EHDN & Enroll-HD 2024

Strasbourg, France

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Overview

More than 1,100 delegates convened in the city of Strasbourg, France, for EHDN & Enroll-HD 2024. This marked 20 years since the founding of EHDN and was also the first collaborative event to combine the bi-annual EHDN Plenary Meeting (Day 1), EHDN and Enroll-HD joint programme (Day 2) with the Enroll-HD Congress (Day 3). A range of scientific and clinical presentations, special meetings, networking opportunities, and social events took place over three days.

Abstracts have been published in the *Journal of Neurology, Neurosurgery, and Psychiatry*: https://jnnp.bmj.com/content/95/Suppl_1. Presentations from Day 1 and Day 2 can be viewed on the EHDN YouTube channel and photos can be viewed at http://www.artifox.com/ehdn-enroll-hd-2024-strasbourg/. Presentations from the Enroll-HD component of the meeting will be made available at https://www.enroll-hd.org/ and posters can be viewed at https://ehdn.org/ehdn2024/#posters.

Wednesday 11 September

Evening Session: Social Cognition in HD

This session for early arrivals was chaired by **Sarah Mason** (University of Cambridge) and **Hugh Rickards** (Birmingham and Solihull Mental Health NHS Foundation Trust).

Esther Cubo (Hospital Universitario Burgos) discussed the biomarkers that are associated with social cognitive deficits in HD. **Asmus Vogel** (Danish Dementia Research Center) described different dimensions of social cognitive processing and the impact that social cognitive deficits could have on everyday functioning in HD. He also introduced different methods to assess social cognition in HD, including behavioural observations and neuropsychological tests. Finally, **Sarah Mason** (University of Cambridge) presented on living with the real-world consequences of social cognitive deficits in HD. She talked about the lived experience of supporting someone with HD as shared by HD caregivers, the meaning they attributed to changes in social cognition, and the practical and emotional impact of supporting someone with HD who navigated the social world differently.

A panel discussion was held after the presentations.

Thursday 12 September

Welcome and Introduction

A warm welcome from **Anne Rosser** (Cardiff University), **Astri Arnesen** (European Huntington Association), **Christine Tranchant** (Strasbourg University Hospitals), and **Patrick Weydt** (Bonn University) set the stage for the presentations from experts across different aspects of HD.

Experiences from HD Family, Clinic, and Laboratory

Chaired by **Filipa Júlio** (European Huntington Association) and **Åsa Petersén** (Lund University).

Anne Elizabeth Saldarriaga Velez Magnusson (former caregiver, at-risk, HD representative) shared a moving, personal account of her experiences and her inspiring vision for the future. **Alexandra Durr** (Sorbonne University) discussed her pioneering work on pre-sypmptomatic genetic testing in France and work with HD families. Finally, **Erich Wanker** (Max Delbrück Center for Molecular Medicine) discussed his work as a protein scientist, and in particular, the role of Huntingtin protein in HD.

Keynote Lecture: History of Unstable Repeat Expansions

Chaired by **Frédéric Saudou** (Université Grenoble Alpes).

Jean-Louis Mandel (Institute of Genetics and Molecular and Cellular Biology, University of Strasbourg) presented an enthralling account of what we have learnt about unstable repeat expansions across different diseases over the past 30 years. Of particular interest was the timeline of repeat expansion discovery in human disorders along with discussion on what we have yet to learn.

20 Years of EHDN

Chaired by **Patrick Weydt** (Bonn University).

This special session featured insights and reflections from three EHDN members who have been instrumental in the inception and development of the organisation: **Bernhard Landwehrmeyer** (Ulm University), **Patrik Brundin** (Roche) and **Anne Rosser** (Cardiff University). Each speaker shared their personal recollections of the formation of EHDN and the trajectory to where we are now, sharing anecdotes, photographs, correspondence, and even previous meeting programmes, much to the appreciation of the audience. Key insights across the presentations included the importance of collaboration in the HD field, the necessity of adapting to the changing landscape, and the need to plan for future success.

Short Communications

Chaired by **Kathrin Reetz** (RWTH Aachen University) and **Eric Reits** (University of Amsterdam).

