CHDI
Accelerating therapeutic development for Huntington's disease

HUNTINGTON'S DISEASE CENTRE

UCL

HDClarity V004.1

Kat Schubert- Study Coordinator

Inaugural Investigator Meeting
Bologna 18th September 2022

HDClarity

Objectives

- Generate a high-quality CSF collection to evaluate biomarkers and pathways to enable development of novel treatments for HD
- Generate high-quality plasma sample collection matching the CSF collection
- Collect high-quality phenotypic data for each participant

Study Overview

HDClarity is funded by CHDI Foundation

- Site agreements
- Site payments

University College London

- Study sponsor
- Location of HDClarity Central Coordination

Study Overview

Multiple sites in Europe, North and South America and Australasia

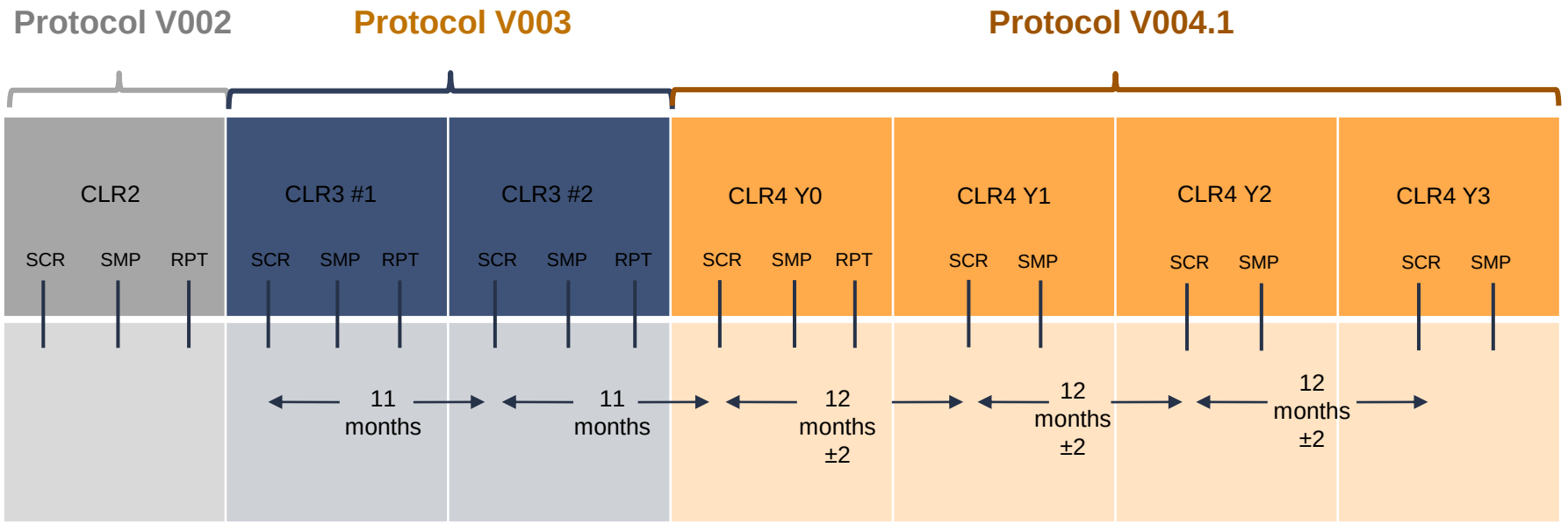
Equally spread across participant cohorts

Protocol VerNo002: up to a minimum of 600 participants

Protocol VerNo003: up to a minimum of 1200 participants

Protocol VerNo004.1: up to a minimum of 2500 participants

Study Design



V002 V003 V004.1

Participant cohorts

- Control
- Early Premanifest
- Late Premanifest
- Early Manifest
- Moderate Manifest
- Late Manifest

Protocol V002 and V003

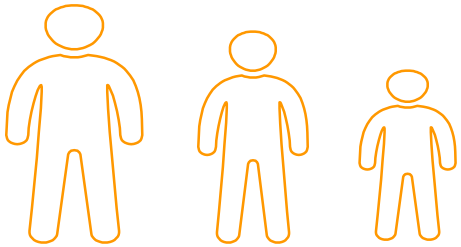
- **Juvenile Manifest**
- **Incomplete Penetrance**

