HDClarity

Overview and protocol

EHDN Biomarkers Meeting

London, 15 Jan 2016

CHDI

Accelerating therapeutic development for Huntington's disease

HUNTINGTON'S DISEASE CENTRE

UCL

History

- **2005** (?) HighQ Foundation commissions Leavitt CSF
- **2006** EHDN Biomarker Working Group (Blankenberg) challenged to quantify mHTT in CSF
- **2009** Discussions begin (CHDI, UCL, Ulm, UBC) re designing a multi-site CSF collection
- **2013** Biomarker Working Group meeting in Frankfurt: GBL proposes CSF as top priority
- **2014** "CHDI-003" protocol draft 1
- **2015**
  - first quantification of CSF KP metabolites by LC/MS-MS
  - first quantification of CSF mHTT
  - first 'gene silencing' trial begins
  - HDClarity protocol finalised and ethics permission granted at UCL

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And so

Crucially

The work, contributions, ideas and discussions of the EHDN Biomarker Working Group since its inception have been **pivotal** to the development of HDClarity

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Overview

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

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Objectives

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

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Principal research exemplars

1. **Kynurenine pathway**
   - Metabolites to be quantified by MS
   - Diet, medications, time of day, inflammatory state
2. **Huntingtin**
   - Protein to be quantified by novel immunoassays
   - Extremely low concentration which we hope to reduce further
   - Consistency
   - Contamination especially by blood

- Shared considerations
  - Stability over time
  - Sample size
  - Urgency

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Sites and participants

- Up to 30 sites, targeting 20 participants per site
- 600 participants

	n	CAG	DCS	BOP	TFC
Healthy control	100				
Premanifest HD		≥ 40	< 4		
Early	100			< 250	
Late	100			≥ 250	
Manifest HD		≥ 36	4		
Early	100				7-13
Moderate	100				4-6
Late	100				0-4

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Inclusion overview

- 21-75 years of age
- Enroll-HD participant
- Capable of consenting or have legal representative
- Capable of complying with study procedures

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Exclusion overview

- Drug trial within 30 days of sampling
- Drug / alcohol abuse
- Unstable medication regime within 30 days
- Significant comorbidity
- Needle phobia, headache, spinal surgery / deformity
- Antiplatelet or anticoagulant therapy within 14 days
- Clotting or bruising disorder
- Screening blood test abnormalities
- Predictable non-compliance or unwillingness
- PI judgement re safety

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Visits

1.	Screening	-30	to	-1
2.	Sampling	0		
3.	Telephone followup	+1	to	+3
4.	Optional repeat sampling	+ 28	to	+56
5.	Telephone followup	++1	to	++3

- Additional visits for screening
- Unscheduled visits

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HDClarity  Enroll-HD

- Enroll-HD provides the phenotypic data for HDClarity
- Sites must be active in Enroll-HD
- Participants must be in Enroll-HD
  - Can join Enroll in order to participate in HDClarity
- Enroll-HD core within 2 months of screening
  - Few exceptions where this is essential to individual recruitment
  - CI waiver must be granted for such exceptions
- Enroll-HD EDC is used for HDClarity data capture
  - Enroll forms
  - Shared forms
  - HDClarity forms

- Remote and onsite data monitoring and queries

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Organisation

Sponsor

Funding and support

Central coordination

EDC and monitoring

Biokits and biorepository

Site visits

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Screening visit

- Informed consent
- Inclusion and exclusion review
- Demographics update
- Confirm (or perform) Enroll-HD assessments
- Physical and neuro exam
- Medical history
- Medications / supplements
- Bloods for safety

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Safety bloods

• White cell count	in range
• Neutrophil count	in range
• Lymphocyte count	in range
• Haemoglobin	in range
• Platelets	in range
• Prothrombin time	in range
• APTT	in range
• CRP	< 2× ULN

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Sampling visit

- Confirm consent
- Inclusion and exclusion review
- Physical and neuro exam
- Medications and supplements
- UHDRS TMS
- Vital signs
- CSF collection
- Venous blood draw
- CSF and blood sample processing
- CSF triplicate cell count

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Phone followup

- Medications and supplements
- AE review

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Optional repeat visits

- Procedures identical to sampling and followup

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Sampling procedure

- Carefully standardised and trained
- Fasted (water from midnight)
- 08:00 – 10:30 am
- Biokit provides all equipment
  - (except lidocaine and Chloraprep swabs)
- Whitacre 20G spinal needle
- 20 mls CSF collected
- 46 mls blood (4 × 10ml LiHep + 1 × Serum)

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Biofluid processing

- Should begin within 15 mins of CSF collection
- On ice
- All plasticware polypropylene
- CSF
  - Triplicate cell count by GLP-accredited personnel for QC
  - Centrifugation to separate cells
  - 300 µL aliquots (approx 67)
  - Cells preserved in RNALater
- Blood
  - Spin and aliquot
  - Serum 1500 µL aliquots × 2
  - Plasma 300 µL aliquots (approx 80)
- Everything frozen immediately to -80°C

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Shipping

- Within 2 months or as advised by CC
- Requested and logged via EDC

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Monitoring

- Remote
  - Enroll-HD and shared data: Enroll-HD monitors
  - HDClarity data: HDClarity CC
  - Site assessment: HDClarity CC
- Onsite
  - Site initiation and training (Jan Lewerenz)
  - Enroll monitors will also monitor HDClarity source
- Medical monitor
  - Tiago Mestre

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Timelines

• Protocol finalised	October 2015	✓
• Sponsor ethics approval	November 2015	✓
• EDC goes live	March 2015	
• First participant	March 2015	

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Interested?

- Enthusiasm for CSF biomarker research
- Active Enroll-HD site or about to be one
- Willing and able to collect CSF
- Commitment to recruitment and quality
- Lab capable of processing
- PI and team enjoy Indian food

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