

SUNDAY MAY 20, 2018		
2:00pm–6:30pm	Registration	Verchères
5:00pm–6:30pm	Resource fair, including clinical studies & initiatives	Frontenac Room
6:30pm–7:00pm	Welcome and opening comments - Enroll-HD: Back to the Future! Cristina Sampaio, MD, PhD, <i>CHDI</i>	Salle De Bal
7:00pm–7:50pm	Keynote speaker Moving the mission along: Drug development for neurodegenerative diseases without subtexts and silos Rachelle Doody, MD, PhD, <i>Roche Pharmaceutical Company/Genentech</i>	Salle De Bal
7:50pm–8:15pm	Thank you to committee members	Salle De Bal
8:15pm–11:00pm	Buffet dinner reception	Terrasse Level
MONDAY MAY 21, 2018		
8:30am–10:30am	SESSION I: BEYOND ENROLL-HD 1.0 We will recap the main features of the Enroll-HD platform and status of the study, introduce the concept of forecasting tools, and outline plans to develop Enroll-HD 2.0. Also covered will be strategies to increase recruitment of premanifest and early-manifest participants, piloting mobile technologies, Enroll-HD Lite for participants with advanced disease, Enroll-HD platform services, and the new governance structure. Chaired by: Cristina Sampaio, MD, PhD, <i>CHDI</i> G. Bernhard Landwehrmeyer, MD, FRCP, <i>Ulm University Hospital</i> Speakers: Joaquim Ferreira, MD, PhD, <i>Instituto de Medicina Molecular</i> Claudia Perandones, MD, MSc, PhD, <i>Enroll-HD/National Laboratories and Institutes of Health of Argentina</i> Michael Lindemann, PhD, <i>Roche Innovation Center Basel</i> Martha Nance, MD, <i>Struthers Parkinson's Center</i> Jenny Townhill, PhD, <i>Enroll-HD</i> Francis O. Walker, MD, <i>Wake Forest School of Medicine</i>	Salle De Bal
10:30am–11:00am	Break	Verchères & Frontenac Room
11:00am–12:30pm	SESSION 2: NEXT GENERATION HD ASSESSMENTS: IS THERE A ROLE FOR PATIENT-REPORTED OUTCOMES IN HD STUDIES? FuRST2.0 is a patient-reported outcome (PRO) measure to evaluate functional outcomes in HD developed using standard rating scale development methodology. We evaluated respondents' comprehension of instructions, items, and scoring through cognitive pretesting techniques and compared the responses of HDGECs and their companions. These results will be presented along with a panel discussion on the role of the patient's perspective in HD research. Chaired by: Glenn T. Stebbins, PhD, <i>Rush University Medical Center</i> Rebecca Fuller, PhD, <i>CHDI</i> Speakers: Astri Arnesen, <i>European Huntington Association</i> Elizabeth A. McCusker, MB BS (Hons) FRACP, <i>Sydney University Medical School</i> Tiago Mestre, MD, <i>University of Ottawa</i> Glenn T. Stebbins, PhD, <i>Rush University Medical Center</i> Rebecca Fuller, PhD, <i>CHDI</i>	Salle De Bal
12:30pm–2:00pm	Lunch Enroll-HD principal investigators assemble to elect committee members.	Frontenac Room



2:00pm-3:30pm	<p>SESSION 3: ENROLL-HD STUDY COORDINATOR TRIVIA GAME!</p> <p>Study coordinators will be divided into teams to play a trivia-style game highlighting frequent questions related to the study protocol, EDC, study conduct, biosamples, etc., followed by a review of all questions and answers. Show us your knowledge of Enroll-HD, have your burning questions answered, and help your team win prizes!</p> <p>Chaired by: Selene Capodarca, <i>Enroll-HD</i> Jenny Callaghan, <i>Enroll-HD</i> Shilpa Deshpande, <i>CHDI</i> Ruth Fullam, <i>Enroll-HD</i></p>	Jacques-Cartier Room	<p>SESSION 4: ENROLL-HD LITE - WHY, WHAT, AND WHEN?</p> <p>Enroll-HD Lite will be a new longitudinal observational study protocol of mid- to late-stage HD. We will introduce the rationale behind the study protocol, give an outline of the assessments that will be included, and the operational considerations for roll out.</p> <p>Chaired by: Martha Nance, MD, <i>Struthers Parkinson's Center</i> Sam Frank, MD, <i>Beth Israel Deaconess Medical Center</i></p> <p>Speakers Martha Nance, MD, <i>Struthers Parkinson's Center</i> Jeffrey Long, PhD, <i>University of Iowa</i> Daisy de Abreu, MSc, <i>Associacao para a Investigacao e desenvolvimento da Faculdade de Medicina de Lisboa</i> Michael Orth, MD, PhD, <i>Ulm University Hospital</i> Selene Capodarca, <i>Enroll-HD</i> Olivia Handley, PhD, <i>Enroll-HD</i></p>	Salle De Bal
3:30pm-3:45pm	Break			Verchères & Frontenac Room
3:45pm-5:15pm	<p>SESSION 5: NEW TOPICS IN ENROLL-HD</p> <p>We will cover aspects important to Enroll-HD conduct, including detecting suicidality and administration of the CSSRS, study co-participation, guidance on dealing with intermediate alleles, and introduce new topics - site metric cards, plasma collection, and the blue card system.</p> <p>Chaired by: Jamie Levey, <i>Enroll-HD</i> Tim McLean, <i>Enroll-HD</i></p> <p>Speakers Erik van Duijn, MD, PhD, <i>Leiden University Medical Center</i> Mark Guttman MD, FRCPC, <i>University of Toronto</i> G. Bernhard Landwehrmeyer, MD, FRCPC, <i>Ulm University Hospital</i> Selene Capodarca, <i>Enroll-HD</i> Anka G. Ehrhardt, PhD, <i>CHDI</i> Mette Gilling Nielsen, MSc, PhD, <i>Enroll-HD</i> Lesley Jones, PhD, <i>Cardiff University</i></p>			Salle De Bal
5:15pm-6:00pm	<p>Featured speaker</p> <p>The results of the IONIS-HTT_{Rx} study</p> <p>Blair R. Leavitt, MDCM FRCPC (C), <i>University of British Columbia</i></p>			Salle De Bal
6:00pm-7:30pm	Resource fair & cocktail reception			Place D'Armes
<p><i>Dinner on your own. There will be no hosted dinner this evening. There are many restaurants within walking distance of the hotel. Please check with the concierge desk in Verchères for restaurant recommendations and reservations.</i></p>				
TUESDAY MAY 22, 2018				
8:30am-10:15am	<p>SESSION 6: STATISTICAL MODELLING IN HUNTINGTON'S DISEASE</p> <p>Overview of the application of statistical methodologies to HD clinical datasets (including from Enroll-HD) and their relevance in improving the validity of inferences and clinical trial planning. Short talks interspersed with Q&A.</p> <p>Chaired by: Amrita Mohan, PhD, <i>CHDI</i> Jeffrey Long, PhD, <i>University of Iowa</i></p> <p>Speakers Mette Gilling Nielsen, MSc, PhD, <i>Enroll-HD</i> Marika Suttorp Booth, MS, <i>RAND Corporation</i> Zhaonan Sun, PhD, <i>IBM Watson Research Center</i> Klaus Romero, MD, MS, <i>Critical Path Institute</i></p>			Salle De Bal