Protocol V004.1

Age Range

Protocol V002/003

- **21-75 years** for all cohorts



Protocol V004.1

- **18-75 years** - controls, early/late premanifest HD and incomplete penetrance HD
- **21-75 years** – early/moderate/advanced manifest HD
- **≥11 years** - juvenile HD

Inclusion Overview – Subgroups

Group	Local CAG V002	Local CAG V003	Local CAG V004.1
Control	<36 (or no known family history)	<36 (or no known family history)	<36 (or no known family history)
Early Premanifest	≥ 40	≥ 40	≥ 40
Late Premanifest	≥ 40	≥ 40	≥ 40
Early Manifest	≥ 36	≥ 40	≥ 40
Moderate Manifest	≥ 36	≥ 40	≥ 40
Late Manifest	≥ 36	≥ 40	≥ 40
Juvenile Manifest HD	-	-	≥ 40
Incomplete Penetrance HD	-	-	36-39

Protocol Version 004.1

Inclusion/Exclusion Overview

Participant Scheduling

Study Procedures

Payments

Inclusion Overview

- Enroll-HD participant
- Capable of consenting or have a legal representative (parent/guardian for juveniles)
- Capable of complying with study procedures
- All participants other than family and community controls must have had a genetic test for HD

Exclusion Overview

- Drug trial within 30 days of sampling
- Changes in medication within 30 days of sampling
- Antiplatelet or anticoagulant therapy within 14 days of sampling
- Significant comorbidity
- Needle phobia, headache, spinal surgery / deformity
- Clotting or bruising disorder
- Screening blood values outside normal range (up to >10%)
- Drug / alcohol abuse
- Predictable non-compliance or unwillingness
- Serious adverse event related to HDClarity study procedures or any lumbar puncture in previous 12 months

Roche Study Participants

- Participants who have received Tominersen (previously IONIS-HTTRx or RG6042) as part of GENERATION HD1, GEN-EXTEND or GEN-PEAK, will need to be excluded from HDClarity
- The data released so far indicates that Tominersen treatment produced physical brain changes distinct from the natural progression of Huntington's disease
- It is not yet clear whether, or over how long, those treated patients may return to their pre-treatment trajectory
- Including these subjects in HDClarity risks introducing unknown variability into any analyses
- Participants who received only placebo injections as part of the Tominersen program will remain eligible for participation in HDClarity

Participant Scheduling – V004.1

Screening (Year 0)	Sampling	Phone Contact	Optional Repeat Sampling	Phone Contact	Screening (Year 1)	Sampling	Phone Contact
-30 to -1	0	1 to 3	28 to 56	31 to 59 (1 to 3 days after optional repeat sampling)	-30 to -1	0	1 to 3

- Annual Screening Visit (**within 90 days of last Enroll-HD visit)**
- Annual Sampling Visit within 30 days of the Annual Screening Visit
- Phone Contact approximately 24-72 hours after the Annual Sampling Visit
- Optional Repeat Sampling Visit 4-8 weeks following the Annual Sampling Visit **(Year 0 only)**

Study Procedures – V004.1

Visit	Investigations Completed
Screening	• Confirm eligibility and obtain written consent • **Urinary pregnancy test for females of child-bearing potential** • Full Neurological and Physical examination • Safety bloods
Sampling and RPT Sampling	• Confirm consent, eligibility and fasting status **(6hrs**) • **Urinary pregnancy test for females of child-bearing potential** • UHDRS motor • Focused Neurological and Physical examination • Lumbar puncture and CSF collection • Blood draw (Only if CSF is collected)
Phone Contact	• Participant Welfare • Update of AE and Con-Med logs

