Huntington's Disease Young Adult Study 2.0

7th September 2023

Full/long title of study	Huntington's Disease Young Adult Study 2.0
Short title	HD-YAS 2.0
Version and date of protocol	Version 3.1 7th Sept 2023
Sponsor:	University College London (UCL)/University College London NHS Foundation Trust (UCLH)
Sponsor reference number:	145646
Funder (s):	Wellcome, CHDI
IRAS Number:	303499
UCL Data Protection Number:	Z6364106/2016/06/74

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PROTOCOL VERSION HISTORY

Version Stage	Versions Number	Version Date	Protocol updated & finalised by;	Reasons for Update
Current	**Version 3.1**	**7th Sept 2023**	**Dr Rachael Scahill** **Ms Kate Fayer**	**Minor change to recruitment numbers to allow more new recruitment**
Previous	**Version 3.0**	**8th Jun 2022**	Dr Rachael Scahill Ms Kate Fayer	**Addition of fluoroscopy-guided lumbar puncture. Increased time for CSF collection**
Previous	Version 2.0	8th Mar 2022	Dr Rachael Scahill Ms Kate Fayer	Add National Adult Reading Test
Previous	Version 1.0	14th Dec 2021	Dr Rachael Scahill Ms Kate Fayer UCL JRO	[include appendix no., if applicable] NB: Appendix is to be attached to current version of the protocol

DECLARATIONS

The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the U.K. Policy Framework for Health and Social Care Research 2017 (3rd edition) (as amended thereafter), the EU General Data Protection Regulation (2016/679) and the UK Data Protection Act (2018), Sponsor SOPs and applicable Trust policies and legal frameworks.

I (investigator) agree to ensure that the confidential information contained in this document will not be used for any other purposes other than the evaluation or conduct of the research investigation without the prior written consent of the Sponsor.

I (investigator) agree to ensure that no research activity or recruitment will commence at participating research sites until the appropriate regulatory approvals and NHS confirmations of Capacity and Capability have been issued, and Sponsor green light confirmed.

I (investigator) also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given. Any deviations from the study as planned in this protocol will be explained and reported accordingly.

Chief Investigator:

Signature: 

…… Date14/12/2021

Print Name (in full): Sarah J Tabrizi

Position: Professor of Clinical Neurology, Hounoury Consultant Neurologist and Director of the UCL Huntington's Disease Centre

On behalf of the Study Sponsor:

Signature:  **Date. 17/12/2021**

Print Name (in full): Pushpsen Joshi

Position: Research Governance Manager, Joint Research Office, University College London

STUDY SUMMARY

IDENTIFIERS	
IRAS Number	303499
REC Reference No.	22/LO/0058
Sponsor Reference No.	145646
Other research reference number(s) (if applicable)	Z6364106/2016/06/74
Full (Scientific) title	Huntington's Disease Young Adult Study 2.0
Health condition(s) or problem(s) studied	Huntington's Disease
Study Type i.e. Cohort etc.	Case control
Target sample size	<161
STUDY TIMELINES	
Study Duration/length	4 years
Expected Start Date	March 2022
End of Study definition and anticipated date	April 2026
Key Study milestones	Protocol and study document development, study submission, budget and contract to be finalised, ethics and HRA approval, first participant recruited, completion of data collection, analysis, publication.
FUNDING & OTHER	
Funding	Wellcome Trust, CHDI
Other support	Huntington's Disease Association, Huntington's Disease Youth Organization
STORAGE of SAMPLES / DATA (if applicable)	
Human tissue samples	UCL Institute of Neurology (Professor Sarah Tabrizi) Queen Square House Queen Square London WC1N 3BG Glasgow University (Professor Darren Monckton) Institute of Molecular Cell & Systems Biology R424 Level 4, Institute of MC&SB, Davidson Building, Glasgow G12 8QQ BioRep srl (CHDI's designated biobank storage facility) c/o DIBIT2 Palazzina San Michele Via Olgettina 60 20132 Milano Italy
Data collected / Storage	All data: UCL HD Centre University College London (Professor Sarah Tabrizi), Russell Square House, 10-12 Russell Square, London WC1B 5EH

	Coded data (basic demographics, CSF and blood assay results, motor and cognition assessments and image analysis variables): CHDI, a non-profit organization (Professor Cristina Sampaio), 155 Village Boulevard, Suite 200, Princeton New Jersey, USA Cambridge University (Prof James Rowe), University of Cambridge Downing St. Cambridge CB2 3EB University of Iowa (Prof Doug Langbehn), 1-290 Medical Education Building Iowa City IA 52242, USA
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Committees	Steering Committee: Prof Sarah Tabrizi Prof Geraint Rees Prof Gill Bates Prof Barbara Sahakian Prof Trevor Robbins Prof James Rowe Prof Ed Wild Prof Doug Langbehn

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Other relevant study personnel	CHDI, a non-profit organization (Professor Cristina Sampaio)155 Village Boulevard, Suite 200, Princeton New Jersey, USA

KEY ROLES AND RESPONSIBILITIES

SPONSOR: Prior to the start of the study, the sponsor is responsible for ensuring that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also must be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

FUNDER: The funder is the entity that will provide the funds (financial support) for the conduct of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work.

CHIEF INVESTIGATOR (CI): The person who takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than once site, the CI takes on the primary responsibility whether he/she is an investigator at any particular site.

The CI ensures that all relevant regulatory approvals and confirmations of NHS Capacity and Capability are in place before the study begins. Furthermore the CI ensures that arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, and that study staff receives adequate training for the conduct of the study as per the protocol and relevant standards.

The CI is responsible for submission of annual reports as required. The CI will notify the Research Ethics Committee and Joint Research Office of the end of the study (including the reasons for premature termination, where applicable). Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC and JRO.

PRINCIPLE INVESTIGATOR (PI): Individually or as leader of the researchers at a site the PI ensures that the study is conducted as per the approved study protocol, and report/notify the relevant parties – this includes the CI of any breaches or incidents related to the study.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
APTT	Activated partial thromboplastin time
CAG	Cytosine-arginine-glutamine codon whose count in the HTT gene determines the genetic diagn
CRP	C-reactive protein
CSF	Cerebrospinal fluid
DBS	Disease Burden Score
eCRF	electronic Case Report Form
GCP	Good Clinical Practice
Hb	Haemoglobin
HD	Huntington's disease
HTT	huntingtin protein
HDGEC	huntington's disease gene expression carriers
ICH Guidelines	International Conference on Harmonisation Guidance for Industry
ICF	Informed Consent Form
KMO	kynurenine mono-oxygenase
KP	kynurenine pathway
MPM	Multi parametric Mapping
MRI	Magnetic Resonance Imaging
NART	National Adult Reading Test
NODDI	Neurite orientation and Dispersion and Density Imaging
PIS	Participant Information Sheet
PT	Prothrombin time
rsfMRI	Resting state functional Magnetic Resonance Imaging
REC	Research Ethics Committee
SAE	Serious Adverse Event
TFC	Total Functional Capacity
TMS	Total Motor Score
UHDRS	Unified Huntington's Disease Rating Scale
VBM	Voxel-based morphometry

Contents

1 INTRODUCTION

Huntington's disease (HD) is an autosomal dominantly inherited, progressive neurodegenerative disorder characterized clinically by a movement disorder (typically chorea), neuropsychiatric disturbances, and cognitive impairment. The clinical features of HD usually emerge in adulthood (mean age of 37 years), after which illness progresses steadily over a period of 15-25 years. Genetic testing (preceded by genetic counselling according to internationally accepted guidelines) allows one to determine whether a clinically normal person harbours the HD mutation and thus predict that a person will go on to develop HD before he or she shows clinical symptoms and signs. HD has a prevalence of approximately 12 per 100,000 in the UK (Evans et al., 2013). HD affects at least 40,000 people living in Europe. In addition, an estimated 80,000 individuals carry the HD mutation but remain as yet unaffected. HD is caused by an expansion of a cytosine-adenine-guanine (CAG) trinucleotide repeat stretch in exon 1 of the HD gene on chromosome 4 (Macdonald et al., 1993). Individuals who have 36 CAG repeats or more may develop the clinical symptoms and signs of HD including motor, cognitive and neuropsychiatric abnormalities that cause a progressive loss of functional capacity and shorten life (Bates et al., 2015). The course of HD is relentless; to date, there is no treatment which has been shown to alter the progression of the disease (Tabrizi et al., 2020).

Since the gene mutation responsible for HD was identified in 1993 (Macdonald et al., 1993), considerable progress has been made in understanding the pathogenesis of this disorder and in identifying targets for potential therapies modifying the natural course of the disease (Tabrizi et al., 2020). Currently the only approved treatment for HD is tetrabenazine, but several clinical trials exploring novel therapeutic approaches to treating this disease are already in progress. It is expected that early intervention with therapeutic agents in a pre-manifest cohort will have the greatest clinical benefit when treating the disease.

2 BACKGROUND AND RATIONALE

Our previous work in the Huntington's Disease Young Adult Study (HD-YAS) used structural and functional MRI, cognitive, behavioural and neuropsychiatric measures and blood and CSF biomarkers to characterise the HD phenotype many years before symptom onset (premanifest) and detected signs of neuronal damage ~24 years before predicted onset (Scahill et al., 2020). Moreover, we detected reduced striatal volume in young HD adults that may be indicative of abnormal development, as supported by other recent work. We have also shown that somatic expansion of the *HTT* CAG repeat is a major driver of disease progression (Lee et al., 2019). However, there remains a significant gap in our knowledge about the dynamics of early HD pathogenesis, the relationship between neurodevelopment and neurodegeneration, and how this might inform the development of effective treatments to delay or prevent symptom onset. HD-YAS 2.0 aims to characterise the earliest neurodegenerative signs at molecular and systems levels and resolve their longitudinal progression in order that our mechanistic investigation can facilitate treatment delivery decades before symptom onset.

