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Enroll!

Updates from the Enroll-HD global community

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DECEMBER 2024

WELCOME TO *ENROLL!* 2024

Cristina Sampaio

The atmosphere at EHDN & Enroll-HD 2024 was lively and uplifting

2024 has been an incredibly busy year for Enroll-HD! Work developing and finalizing the updated protocol for Enroll-HD 2.0 has almost been completed, and this will modernize HD research. The EHDN & Enroll-HD 2024 meeting in Strasbourg provided an important opportunity to share these updates with the wider HD community, and it was wonderful to see so many of you there. The vibrant and dynamic atmosphere shared by clinicians, researchers, and those affected by HD ensured that the meeting created lasting memories as well as a renewed sense of purpose.

There is no doubt that HD research is robust. Enroll-HD data from more than 30,000 participants in the database—of whom more than 21,000 are still currently enrolled at more than 150 sites in 23 countries worldwide—has been used to support the design and implementation of more than 25 clinical trials, among other projects. We are very proud of what has been achieved by Enroll-HD over the past 12 years. As we roll out Enroll-HD 2.0 in 2025, we look forward to making even greater strides in advancing HD research.

Cristina Sampaio
Chief Medical Officer, CHDI

EHDN & Enroll-HD 2024

In September this year, Enroll-HD and EHDN collaborated to create a unique event combining the bi-annual EHDN Plenary Meeting (Day 1), EHDN and Enroll-HD joint program (Day 2) with the Enroll-HD Congress (Day 3). More than 1,100 delegates convened in the city of Strasbourg, France, to enjoy scientific and clinical presentations, special meetings, networking opportunities, and social events. We share some highlights from the Enroll-HD component of the meeting here.

KEYNOTE LECTURES

Sarah Tabrizi (University College London) discussed mechanisms of pathogenesis, therapies under development, HD-YAS (longitudinal study of young adults who have the expanded gene), and promising feedback from the Food and Drug Administration (FDA) on biomarker integration into the drug development process.

Harry Orr (University of Minnesota) presented on CAG-repeat disorders and proposed that if we can better understand the pathogenic similarities and differences between HD and other inherited conditions such as spinocerebellar ataxia type 1 (SCA1), we can move closer towards the overarching goal of developing effective treatments.

Michael Panzara (Neurvati Neurosciences) delivered a stimulating lecture on the use of innovative trial designs to accelerate drug development, drawing on his extensive experience in developing therapies for neurological disorders.

Genetic Modifiers and Somatic Mosaicism (Parallel Session)

Bob Handsaker (Harvard Medical School) presented on the "ticking DNA clock" of somatic instability, the process through which the already expanded region of CAG repeats in the mutant huntingtin (mHTT) gene grows even larger over time.

Davina Hensman Moss (University College London) discussed a recent project looking at the DNA of sperm and blood of men with HD (Sperm-CAG) and how this work might develop.

Development and Aging in HD (Parallel Session)

Oliver Bartley (Cardiff University) described work using medium spiny neurons derived from human pluripotent stem cells and reminded us of the need to understand the advantages and disadvantages of different experimental models.

Sandrine Humbert (Paris Brain Institute) took a neurodevelopmental approach in tracing a path from embryonic and post-natal development to before and after clinical motor diagnosis in adulthood.

Practical Deployment of HD-ISS in Clinical Research

Cristina Sampaio (CHDI) recapped on the development of the Huntington's Disease Integrated Staging System (HD-ISS) and considered the opportunities and challenges it now offers as a research tool.