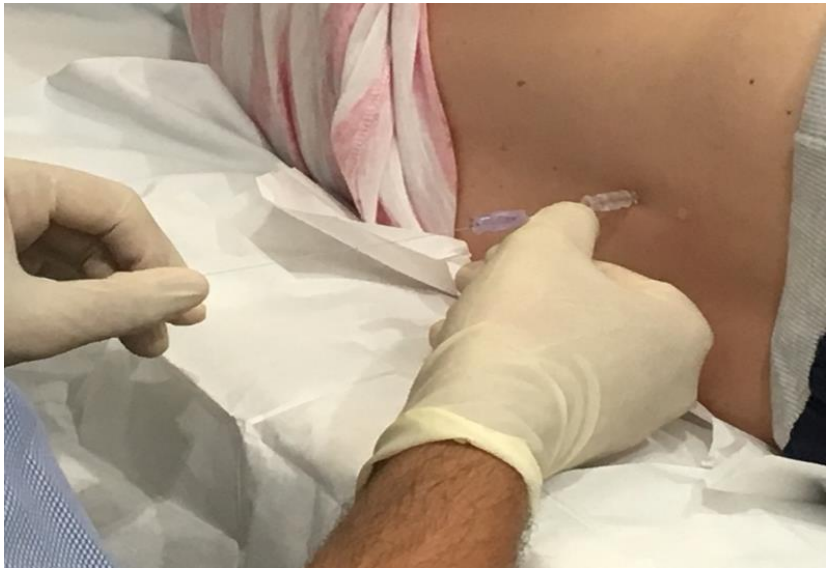
Waivers and Repeated Procedures

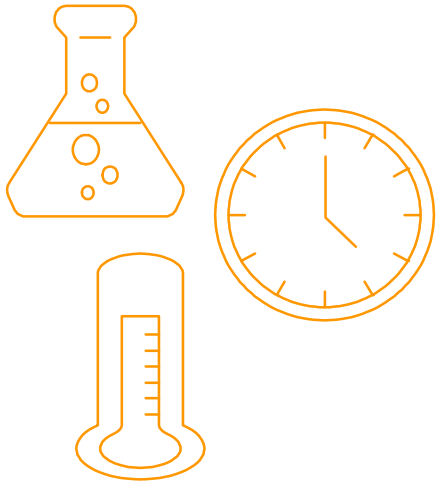
- Indications for a waiver:
  - Variations to the Inclusion and/or Exclusion criteria, e.g. safety bloods out of range
  - >30 days between the HDClarity Screening and Sampling visits

- **Waivers are no longer given to repeat the Enroll-HD core assessments. If it is >90 days since the last Enroll-HD visit, the HDClarity cannot take place**

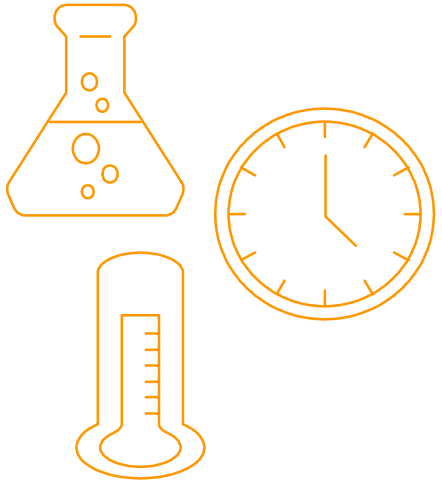
- Repeat screening and sampling attempts do not require a waiver, but do require permission in advance from the chief investigator

Lumbar Puncture Procedure





Sample Processing



Site Payments – Visit Payments

Visit Type	Definition
Screening Visit	Conducted on the same day as an Enroll-HD annual visit or within 90 days of the Enroll-HD annual visit
Sampling Visit and Optional Sampling Visit - Complete	Visit is complete – all assessments outlined In the protocol have been completed
Sampling Visit and Optional Sampling Visit – Partially Complete	At least one assessment is completed and signed. Either a premature end form is completed or some of the CRFs have been deactivated.
CI Approved Assessments	Procedures and fees that require prior approval of the Chief Investigator, e.g. repeat screening procedures