Using non-invasive MRI measures of brain atrophy combined with structural, functional and effective connectivity we aim to detect and characterise any early disease-related effects. In parallel we will characterise any functional deficits using targeted cognitive testing. In addition to the HD core

assessments, a battery of computerised neuropsychological tests, CANTAB, has been used previously in studies of pre-HD and manifest HD (Lawrence et al., 1996, 1998). CANTAB planning test scores are neurobiologically-based, validated with good reliability (Insel et al., 2013) and have a significant relationship to the Functional Assessment subsection of the Unified Huntington's Disease Rating Scale (UHDRS) (Huntington Study Group, 1996). Whilst CANTAB tests 'cold', or non-emotional, cognition, EMOTICOM (developed by Sahakian, Robbins and colleagues) tests 'hot', or social and emotional cognition. EMOTICOM also contains motivation and impulsivity tests, relevant to the behavioural problems of HD, plus the objective measures of aggression and disgust (Calder et al., 2010). We will also use the National Adult Reading Test (Nelson, 1982) to estimate premorbid Intelligence Quotient (IQ) if the participant did not take part in the original HD-YAS 1.0 study.

In a subset of participants who've donated longitudinal CSF, ultra-high field (UHF) 7T MRI will be used to investigate structural myelin differences in cortical layers. MEG, which measures magnetic fields produced by neuronal activation, will be used to assess cortical layer function during a visually guided action selection task and at rest. Coherence between these measures will also be investigated.

Will we collect DNA and PBMC buffy coat samples from HDGEC at each time point to test somatic instability in this cohort.

For the first time a battery of validated CSF and blood biomarkers will be tracked over time in this very early premanifest cohort.

3 AIM(S) AND OBJECTIVES

We aim to facilitate the delivery of disease-modifying therapeutic trials in HD. We will do this by mapping the progression of early HD pathology and understanding its impact on symptomatology in young adult HD mutation carriers. Elucidating this early disease progression will help identify the optimal time to deliver therapies with potential to delay or even prevent the onset of symptoms. In addition, we will generate robust biomarkers with utility as efficacy measures in future disease-modifying trials.

HD-YAS far-from-onset premanifest mutation carriers (n=64) and controls, matched for age, sex and education (n=67), will undergo neuroimaging, cognitive, behavioural and psychiatric assessments and biofluid assessments ~5 and 7 years after their baseline assessment from HD-YAS. In addition, up to 30 new participants may be recruited across the groups to account for participant drop out or unwillingness/inability to complete all study assessments. We will compare change over time in HDGEC and control groups and model disease burden influence (an early natural history proxy) within the HDGEG group. These analyses will incorporate previous baseline measurements (providing three timepoints). We will create a data-driven natural history of pathological changes across the pre-clinical period in HD and estimate longitudinal models of age and CAG-dependence on the outcomes, providing a critical tool to increase power.

3.1 Primary Objective

To highlight the earliest timepoint to target intervention, prior to widespread neuronal damage with the aim of delaying or preventing the onset of symptoms. We will determine whether young adult gene carriers with a disease burden score (DBS) at baseline ≤ 240 (Penney et al. 1997) in the Huntington's Disease Young Adult Study exhibit longitudinal differences in:

- Regional brain volumes;
- Structural brain connectivity;
- Functional/effective brain connectivity;
- Grey matter and white matter microstructure;
- Myelination;
- Mutant huntingtin levels in the CSF;
- Cognition:
- Nfl in CSF and blood,
- Structural myelin measures in deep and superficial cortical layers;
- Functional measures in deep and superficial cortical layers during cognitive tasks and at rest;
- Coherence between cortical layer structure and function.

3.2 Secondary Objectives

To determine which metrics (or combination of metrics) demonstrate the most robust measures with potential utility in clinical trials. By integrating information from multiple imaging and functional modalities we will determine when biomarkers deviate from the normal range in terms of their change over time.

4 STUDY DESIGN & METHODS OF DATA COLLECTION

4.1 Study Population

Eligible participants who completed the HD-YAS study will be invited to take part;

- Healthy controls, n= ≤67
- Young Adult Premanifest HD, n=≤64

In addition, up to 50 new participants may be recruited across the groups to account for participant drop out or unwillingness/inability to complete all study assessments.

4.2 Recruitment

Eligible participants who completed the HD-YAS study will be invited to take part. New participants may be included to account for drop-out. We may recruit up to 25 new premanifest participants and 25 new control participants who meet eligibility criteria. These participants will be identified through our HD clinic and through advertising/social media advertising with assistance from the Huntington's Disease Association and the Huntington's Disease Youth Organisation or through Participant Identification Centres across the UK.

Longitudinal CSF collection is a vital part of the study. All participants will be invited to donate CSF at two time points in this study.

Participants who donated CSF at baseline in the original HD-YAS study and have subsequently agreed to donate CSF in this study will be invited to participate in 7T and MEG scanning. We want to achieve 20 HDGEC and 20 Control participants with 7T and MEG scanning. Participants will be invited based on their willingness and tolerance of MRI scanning as assessed by the participant and investigators. 7T and MEG scanning is an optional component for the participants.

4.3 Study Visit and Assessments

Participants will attend two study visits. For participants who took part in HD-YAS these visits will occur approximately 5 years and 7 years from Baseline assessment in the HD-YAS study. This interval was selected to provide power to detect specific and mechanistically relevant measures of longitudinal change that will allow us to identify early dynamic neurodegeneration. For new participants these visits will occur approximately 2 years apart. Participants will undergo:

COGNITIVE, IMAGING ASSESSMENTS AND BLOOD SAMPLES (DAY 1)

- Cognitive tasks (CANTAB and EMOTICOM batteries)
- 3T Volumetric MRI
- rsfMRI
- NODDI
- MPM
- Huntington's disease core research assessments.
- National Adult Reading Test (New participants at first visit only)
- Blood sample collection for research genotyping (new HDGEC participants at first visit only)
- Blood samples collection for biomarker analyses
- Blood sample collection for DNA extraction, buffy coat isolation and assessment of somatic instability in all HDGEC
- Clinical review and screening blood sample for CSF collection in eligible participants

CSF COLLECTION AND NEUROPSYCHIATRIC QUESTIONNAIRES (Day 2)

Participants meeting the eligibility requirements for the CSF collection will go on to have the lumbar puncture, CSF collection and venous blood draw on a separate day starting at 8:30 am. Overnight hotel accommodation will be offered in a local hotel.

- CSF and complementary fasted blood sample collection
- Neuropsychiatric self-report questionnaires

OPTIONAL 7T and MEG scanning

- 7T
- MEG

A subset of eligible and willing participants will be invited to undergo 7T and MEG scanning on an additional study day. Participants who choose to take part will complete the study visit over three days instead of two. The protocol allows a degree of flexibility with regards to positioning of this day to best accommodate the participants' schedules. For example, 7T and MEG could occur on a separate day prior to either cognitive and core imaging assessments or prior to the CSF collection. The only limitation is that we would not perform scanning on the day after CSF collection.

The study visit is summarised in table 1 below:

Day 1

Estimated Time	Assessment Type	Details	Type of Test	Rating Type	Approximate Duration
09:00	Informed Consent	Consent to HD-YAS taken by researcher	-	Study Doctor	30 min
09:30	Clinical Review and Blood Collection	≤40 ml biomarker blood collection Optional 15 ml CSF screening blood sample (safety) 10 ml EDTA for DNA extraction 10 ml EDTA for research genotyping (new HDGECs only)		Study Doctor	45 mins
10:15	BREAK				
10:45	Cognitive	CANTAB EMOTICOM Other	Computerised tablet and paper forms	Objective, computerised. Psychologist administered	110 min. Short break can be offered during the cognitive battery.
13:00	LUNCH				
14:00	Imaging	Positioning 3T Volumetric MRI rsfMRI NODDI MPM	MRI	Radiologist/Imaging Team	90 mins
15:30	BREAK				
16:00		Demographics, Lifestyle		Clinician/psychologist rated	60 mins

	HD core research assessments	HD history, PMH and conmeds UHDRS (TMS, TFC, IS) PBA-s (& C-SSRS if relevant) SDMT Verbal fluency test (category) Stroop (colour, work, interference)	Psychologist/clinician led interview/questionnaires		
17:00	END OF STUDY VISIT				

Overnight hotel stay near study site following Day 1 assessments. Fasting from midnight for CSF and blood collection (water only)

Day 2

8:00 - 9:30	CSF collection Blood collection**	Lumbar Puncture and venous blood collection	Biomarkers	Clinician	45 min procedure, plus resting time
9:30 - 10:15	Neuropsychiatric self-report assessments	To be completed at home within a week of study visit, or following main study visit	Tablet based questionnaires	Participant self-administered	45 mins

1-3 days after CSF collection	Telephone follow-up to check for adverse events following the optional CSF collection. Follow-up details to be entered on to paper CRF by researcher.

Optional 7T and MEG collection

Estimated Time	Assessment Type	Details	Type of Test	Rating Type	Duration
13:00	Safety screening	Performed by researcher and radiographer	-	-	30mins
13:30	MEG Task practice	Practice of computer game task used during MEG scanning	-	-	30mins
14:00	MEG Scanning		MEG	-	60-90mins

15:00	BREAK				60mins
15:30	7T MRI				60 mins
16:30	Participant feedback questionnaire / END OF STUDY VISIT				

5 STUDY SCHEDULE

Participants who were enrolled in the HD Young Adult Study will be recruited for a follow-up and attend two separate study visits approximately **5** and **7** years after baseline. New participants will undergo the same two study visits.

