Huntington's Disease Regulatory Science Consortium (HD-RSC) Inaugural Meeting Summary

Introduction

Huntington's Disease Regulatory Science Consortium (HD-RSC)

Inaugural Meeting Summary

April 29 & 30, 2019 – Rockville, Maryland

The Huntington's Disease Regulatory Science Consortium (HD-RSC), created in partnership with the CHDI Foundation and the Critical Path Institute (C-Path), was formally launched on March 28, 2018 with the primary goal of defining the regulatory science needs in order to accelerate and de-risk HD therapeutic development by all stakeholders. HD-RSC provides the forum and structure to bring together necessary participants from the HD community for data contribution and tool development, leading to efficiencies in the development of new therapies. HD-RSC is comprised of participants from government, academia, industry, non-profit science research, and patient advocacy organizations.

The five sessions included in this meeting were:

- C-Path Data Sharing Initiative in Neuroscience
- Quantitative Solutions to HD Drug Development
- Biomarker Solutions to HD Drug Development
- Regulatory Feedback on Novel COAs (FuRST 2.0 and HD-CAB)
- Considerations for Pre-Manifest Trials in HD

Who attended?

GOVERNMENT	EMA, FDA, NIH, NINDS
ACADEMIA	University College London, University of Iowa, University of Rochester, Wester other Scientific Advisors
INDUSTRY	IBM, Ixico, NeuraMetrix, Pfizer, Prilenia, PTC, Roche, Sanofi, Takeda, Teva, Tr Voyager, Wave Life Sciences
NON-PROFITS, PATIENT ADVOCACY	CHDI Foundation, European Huntington Association, Huntington's Disease Soci Study Group, Huntington's Society of Canada

This meeting brought together over 80 in-person attendees representing the above groups (Table 1), with

many others joining remotely.*Table 1: HD-RSC Partners from Government, Academia, Industry, and Non-Profit and Patient Advocacy Organizations*

C-Path Data Sharing Initiative in Neuroscience

There is a strong need for data-informed clinical trial design, particularly as trials target earlier disease stages where information is limited. A disease progression tool spanning a disease from pre-manifest to late stages is contingent on data sharing and transparency. Successful instances of data sharing from other neurologic fields include:

- The **Alzheimer's Disease Clinical Trial Simulation tool**, which includes information from over 13,000 patients in 37 trials submitted to C-Path. Applicants from over 350 institutions have completed the process to use this aggregated database for research purposes.
- Industry leaders committing to data sharing initiatives, including Biogen's **Clinical Trial and Transparency and Data Sharing** initiative, which addresses the need for a better-informed basis on which to design clinical trials in neuroscience.
- The **FDA's recent systematic analyses of partial onset seizure data** found similar exposure-response profiles in adult and pediatric populations, leading to a **surge in new drug applications and rapid approvals**.

Contemporary large and deep datasets provide an unprecedented opportunity to realize the vision of developing an early HD progression model. C-Path has a legacy of partnering with industry for data sharing and is uniquely positioned to make a great impact in this area as a trusted, neutral third party that can convene scientific consortia to bring together the best science and broadest experience. Take home message of the C-Path Data Sharing Initiative in Neuroscience: **Commit to the hypothesis, commit to a central repository, commit to engage your organization, and commit to sharing your data with C-Path.**

Quantitative Solutions to HD Drug Development

Overview: Commonly posed questions critical to clinical trial design are quantitative in nature, including sample size estimations, trial duration, assessment frequency, inclusion and exclusion criteria, and biomarker selection. Disease modeling serves to understand the progression of a given disease by quantifying sources of variability (e.g., CAG expansion) in the patient population. *Ideally, we only want a trial to fail because the intervention was not effective, rather than because of poor trial design.*

The overarching aim of the **HD-RSC Modeling & Simulation Working Group** is to develop a clinical trial simulation (CTS) tool for manifest HD, with multiple models underlying the final CTS tool: disease progression models, symptomatic or disease-modifying drug models, and additional models related to the trial (i.e., placebo effects, dropout).

Progress:

- Drafted the **context-of-use statement for the CTS tool**, which, analogous to a drug label, defines the target population, endpoints to be modeled, and a description of the intended application.
  - The tool will perform clinical trial simulations to help inform trial design, including inclusion/exclusion criteria, enrichment and stratification approaches, and power calculations.
- Developed and **refined a modeling analysis plan** based on preliminary modeling and discussion.

- ○ Current modeling efforts seek to capture **TMS and TFC as linear models.**
- ○ Current covariates include: CAP score, CAG length, age, and sex.

<div style="background:#d6e4f0;">

Challenges and Next Steps:

- HD exists as a continuum and not in discrete stages, and the conceptualization of disease progression is likely **addressing changes in genetics, biofluids, and imaging biomarkers** alongside clinical presentation.
- The ability to successfully model the entire HD continuum, including prodromal or pre-manifest HD, will req
  - ○ **randomized, interventional clinical trial datasets**
  - ○ **exploratory endpoint data from these trials, including biomarkers and clinical outcome assessmen**
  - ○ incorporation of **these measures as covariates to explain sources of variability** in disease progression

</div>

Biomarker Solutions to HD Drug Development

<u>Overview</u>: Across chronic neurological disorders, biomarkers, COAs, and approved treatments primarily, if not exclusively, are targeted toward the manifest stage of the disease. There is an unmet need to identify biomarkers to detect the earliest stages of the disease which will allow for better disease progression modifying or preventative trials. These biomarkers can be categorized as pharmacodynamic/response, monitoring, or prognostic biomarkers, with the long-term goal of linking these biomarkers to clinically meaningful outcomes. The Imaging and Biofluid subgroups have already identified leading candidate biomarkers for HD (Table 2), drafted preliminary COU statements, and are in the process of assessing regulatory readiness of these candidate biomarkers.