Jeffrey Long (University of Iowa) continued on this theme and showed how the HD-ISS may be used in the planning of clinical trials. The session concluded with a stimulating panel

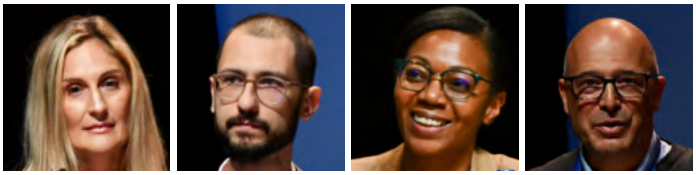
From left to right: Sarah Tabrizi, Jeff Long, Cristina Sampaio, Amy-Lee Bredlau, Abi-Saab Walif, Peter McColgan, Glenn Morrison, Chris Ross

discussion involving **Abi-Saab Walid** (uniQure), **Peter McColgan** (Roche), **Amy-Lee Bredlau** (PTC Therapeutics), and **Glenn Morrison** (Annexon Biosciences).

Advances Obtained Through Enroll-HD

Three sessions were specifically dedicated to advances gained through the Enroll-HD study and clinical research platform.

In the first, **Katrin Barth** (EHDN), **Jong-Min Lee** (Harvard Medical School), **Douglas Langbehn** (University of Iowa), and **James Mills** (University of Iowa) presented on biomarkers and modeling.



In the second session, **Jenny Townhill** (EHDN), **Marcelo Boareto** (Roche), **Jamie Hamilton** (CHDI), and **Joaquim Ferreira** (University of Lisbon) discussed different aspects of support for clinical trials and clinical studies in HD.

In the third session, **Priyantha Herath** (Alnylam), **Andrew Wood** (CHDI), and **Tiago Mestre** (University of Ottawa) discussed novel approaches to clinical trial design, providing exciting insights into the future of HD research. **Patrick Weydt** (Bonn University and EHDN) concluded the sessions with an insightful discussion on the next steps toward achieving clinical benefit from clinical research.

Additional coverage of EHDN & Enroll-HD 2024 has been published in the November issue of EHDN News (see https://ehdn.org/ehdn-newsletter-53rd-edition), and recorded presentations from the Enroll-HD component of the meeting are now available on the Enroll-HD website (https://www.enroll-hd.org).

From left to right: Fiona Loveday, Jolie Lewis, and Marta Laciak (Language Area Coordinators)

Enroll-HD 2.0: Why, What, When?

Swati Sathe is the Medical Vice President at CHDI. In addition to heading up the statistics and modeling team, her role includes providing input on key medical and scientific issues relating to clinical research across a multitude of studies. As presented at EHDN & Enroll-HD 2024, Enroll-HD 2.0 brings some very exciting developments to HD research. We caught up with Swati to find out more about what Enroll-HD 2.0 means for participants.

Why is Enroll-HD changing?

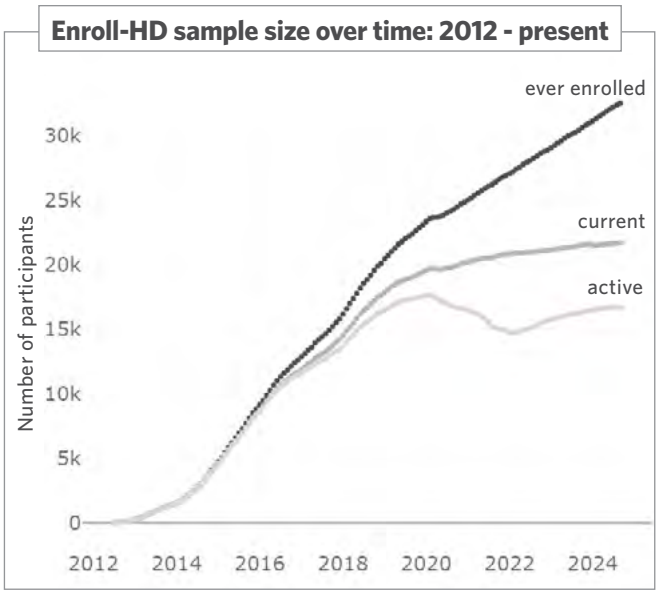
Enroll-HD has been a success story—it has met its objectives, recruited a tremendous number of participants, and provided valuable data and outputs over the past 12 years. We now need to change Enroll-HD to move with the changing landscape of HD research. In particular, clinical trials are focusing on participants much earlier in the course of their disease, so Enroll-HD should be prepared to meet this need.