DAY 1 STUDY ASSESSMENTS

Cognitive Tasks

Overview:
CANTAB

- ID/ED Attentional Set Shifting (7 minutes)
- One Touch Stockings (10 minutes)
- Spatial Working Memory (10 minutes)
- Paired Associates Learning (10 minutes)
- Rapid Visual Information Processing (10 minutes)
- Stop Signal Task (SST) (20 minutes)

EMOTICOM

- Emotional Intensity Face Morphing (5 minutes)
- Moral Judgement (10 minutes)

Other

- Goal Priors Assay Task (25 minutes)
- National Adult Reading Test (3 minutes) (New participants only)

ESTIMATED TOTAL TIME: 110 minutes

Description:
CANTAB battery (67 minutes)

The CANTAB computerised neuropsychological tests (http://www.camcog.com) have been used previously in studies of premanifest and manifest HD and are neurobiologically-based and validated,

with good reliability.

The following CANTAB tests are proposed for inclusion in the battery:

- Intra-dimensional and extra-dimensional (ID/ED) Attentional Set Shifting

  Measure of cognitive flexibility that involves rule acquisition and reversal learning in response to simple and compound visual stimuli. Participants are required to adapt their responding to changes in outcome contingency and shift their attentional focus within the same (ID) or different (ED) stimulus dimensions. Previously shown to be sensitive to deficits in both early (Lawrence et al., 1996) and premanifest HD (Lawrence et al., 1998).

- One Touch Stockings

  A test of visuospatial planning and working memory based on a modified version of the Tower of London. Participants are shown example configurations of three coloured balls and must determine the minimum moves required to match their display to the example without actually moving the balls. Previously shown to be sensitive to disease progression and to correlate with functional assessment scores in early HD (Ho et al. 2003).

- Spatial Working Memory

  Examines memory for spatial locations already visited in an array of visual stimuli, assessing an individual's ability to retain and manipulate visuospatial information and to apply an effective search strategy. These aspects of visuospatial working memory have been found to be impaired in premanifest HD (Tabrizi et al., 2009).

- Paired Associates Learning

  A sensitive measure of episodic memory and new learning. Patterns are briefly displayed at various locations on the screen, before they are hidden and the participant must recall their location. The number of patterns to be recalled increases from 2, 3, 6, to 8. Elevated error rates on this task are apparent in manifest HD (Lawrence AD, Watkins LH, Sahakian BJ, Hodges JR, 2000)and predictive of time to disease onset in premanifest HD (Begeti et al., 2016).

- Rapid Visual Information Processing

  Measures sustained attention by presenting a rapid stream of digits and requiring participants to detect target sequences. Accuracy measures indicate sustained attention ability and reaction times provide a measure of visuomotor processing speed.

- Stop Signal Task

  Measures response inhibition (impulse control). Participants respond to an arrow stimulus, however if an audio tone is present the subject must inhibit that response. Performance indicates how quickly and efficiently participants can inhibit a prepotent motor response.

EMOTICOM battery (15 minutes)

EMOTICOM is a newly develop battery to assess social cognition and motivational/emotional functioning which has been standardised on 300 volunteers (Bland et al., 2016).

The following EMOTICOM tests are proposed for inclusion in the battery:

- Emotional Intensity Face Morphing

  Assesses emotion recognition by determining the point of emotional intensity at which participants can recognise a facial emotion. Participants view faces that either increase or decrease in emotional intensity and are asked to respond at points when they can detect (or no longer detect) a given emotion. It is anticipated this task will be sensitive to emotion recognition deficits documented in early and premanifest HD (Henley et al., 2008).

- Moral Judgement

  Examines emotional responses to social situations. Cartoon figures depict a range of moral scenarios involving accidental or intentional harm. Participants are required to imagine how they would feel as either the victim or actor and to rate their feelings across a range of emotions including guilt, shame, anger and feeling "bad". This task will provide a detailed measure of emotional responsiveness and social processing.

Other

- Goal Priors Assay Task

  This task examines the integration of predicted consequences of one's actions with sensory evidence, in the context of effortful, goal-directed behaviour. Participants press their finger on a force sensor button, to subsequently trigger a ballistic ball movement on the screen (like a catapult, in the popular Angrybirds game), aiming for the ball to stop on the target. For a subset of trials, the ball movement is not shown, and participants are asked to estimate where the ball would have stopped (see Figure 1). The relationship between the participant's estimates of performance and their true performance is used to infer the relative weighting of predictions for the perception of action outcomes. Normative goal-directed behaviour uses strong predictions which "explain away" sensory evidence, including evidence of errors. Reduced precision (or weighting) of the priors is associated with apathy (Hezemans et al., 2020) in health and Parkinson's disease (Hezemans et al., 2021).

- National Adult Reading Test

  Reading test used as an estimate of premorbid Intelligence Quotient (IQ)

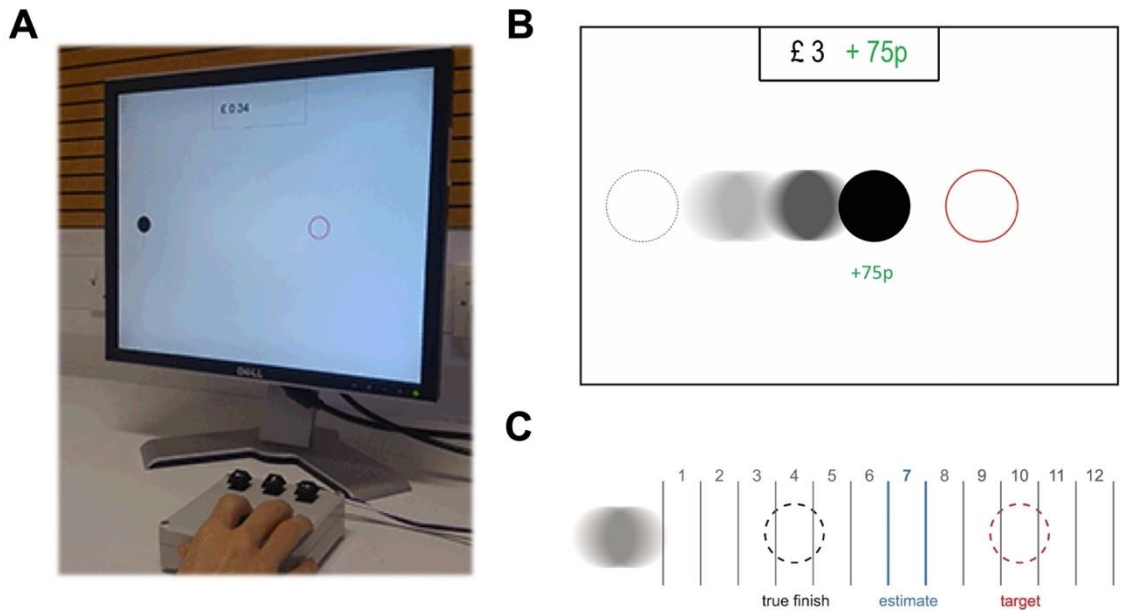


Figure 1: Overview of the visuomotor task. (A) Example of a participant performing the task. The participant presses their index finger on a force sensor button that determines the speed of a "catapulted" black cursor towards the target (red outline). The distance travelled by the ball increases with the force exerted on the sensor (relative to the participant's maximum force). (B) For the majority of trials, participants view the outcome of their action – that is, the ball's full trajectory to its final position on the screen. (C) For a subset of trials, the ball's trajectory is not shown, and participants are asked to estimate where the ball would have stopped. Participants are shown a grid of 12 evenly spaced response options, where one of the response options is centred on the true final ball position.

Clinical review

A standard neurological examination will be performed prior to CSF collection as well as a brief general physical examination. Evidence of possible bleeding tendency such as bruises or petechial rash should be noted if the participant has consented to participate in CSF collection.

- 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

ESTIMATED TOTAL TIME: 25 minutes

Venous Blood Collection Procedure

Venous blood is drawn on the morning of the study visit. Participants are not required to fast. Collection time is recorded. The following samples are acquired:

- Up to 4 × 10 ml blood in lithium heparin tubes. Gently invert each tube 10 times immediately after collection, and place on ice.
- 1 X 10 ml EDTA blood tube for DNA extraction (HDGECs only)
- 1 x 10 ml EDTA blood tube for research genotyping (new HDGECs only)
- 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.

Plasma Sample Processing

- Spin lithium heparin tubes at 1300×g for 10 min at 4°C immediately on arrival.
- Discard any tubes whose plasma is pink due to haemolysis.
- Combine the supernatant in one tube labelled “plasma” and mix by inverting 10 times. Store on crushed ice.
- Divide lithium heparin plasma into 300 µl aliquots using supplied pipette tips and cryovials labelled ‘plasma’.
- Freeze samples on dry ice and store at -80°C.
- Record time of freezing.

Imaging assessment

All participants will undergo structural (T1, NODDI and MPM) and functional (resting state) MRI on a 3T scanner. Protocol details will be provided in the Standard Operating Procedure (SOP) documents. The structural T1 modality was chosen because it can provide volumetric images suitable for the most widely used and discriminating analysis techniques (e.g. Aylward et al., 1994; Henley et al., 2006). NODDI, MPM and rsfMRI are exploratory techniques which were included at baseline to provide complementary assessments of hallmarks of HD. NODDI has the ability to highlight subtle changes in tissue microstructure (H. Zhang et al., 2012; J. Zhang et al., 2018) and MPM provides a measure of myelination within the white matter (Johnson et al., 2021). These measures, together with the rsfMRI will be used to identify any alterations in network connectivity (Klöppel et al., 2015). These follow-up imaging techniques will be acquired on the same 3T Siemens PRISMA used at baseline, providing the opportunity to explore changes over time in all these metrics.

