sponsor has been negligent. However, if this study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the study. The Sponsor does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

16.4 Informed Consent Procedure

All participants must give informed consent prior to undertaking study procedures and these informed consents must be obtained by clinical site staff using approved processes according to all applicable laws and regulations on GCP. At a minimum, the consent process will involve:

1. Provision of written, ERB and/or IRB-approved information about the study to potential participants;
2. Potential participants permitted sufficient opportunity to read the information and consider the options without maximum but with a recommended minimum of 24 hours;
3. Potential participants permitted sufficient opportunity to ask questions and receive satisfactory answers from the site study team;
4. Potential participants' comprehension verified before signing a consent form; and
5. The voluntary signing of a consent form and countersigning by the study site personnel undertaking the consent process.

In the event that a site wishes to enroll participants with impaired capacity, specific ERB and/or IRB approval will be sought in advance before such participants are enrolled and a Legally Authorised Representative will sign on behalf of the participant.

Signed consent forms will be maintained in a secure designated location at the site.

16.5 Data Collection, Retention and Monitoring

16.5.1 Data Entry/Electronic Data Capture System

The data are entered electronically via secure internet-based technology. Access to the eCRFs is limited by password and can only be authorized by the Chief Investigator and issued by the study administrator. Each Site Principal Investigator in this study can only see data on participants from their own site. The data managers who are responsible for the data quality and integrity have access to all sites' data. Clinical research monitors, who are responsible for monitoring data for site that are assigned, can only review the data from those sites. They are responsible for study monitoring and ensuring compliance with the study protocol.

16.5.2 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Query reports pertaining to data omissions and discrepancies will be forwarded to the Site Principal Investigator and Study Central Coordination for resolution. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

16.5.3 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

UCL and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol).

The Chief Investigator will archive the study master file at UCL for at least 20 years and in line with all applicable legal and statutory requirements. The Site Principal Investigator at each participating site agrees to archive his/her respective site's study documents for the period of time specified in the site agreement and in line with all applicable legal and statutory requirements.

16.5.4 Investigator Site Files

Each site will maintain an Investigator Site File (ISF) containing all applicable regulatory, ethical and GCP documentation relating to the conduct of the study at the site. It will be the responsibility of each site's Principal Investigator to maintain this ISF.

16.5.5 Source Documents

The Site Principal Investigator should maintain source documents for each participant enrolled in the study. Source documents such as local laboratory ranges and reports, participant charts and doctors' notes will be kept as part of the participants' medical records. For participants who do not have a medical record per se, another method of documentation and record keeping will be employed, along with the obligation to retain source documents, such as laboratory reports, for the period of time specified in the site agreement. Participant files including medical records and signed participant informed consent forms must be available for review in the event the site is selected for monitoring, audits, or inspections.

16.5.6 Monitoring

The Sponsor is responsible for ensuring the proper conduct of the study with regard to ethics, protocol adherence, site procedures, integrity of the data, and applicable laws and/or regulations. At regular intervals during the study and following completion of the study, the Sponsor's study monitors will contact the study site via visits to the site, telephone calls, and/or letters in order to review study progress, eCRF completion, and address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: informed consent of participants, participant recruitment, participant compliance with the study procedures, source data verification, use of concomitant therapy by participants, AE and SAE documentation and reporting, and quality of data. Records pertaining to these aspects are expected to be kept current.

The Site Principal Investigator must make study data accessible to the clinical monitor, to other authorized representatives of the Sponsor, and to regulatory inspectors.

16.5.7 Data transfer

In the study, data will be collected from participants in accordance with the participant consent form, participant information sheet (as applicable) and of this protocol.

The data will be appropriately sent to the data repository held and managed by service providers engaged by CHDI for storage and data monitoring, and for the purposes of the EU General Data Protection Regulation (GDPR), both CHDI and UCL will act as joint data controllers of such data for the study. Both CHDI and UCL have an appointed Data Protection Officer to assist with their respective responsibilities and as part of their obligations under the GDPR, will provide participants with information about data protection and privacy and transfer of data outside of the EU. Participants who were consented into the study before GDPR was in force will be provided with a supplemental notice containing this information.

The service providers engaged by CHDI will process, store and dispose of all study data in accordance with all applicable legal and regulatory requirements, including, as applicable, the Data Protection Act 1998 and the General Data Protection Regulation and any amendments thereto. All paper and digital records not uploaded to the study data repository will be retained at individual study sites in locked and/or password-protected form under the control of the Site Principal Investigators.