Enroll-HD 2.0 is an amendment to the original protocol rather than a new study, and the key changes will be to enrollment, recruitment, cohorts, and assessments.

How will enrollment and recruitment change in Enroll-HD 2.0?

Rather than recruit as many participants as possible, Enroll-HD 2.0 will aim to recruit a manageable number of participants, around 25,000 active participants in total, and, using the HD-ISS, implement a strategy to ensure that more participants in the early stages of the disease take part. The HD-ISS was designed to objectively describe the trajectory of HD over the lifespan to facilitate clinical research (for more details on HD-ISS, see our interview with Swati

EHDN & Enroll-HD 2024 delegates were keen to hear about Enroll-HD 2.0



Enroll-HD has recruited extensively over the past 12 years

in 2023: https://www.enroll-hd.org/enrollhd_documents/newsletters/winter-2023.pdf).

How will cohorts change?

Participants will initially be placed into one of three cohorts (A, B or C). For participants with HD, this assignment will be based on their HD-ISS score (i.e., Stages 0–1: before clinical motor diagnosis; Stage 2: early; Stage 3: late). The transition between cohorts will be determined by each participant's clinical status and assessment scores, and fully explained before recruitment and throughout the duration of the study. As always, participants will have the opportunity to ask questions.

How will assessments change?

A major benefit of placing participants into cohorts is that assessments will now be tailored to each cohort, meaning that the utility of the data collected, such as imaging and biosamples, will be maximized while the testing burden on participants is reduced. Increased flexibility will also be offered with the introduction of online/telephone visits for some participants.

Alongside Enroll-HD 2.0, a new biobanking protocol will enable CHDI to store and distribute vital data as well as collect additional biosamples. The CHDI Biobank will create a standardized and clearly defined process for the collection, storage, and sharing of biological samples and data from participants with HD and control participants. These changes will meet evolving regulatory requirements and also expand available data to meet research needs. We believe that the CHDI

The breaks offered a great exchange platform

Biobank will help accelerate the development of biomarkers in HD research, allow further investigation into the genetic and environmental factors that affect HD pathophysiology, and inform the development of disease progression models and clinical assessment tools.

When will these changes take place?

The planning for Enroll-HD 2.0 started in 2023, and preparation took place throughout 2024. As we move into 2025, we hope that study sites will start with the new protocol. We look forward to seeing the implementation of these important developments and sharing updates in due course.

FuRST 2.0: A Scientifically Validated Measure of Functional Ability

Neha Sinha, PhD, is the Director of Clinical Assessment Methodology at CHDI. She plays a key role in developing and evaluating clinical outcome assessments to better understand HD pathophysiology and assess the impact of interventions on disease progression. We spoke with Neha to find out more about the development and introduction of FuRST 2.0.

Why is functional ability in HD important to study?

Functional ability refers to an individual's capacity to carry out daily activities essential for independence and well-being. This includes meeting basic needs, fulfilling roles within family and society, performing occupational tasks, managing financial responsibilities, and maintaining overall health. In HD, functional ability is vital to assess because it reflects the practical impact of disease progression on quality of life (QoL).

What are the pressing questions about functional ability in HD?

In HD, progressive neurodegeneration leads to motor, cognitive, and behavioral impairments that directly impact functional abilities. Loss of these skills often signals the transition to greater dependence on caregivers and a decline in overall QoL. As such, functional ability is a meaningful participant-oriented health outcome, and when combined with other outcome measures in clinical trials, it can provide data that connects neuropathological change with its impact on everyday life.

In people with HD, a decline in functional ability begins subtly in the period before clinical motor diagnosis and progresses throughout the disease; the timing and trajectory of these functional changes in early HD are not fully understood. However, currently there are no assessments of functional ability sensitive to the changes in the stages of HD prior to clinical motor diagnosis.

How can FuRST 2.0 help address these questions?