10:15am-10:45am	Break		Verchères & Frontenac Room	
10:45am-12:30pm	<p>SESSION 7: CLINICAL STUDIES AND TRIALS: LEVERAGING THE ENROLL-HD ECOSYSTEM</p> <p>We will highlight the variety of services that the Enroll-HD platform offers to our commercial and academic collaborators to support the planning and conduct of clinical studies and trials. We will then showcase results from several studies and trials that have successfully leveraged the Enroll-HD ecosystem.</p> <p>Chaired by: Jen Ware, PhD, <i>CHDI</i> Juliana Bronzova, MD, <i>Enroll-HD</i></p> <p>Speakers Jenny J. Townhill, PhD, <i>Enroll-HD/Cardiff University</i> & Tim McLean, <i>Enroll-HD</i> Andrea Varrone, MD, PhD, <i>Karolinska Institutet</i> Marielle Delnomdedieu, PhD, <i>Pfizer, Inc.</i> Maurice Zauderer, PhD, <i>Vaccinex, Inc.</i></p>		Salle De Bal	
12:30pm-2:00pm	Lunch		Frontenac Room	
12:45pm-1:45pm	<p>Lumbar puncture demonstration skills workshop</p> <p>with Mark Guttman, Francis Walker, Filipe Rodrigues, & Jan Lewerenz (due to capacity this is only open to those who have already signed up)</p>		Salle De Bal	
2:00pm-3:30pm	<p>SESSION 8: ENROLL-HD STUDY COORDINATOR Q&A PANEL</p> <p>Study coordinators from sites around the world will give short presentations that focus on their site organization, study conduct, primary challenges and solutions, followed by a Q&A panel where all study coordinators can ask questions and share their own experiences.</p> <p>Chaired by: Selene Capodarca, <i>Enroll-HD</i> Jenny Callaghan, <i>Enroll-HD</i> Shilpa Deshpande, <i>CHDI</i> Ruth Fullam, <i>Enroll-HD</i></p> <p>Speakers Anna Castaldo, MS, <i>Istituto Neurologico Carlo Besta</i> Paula Wasserman MA, CCRC, <i>Columbia University</i> Natalia Rojas, MS, <i>Centro de Trastornos del Movimiento (CETRAM)</i></p>	Jacques-Cartier Room	<p>SESSION 9: ADVANTAGES AND CHALLENGES TO OPEN SCIENCE: APPROACHES AND SOLUTIONS</p> <p>The scientific benefits of transparency, collegiality, collaboration, and rigor that open science provides is an increasingly important topic of conversation in the clinical sciences. We will bring together open-science experts, with particular emphasis on data sharing, dataset aggregation, dataset provenance acknowledgment in scientific publications, data-sharing logistics, and the introduction of CDISC data standards for HD that will enable data comparison and re-use across different trials and studies. There will be short presentations followed by an interactive discussion.</p> <p>Chaired by: Andrew Wood, PhD, <i>CHDI</i> Simon Noble, PhD, <i>CHDI</i></p> <p>Speakers Christine Suver, PhD, <i>Sage Bionetworks</i> Heather H. Pierce, JD, MPH, <i>Association of American Medical Colleges (AAMC)</i> Diane Stephenson, PhD, <i>C-PATH/Huntington's Disease Regulatory Science Consortium</i> Matthieu Schapira, PhD, <i>University of Toronto/Structural Genomics Consortium</i></p>	Salle De Bal