Participant Reimbursement

Visit Type	Participant Travel Allowance	Participant Meal Allowance	Participant Lodging Allowance	Participant Compensation	Companion
Screening Visit on the same day as your Enroll-HD visit	Covered by your Enroll-HD visit allowance	None	None	None	None
Screening Visit on a different day to your Enroll-HD visit	Under 25 miles= XX 25-50 miles= XX Over 80 miles = XX	None	None	None	None
Sampling Visit or Optional Repeat Sampling Visit	Under 25 miles= XX 25-50 miles= XX Over 80 miles = XX	XX	XX	XX	Receives the same travel and meal allowances as the participant, but no additional lodging allowance

Summary of Changes

Protocol Overview	Protocol V002 Jun 2016	Protocol V003 Dec 2018	Protocol V004.1 Dec 2021
Longitudinal	N	Y	Y
Consent	initial screening only	annually	every 4 years
Total recruitment	600	1200	2500
Number of cohorts	6	6	8
Enroll-HD window	60 days	60 days	90 days
Age range	21-75	21-75	11-75
Time of LP	a.m.	a.m.	any
Fasting	overnight	overnight	6 hours
Pregnancy testing	N	N	Y
Blood test	within local range	within 10% of the local range	within 10% of the local range
Optional repeat sampling	Y	Y	Y0 only