ESTIMATED TOTAL TIME: 90 minutes

Local Radiologist Read
A radiological read will be performed for any incidental pathology, this will ideally be done within five working days of image collection. If abnormalities are seen UCL will liaise with the recruiting site and ensure the participant's GP and/or local neurologist are informed if relevant.

The following analysis will be performed by the dedicated image analysis team at UCL:

- Whole brain, ventricular, caudate and putamen volumes and change over time (P A Freeborough & Fox, 1997; Hobbs et al., 2009).
- Assessment of neurite density using Neurite Orientation and Dispersion Diffusion Imaging (NODDI) (H. Zhang et al., 2012) to detect subtle changes in microstructure which are complementary to macrostructural information provided by volumetric imaging, and change over time.
- Change in grey- and white-matter density using within-subject non-linear registration (Peter A. Freeborough & Fox, 1998) and voxel-based morphometry (VBM) (Ashburner & Friston, 2000)
- Resting state fMRI region analyses and principal component analyses. Seed connectivity will be used to identify brain regions which are simultaneously activated at rest. Dynamic causal modelling (Johnson et al., 2019) will be used to explore causal interactions between the brain and these regions. Changes in these metrics over time will be estimated.
- Brain cellular microstructure and structural connectivity will be examined using volumetric MRI combined with NODDI. Computational approaches will be applied to visualize neural tracts and to determine the relative strength of anatomical connections between brain regions. Graph theory (McColgan et al., 2015) will be used to detect changes in the organization of brain networks such as integration and efficiency. Statistical parametric mapping will be used to

identify any differences in myelination within gene carriers. Change over time in these metrics will be estimated.

HD Core Research Assessments

The following assessments will be completed as part of the core HD core research assessments at the study visit. These validated assessments are commonly used in HD research.

Unified Huntington's Disease Rating Scale (UHDRS)

The Unified Huntington's Disease Rating Scale (UHDRS), developed by the Huntington Study Group to provide a uniform assessment of the clinical features and course of HD has undergone reliability and validity testing that support its use in longitudinal studies (Huntington Study Group, 1996). The scale assesses four domains associated with HD: motor function, cognitive function, behavioural abnormalities and functional capacity.

UHDRS Total Functional Capacity Scale (TFC)

The TFC represents the Investigator's assessment of the participant's capacity to perform a wide range of activities of daily living including working, chores, managing finances, eating, dressing and bathing. It is based on a brief interview with the participant and the study partner (if relevant). Scores range from 0 to 13, and higher scores represent better functioning.

UHDRS Independence Scale

The patient's independence scale is the Investigator's assessment of the participant's degree of independence. The scale consists of 19 discrete levels ranging from 10 to 100 (by 5) where no special care needed corresponds to a scale of 100 and tube fed and total bed care corresponds to a scale of 10.

UHDRS Total Motor Scale (TMS)

The TMS is the sum of the individual motor ratings obtained during administration of the motor assessment portion of the UHDRS. Scores range from 0 to 124, and higher scores represent more severe impairment.

Problems Behaviour Assessment for Huntington's Disease – Short Form (PBA-s)

The PBA-s assesses common behavioural and psychiatric manifestations of HD, including affect, irritability, loss of motivation, perseverative phenomena and psychotic symptoms. The test administrator interviews the participant (and companion if relevant) and rates the participant's behaviour over the prior four weeks according to the guidelines for the test. The C-SSRS will also be activated and completed if triggered by responses to items in the PBA-s which relate to self-harm and suicidal ideation. If the responses to the C-SSRS indicate the subject is at risk, in line with local standard operating procedures, the clinical care team will be informed and the relevant referrals made.

Verbal Fluency (Category)

Verbal fluency is a commonly used neuropsychological test which examines the ability to spontaneously produce words orally within a fixed time span. For category fluency, words must be produced according to semantic constraints. The measure of performance used will be the number of correctly generated words within 60 seconds.

Stroop (Colour, Word and Interference)

The Stroop Reading tests are commonly used neuropsychological tests. They involve naming colours (e.g., red, green, blue) and reading the words for colours in black and different coloured ink. Each Stroop test takes 45 seconds.

Symbol Digit Modality Test (SDMT)

SDMT involves a simple substitution task. Using a reference key, the examinee has 90 seconds to pair specific numbers with given geometric figures. The score is the number of correct responses achieved in 90 seconds.

ESTIMATED TOTAL TIME: 60 minutes

DAY 2 STUDY ASSESSMENTS

CSF and associated venous blood sample Collection (Optional)

Lumbar puncture is 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 will be recorded.

The participant's continued consent to participate will be confirmed and recorded in the medical notes prior to CSF and blood collection, and the results of the routine laboratory examination are to be reviewed and recorded together with measurement of vital signs. Venous blood sampling is performed immediately after CSF collection is complete. (See Venous blood collection procedure on page 21 for complete instructions).

Lumbar CSF Collection Procedure

- Ensure that all equipment is on hand and that ice is available for CSF collection and transportation of samples to the lab.
- Ensure availability and settings of centrifuges for appropriate temperatures and timely processing of CSF and blood samples.
- Pre-cool CSF collection tubes on ice.
- Prepare a sterile field containing all equipment needed, label tubes.
- Place participant into lateral decubitus position with pillow between knees.

- Identify L4/5 or L3/4 space using surface markings.
- Disinfect skin using pre-filled antiseptic sponge.
- 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 using the 21G needle.
- Obtain CSF using a 24G spinal needle. The 20G spinal introducer needle should be placed along the intended angle of injection and advanced until in position. 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).
- If CSF cannot be obtained, up to three needles may be used.
- An adjacent space may be used (with further lidocaine, max. total 10 ml, if needed).
- 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.
- Document the space used for lumbar puncture, the number of attempts and volume of lidocaine used in the eCRF.
- Omit pressure measurement for all participants (because polypropylene spinal manometers are not available).
- CSF is collected in 50ml tubes placed on ice in the paper cup.
- 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 20 ml, 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 19 ml. If the second separately collected ml of CSF is also macroscopically bloody, discard the tube, and continue to collect 18 ml of CSF in a third pre-cooled 'CSF' tube. Stop collecting CSF when sampling time exceeds 40 minutes. Document these details in the eCRF.
- Place cap on tube and leave on crushed ice until further processing.
- Reinsert the stylet before withdrawing the needle.
- Cover the puncture site with sterile dressing.
- Record time of CSF collection.
- Participants can mobilise or remain lying for an hour at their discretion.
- Transport samples immediately to biomarker laboratory for processing.

Fluoroscopy -guided Lumbar CSF Collection

In rare cases where it is not possible to obtain the CSF sample via regular LP, due to participant obesity or difficult anatomy, the participant will be asked to return to the site on another day and under go fluoroscopy-guide lumbar puncture to obtain the CSF sample. The participant will be given a separate information sheet, which includes full details of the procedure including the risks of exposure to ionising radiation, and will be asked to give additional informed consent to under go this.

Neuropsychiatric self-report assessments

All questionnaires are self-report and designed to be completed by participants independently on a tablet that will be provided.

- Frontal Systems Behaviours Inventory (FrSBe) (7 minutes)
- Toronto Alexithymia Scale (TAS-20) - 20 items (4 minutes)
- Toronto Empathy Questionnaire (TEQ) - 16 items (3 minutes)
- Zung self-rating depression scale (SDS) - 20 items (3 minutes)
- State/Trait Anxiety (STAI) - 40 items (5 minutes)
- Barratt Impulsivity scale (BIS-11) - 30 items (4 minutes)
- Obsessive-Compulsive Inventory (OCI-R) - 18 items (3 minutes)
- Apathy-Motivation Index - 18 items (3 minutes)
- Pittsburgh Sleep Quality Index (PSQI) -19 items (3 minutes)
- MOS 36-Item Short-Form Health Survey (SF-36) - 36 items (4 minutes)

ESTIMATED TOTAL TIME: 40 minutes

Description:

- FrSBe

The goal of the FrSBe is a 46-item behaviour rating scale that is intended to measure behaviour associated with damage to the frontal systems of the brain. Separate rating forms are available for the participant (Self-rating) and the companion (Family Rating). Each FrSBe form yields a Total score and scores for subscales measuring Apathy (14 items), Disinhibition (15 items), and Executive Dysfunction (17 items). Each item is rated on a 5-point Likert scale.

The FrSBe has been used in the Predict HD study and preliminary analyses demonstrate some sensitivity in premanifest HD. Hamilton and colleagues showed that this rating scale was sensitive to changes occurring between the premanifest period and early HD (Hamilton et al., 2003).

- TAS-20

Widely used and validated self-report instrument to measure the construct of alexithymia, i.e., difficulties in identifying and describing emotions, reduced emotional engagement and tendencies towards externally focused attention. Items are scored on a five-point scale from 'strongly disagree' to 'strongly agree' (Bagby et al., 2021).

- TEQ

Validated brief self-report measure that covers multiple facets of empathy, including its cognitive and affective components. Items are scored on a five-point scale ranging from 'never' to 'often' (Sprens et al., 2009).

- SDS

Self-rated scale that is a well validated screening tool for depression. Covers affective, psychological and somatic symptoms associated with depression, items are scored on a four-point scale (Zung et al. 1965).