3:30pm–4:00pm	Break	Verchères & Frontenac Room
4:00pm–5:30pm	<p>SESSION 10: LOOKING AHEAD – THE FUTURE IS BRIGHT</p> <p>Human genetics and genomics investigations are improving understanding of the genotype:phenotype relationship in HD. We will cover the technology and experimental approaches being enabled by the Enroll-HD platform, results of genetic analysis at the HTT locus, epigenetic studies of human HD gene expanded DNA, and human genome-wide association studies (GWAS) identifying genetic modifiers of HD phenotypes. Emerging results provide insight into the identification of candidate biomarkers, candidate drug discovery targets, the design of clinical trials, and the clinical assessment and future treatment of HD patients. Presentations will each be followed by a Q&A.</p> <p>Chaired by: Seung P. Kwak, PhD, <i>CHDI</i> Thomas F. Vogt, PhD, <i>CHDI</i></p> <p>Speakers: Darren G Monckton, PhD, <i>University of Glasgow</i> Steve Horvath, PhD, ScD, <i>University of California, Los Angeles</i> James F. Gusella, PhD, <i>Massachusetts General Hospital</i></p>	Salle De Bal
5:30pm–6:00pm	Break	Verchères & Frontenac Room
6:00pm–6:45pm	<p>Featured speaker</p> <p>Ethical considerations in HD research Robert Klitzman, MD, <i>Columbia University</i></p>	Salle De Bal
6:45pm–7:00pm	<p>Closing remarks Cristina Sampaio, MD, PhD, <i>CHDI</i></p>	Salle De Bal
7:00pm–7:30pm	Walk to cocktail reception	
7:30pm–10:00pm	Farewell dinner	Séminaire de Québec
WEDNESDAY MAY 23, 2018		
9:00am–12:00pm	<p>Workshop: Best practices in the analysis of observational HD data (Open to all, prior sign-up required)</p> <p>We will provide practical advice about analyzing observational data, with a specific focus on HD studies. We will discuss the benefits and limitations of observational research, identify preferred analytical methods, describe considerations specific to HD observational data analysis, outline best practices in reporting of methods and results, and provide an overview of methods that can be applied to observational data to improve causal inference. Practical examples will be provided throughout based on Enroll-HD data.</p> <p>Chaired by: Jen Ware, PhD, <i>CHDI</i></p>	Jacques-Cartier Room
7:30am–3:30pm	<p>Global Enroll-HD Team staff meeting Invitation to staff only</p> <p>Chaired by: Eileen Neacy, <i>CHDI</i> Jamie Levey, <i>Enroll-HD</i> Tim McLean, <i>Enroll-HD</i></p>	Montmagny Room

KEYNOTE SPEAKER

Moving the mission along: Drug development for neurodegenerative diseases without subtexts and silos

Rachelle Doody, MD, PhD

Genentech & Roche

Huntington's disease (HD) is a fatal, autosomal dominant neurodegenerative disorder that manifests with motor, cognitive, and psychiatric symptoms. Dynamic collaboration is essential to overcome technical, epidemiologic, and funding limitations inherent to HD research, and to more quickly enable successful drug development. No disease-modifying therapy for HD exists, and symptomatic therapy is often ineffective, with few FDA-approved treatment options on the market. However, the identification of and basic research on several potentially important disease mechanisms in HD have increased optimism for more successful drug development in the short-term future. This presentation reviews Roche's ongoing collaboration with Ionis Pharmaceuticals on an antisense oligonucleotide (ASO) that may interfere with targeted mRNA and thus decrease the production of the abnormal protein believed to be at the heart of HD. It also considers parallels and differences between research in HD and Alzheimer's disease (AD), and how learnings from collaborative AD research may be applied to similar efforts in HD. Finally, this presentation makes an argument for collaboration across industry, non-profit organizations, clinical trials enterprises, and academia as part of the solution to many of the barriers limiting HD research today.

Sunday May 20th, 2018

7:00pm–7:50pm



FEATURED SPEAKER

The results of the IONIS-HTT_{Rx} study**Blair R. Leavitt, MDCM FRCP (C)**

University of British Columbia

On behalf of Sarah Tabrizi, Holly Kordasiewicz, Christian Czech, Eric Swayze, Daniel A. Norris, Tiffany Baumann, Irene Gerlach, Scott Schobel, Anne Smith, Roger Lane, C. Frank Bennett and the IONIS-HTT_{Rx} Investigators

This study assessed the safety and tolerability of intrathecal (IT) administration of IONIS-HTT_{Rx} (RG6042), an antisense oligonucleotide (ASO) targeting huntingtin mRNA, in patients with Huntington's disease (HD) and characterized its pharmacokinetic (PK), pharmacodynamic (PD), clinical, and biomarker effects. Production of mutant huntingtin protein from the expanded *HTT* allele is considered the proximal cause of HD pathology. IONIS-HTT_{Rx} (RG6042) is a selective ASO that potently suppresses HTT and is the result of a comprehensive drug discovery effort, including extensive preclinical efficacy and safety studies. In this double-blind ascending dose phase 1/2a trial (NCT02519036), 46 people with early stage HD were randomized (3:1) to receive either four monthly IT injections of 10 mg, 30 mg, 60 mg, 90 mg or 120 mg of IONIS-HTT_{Rx} (RG6042) or placebo. Prior to increasing dose, an independent data safety monitoring board reviewed available safety, PK and target engagement data for previous doses. All subjects completed the study, the rate of adverse events was not different between ASO and placebo treated subjects, and no clinically relevant changes in safety lab parameters were observed. Significant, dose-dependent reductions in mHTT were observed in CSF of treated participants, with mHTT reductions of up to approximately 60% and mean reductions of approximately 40% in CSF observed at the two highest doses, 90 mg ($p < 0.01$) and 120 mg ($p < 0.01$). Results of clinical outcome measures will also be presented. IONIS-HTT_{Rx} (RG6042) was well-tolerated at all doses tested, with no study drug-related adverse safety signals during the treatment or follow-up periods. Significant dose-dependent reductions in CSF mHTT provide evidence for CNS target engagement. This study supports further development of IONIS-HTT_{Rx} (RG6042) in a phase 3 trial to determine clinical efficacy.