Nicola Hobbs (University College London) described insights into early stage brain atrophy and white matter changes in the absence of clinical symptoms that have been gained from neuroimaging conducted as part of the HD Young Adult Study (HD-YAS). **Nellie Georgiou-Karistianis** (Monash University) discussed brain-predicted age (the apparent age of an individual's brain as opposed to their actual age) as a sensitive measure of HD disease progression that can also be used to stratify individuals with HD. **Christelle Langley** (University of Cambridge) presented data obtained via HD-YAS, focusing on subtle changes in cognitive aspects of function in HD, even at the early stages, as identified with a range of neuropsychological assessments. **Cali Rioboit** (Monash University) considered whether the measures of cognition commonly used in HD research effectively capture the cognitive symptoms that are clinically meaningful to individuals with HD and their caregivers. **Una Jones** (Cardiff University)

presented on behalf of EHDN's Physiotherapy Working Group. She described work following the 2020 publication of clinical guidelines, which assessed the extent of implementation of these and the next steps in supporting wider accessibility and promotion. **Selene Capodarca** (EHDN and Director of Art4HD) concluded the session by presenting the valuable work of Factor-H in improving the lives of HD families in vulnerable communities through art.

Parallel Sessions I

A. Novel Disease Mechanisms and Corresponding Therapeutic Targets

Chaired by **Nicole Déglon** (Lausanne University Hospital) and **Romina Aron Badin** (François Jacob Institute of Biology).

Manuel Seefelder (Ulm University) started with key updates on the role of Huntingtin-associated protein 40 (HAP40) and its role in HD. Ongoing work is confirming some of the identified HAP40 interactors using complementary approaches, examining the role of HAP40 in mitochondria, and more closely looking at the role of the identified interactors in HD. Next to speak was **Karine Merienne** (Strasbourg University/CNRS), who discussed new insights into epigenetic dysregulation in HD. Recent research from her group indicates that the HD mutation accelerates epigenetic ageing in striatal neurons, promoting repression of identity genes as well as derepression of developmental genes. Finally, **Nicole Déglon** (Lausanne University Hospital) illustrated the potential application of gene transfer and editing technologies in HD. This included the use of adeno-associated vectors and the KamiCas9 self-inactivating gene editing, as well as research into the long-term consequences of wild-type HTT inactivation in striatal and projection neurons of adult mice.

B. Cognitive Symptoms and Rehabilitation

Chaired by **Anne-Catherine Bachoud** (Paris Est University) and **Saul Martinez-Horta** (Sant Pau Hospital).

The session was opened by **Katharine Huynh** (Monash University) who presented results from a pilot trial of computerised cognitive training in Huntington's disease. Results from this pilot trial suggest the feasibility of a larger-scale trial, as well as the potential benefits of cognitive training to executive functions and grey matter volumes in the brain. She was followed by **Remy Nguyen** (AP-HP), who discussed speech as a predictor of clinical features in HD, and how this was the first step in developing new tools to assess individuals with HD in daily life remotely. **Arnau Puig-Davi** (Hospital de la Santa Creu i Sant Pau) focused on language disintegration in HD. He demonstrated how language impairment is an integral part of the cognitive phenotype of HD, with severity associated with structural disintegration and functional abnormalities in large brain territories. He concluded that language assessment is an accessible and potentially useful tool to detect early cognitive changes based on the biology of HD.

Parallel Sessions II

A. Metabolic Dysfunction in HD and Related Neurodegenerative Disorders

Chaired by **Luc Dupuis** (University of Strasbourg) and Patrick Weydt (Bonn University).

First to speak was **Maria Pennuto** (University of Padova), who described spinal and bulbar muscular atrophy (SMBA; also known as Kennedy disease) and drew parallels between this neuromuscular disease and other polyglutamine (polyQ) diseases, including HD. Her research in animals points to skeletal muscle and peripheral tissues as a therapeutic target in SMBA and beyond. **David Vilchez** (University of Cologne) explained the beneficial effects of moderate cold temperatures in extending

the lifespan of several species (e.g., mice) and the importance of the proteasome activator PSME3 in this. Critically, for understanding human disease prevention, he presented a rationale for studying plants, which express hundreds of polyQ proteins but do not develop pathologies such as HD. Finally, **Erik Storkebaum** (Radboud University) focused on the hypothesised role of an imbalance between the amount of tRNA available in a cell to balance the demand for codons from messenger RNA (mRNA) in triggering peripheral neuropathy in HD. Suported by experimental evidence, he also discussed the implications for novel therapeutic approaches.

B. Palliative Care in HD: Myths and Potentials

Chaired by **Jaime Kulisevsky** (Sant Pau Hospital) and **Alzbeta Mühlbäck** (Ulm University).