- *STAI*

Well validated and commonly used self-report measure of anxiety, providing assessment of both state and trait levels of anxiety. Items are scored on a four-point scale that reflects frequency of anxious thoughts/behaviours (Spielberger et al., 1970).

- BIS-11

Self-report questionnaire designed to assess the personality/behavioural construct of impulsiveness. Measures three factors, including attentional, motor and non-planning impulsivity, items are scored on a four-point scale relating to frequency of behaviours (Patton et al., 1995).

- OCI-R

Brief self-report instrument to determine severity of obsessive and compulsive behaviours. Items are scored on a five-point scale identifying how often an individual is distressed by behaviours relating to washing, checking, ordering, obsessing, hoarding, neutralising (Foa et al., 2002).

- AMI

The Apathy-Motivation Index (AMI) is an 18 item scale that assesses motivation, which was developed for use in healthy participants. Based on the Lille Apathy Rating Scale (LARS) (Sockeel et al., 2006) the AMI had been modified to be sensitive to variations in motivation in healthy people. The scale covers behavioural, social and emotional domains of apathy, and can identify profiles of apathy that are associated with depression, anhedonia and fatigue.

- PSQI

Self-report questionnaire assessing several sub-categories including, subjective quality of sleep, sleep onset latency, sleep duration, sleep efficiency, presence of sleep disturbances, use of hypnotic-sedative medication and presence of daytime sleepiness (Buysse et al., 1989).

- SF-36

Self-report scale assessing eight health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical/emotional problems; 3) limitations in usual role because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions (Ware & Sherbourne, 1992).

CSF Participant Discharge

Participants are observed for potential complications for at least an hour and discharged once appropriate. Any AEs are recorded.

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

CSF Follow-up Telephone Call

Participants will be contacted 24 to 72 hours following the Sampling Visit to collect any AE and/or concomitant medication data.

CSF Sample Processing

- All CSF processing should be done on ice, beginning within 30 minutes of completion of collection.
- Agitate the entire CSF sample for 10 seconds to homogenise CSF.
- Use 200 µl of the CSF to determine white blood cell count and erythrocyte count per µl according to local GLP-approved laboratory practice. This should be done in triplicate within 60 minutes of collection and all values recorded in the eCRF.
- Centrifuge the 50 ml tube containing residual CSF at 400 × g for 10 min at 4°C to remove cells.
- Pipette supernatant into a single tube labelled “CSF supernatant” and agitate for 10 seconds to homogenise CSF
- Aliquot the CSF into 300 µl aliquots, using supplied pipette tips and cryovials labelled “CSF”.
- Gently resuspend pellet in 300µL of supplied preservative solution and transfer to the cryovial labelled “Cells from CSF”.
- Freeze CSF aliquots and resuspended cells on dry ice and store at -80°C.
- Record time of freezing

Venous Blood Collection Procedure

Venous blood is drawn immediately after CSF collection is complete, recording the time. The following samples are acquired:

- 1 × 8.5 ml serum tube.

- 4 × 10 ml blood in lithium heparin tubes. Gently invert each tube 10 times immediately after collection, and place on ice.
- 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.

Serum Sample Processing

- Spin serum tube at 2000×g at room temperature for 10 min immediately upon arrival in the biomarker laboratory
- Transfer 1500 µl of the supernatant into each of 2 separate 2 ml cryovials labeled "serum", freeze on dry ice and store in -80°C.
- Record time of freezing

Plasma Sample Processing

- Spin lithium heparin tubes at 1300×g for 10 min at 4°C immediately on arrival.
- Discard any tubes whose plasma is pink due to hemolysis.
- Combine the supernatant in one tube labelled "plasma" and mix by inverting 10 times. Store on crushed ice.
- Divide lithium heparin plasma into 300 µl aliquots using supplied pipette tips and cryovials labeled 'plasma'.
- Freeze samples on dry ice and store at -80°C.
- Record time of freezing.

Sample storage

- Store samples in a -80°C freezer.
- Log samples on paper CRF and secure HD-YAS database.

Sample Quality Control

The following quality control measures will be carried out to identify and flag samples subject to potential confounders:

- Microscopic erythrocyte count in CSF is performed locally in triplicate and recorded on the secure HD-YAS database. Cut-off for flagging: > 1000 cells/µl.
- Microscopic leukocyte count in CSF is performed locally in triplicate and recorded on the secure HD-YAS database. Cut-off for flagging: ≥ 5 cells/µl.

Analysis of DNA, CSF and plasma samples

DNA, CSF and plasma samples will be analysed locally at UCL Institute of Neurology or by collaborators authorised by the Principal Investigator or CHDI. This may include collaborators outside the UK from

academic or commercial entities for the purpose of research (1) to better understand HD or other diseases being studied, (2) that furthers the development of treatments for HD or other diseases or (3) that furthers biomedical research. Any shared samples will be coded and linked-anonymised.

Analyses of total and mutant huntingtin protein in CSF and plasma, Neurofiliment light chain in CSF and Plasma are specifically planned. In addition, the plasma levels of tryptophan will be determined in the fasted plasma collection, which will allow for an additional control for lack of compliance with the stipulation of an overnight fast.

Additional measurements, including but not limited to the levels of soluble HTT, and other putative biomarkers may also be measured at appropriate laboratories.

The primary outcome measurements are of unknown clinical significance. The detailed analysis may include measurements of potential clinical significance in relation to conditions other than HD, such as oligoclonal bands. However, patients with other neurological diagnoses or unexpected examination findings will be excluded. Therefore any abnormal results, obtained on a linked-anonymised basis, will remain of indeterminate clinical significance and will not be fed back to the participant.

A portion of each participant's CSF and fasted blood samples will be shared alongside phenotypic data with CHDI Foundation Inc. a collaborator of the Principal Investigator and partial funder of HD-YAS to investigate the huntingtin protein and other biomarkers and pathways of relevance to HD.

CSF and blood draw Safety

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

Study-related risks are explained in the informed consent document. In particular, the following risks may be associated with lumbar puncture: pain; headache (approximately 19%), 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.

Optional 7T and MEG scanning

7 Tesla MRI

7T MRI will be acquired at 600µm. R1 will be used as a measure of myelin structure and these will be derived at varying cortical depths, allowing investigation of layer structure.

ESTIMATED TOTAL TIME: 60 minutes

MEG Scanning

Participants will undergo MEG imaging. Recordings will be performed at rest and during a cognitive task. This task has been designed to induce low and high-frequency activity in the visual and sensorimotor cortices.

ESTIMATED TOTAL TIME: 90 minutes

Criteria for Termination of the Study

If the study is prematurely terminated or suspended for any reason, the Principal Investigator/institution will promptly inform the study participants and should assure appropriate follow-up for them. The Principal Investigator will also inform the appropriate Research Ethics Committee and Trust R&D Office.

Any decisions will be subject to immediate informing the Sponsor as detailed in Section 15 RECORDING AND REPORTING OF EVENTS AND INCIDENTS.

6 ELIGIBILITY CRITERIA

Inclusion Criteria

Healthy controls as well as young adult HD gene expansion carriers will be enrolled.

For the Healthy Control group, participants eligible are persons who meet the following criteria:

a. Are capable of providing informed consent and
b. Are capable of complying with study procedures and
c. Are aged between 18-47 years old and
d. Have no known family history of HD (gene negative); or
e. 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*) (family control or community control)

For the Young Adult Premanifest HD group, participants eligible are persons who meet the following criteria:

a. Are capable of providing informed consent and
b. Are capable of complying with study procedures and
c. Are aged between 18-47 years old and
d. Have CAG expansion ≥ 40;
e. New participants must have a DBS <240

Exclusion Criteria:

For all groups, participants are ineligible if they meet any of the following exclusion criteria:

a. Current use of investigational drugs or participation in a clinical drug trial within 30 days prior to study visit; or

b. Current intoxication, drug or alcohol abuse or dependence; or

c. If using any antidepressant, psychoactive, psychotropic or other medications or nutraceuticals used to treat HD, the use of inappropriate (e.g., non-therapeutically high) or unstable dose within 30 days prior to study visit; or

d. Significant medical, neurological or psychiatric co-morbidity likely, in the judgment of the Principal Investigator, to impair participant's ability to complete essential study procedures; or

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

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

g. Needle phobia: or

h. Contraindication to MRI, including, but not limited to, MR-incompatible pacemakers, recent metallic implants, foreign body in the eye or other indications, as assessed by a standard pre-MRI questionnaire; or

i. Pregnant (as confirmed by urine pregnancy test); or

j. Claustrophobia, or any other condition that would make the subject incapable of undergoing an MRI.

For CSF collection:

a. Needle phobia, frequent headache, significant lower spinal deformity or major surgery; or

b. 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

c. Clotting or bruising disorder; or

d. Screening blood test results outside the clinical laboratory's normal range for the following: white cell count, neutrophil count, lymphocyte count, haemoglobin (Hb), platelets, prothrombin time (PT) or activated partial thromboplastin time (APTT); or

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

f. Exclusion during history or physical examination, final decision to be made by the 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 operator or the Principal Investigator, it is felt that lumbar puncture is unsafe.

For Optional 7T MRI and MEG

a. Contraindication to MRI, including, but not limited to, MR-incompatible pacemakers, recent metallic implants, foreign body in the eye or other indications, as assessed by a standard pre-MRI questionnaire; or

b. Pregnant (as confirmed by urine pregnancy test); or

c. Claustrophobia, or any other condition that would make the subject incapable of undergoing an MRI; or

d. Tattoos that fall above the line defined by the crease of the elbow or on the genitals.