Monday May 21st, 2018

5:15pm–6:00pm



FEATURED SPEAKER

Ethical considerations in HD research

Robert Klitzman, MD

Columbia University

Bioethical principles can help in addressing critical dilemmas that arise concerning data and biospecimen sharing, access to treatments, drug company pricing, and informed consent. In addressing each of these dilemmas, basic bioethical principles of respect for persons (autonomy), beneficence, non-maleficence and justice are vital. Especially across national borders, sharing data and biospecimens pose challenges, partly since law and regulations vary regarding data privacy generally, health and genomics data, and biosamples leaving the country. Key questions emerge of under what conditions data might be shared – e.g., if it is de-identified, anonymized, or coded. Challenges surface since laws and regulators are usually written “in the abstract”, without considering the particular circumstances of HD, and university and other institutional lawyers are often “risk adverse”. Institutional Review Boards (IRBs)/ Research Ethics Committee (RECs) also face dilemmas of how much to reduce privacy risks, and how “secure” is “secure” enough. But these committees vary widely, and often need education on these issues. Access to treatments can pose challenges, too, since sharing the burdens and benefits of research is a fundamental ethical principle. But drug company prices are increasing, with certain new drugs costing \$1 million per person per year. Questions thus emerge of whether certain prices are “too” high, who should decide and how. Commentators have suggested that certain levels of drug company profit are acceptable (e.g., 8 times the cost of research and development, or R&D), but R&D may be calculated in different ways (e.g., including failed trails of other drugs). Disease advocacy organizations face challenges, too, concerning whether and how to partner with pharmaceutical companies. In addressing pricing issues in these situations, statements of ethical principles can be helpful. Stakeholder groups need to address these policy issues institutionally, nationally and internationally. These issues highlight critical needs for research, policy, and education of policymakers, clinicians, researchers and others.

Tuesday May 22nd, 2018
6:00pm–6:45pm



ENROLL-HD: EVOLVING TO MEET THE RESEARCH CHALLENGES OF 2025

Enroll-HD was designed to be an integrated infrastructure to facilitate the execution of Huntington's disease (HD) clinical studies and to generate high-quality biomedical data. The Enroll-HD platform includes several ongoing and planned interconnected studies, with the Enroll-HD study being the largest and the clinical pillar of the platform that encompasses collection of longitudinal phenotypic data and blood-derived biosamples. Its current protocol and overall structure closely follow its direct predecessors, COHORT and REGISTRY. Participants from REGISTRY who consent continue to seamlessly transition to Enroll-HD, linking the longitudinal data collected in REGISTRY to Enroll-HD study data. The first participant entered the Enroll-HD study on July 23, 2012, and now there are over 15,000 active participants from 18 nations and 161 clinical study sites. After six years of growth we now need to adapt the Enroll-HD platform to meet the challenges of the new HD clinical research and development environment that we have all shaped. These changes have three overarching goals:

Optimize the composition of the Enroll-HD cohort

Enroll-HD began as an open-ended, prospective, natural-history study without pre-defined constraints on participation. Transitioning REGISTRY participants over to Enroll-HD significantly increased the total population as well as the longitudinal depth of data. Overall, the current cohort mainly comprises individuals with manifest disease (55%), a population with a low dropout rate (~5% annually). Current forecasts indicate that, left unchanged, over the next ten years the cohort would be heavily skewed towards the later disease stages. However, it is clear that future clinical studies and trials will require participants in early-manifest and premanifest disease stages. Additionally, successful conduct of clinical studies in these earlier stage populations will require the development of well validated prognostic, predictive and responsive biomarkers. A large cohort of study-ready, pre- and early-manifest participants will be needed to meet the requirements of upcoming clinical trials and biomarker studies. Two major initiatives to reshape the composition of the Enroll-HD cohort are currently underway:

- ***Modify recruitment and retention strategy to increase the number of premanifest and early-manifest participants***

This involves working with lay associations and genetic-counselling centers to identify eligible participants, establishing recruitment targets, refining forecast modelling, and assessing new technologies such as mobile technology.

- ***Enroll-HD Lite, a study protocol that caters to moderate- to advanced-stage participants***

This new protocol will reduce participant burden while maintaining continuity of critical Enroll-HD data by offering a lighter assessment battery and, whenever possible, assessments specific for moderate- to advanced-stage HD participants.

Create new resources for research

Enroll-HD will continue to provide researchers with innovative resources to develop and test novel hypotheses. Two new projects will augment the current extensive biosample collection and phenotypic datasets. The first will build a large, longitudinal, high-quality plasma sample collection spanning all disease phases (and including family controls and gene-negative family members) to fully explore the growing interest in peripherally-expressed biomarkers to use in mechanistic and discovery research. Currently, high-quality HD plasma collections are scarce and being quickly depleted.

The second project will look for unusual or extreme phenotypes, since such anomalous cases could be the key to understanding new molecular mechanisms or environmental exceptions. Two distinct approaches have been used in such analyses; a statistical approach that defines outliers based on specific distributions, and a more qualitative method that relies upon clinical experience and insight to identify uncharacteristic traits. We will introduce what we are calling a blue card system (in reference to the UK's adverse-reaction reporting yellow card system) to flag unusual clinical cases in the EDC and enable in-depth review by a team of expert clinicians and geneticists to gauge whether the individual merits further study, namely whole genome sequencing.

- ***Create a high-quality plasma collection***

A longitudinal plasma collection of approximately 2,000-3,000 participants (spanning all disease stages, including control participants) for a minimum of 5 consecutive years.

- ***Identify unique phenotypes – blue card system***

A system to flag unusual or extreme phenotypes for review and potential further study.