As HD research and clinical trials are increasingly targeting earlier stages of the disease, there was a need to develop a more sensitive functional measure. The Functional Rating Scale 2.0 (FuRST 2.0) was developed to provide a fit-for-purpose, scientifically validated, functional patient-reported outcome (PRO) measure sensitive to the earliest functional decline in HD.

What will FuRST 2.0 assessments involve for participants?

The FuRST 2.0 is a 24-item PRO that assesses functional ability without considering the underlying cause. It covers the respondent's functional ability over the past two weeks and assesses a range of functional abilities, including the ability to work, manage finances, social interactions, and independence in the home environment.

Have these assessments been validated?

The development of FuRST 2.0 followed a rigorous, data-driven, iterative process to ensure its content validity, which, more simply, means that it accurately measures what it is intended to measure. This process included focus groups to identify symptoms currently experienced or starting to appear, Delphi Panel consultations to gather consensus from experts, multiple rounds of interviewing with HD participants and their companions to assess usability and comfort with sensitive topics, and input from a steering committee and regulatory agencies such as the FDA.

How will the data be used?

Participants in the Enroll-HD study are completing the FuRST 2.0 at their study site. These data will be analyzed to further evaluate the properties of the scale to support refinement and application in broader research and clinical contexts.

How will the introduction of FuRST 2.0 benefit HD research more broadly?

PROs play a crucial role in capturing participant perspectives on disease impact and assessing the benefits of therapeutic interventions. Despite their importance, PROs have been underutilized in HD clinical trials, largely due to concerns about meeting the rigorous methodological standards required by regulatory agencies.

The development of FuRST 2.0 highlights the value of iterative engagement with both the target population—in this case, people with HD—and regulatory agencies throughout the PRO development process. By exemplifying this patient-centered and methodologically sound approach, FuRST 2.0 sets a precedent for future PRO development and the broader adoption of such measures in HD research.

Reaching out about Enroll-HD

Key to the success of Enroll-HD is the work of dedicated site staff who reach out to meet new participants and maintain relationships with established participants. We met with team members across the Enroll-HD map to find out more about their roles and responsibilities.

Julie Koeppel undertakes the roles of Research Specialist and Enroll-HD Coordinator at the University of Iowa Huntington's Disease Center of Excellence.

What does a typical working day look like for you?

I start Enroll-HD visits by having a catch-up with the participant. I love hearing about what's happened over the past year and appreciate the opportunity to reconnect with participants.

From left to right: Peggy Nopoulos, Julie Koeppel, Amy Lemke, Annie Killoran

Everyone has an important story to tell. When the visit is completed, I like to enter data as quickly as possible after visits while it is all still fresh in my memory.

On days I don't have Enroll-HD visits, I spend the day reaching out to participants and liaising with them to coordinate clinic visits (or any other events that are happening for them) with Enroll-HD visits. I also stay in very close communication with our HD clinic coordinator—as we have a range of studies happening at any one time, I meet a lot of individuals and families affected by HD, and if they aren't already involved, I can always put people in touch with an Enroll-HD site close to home. Essentially, we work to ensure the research fits around what is best for participants.

How does Enroll-HD fit in with other studies at your clinic?

We have lots of other studies in HD, including drug trials. I think Enroll-HD provides a useful way to let people know about these other studies, and participants in Enroll-HD often share information about the study with family members and friends. Here in the Midwestern USA, our families are often big and connected, and extremely dedicated to HD research, where Enroll-HD plays a key role.

What stands out for you in terms of working with the HD community?

I've done lots of research, and throughout all of this, the hardest part is usually recruitment. In the past, I would sometimes feel like a salesperson giving a spiel in the hope of gaining another participant. With Enroll-HD participants, it's the complete opposite. These people are incredibly eager and energized about taking part in research because they want to make a difference for future generations. I don't think you often find that in research, and the endless dedication, perseverance, and courage that I see every day in our participants is incredibly inspiring.