Participant Categories

All gene carriers will be defined as;

Premanifest HD Gene Expression Carriers: Gene carriers without clinical features regarded as diagnostic of HD

Healthy control participants will be further divided into one of three sub-categories during data acquisition;

Genotype negative: This group includes a first or second degree relative i.e., related by blood to a carrier, who has undergone predictive genetic testing for HD and is known not to carry the HD expansion mutation.

Family Control: Family member or individual not related by blood to carriers (e.g., spouses, partners, caregivers).

Community Control: Individuals unrelated to HD carriers who did not grow up in a family affected by HD.

7 CONSENT

Informed consent will be obtained prior to the participant undergoing any activities that are specifically for the purpose of this research study. The process of informed consent will involve:

- Discussion between the potential participant and a member of the research team about the nature and objectives of the study and possible risks and benefits associated with their participation at least 2 weeks prior to any planned visit. Following this discussion the potential participant will be sent the Participant Information Sheet (PIS) and Informed Consent Form (ICF) so that they have the opportunity to discuss the study with the researcher, family and friends etc if they wish to do so.
- One week before the planned study visit the potential participant will be contacted by a member of the research team to discuss any queries arising from the PIS and ICF and if appropriate confirm the visit date. If any clinical concerns are raised, the participant will be contacted by the study clinician for further discussion.

- One day before the study visit the participant will be contacted by a member of the research team to discuss any last minute concerns regarding the visit and again where appropriate may be referred to the study clinician for discussion
- On the day of the visit the participant will first of all meet with the study clinician and have the opportunity to raise any final questions. If the participant is happy to provide consent this will be taken by the study clinician in the outpatient department.
- Informed consent will be documented in the source notes and a copy of the signed consent form will be shared with the participant to take home as well as stored in the Investigator Site File and participant notes.

8 DATA ANALYSIS

The HD Young Adult Study collected baseline data between April 2017 and April 2019 for 64 premanifest gene carriers and 67 healthy controls. We conducted clinical assessments, 3T imaging including volumetric, NODDI, multiparametric mapping and resting state fMRI as well as cognitive testing and blood and CSF sampling. Power calculations for the baseline sample suggested that with a type 1 error rate of 5%, a sample of 60 participants/group would provide 80% power to detect a mean difference versus controls of 0.53 adjusted within-group standard deviations (effect size), allowing for 5 covariates. Similarly, after allowing for 5 covariates, the sample of 60 CAG-expanded participants allows the same statistical power for detecting a partial Pearson correlation of 0.36 among outcome measures and between these measures and the CAG-length Age Product (CAP) score or other potential predictors of HD risk. We found significant volume reduction in the putamen in the absence of any other differences in brain macro- or microstructure, connectivity or function (Scahill et al., 2020) . Cognition was intact but there were elevated levels of Neurofilament light protein (NfL) suggestive of neuronal injury. We suggest this provides an optimum time window to administer treatments prior to widespread neuronal damage in order to delay or prevent the onset of symptoms.

In order to understand whether the putaminal volume reduction present in the premanifest gene carriers is neurodevelopmental or neurodegenerative it is necessary to obtain longitudinal data to establish whether there is ongoing atrophy. Longitudinal data will also provide information on the stability of other brain measures and identify a time at which they start to deviate from the normal range. We anticipate that after this time interval of ~5 years those participants with the highest disease burden i.e. those who are closer to expected disease onset may start to show subtle early signs of structural loss, breakdown in connectivity and cognitive deficits. This time interval was selected following power calculations by our statistician Professor Doug Langbehn of the University of Iowa who determined that this would provide 80% power to detect mean case-control differences in change over time.

We will test for adjusted mean differences between groups, typically via covariate-adjusted least square comparisons. Covariates will include age, gender, and IQ and, nested within the gene-carrier group, CAG length and its interaction with age. We will adjust for potential group differences in residual variances, and if substantial violations of test-assumption data distributions are noted we will adjust the analyses by outcome-variable transformation if possible. Failing this, we will use nonparametric bootstrapping for inference and confidence level estimation. In secondary analyses, we will assess correlations between outcomes and the CAP statistic that has proved a powerful

predictor of HD progression in older participants (Ross et al., 2014). We will assess longitudinal neurodegeneration using mostly linear models with participant random effects. Broadly, we will compare the premanifest gene carriers to controls and test disease burden influence within the CAG-expanded. We will protect against multiple comparison and reporting bias by designating a limited set of primary outcomes based upon established relevance to HD and high measurement reliability (e.g., NfL, putamen volume). We will calculate family-wise error and false discovery rates (FDR) for these measures. We will group all other outcomes by measurement class (e.g., serum assays) and report FDR estimates per class. In the event of substantial missing predictor data, we will use multiple imputation. We will subject critical data with plausible informative missingness to sensitivity analyses. All analyses will be prespecified in the Statistical Analysis Plan prior to initiation of data analysis.

9 PATIENT AND PUBLIC INVOLVEMENT (PPI)

We have maintained regular contact with our HD-YAS participants through a newsletter, email and direct telephone calls and have kept them informed about the results of the baseline study and our plans for future visits. Participants commented on how grateful they were to receive updates on our findings and our plans for future visits.

When considering the design of the next YAS visit we convened a focus group to get feedback on their experience and see where improvements could be made. In response to their comments we have made the following amendments to the assessment visit:

- Start time 20 minutes before assessment to give the participants chance to compose themselves and have a drink and a snack beforehand
- For those travelling from further away offer the option of an overnight stay beforehand
- Provide more refreshments in the testing room, particularly during the cognitive session
- More breaks throughout the day and an opportunity to get fresh air
- A full lunchbreak of at least one hour
- If possible reduce the cognitive battery.
- Provide more real time feedback about how long is left in each session (e.g. cognitive, imaging)
- Advice in advance that in the event of an LP headache this can require bed rest and if it is possible the participant should arrange to have a clearer schedule the few days following the LP.
- Provide a post LP care summary in writing and give clear guidance about how best to recover
- Clearer information about how long and tiring the tests can feel in the Participant Information Sheets and in screening telephone calls.
- Breaks during scanning to be offered and participants can have the choice between longer scanning sessions or a break
- Additional 7T and MEG scanning sessions to be on a separate day

In addition when writing our grant we got feedback from two participants on the lay summary and made amendments in response to their suggestions.

10 FUNDING AND SUPPLY OF EQUIPMENT

The study funding has been reviewed by the UCLH/UCL Joint Research Office, and deemed sufficient to cover the requirements of the study. NHS costs will be supported via the Local Clinical Research Network.

The research costs for the study have been supported by the Wellcome Trust to the sum of £3,313,863 to run from 1st January 2022 for 60 months. CSF collection is funded by CHDI, a not-for-profit foundation supporting research into HD.

The following will occur prior to the research activity or related transfers at the subcontractor beginning:
A subcontract for statistical support will be set up with the University of Iowa for the sum of £96,542.

Neither the CI nor any other co-investigators or collaborators have direct personal involvement with those funding the research and there are no conflicts of interest to declare.

11 DATA HANDLING AND MANAGEMENT

The study is compliant with the requirements of General Data Protection Regulation (2016/679) and the UK Data Protection Act (2018). All investigators and study site staff will comply with the requirements of the General Data Protection Regulation (2016/679) with regards to the collection, storage, processing and disclosure of personal information, and will uphold the Act's core principles. UCL is the data controller; the UCL Data Protection Officer is data-protection@ucl.ac.uk. The data processors are the UCL HD centre, CHDI, University of Glascow (Prof Darren Monckton), University of Cambridge (Prof James Rowe) and University of Iowa (Prof Doug Langbehn). The study will be collecting the following personal data in accordance with the participant consent form and participant information sheet: name, date of birth, medical history, ethnicity, cognitive and neuropsychiatric data. Participant data will be stored securely at the UCL Institute of Neurology and UCL will act as the data controller of such data for the study.

The Principal Investigator and her delegated representatives will process, store and dispose of participant data in accordance with all applicable legal and regulatory requirements, including the Data Protection Act 2018, UK GDPR and any amendments thereto. Data held on paper will be stored at the UCL Institute of Neurology Huntington's Disease Research Centre under secure access control, in a locked filing cabinet controlled by the Investigator.

The Principal Investigator will 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.

All HD-YAS assessments will be collected on paper case report forms, scored and filed in the participants medical notes, the scores will be entered onto a secure database dedicated to the HD-

YAS study. For the CANTAB and EMOTICOM data is recorded electronically direct into a tablet as the participant completes the assessments. Data will be stored securely on a drive dedicated to the HD Centre and managed and backed up by the UCL Insitutite of Neurology Computing Unit.

In order to maintain subject privacy, all case report forms (CRFs), study reports and communications will identify the subject by initials and the assigned Subject number or HDID (a 9-digit unique identifier assigned at first visit). The investigator will preserve the confidentiality of participants taking part in the study in accordance with the Data Protection Act. Access to data will be limited to designated members of the research team who have all completed GDPR training.

The Principal Investigator will archive the study master file at University College London and retain all study documentation for 20 years and in line with all relevant legal and statutory requirements.

A senior member of the HD Research centre who is not involved with the study directly will carry out HD-YAS data monitoring and will ensure compliance with the study protocol. The Principal Investigator will make study data accessible to the designated study monitor, to other authorised representatives of the Sponsor, and to regulatory inspectors.

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality.