Automate, communicate and reorganize for better efficiency

Several projects are underway to reduce the resources needed to operate and manage the Enroll-HD study and to enhance overall data quality. These important changes include:

- ***Provide timely feedback to sites***

Sites need timely feedback to improve performance. New easy-to-read site report cards that highlight the most critical aspects of study management—recruitment, retention, safety, and data quality—will soon be introduced.

- ***Reorganize Enroll-HD governance***

Consolidating Enroll-HD governance maximizes productivity of committees without undue burden to the members or detracting from the resources needed to run the platform. The reorganization also incorporates a structured process of membership rotation.

- ***Statistical monitoring and EDC changes to enhance data quality***

Using statistical algorithms to check all data points, combined with revisions to several forms in the EDC and added edit checks, will further enhance data quality and reduce queries to sites.

Summary

You will hear more during the Congress about these strategic changes that are currently underway to better position Enroll-HD to meet the challenges of near- and mid-term HD clinical research. The dedication and commitment of the numerous HD clinicians, study coordinators, and other site staff worldwide, as well as the participants and their families, are responsible for the enormous success of the Enroll-HD platform. Thank you all for your continued contribution as we work together to meet Enroll-HD's goals and improve the lives of individuals with Huntington's disease.



A NOTE ON CHDI'S STRATEGY FOR CLINICAL DEVELOPMENT - THE CENTRAL ROLE OF ENROLL-HD

Two goals drive CHDI's clinical-development activities: To provide infrastructure, tools, and biomarkers to efficiently develop HD therapeutics, and to validate therapeutic targets using clinical data to better understand the human biology of HD. To achieve these goals we are pursuing four types of activity:

- **Elucidate the mechanisms integral to HD etiology and progression, including mechanistic (such as genome-wide and phenome-wide association) studies, experimental medicine, and epidemiology studies.**
- **Develop and validate clinical biomarkers of disease progression and therapeutic response, including biomarkers for diagnosis, enrichment, prognosis, prediction, and target engagement.**
- **Establish a clinical research platform and attendant tools (including regulatory science procedures) to enable the design and conduct of clinical trials and studies.**
- **Provide third parties with expertise and support for the execution of therapeutic development trials.**

CHDI maintains a dedicated clinical operations infrastructure to support these activities. A network of 161 Enroll-HD **clinical sites** worldwide collect clinical data and biosamples—DNA, plasma, CSF and, in the near future, semen—from more than 15,000 active research participants. These data and biosamples are stored in various **repositories** from which they may be accessed by interested researchers. The data are monitored, queried, cleaned and analyzed through an **integrated data and statistical** approach to ensure participant privacy and data quality. Some of the statisticians involved are also available for consultation regarding use of the data and experimental design. All of this is tied together by **information technology services** that ensure data from disparate sources is seamlessly collected, combined into a coherent whole and made available to researchers to pursue the objectives above. HD clinical sites, data and biosample repositories, clinical study support services, statistical analysis and support, and IT services – these constitute the Enroll-HD **platform**.

In the Congress presentations we will hear about some of the innovative ways that the platform is now being used to further HD therapeutic development, including genome-wide association studies, disease modelling, experimental design and statistical rigor, next-generation HD assessments, study/trial feasibility, *in silico* recruitment, and open science. There will also be a resource fair on Sunday and Monday evening that showcases some of the resources available to aid your own research, including posters outlining some of the ongoing and upcoming platform studies (see Studies & Initiatives section in this program book). We hope that at Congress you will find new resources and collaborators to inspire your own research ideas.



CLINICAL STUDIES AND OTHER INITIATIVES

Platform studies are an integral part of the Enroll-HD ecosystem. At the Congress there will be posters at the Sunday and Monday evening resource fairs that describe in detail some of the ongoing and upcoming clinical studies and aligned initiatives that can help your research, and abstracts describing those studies and initiatives are collected here. At the resource fairs you can also find details of the communal resources and services that Enroll-HD offers, including support for clinical trial sponsors to aid study site selection and management, and participant eligibility and recruitment.

Enroll-HD

Enroll-HD is a clinical research platform that includes at its core a prospective observational study of HD. The objectives of Enroll-HD are: 1) enhance the design and expedite the conduct of clinical trials; 2) improve the understanding of the phenotypic spectrum and disease mechanisms; 3) foster good clinical care.

Over 15,000 currently active participants have been recruited from 18 countries and 161 study sites. The data collected from these participants is monitored using a rigorous risk-based process. Recoded data and biosamples are made available to researchers. Enroll-HD also serves as a registry that can be used to facilitate recruitment by identifying potentially eligible participants who can be invited by investigators to participate in clinical trials. To improve support for future clinical trials, the study will now begin to prioritize the recruitment of premanifest and early-stage disease participants. Platform studies are additional clinical studies that utilize at least one or more Enroll-HD platform service, which include site feasibility, study guidance documents and templates, potentially eligible participant listings, study set-up support, monitoring and data management.

The Enroll-HD Clinical Training Portal is an online resource launched in January 2017 where HD research personnel can complete and maintain study-relevant training, presently UHDRS Motor Certification (all users) and GCP (Enroll-HD Study users only). There are currently more than 1300 registered users, and it enables faster, more cost-effective start-up of clinical trials and studies, standardizes the quality of training, and reduces workload at sites.

Enroll-HD plasma collection

Increasing demand for high-quality plasma samples has led to a change in the Enroll-HD biosample collection—in addition to PBMCs, from late 2018 EDTA plasma samples will be collected from select sites. The goal is to collect longitudinal EDTA plasma samples annually from 2-3000 HDGECs at all disease stages, with a focus on premanifest and early-stage participants, plus another 10-15% of EDTA plasma samples from gene-negative family members and family-control participants.