Joie Hucko is the Outreach Coordinator at The Huntington Disease Care, Education, and Research Center at Georgetown. Joie joined this Centre of Excellence in 2022.

What does your role involve?

I'm the outreach coordinator for the center, which means that I'm responsible for getting the word out! If anything changes with any of the studies or if we have a new study, my job is to keep everyone informed, and I do this by sending out press releases, updating our monthly newsletter, and so on. When I started, a key goal was to reconnect with participants and families post-COVID-19. This kind of role didn't previously exist at the center so I've had a lot of agency in developing it.

When I meet individuals with HD and their families for the first time, I tell them how Enroll-HD is a great introductory study for people looking to get involved in research. The vast majority of participants in Enroll-HD are also involved in other studies—Enroll-HD is integral to all our research efforts.

On a day-to-day basis, my focus is on communicating with participants and families and also community providers such as long-term care facilities, therapists,

Community events are popular in Georgetown

and other teams we might make referrals to. The development of these relationships involves sharing knowledge about HD and working to streamline the referral process.

We have a number of support groups and I run one on virtual education, another for caregivers, and a young adults group. We also have quarterly community events, which are free events like bowling, 'paint and sip'—which is led by an instructor with drinks and snacks!—and games and trivia nights. Our main aim is to bring everyone together and provide the opportunity to talk, ask questions, and hear more about our research and what we do.

How many participants do you work with?

We work with about 250 individuals with HD and their families. As we serve Maryland, Virginia, and Washington DC, we have a very large service area. We also reach out to neighboring states and have individuals coming to us from further afield for clinical care. Our existing participants are very connected and engaged—which is wonderful! We are also committed to making sure that those who do not currently have access to this specialized care know who we are and what we do.

How do you keep in touch with so many participants?

I frequently keep in touch with participants through email, and we have a few different avenues for communication, including a YouTube channel (https://www.youtube.com/channel/UCA1dvafgh08rP17DlGTt2wg), where we post talks by people at our center on topics such as education, research, and the work that takes place at our site. I also run an Instagram page (https://www.instagram.com/georgetown_hd_cerc/) and post all our updates, including newsletters, there.

What does the future hold for HD research?

Across the board, we are seeing a shift towards studying the earlier stages of HD in younger people. This is key to Enroll-HD 2.0, and all sites will be thinking about how best to facilitate this. As I mentioned, we have a young adult support group—and this isn't a traditional support group; we primarily use a messaging app to keep in touch. This approach seems a lot more accessible and engaging for our young adults and allows us to build up a shared rapport. We know that for most young adults, symptoms won't appear for at least another 5 to 10 years, so Enroll-HD 2.0 will provide a low-burden way to get involved, allowing participants to continue their working and family lives while making a tangible contribution to research.


Danielle Buchanan and **Elizabeth Huitz** are key members of the Huntington's Disease Program at Vanderbilt University Medical Center, which received a Level 1 Center of Excellence designation from the Huntington's Disease Society of America in 2017.

How many people do you see at the clinic?

Elizabeth: We have about 400 individuals with HD who come into our clinic and about 500 individuals taking part in Enroll-HD, as this includes family members as well. While we primarily cover the southeast of America, people also come all the way from Florida, North Carolina, Pittsburgh, and Illinois.

Danielle: People have even joined us from Canada! Some of our families are quite big and have multiple generations. Even if they don't live in close proximity to one another, people still refer their family members to Vanderbilt on the basis of their positive experiences here and the opportunities to get involved in research.

How do you keep in touch with so many participants?

Danielle: If someone is coming in for an Enroll-HD visit, I like to pop in and see how they're doing. As I've worked with each person for the last seven years, we've built up a connection, and it's great to catch up in person. There is a weekly support group that our social work team hosts called "happy hour" that patients and caregivers can attend which has gotten great feedback and attendance.

How do you work with individuals who haven't been to the clinic before?