The Chief Investigator will inform the sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

All transfers of data and/or samples will be covered by materials transfer agreements (Section 0

Data and Sample Flow Chart**).**

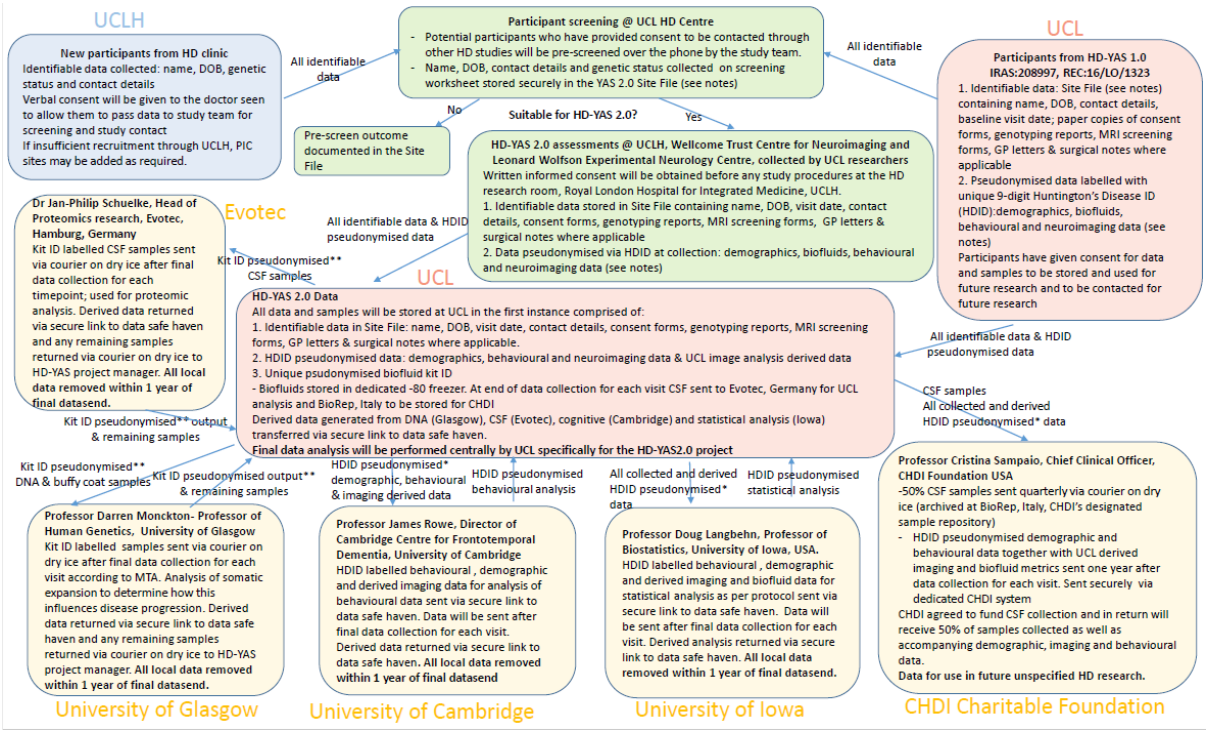
The following agreements have been created by the Sponsor (UCL) to cover the relevant study research activity:

- **UCL -> CHDI**
- **Site agreements**

The following agreements are yet to be created and will drawn up by Sponsor (UCL) during the study:

- **UCL -> Evotec (Germany)**
- **UCL -> University of Glasgow**
- **UCL -> University of Cambridge**
- **UCL -> University of Iowa**

11.1 Data and Sample Flow Chart



12 MATERIAL/SAMPLE STORAGE

Biological material from the blood collection (whole blood, plasma and DNA), as well as CSF and associated fasted blood from the optional CSF collection, will be collected from participants in accordance with the participant consent form and participant information sheet and shall include all biological materials and any derivatives, portions, progeny or improvements as well as all participant information and documentation supplied in relation to it. These biological samples will be stored at UCL Institute of Neurology for the processing described in this protocol, and for use in future HD research.

Samples will be processed, stored and disposed in accordance with all applicable legal and regulatory requirements, including the Human Tissue Act 2004 and any amendments thereafter, and the applicable HTA Codes of Practice Departmental SOPs will be followed to facilitate regulatory compliance.

This will prepare samples for shipment to collaborators in accordance with the analytical plan agreed with the Principal Investigator. A portion of the coded samples will be shared with CHDI, and these samples will be stored at a biological storage facility called BioRep, located in Milan, Italy. The PI and his delegated representatives will process, store and dispose of samples in accordance with all applicable legal and regulatory requirements, including the Human Tissue Act 2004 and any amendments thereto.

Details on conditions of sample sharing with CHDI are contained in the separate contract agreement (REFERENCE/DATE).

DNA for Research Genotyping

Only participants with a confirmed predictive genetic test result are eligible for HD-YAS. Participants will have undergone extensive genetic counselling prior to predictive testing through their local service and all participants will be aware of their genetic status i.e., whether they will go on to develop HD or not. The exception to this are family and community controls who are not at risk of inheriting the expansion mutation, and therefore, predictive testing is not necessary.

All pre-manifest HD participants who already have a positive predictive genetic test will donate a sample for research genotyping to confirm the HD expansion mutation size. The purpose of this is to standardise the way the test is performed for study analyses. A DNA sample will not be collected from control participants.

Ten ml of peripheral blood will be collected in 2 x 5ml purple topped EDTA tubes. Samples will be transported on the day of collection to the Neurogenetics Laboratory, National Hospital for Neurology and Neurosurgery for DNA extraction and research genotyping. DNA extraction and genotyping will be performed according to standard procedure. The results will be fed back to Professor Tabrizi and the study team, but since these are obtained for research they will not be fed back to the participant.

DNA will be stored at UCL Institute of Neurology under custodianship of the PI. Samples will be donated with the understanding that it is used for HD-related research. In addition to re-sizing of the CAG expansion mutation within the HD gene, DNA may also be used to identify somatic expansion and genetic modifiers of HD, in particular genetic modifiers of age of onset, rate of progression and phenotypic characteristics presentations. This DNA may also be stored for future use and HD related genetic research.

13 PEER AND REGULATORY REVIEW

The study has been peer reviewed in accordance with the requirements outlined by UCLH/UCL. The Sponsor considers the procedure for obtaining funding from (insert funder name) to be of sufficient rigour and independence to be considered an adequate peer review.

The study was deemed to require regulatory approval from the following bodies (REC Favourable Opinion and HRA Approval). **Before any site can enrol patients into the study,** the Chief Investigator or designee will ensure that the appropriate regulatory approvals have been issued, and NHS Confirmations of Capacity and Capability and Sponsor green lights are in place.

For any amendments to the study, the Chief Investigator or designee, in agreement with the Sponsor, will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments as well as the study delivery team) to confirm ongoing Capacity and Capability for the study.

All correspondence with the Sponsor, REC and HRA will be retained. The Chief Investigator will notify the Sponsor and REC of the end of the study.

It is the Chief Investigator's responsibility to produce the annual progress reports when required; an annual progress report (APR) will be submitted to the Sponsor and REC within 30 days of the anniversary date on which the favourable opinion was issued, and annually until the study is declared ended.

If the study is ended prematurely, the Chief Investigator will notify the Sponsor and REC, including the reasons for the premature termination.

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the Sponsor and to the REC and HRA.

14 ASSESSMENT AND MANAGEMENT OF RISK

Blood Collection

There is a small risk of discomfort, bruising or bleeding associated with having a blood sample taken. Participants may feel faint or light-headed during or shortly following blood collection. Participants may lie down for blood collection, drinks and snacks may be offered and participants will have the opportunity to rest.

MRI scan

Participants may find MRI scanning uncomfortable because of the enclosed space and the need to stay still during the scanning process. A 2-way communication system will allow the participant to communicate with the MRI operator during the scan.

A safety assessment will be performed by trained personnel to ensure that it is safe to perform an MRI. As long as this questionnaire is correctly completed, MRI is safe.

Assessments and questionnaires

When completing the clinical, behavioural and cognitive assessments for HD-YAS, participants may experience low mood or psychological discomfort (such as stress or anxiety). A risk assessment will be completed and all staff trained on how to handle any incidences of psychiatric distress or risk factors.

Lumbar Puncture

Some participants experience brief pain, either in the back or down one leg, when the needle is close to the spinal fluid. This pain usually stops after a few seconds.
Risk of back pain following the CSF collection.
Risk of headache following the CSF collection. Participants will be given instructions on how to manage this if it occurs. The risk of headache is about 19%. Occasionally the headache doesn't go away on its own and a second hospital procedure called a "blood patch" may be recommended to help it resolve. This is rare – the chance is less than 1% overall.
Hypersensitivity (allergic) reaction to the anaesthetic.

Risk of infection caused by the needle going through the skin. This is very rare; the risk is much less than 1 in 1,000.
Risk of damage to the nerves in the lower back, which could cause numbness, pain or altered function in the legs, bowels, bladder or genitals. This may be caused directly by the needle or by blood leaking into the fluid. It is very rare (much less than 1 in 1,000).

Fluoroscopy-guided lumbar puncture
There is an additional risk associated with exposure to ionising radiation. This will fully explained to participants in an additional information sheet.

Collection of private / personal information
GDPR and Data Protection regulations will be followed closely

Unexpected findings

It is possible that an MRI scan, blood test or a lumbar puncture may reveal an unexpected finding of possible medical importance. If this happens, we will inform the participant and their General Practitioner (GP) who will be able to take any necessary action through the usual NHS care pathways.

15 RECORDING AND REPORTING OF EVENTS AND INCIDENTS

15.1 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 unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of study procedures.

The Principal Investigator or appointed delegate(s) 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 on paper CRFs and in the HD-YAS secure database. 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.