The current Enroll-HD study protocol and informed consent forms already include plasma collection, but a minor site agreement change will be necessary to allow for an additional extended procedure payment to sites. Enroll-HD sites will be identified according to eligibility criteria (including having trained staff to collect and process the samples, a 4°C centrifuge, and a -80°C freezer to store aliquoted samples until shipment) and invited to participate in the plasma collection.

Enroll-HD Lite

Enroll-HD Lite will be a new observational study protocol that includes a leaner assessment battery designed to continue to follow Enroll-HD study participants longitudinally as they progress into moderate- to late-stage disease, offering a reduced visit burden whilst collecting critical milestones of disease progression. Participants will transition from the established Enroll-HD protocol and there will be no biosample collection. Enroll-HD Lite baseline study assessments will take place at the study site, and annual follow-up visits may take place either at the study site or via a phone contact visit. Eligible participants will include moderate- to late-stage HDGECs and control participants, and the study will have a phased roll out with the first wave expected to recruit between 500-800 participants from approximately 15 Enroll-HD sites. After this initial phase an interim analysis of the Enroll-HD Lite dataset will guide the overall study population size and global reach.

HD-Charge: Indirect and out-of-pocket costs of HD in the US

As HD progresses patients require more medical care, caregiver support and long-term care. From a societal perspective the economic burden associated with HD needs to be considered to provide guidance and resources for health policy development, but there is very little data available on the direct or indirect costs of the disease. A previous retrospective study summarized the direct medical costs of HD in the US using commercial and Medicaid claims data, but other economic aspects of HD have not been analyzed. HD-Charge aims to quantify the indirect and out-of-pocket costs of disease on both HDGECs and companions in the US to produce inputs for an interactive burden of illness model for HD. HD-Charge is a single-assessment, cross-sectional online survey administered to HDGECs

and companions. Approximately 240 participants will be recruited across 8-14 active Enroll-HD sites representing diverse geographical US regions. An equal number of HDGECs (CAG length ≥ 40 , diagnostic confidence level = 4, adult onset of disease) and companions from each stage of the disease (early, middle, late) will be targeted. A resource utilization questionnaire to capture information on medical services used by HDGECs and their comorbid conditions will also be completed by the site. Study recruitment is expected to start in Fall 2018 and continue for around 2.5 years.

FuRST 2.0: Cognitive pre-testing study for a new functional rating scale for HD

Many HD therapeutics in development aim to intervene earlier in disease course and slow progression. The Total Functional Capacity (TFC) is part of the Unified Huntington's Disease Rating Scale (UHDRS) and is most commonly used to measure function in manifest HD patients. However, for early-stage HD there is a ceiling effect and new functional rating scales that are more sensitive for earlier disease stages are needed. Advocacy groups and regulatory agencies have endorsed collecting patient-reported outcome (PRO) data.

The overall goal of the FuRST 2.0 program is to use clinimetric techniques to develop a valid and reliable functional rating scale to evaluate premanifest and early-manifest HD. FuRST 2.0 is being developed using PRO methodologies including focus groups, Delphi panel, cognitive pre-testing (CPT) and validation, and these are being implemented using Enroll-HD platform resources such as recruitment sites, participants, and monitoring capabilities. CPT is an iterative process with the main objective being to test items for understanding and determine the need for refinements. CPT Round-1 was successfully completed 3 months ahead of schedule and included 75 participants: 20 early-manifest HDGECs (CAG ≥ 36 , TFC ≥ 7 , Diagnostic Confidence Level (DCL) = 4) and 20 of their companions, 20 premanifest HDGECs (CAG ≥ 40 , DCL ≤ 3 , Disease Burden Score (DBS) ≥ 250) and 15 of their companions. Scale items were modified, and second round CPT is expected to start in Q4-2018.

HD-CAB Longitudinal Study

Cognitive impairment is a core feature of HD, affects quality of life, and has been targeted for treatment in clinical trials. The HD-Cognitive Assessment Battery (HD-CAB) consists of 6 tests evaluating attention, processing speed, visuospatial processing, timing, emotion processing, memory, and executive function in HD and was designed for use in clinical trials. Following the guidance of the clinical outcome assessment qualification process of the FDA, the HD-CAB Longitudinal Study will evaluate the longitudinal measurement properties of the HD-CAB in 250 HDGEC participants (50 early-manifest, 100 premanifest, and 100 comparison participants) for use in premanifest and early-manifest HD. HDGEC inclusion criteria include current Enroll-HD participants 18 years or older with a Total Functional Capacity score of 7-13, CAG-repeat length ≥ 36 . Initial recruitment will take place at 40 Enroll-HD sites in 8 countries comprising English speakers and at least 2 other languages. The study is expected to run 2019 through 2023 and will mimic a clinical trial with study visits every 4 months for 36 months. HD-CAB longitudinal measurement properties will be evaluated, including longitudinal construct validity, ability to detect change, and to provide a methodology to evaluate individual change in premanifest and early-manifest HD on the HD-CAB composite score and each of its six individual tests.

iMarkHD

iMarkHD is a longitudinal adaptive study of molecular pathology and neuronal networks in HDGECs and healthy controls (HC) using positron emission tomography (PET) and multi-modal magnetic resonance imaging (MRI). The study's primary goal is to establish a comprehensive understanding of disease-related changes taking place across the basal ganglia and cortex during HD progression. Molecular expression data acquired from four (CB_1R , PDE-10A, 5HT_{2A}R and H₃R) PET ligands will provide an assessment of change in key signaling pathways known to be affected during HD. The multi-modal MRI protocol (sMRI, fMRI (BOLD and ASL), dMRI and QSM) will assess changes in structural and physiological parameters co-occurring with molecular change measured by PET in the same participants. Approximately 113 participants (HDGECs and HC) are planned in total to be enrolled within 2 cohorts and three groups spanning premanifest, perimanifest and manifest HD; the study will run approximately 5 years and includes baseline, year 1 and year 2 longitudinal assessments. The study will recruit adults between 21 and 75 years of age at time of screening and take place in the UK. The combined collection of molecular, structural and functional measures is unprecedented and is expected to identify novel markers of disease progression and treatment response in HD therapeutic development.