IMAGING	
	MRI (caudate, white matter, & whole brain volumes)
	DTI (white matter integrity)
	PET (mHTT, PDE10)
	MRS (myoinositol, NAA)
BIOFLUIDS	CSF (mHTT, NfL, total HTT)
	Plasma (NfL)

Table 2: Candidate Biomarkers for Huntington's Disease

<u>Imaging Progress</u>:

- A **review article is in progress on caudate volume** use in clinical trials. Attention is given to the

technical aspects and analysis across vMRI collections.

- Observational study data to support analysis of caudate volume is in-house, but further efforts cannot yet be supported by HD-RSC without caudate volume data from interventional clinical trials.
- The group may consider seeking a **Letter of Support for other early-stage biomarker candidates**, such as PDE10 PET or mHTT PET, pending review of emerging data.

Biofluids Progress:

- The Biofluids Biomarker Working Group is prioritizing efforts to **advance the mutant HTT (mHTT)** assay, as more development work has been done on the mHTT assay to make it ready for use compared to the total HTT assay or NfL, there is clear biologic plausibility, and clinical data already exists.
- The group has formed the mHTTAssay Task Force, the focus of which is **comparing the available mHTT assays to ensure assay interoperability**, with a possible follow-up inter-lab validation study under consideration.
- Ongoing natural history studies and early phase clinical studies will soon provide much needed clinical data for these analytes to support pursuing regulatory acceptance of these biomarkers for use as prognostic or monitoring biomarkers.

Challenges and Next Steps:

- Currently, **data acquisition is the rate-limiting step** to pursuing regulatory acceptance of any leading candidate biomarker.
- Once clinical trial data is received, C-Path will be able to better assess what pathway and context of use the data will be able to support.

Regulatory Feedback on Novel COAs (FuRST 2.0 & HD-CAB)

Overview: There is an unmet need for clinical outcome assessments (COAs) that are capable of capturing the earlier decline in motor and non-motor symptoms in order to advance potential therapeutics in pre-manifest or early-manifest HD. An informal meeting was held with the FDA Division of Neurology Products to receive feedback for two novel COAs under development for use in HD clinical trials.

FuRST 2.0:

The Functional Rating Scale 2.0 (FuRST 2.0) is a 24-item patient-reported outcome (PRO) measure developed to assess *functional* ability in pre-manifest and early-manifest HDGECS.

- Recommendations were obtained on the administration and target population for the FuRST 2.0, further scale development, and application in clinical trials, and proposed future validation work.
- FuRST 2.0 has the **potential to serve as a possible primary endpoint** if it is sensitive to changes and performs well in the target population as it has inherent clinical meaningfulness.
- Suggestions were focused on modifying anchors to:
  - avoid quantification
  - have more inherent meaning to improve interpretability

- distinguish if the HDGEC has never performed an activity (no ability to lose that function) from no longer being able to perform the activity (loss of function) where applicable

<u>HD-CAB:</u>

The HD Cognitive Assessment Battery (HD-CAB) is a battery of six performance outcome tests to assess a range of *cognitive* functions in HD.

- **Recommended an alternative to z-score composite** to aid in establishing clinical meaningfulness.
- Consider **time-to-event strategies** to determine timeframe for a given test to remain stable while observing measurable decline in tests in placebo controls.
- Consider **novel cognitive assessments** such as structured comprehension/conversation test or a virtual reality-based performance assessment.

Challenges and Next Steps:

- Round 2 of cognitive pretesting with modified anchors in FuRST 2.0 is currently underway.
- Team is in process of designing a pre-specified sensitivity analysis for FuRST 2.0.
- Discuss **endpoint strategy of HD-CAB in conjunction with FuRST 2.0 with sponsors.**
- Design comprehensive but feasible **co-validation study which includes FuRST 2.0, HD-CAB, and novel cognitive assessments.**
- Seek a **SAWP with EMA on the HD-CAB and FuRST2.0** and continue dialogue with the FDA through HD-RSC.

Considerations for Pre-Manifest Trials in HD

<u>Lessons from DIAN-TU on Innovative Trial Design:</u>

Dr. Randall Bateman shared his experience with [the Dominantly Inherited Alzheimer Network (DIAN)](), which was established in 2008 to study individuals with dominantly inherited AD (DIAD). DIAD shares similar challenges for disease modification with HD; thus, adapting lessons from DIAN to HD could streamline biomarker identification, trial enrollment, and therapeutic discovery.

- Researchers need to maintain a high degree of flexibility for multi-year studies and observational periods.
- **Trial design should be as inclusive as possible** and other approaches should be considered such as pooled placebo, run-in periods, the use of external controls, and the prioritization of experimental treatments.
- The HD community will need to come to a **consensus on disease staging** based on natural history data to define which populations to treat in a trial.
- Important considerations include: the **stage of the disease to target,** whether there is **enough target engagement** for disease modification, and whether the target is the **"right" target.**
- If a biomarker like CSF mHTTcould be reliably linked to a future disease outcome, such a biomarker could serve as a surrogate marker and decrease the trial duration significantly.

Many of the above discussion points will be explored through HD-RSC's newest endeavor, the **Regulatory Science Forum**

working group, which will be responsible for developing white papers or publications based on HD community input to outline key points to consider for enabling clinical trials and the development of therapeutics targeting pre-manifest HD.

For more information about HD-RSC, contact Ariana Mullin, Ph.D. (amullin@c-path.org) or visit:

Critical Path Institute: https://c-path.org/

Huntington's Disease Regulatory Science Consortium: https://c-path.org/programs/hdrsc