15.1.1 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 1Mild AE

Grade 2Moderate AE

Grade 3Severe AE

Grade 4Life-threatening or disabling AE

Grade 5Death related to AE

15.1.2 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.

15.2 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

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 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.

15.2.1 Serious Adverse Event Reporting

SAEs (as defined in Section 4.2) must be reported to the study Sponsor immediately 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 time of informed consent until all the study procedures have been completed, unless further follow-up is requested by the Investigator.

In accordance with the standard operating procedures and policies of the REC, the Principal Investigator will report SAEs to the REC.

15.3 Post-study Follow-up of Adverse Events

Any AE, including clinically significant physical examination findings, must be followed until the event resolves, the condition stabilises, the event is otherwise explained, or the participant is lost to follow-up. If resolved, a resolution date should be documented on the secure HD-YAS database and in the source documents. The 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.

All events and incidents (and near misses) that occur to participants and/ or staff that are **unexpected** and directly **related** to the research study will be reported to the Sponsor via UCL: research-incidents@ucl.ac.uk and host sites via their Trust reporting systems (UCLH Datix), and documented in the Trial Master File/Investigator Site File via study-specific incident logs (and related correspondence). This will be completed by the CI or PI. The Sponsor will be responsible for investigating, reviewing, or escalating to a serious breach if required.

15.4 Personal Data Breaches

- Personal data breaches will be immediately reported to the UCL Information Security Group (ISG) and the UCL Data Protection Officer [data-protection@ucl.ac.uk], (as per form and guidance: https://www.ucl.ac.uk/legal-services/guidance/reporting-loss-personal-data), and to the Sponsor via the UCL REDCAP incident reporting form (https://redcap.slms.ucl.ac.uk/surveys/?s=NE5dypTdFo). The following information will be provided: full details as to the nature of the breach, an indication as to the volume of material involved, and the sensitivity of the breach (and any timeframes that apply). Sites will additionally follow their Trust incident reporting mechanisms and will document this within their TMF/ISFs.

15.5 Adverse Events and Serious Adverse Events Sponsor Reporting Requirements

Adverse events are any untoward medical occurrence in a patient or study participant, which does not necessarily have a causal relationship with the procedure involved. These do not require reporting to the Sponsor, but the severity, causality and expectedness will be recorded in the participant's medical records, CRF and AE log with a description of clinical symptoms and the event, including dates as appropriate.

SAEs (any event that results in death, is life-threatening, requires hospitalisation or prolongation of existing inpatient hospitalisation, results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect) that have been determined to be **unrelated** to the research intervention by the CI/PI do not require reporting to the Sponsor, but will be recorded in the participant's medical records, CRF and site file. Additionally, **expected** SAEs that are likely to occur on a regular basis and offer no further new information to the safety profile, or are related to the disease area of the participants, do not require reporting to the Sponsor, but must be recorded as previously stipulated. Sponsors will however be notified where the frequency and severity of unrelated SAEs are unusual; research sites will report as per Sponsor reporting requirements.

In some instances, **unexpected and related SAEs** may occur in observational research All reportable SAEs will be recorded in the medical records and CRF, and reported to the Sponsor via the JRO REDCAP research incident reporting form or research-incidents@ucl.ac.uk, within 5 working days of becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the Sponsor as soon as possible.

15.6 Protocol deviations and notification of protocol violations

Protocol deviations are usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the Sponsor. The CI will monitor protocol deviations, and if found to frequently recur, will discuss in the first instance with the Sponsor to determine re-classification and reporting requirements.

A protocol violation is a breach which is likely to effect to a significant degree: –
(a) the safety or physical or mental integrity of the participants of the study; or
(b) the scientific value of the study

The CI and Sponsor will be notified immediately of any case where the above definition applies via UCL: research-incidents@ucl.ac.uk or UCL REDCAP incident reporting form.

15.7 NHS Serious Incidents and near misses

A serious incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.
b. It is contrary to specified or expected standard of patient care or service.
c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d. It puts the Trust in an adverse position with potential loss of reputation.
e. It puts Trust property or assets in an adverse position or at risk.

Serious Incidents and near misses will be reported to the Sponsor and Trust Quality & Safety department as soon as the study team becomes aware of them.

15.8 Complaints from research participants

In the first instance, research participant complaints (patients or healthy volunteers) will be reported to the CI/PI to investigate, as documented in the patient information sheet(s), and to the Sponsor via research-incidents@ucl.ac.uk, following the *UCL Complaints from Research Subjects about UCL Sponsored Studies and Trials* policy for participants who are NHS patients, complaints will be reported to the NHS Complaints Manager at the Trust where the recruitment and study procedures was undertaken. Complaints from NHS patients are handled under NHS complaints policies and procedures, with involvement from PALS and the Sponsor where necessary.

16 MONITORING AND AUDITING

All HD-YAS assessments will be collected on paper case report forms, scored and filed in the participants medical notes, the scores will be entered onto the HD-YAS secure database. For the CANTAB and EMOTICOM data is recorded electronically direct into a tablet as the participant completes the assessments.

Source Documents: The Principal Investigator will 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.

The Principal Investigator, on behalf of 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.

A senior member of the HD Research centre will carry out HD-YAS data monitoring and will ensure compliance with the study protocol. The Principal Investigator will make study data accessible to the designated study monitor, to other authorised representatives of the Sponsor, and to regulatory inspectors.

17 TRAINING

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study. Appropriate training records will be maintained in the study files

18 INTELLECTUAL PROPERTY

All background intellectual property rights (including licences) and know-how used in connection with the study shall remain the property of the party introducing the same and the exercise of such rights for purposes of the study shall not infringe any third party's rights.

All intellectual property rights and know-how in the protocol, the study data and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used independently of the study by each participating site, shall belong to UCL. All intellectual property rights deriving or arising from the material or any derivations of the material provided to UCL by the participating site shall belong to UCL. Each participating site agrees that by giving approval to conduct the study at its respective site, effectively assigns all such intellectual property rights ("IPR") to UCL and discloses all such know-how to UCL.

Nothing in this section shall be construed so as to prevent or hinder the participating sites from using its own know how or clinical data gained during the performance of the study, as its own risk, in the furtherance of its normal activities or providing clinical care to the extent that such use does not result in the disclosure or misuse of confidential information of the infringement of an intellectual property rights of UCL, or their funder. This section does not permit the disclosure of any of the study data, all of which remain confidential until publication of the results of the study.

The following additional agreements with subcontrators and collaborators include information related to the intellectual property of this study:

- **CHDI (Contract ref/date)**
- **Evotec (Germany) (Contract ref/date TBC)**
- **University of Glasgow (Contract ref/date TBC)**
- **University of Cambridge (Contract ref/date TBC)**
- **University of Iowa (Contract ref/date TBC)**

19 INDEMNITY ARRANGEMENTS

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London 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.

Participants may also be able to claim compensation for injury caused by participation in this clinical study without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should be advised to do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical study shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London upon request.

Additionally, UCL does not accept liability for sites such as GP surgeries in primary care; investigators/collaborators based in these types of sites must ensure that their activity on the study is covered under their own professional indemnity.

20 ARCHIVING

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 confirms that he/she will archive the study master file at UCL Library for the period stipulated in the protocol and in line with all relevant legal and statutory requirements. The Principal Investigator at each participating site agrees to archive his/her respective site's study documents in line with all relevant legal and statutory requirements. Study documents will be archived for a minimum of 5 years from the study end, and no longer than 20 years from the study end.

The Trial Master File will be archived at UCL, in accordance with the UCL Retentions Schedule and Policy. It will be archived for a minimum of 5 years from the study end, and no longer than 20 years from study end.

21 PUBLICATION AND DISSEMINATION

Data generated by this study will be owned by UCL 2 years after completion of data collection, pseudoanonymised data will be transferred to CHDI who are co-funding the project. They have extensive experience in curating large datasets and working with international academic and commercial companies on data sharing to further HD research. All data sharing will be done according to our data sharing policy which complies with all information provided in our participant information forms. This policy also complies with the conditions set by our main funders, the Wellcome Trust.

On completion of data collection our results will be tabulated and analysed by our independent statistician, Professor Doug Langbehn of the University of Iowa. Yearly and End of Study Reports will be prepared as required by the Wellcome Trust.

We will endeavour to publish our results in high impact journals. Authorship will be determined depending contributions. Co-investigators will have the right to publish study data relevant to their speciality, but all publications and authorship lists will be agreed with the PI, Professor Sarah Tabrizi. Funding by the Wellcome Trust and CHDI will be acknowledged in all publications but review is not required prior to publication. We also anticipate presenting our findings at international conferences such as the European Huntington's Disease Network Meeting and the Movement Disorders Conference.

We will provide a lay summary of our findings and distribute this information to our participants through our newsletter and the HDBuzz website. We will also email publications and abstracts to the JRO.

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23 APPENDICES

Include here **a list** of the supplementary information and documents that will support the protocol and information contained therein, e.g. PIS, ICF, schedule visit, assessment tools, delegation log, case report forms, questionnaires, scales, tables, charts, diagrams, manufacturer's brochures.

It is not advisable to insert copies of documents such as the PIS and ICF due to version control and document management issues. You may wish to list the document titles here or delete if unnecessary.

23.1 Associated Documents

Include here supplementary information and documents that will support the protocol and information contained therein.

E.g. data dictionary

Document Name	Document Version	Document Date
CHDI Contract	TBC	
HDID license agreement	TBC	
Evotec contract	TBC	
University of Glascow Contract	TBC	
University Cambridge Contract	TBC	
University Iowa Contract	TBC	