16.6 Biological samples (handling, processing and storage)

In the study, cerebrospinal fluid, plasma, serum and cells from CSF will be collected from participants in accordance with the participant consent form and participant information sheet (as applicable) and shall include all tissue samples or other biological materials and any derivatives, portions, progeny or improvements as well as all participant information and documentation supplied in relation to them. The biological samples will be appropriately sent to BioRep, Via Olgettina, 60, c/o DIBIT 2 - Palazzina San Michele 20132 Milan – Italy (or such other selected biorepository), for cataloguing and storage of the samples to be carried out in accordance with the protocol and the informed consents. BioRep (or such other selected biorepository) will process, store and dispose of all samples in accordance with all applicable legal and regulatory requirements, including, as applicable, the Human Tissue Act 2004 and any amendments thereto.

16.7 Amendments

Any amendments to the protocol will be written and approved by the Chief Investigator and CHDI. All amendments must be submitted to the Sponsor and IRB/ERB for approval prior to implementing the changes. In some instances, an amendment may require changes to the informed consent form, which also must be approved by CHDI and submitted for IRB/ERB approval prior to administration to study participants.

16.8 Record Keeping

16.8.1 Participant Health Information

The Site Principal Investigator agrees to comply with all applicable laws and regulations relating to the privacy of participant health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation) and the EU General Data Protection Regulation (GDPR). Where applicable, the Site Principal Investigator shall ensure that study participants authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

16.8.2 Retention of Study Documents

Study-related records must be retained for the period of time specified in the site agreement. The Site Principal Investigator must not destroy any study-related records without receiving approval from the Chief Investigator and CHDI. The Site Principal Investigator must notify the Chief Investigator in the event of accidental loss or destruction of any study records. If the Site Principal Investigator leaves the institution where the study was conducted, the Chief Investigator must be contacted to arrange alternative record storage options.

16.9 Reporting

After completion of the study, an abbreviated clinical study report will be prepared by the Chief Investigator.

17. Appendix A – Site Principal Investigator Obligations

The study protocol and the final version of the participant informed consent form will be approved by an IRB/ERB before enrollment of any participants. The opinion of the IRB/ERB will be dated and given in writing.

The Site Principal Investigator will ensure that the IRB/ERB will be promptly informed of all changes in the research activity and of all unanticipated problems including risk to participants. The Site Principal Investigator will not proceed with changes to the protocol until IRB/ERB approval has been obtained.

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

As described in GCP guidelines, site personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s). Site personnel will not include individuals who (a) are currently and have not ever been, debarred or convicted of a crime for which a person can be debarred or otherwise suspended or disqualified under any applicable laws, regulations or professional guidelines or (b) have ever been threatened to be debarred or indicted for a crime or otherwise engaged in any conduct or activity for which a person can be debarred or otherwise suspended or disqualified. Quality assurance systems and procedures will be implemented to assure the quality of every aspect of the study.

<u>IRB/ERB Review/Approval/Reports</u>

The protocol and informed consent for this study, including advertisements used to recruit participants, must be reviewed and approved by an appropriate IRB/ERB prior to enrollment of participants in the study. It is the responsibility of the Site Principal Investigator to assure that all aspects of the ethical review are conducted in accordance with the current Declaration of Helsinki, ICH, GCP, and/or local laws, whichever provide the greatest level of protection. A letter documenting the IRB/ERB approval which specifically identifies the study/protocol and a list of the committee members must be received by the Chief Investigator and CHDI prior to initiation of the study. Amendments to the protocol and informed consents will be subject to the same requirements as the original protocol and informed consents.

A progress report with a request for re-evaluation and re-approval will be submitted by the Site Principal Investigator to the IRB/ERB at intervals required by the IRB/ERCB. A copy of the report will be sent to CHDI and the Sponsor as well as letters of re-evaluation and re-approval.

After completion or termination of the study, the Site Principal Investigator will submit a final report to the IRB/ERB and to CHDI, if required. This report should include: deviations from the protocol, the number and types of participants evaluated, and significant AEs, including deaths.

<u>Study Documentation</u>

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

documentation includes CHDI/Site Principal Investigator correspondence, IRB/ERB correspondence, protocol and amendments, information regarding monitoring activities, participant exclusion records, eCRFs, and data queries.

Confidentiality

The anonymity of study participants will be protected by using an assigned participant number on eCRFs and other documents relating to the participant. Documents that identify the participant (e.g., the signed informed consent document) must be maintained in strict confidence by the Site Principal Investigator, except to the extent necessary to allow auditing by the Food and Drug Administration and other regulatory authorities or the clinical monitor and others as described in the informed consent.

Study Facilities

The Site Principal Investigator must ensure that there is a robust institutional policy on freezer failure that includes checks, alarms, emergency contact details, backup power supplies, CO2 cylinders and an infrastructure to transfer samples to an off-site facility if necessary.

18. References

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