iRestHD: A multimodal investigation of resting state brain activity through simultaneous PET/MRI in manifest and premanifest HD

One of the most urgent requirements for HD clinical research is the development of biomarkers to evaluate therapeutic interventions. Preliminary work has revealed different glucose metabolism patterns in manifest and premanifest HDGECs when the brain is at rest (i.e., without performing any task), but further research is needed into PET and MRI resting-state biomarkers. iRestHD is a cross-

sectional study that will investigate four functional properties of the brain at rest: (1) glucose metabolism by means of ^{18}F -FDG PET; (2) blood perfusion by means of arterial spin labeling MRI; (3) functional connectivity by means of fMRI; and (4) electrophysiological activity by means of quantitative EEG. To measure the same brain activity, PET and MRI data will be collected simultaneously using a Siemens Biograph mMR scanner. Eighty participants will be recruited from 5-15 North American recruitment sites; 20 premanifest HD, 20 manifest HD, and 40 healthy controls. The stability of the findings will be carefully assessed in a subset of 16 participants with test-retest assessments separated by 24-72 hours. The primary objective is to identify glucose metabolism patterns that differentiate premanifest from manifest HD patients. Secondary objectives include similar research on the other modalities and, importantly, the investigation of inter-modality relationships in search of any modality as a potential biomarker of disease progression. The study will start in 2019 and is expected to run for about 2 years.

iMagemHTT

iMagemHTT is an adaptive PET imaging study that will explore the binding and kinetic properties of two novel PET tracers for mutant huntingtin (mHTT) protein and their suitability for quantification of aggregated mHTT in the brain of HDGECs compared with healthy controls (HC). Currently there is no way to measure mHTT in the brain and a cognate PET tracer would provide a methodology to follow the progression of HD and support the development of mHTT-lowering therapeutics.

Both PET tracers can detect mutant but not normal HTT in HD mouse models and have been tested for safety in animals; this will be the first time these tracers are administered to humans. The study cohort will comprise 84 participants: 18 stage 2, 12 stage 1 (each manifest group CAG \geq 36, burden of disease score (BOD) \geq 250), 12 premanifest (CAG \geq 40, BOD \geq 250) HDGECs, plus 42 HCs; participants of both sexes, age 20-65, BMI 19-35. There will be two phases to the study: Phase 1 will determine whether the tracers are suitable for PET imaging in humans and can detect mHTT in the brain by evaluating binding and kinetics in young HC and stage 2 HDGECs; Phase 2 will focus on quantifying mHTT and test-retest variability of the tracers in premanifest, stage 1 and stage 2 HDGECs compared to age-matched HCs. Study results could lead to the development of a method to quantify mHTT in the HDGEC brain. The study will begin Q4 2018 and run until Q3 2021.

HDClarity: A multisite cerebrospinal fluid collection initiative in HD

Cerebrospinal fluid (CSF) is ideal for assessing HD biomarkers, particularly pharmacodynamic markers, due to its proximity to the brain. HDClarity is a multisite study that aims to establish the largest, highest-quality repository of CSF from well-characterized HDGECs and matched controls to expedite research into biomarkers and evaluate pathways to enable development of novel HD therapeutics.

The study aims to recruit >1200 participants from individuals in Enroll-HD with premanifest HD (UHDRS Diagnostic Confidence Score (DCS) < 4; CAG \geq 40), manifest HD (DCS = 4; CAG \geq 36), and healthy controls. CSF and blood are collected using a standardized protocol and sampling kit. Participants attend a screening visit and a sampling visit and some are invited to return for a repeat sampling visit 4-8 weeks later. Clinical and phenotypic data are also collected. Over 300 CSF samples have already been collected and recruitment is ongoing. Samples have already been distributed to investigators for pre-specified analyses.

ImageClarity

The HDClarity study is collecting high-quality cerebrospinal fluid samples, blood samples, and phenotypic data from an expected 1,200 HD participants in 15 countries, and proteomic and hematic analyses on these samples aim to identify biomarkers that closely track disease progression. However, it is currently unclear whether the anomalies observed in wet biomarkers reflect changes in specific brain regions (i.e., degeneration) or more generic changes throughout the whole brain. Non-invasive neuroimaging might track the same underlying pathological processes and potentially emulate or enhance the predictive value of wet biomarkers. The imageClarity study will image approximately half of HDClarity participants to investigate the relationship between wet biomarkers obtained from HDClarity and the neuroimaging features obtained from MRI. For each imageClarity participant a rich multimodal MRI dataset will be collected, allowing investigation of structural morphometry, white matter microstructure, tract degeneration, demyelination, functional connectivity, oxygen consumption, blood perfusion, and metabolic anomalies. A number of imaging sequences are new to HD research and will provide novel insights on mechanisms of disease progression. Importantly, all sequences are non-invasive to minimize participants' burden. The protocol will be harmonized between sites using the same scanner model (Siemens Prisma 3T). In sum, imageClarity is geared to build a robust dataset and a number of analysis tools that will enable the investigation of complex relationships between wet biomarkers and neuroimaging features. The study is expected to start in 2019.