Elizabeth: People who haven't been before can understandably be very nervous. Our telephone numbers are readily available, and we fully appreciate that making that first call can be petrifying. When someone reaches out, we explain a bit about the clinic, what we do, and the opportunities available. We also invite them to come in, ask questions in person, meet the team, and so on. As we're a multidisciplinary team comprising genetic counselors, social workers, speech pathologists, neurologists, research coordinators, and others, we have something important to offer at every stage of the journey for the entire family.

What stands out for you about working in HD?

Danielle: The hope, resilience, and commitment to research in our HD families are all amazing. Perhaps most importantly, our participants are not taking part in research for themselves but for the next generation and beyond. It's incredible to witness and be part of.

Kate Fayer (Research Coordinator) and **Olivia Thackeray** (Research Assistant) are both based at University College London in the UK, where they work with Professor Sarah Tabrizi on an extensive HD research program.

What does a typical day look like for each of you?

Kate: I work on the project management side of things, which means making sure our files and notes are up to date and that everything is recorded as it should be. I am involved in a variety of research projects, but Enroll-HD is the foundation to most of this work.

Olivia: I work on lots of Enroll-HD day-to-day activities, including scheduling visits with participants and making sure we've got everything in place for these. It's always great to see the participants, and as we get to see each participant every year, we have the opportunity to build up a rapport.

How many Enroll-HD participants do you work with at UCL?

Kate: We have between 300 and 400 participants, and some travel quite a distance to come see us! Professor Tabrizi is well-known in the HD field, so we even have participants traveling from as far as Scotland. The effort that participants put in is amazing and the motivation to work towards progressing knowledge about HD is immense. It's a community effort.

How does Enroll-HD fit with other research projects conducted at UCL?

Kate: I think of Enroll-HD as the first step into research—it provides a really good first experience and allows participants to find out about the research process and hear about other projects going on. I find that our participants build up a sense of community, a sense of being part of something bigger because they know just how many people are involved and that the data are being used to better understand HD.

Olivia: There's definitely a sense of "Enroll-HD community," and participants love to hear about what we're doing. The willingness of participants to get involved in Enroll-HD and other projects really stands out for me. Given the genetic nature of HD, many participants have witnessed family members go through all kinds of hardship, and I think this motivates them to get involved in research and play a part in making a difference.

What does the introduction of Enroll-HD 2.0 mean for you?

Kate: It's an exciting time! With the introduction of Enroll-HD 2.0, big changes are ahead, all of which are aiming to bring us closer to finding treatments for HD.

Olivia: We are currently in the early stages of working towards implementing Enroll-HD 2.0. As always, participants are at the forefront of what we do, so we'll be talking with them, listening to their feedback, and making sure we can answer any questions as these developments progress.

Delegates at EHDN & Enroll-HD 2024

And Finally...

We conclude our 2024 issue of *Enroll!* with reflections from **Eileen Neacy**, Chief Operating Officer at CHDI. Eileen has worked at CHDI since 2007 and is responsible for CHDI's operations, including the Enroll-HD Platform.

This issue of *Enroll!* provides a fascinating snapshot of just how much can be achieved in a year! From the hugely successful meeting in Strasbourg to progress on rolling out the Enroll-HD 2.0 protocol, the collaborative determination and spirit of participants, researchers, and clinicians continue to make Enroll-HD a pioneering landmark study. The achievements of Enroll-HD are not only unique within the field of HD research but also within the study of rare diseases and medical science more broadly

Looking to the future, I am confident that the changes in Enroll-HD 2.0 will provide an even greater catalyst for clinical development and research. Collectively, there is much to be proud of, and I am thrilled to be part of this work.

Enroll! is a publication of CHDI Foundation, Inc., a nonprofit biomedical research organization that is exclusively dedicated to collaboratively developing therapeutics that will substantially benefit those affected by Huntington's disease. As part of that mission, CHDI Foundation sponsors and manages Enroll-HD. More information can be found at: www.chdifoundation.org

Editor: Simon Noble, PhD
Senior Science Writer: Catherine Deeprose, PhD
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Contact us at info@enroll-hd.org