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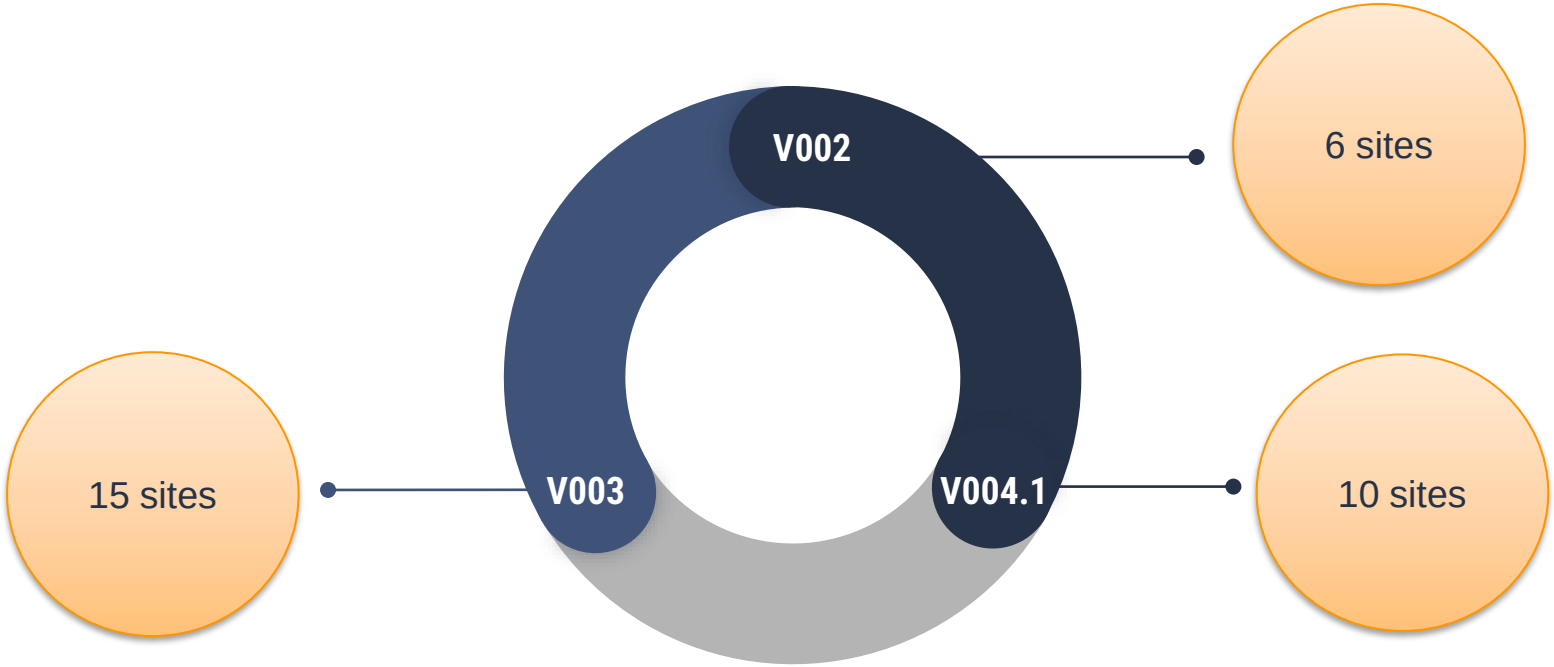
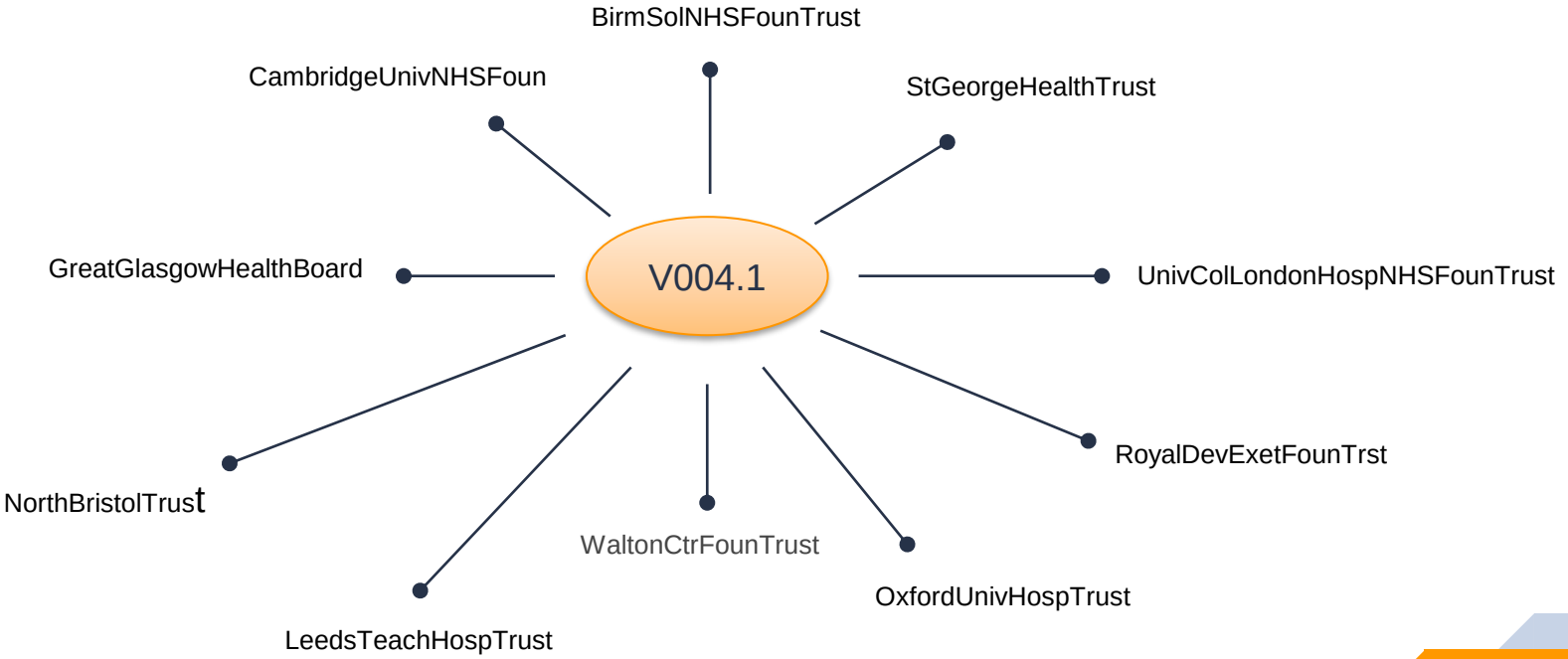
Transition

Sites at Each Protocol Versions



Sites Approved for Protocol V004.1



Central Coordination Team

Edward Wild – Chief Investigator

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THANK YOU!