Origin-HD: Genetic modifiers of HTT CAG intergenerational repeat instability in male HDGECs

Earlier disease onset in subsequent generations, called anticipation, has been observed in HD families and is attributed to an increased CAG-repeat length in the *HTT* gene. CAG-repeat length mutations are referred to as repeat instability and genome-wide

association studies suggest that genomic variants function as genetic modifiers of disease onset, for example by affecting DNA repair mechanisms. Origin-HD aims to investigate CAG repeat instability in germline and somatic cells and evaluate for correlations with putative genetic modifiers. Understanding the mechanisms that modulate repeat instability may yield testable targets for future interventions.

Starting Q2 2019, over 1,000 male HDGECs (ages 18-55) already participating in Enroll-HD will be recruited over about two years using a non-targeted sampling approach, approximately balanced between premanifest and manifest disease. Allele and genotype frequency for each pre-specified variant of interest will be assessed after about 500 participants have been recruited. If the predicted detectable effect size is $d > 0.35$ in the final sample of 1,000 participants, a recall-by-genotype recruitment approach will be adopted in parallel to the original non-targeted approach. The repeat instability in DNA from sperm and blood of study participants will be analyzed, and genetic modifier variants will be determined.

Huntington's Disease Young Adult Study (HD-YAS)

HD-YAS will study a cohort of young adult HDGECs decades before expected symptom onset to characterize the very earliest signs of disease-related brain changes and identify whether there is any identifiable early functional impairment. Currently there is no detailed characterization of such a young adult HDGEC cohort and this represents the earliest time point after predictive genetic testing in which to gain disease insights. HD-YAS will be important in determining the earliest potential time window for therapeutic intervention.

HD-YAS will recruit 120 participants—60 premanifest HDGECs and 60 gene-negative family members or family controls—and will use a cross-sectional comparison with one visit per participant to assess the earliest time-point at which neurodegeneration can be detected. Participants will undergo 3T Volumetric MRI, rsfMRI and task fMRI, NODDI, and cognitive assessments including the CANTAB and EMOTICOM batteries, and biosamples such as CSF, blood and DNA will be collected to investigate biomarkers.

Participants will be 18-40 years old, and at-risk individuals must have a predictive genetic test to determine whether they carry the *HTT* gene (gene-carrier) or not (control). Individuals must not show any clinical symptoms of HD, have a disease burden score of ≤ 240 , and must be willing and able to comply with the study visit and study procedures. HD-YAS began in August 2017 and is expected to complete by July 2019. HD-YAS collaborates with Enroll-HD to identify potentially eligible participants throughout the UK who could be invited to participate.

OTHER INITIATIVES

Huntington's disease progression and stage modeling

There is some evidence that mild and progressive symptoms of HD often emerge 10-15 years prior to formal clinical diagnosis. With the ultimate therapeutic aim to slow HD progression in its earliest stages it is imperative that we have a thorough quantitative understanding of any subtle yet significant clinical signs and symptoms exhibited during this long pre-diagnosis period. In particular, clear knowledge of the dynamic progression of HD through the early stages is critical for strategic timing of therapeutic interventions, particularly at earlier stages, and related clinical trial design. Such knowledge could change the way we think about the course of HD.

Through various interdisciplinary modeling collaborations, the disease progression and stage modeling initiative at CHDI aims to advance development of next-generation statistical and data-mining functions to describe and quantify the time course of HD. The initiative engages with a number of key industry and academic collaborators in order to systematically analyze and develop progression and staging models based on HD natural history study datasets, such as that from Enroll-HD. Due to the interdisciplinary nature of these collaborations we anticipate they will have direct effects on HD clinical practice, as well as be of scholastic interest to clinicians and preclinical researchers alike. Models developed to date have informed about premanifest HD stages and helped identify potential trajectories that different sub-groups of HD patients take over the course of their disease.

Experimental design and scientific rigor

The generally low reproducibility of all scientific research is a serious concern; spurious research findings misdirect research effort and waste resources, often including patient time and goodwill. CHDI has established a number of resources for the research community to improve the quality and reproducibility of HD research, including the formation of a committee of independent experts in research methods and statistics that can provide unbiased evaluation and advice regarding all aspects of experimental design and statistics. The Independent Statistical Standing Committee (ISSC) provides a number of services, including experimental design expertise (e.g., sample size/power calculations) and critical evaluation of study materials (e.g., statistical analysis plans), and CHDI makes this resource available to the HD research community on a priority basis. CHDI is also investing in activities to promote best practice in data analysis and reporting to further improve scientific rigor.



Huntington's Disease Regulatory Science Consortium – HD-RSC

The Huntington's Disease Regulatory Science Consortium (HD-RSC) was launched in March 2018 with the overall goal of accelerating HD therapeutic development. This international collaboration builds upon CHDI's established leadership in HD and C-Path's regulatory science and data science core competencies. Already, more than 20 partner institutions from industry, academia, government, and patient advocacy organizations have joined this initiative to share data and expertise to advance innovation in regulatory science methods and collectively tackle challenges for HD drug development. The HD-RSC will provide a forum and structure to bring together the HD community for data contribution and tool development, and these assets will be made publicly available to develop new therapies more efficiently and to de-risk the drug development pathway. Towards this mission, the HD-RSC has already worked to establish HD specific consensus data standards for clinical trial use, and will acquire patient-level data from HD observational studies and clinical trials to build an integrated database. Through this standardized database, the HD-RSC will advance the development of quantitative modeling tools incorporating disease, drug, and clinical trial features, to select optimal trial designs as well as promising biomarkers and clinical outcome assessments for use in HD trials. The consortium will engage regulators early and often to align on areas of high unmet need and to reach regulatory acceptance of leading drug development tools. The launch of the HD-RSC aligns with recent progress in understanding disease pathophysiology, the identification of new therapeutic targets, and the increase in pharmaceutical companies now advancing therapies for HD.