Berend Feddersen (Ludwig-Maximilians-University of Munich) discussed the importance of advance care planning in HD. **Erik van Duijn** (Leiden University Medical Centre and Topaz) considered the inherent need for an early palliative approach to care in HD, which includes both physical, psychological, social and existential needs. A palliative approach to care is patient-centred, provided proactively by multidisciplinary teams that prioritise the well-being and autonomy of patients and their care partners.

EHDN Business Meeting

Anne Rosser delivered this session and quickly moved to the results of the Executive Committee (EC) elections. We heard that Anne would be stepping down along with Alzbeta Muelbaech, Caterina Mariotti, and Jaime Kulisevksy. Newly elected members Ahmad Aziz, Nayana Lahiri, Esther Cubo, and Hoa Nguyen were congratulated and introduced themselves on stage.

The constitutional amendment to include one person on the EC representing the European community of families with HD as appointed by either the European Huntington's Association or other organisation, as determined by the EC, was accepted by voters.

Anne recapped on key activities since 2022, including the appointment of joint Science Directors Flaviano Giorgini and Julianna Bronzova. We were reminded of the process for endorsing clinical trials and were shown a snapshot of the studies endorsed since the last plenary meeting. We also heard that 10 Lesley Jones Seed Funds have been awarded since 2022, with pilot projects spanning from molecular genetics to much more clinically orientated work.

After a summary of current working groups and task forces, we heard how the Fluid Biomarker working group has undergone a shift in focus and ways of working, illustrating how working groups can adapt over time. In terms of outputs, the Neuroimaging working group has recently published a review paper in the Journal of Huntington's Disease, the Physiotherapy working group has published guidelines which have been translated into different languages, and the Incidental Findings task force has published best practice guidelines on reporting incidental findings in genomic studies. The Advanced Therapies working group has been highly active, and several task forces have been set up to address the various challenges in translating advanced therapies to the clinic.

We were reminded about the success of the Working Groups Virtual Forum held in September 2023 and how new collaborations and ideas have emerged from this. One of these is the EHDN Strategic Fund, which will be piloted over the coming year, aiming to support working groups and task forces in meeting their strategic aims (next round in March 2025). Excitingly, EHDN (led by Flaviano Giorgini) has been developing a Marie Curie Doctoral Network grant application (STRIVE-HD) for submission in November.

We also heard about revisions to EHDN's Scientific Strategy (covering 2023–2028). While EHDN's mission hasn't changed, the aim is to take into account the changing landscape and new opportunities in HD research. Activities related to this include the EHDN Regulatory Science Initiative (EHDN-RSI) seeking to facilitate the implementation of ongoing and future clinical trials on key issues of regulatory importance. The first project is working with the European Medicines Agency on the qualification of the HD Integrated Staging System (HD-ISS). Another initiative is the development of a brain bank for early-stage post-mortem brains. It is also hoped that EHDN Platform Meetings (as held previously with Prilenia and Roche) will continue, and further ideas for this are being discussed by the Think Tank.

As part of the strategic plan, EHDN continues to focus on communication and education. In addition to the usual activities (e.g., EHDN website, newsletter, social media, and supporting Think Tank projects), new projects for the Communication and Education Group include podcasts, the Fellowship Impact Project, and supporting education initiatives.

Friday 13 September

Delegates were welcomed to the second day of the meeting by **Anne Rosser** (Cardiff University), **Jenna Heilman** (Huntington's Disease Youth Organization), and **Cristina Sampaio** (CHDI).

Update on Ongoing Clinical Trials

Chaired by **Ahmad Aziz** (German Center for Neurodegenerative Diseases) and **Tiago Mestro** (University of Ottawa).

First to speak was Raúl Insa (**SOM Biotech**), who described SOM's artificial intelligence platform used to identify known drugs suitable for repurposing in HD. On this basis, the VMAT2 inhibitor bevantolol (SOM3355) was selected and has undergone pre-clinical studies and a clinical phase 2a proof-of-concept study (completed in 2021), which demonstrated that SOM3355 was safe and reduced chorea. The phase 2b study testing two doses over 12 weeks in a double-blind, placebo-controlled trial started in 2022 and was completed this summer. Results are planned for release in November 2024.

Michael Hayden (**Prilenia**) discussed the open-label extension to PROOF-HD, showing the persistence of effects of pridopidine for up to 2 years for the primary efficacy population [participants who were off antidopaminergic drugs (ADMs)] across several outcome measures, including the composite Unified Huntington's Disease Rating Scale (cUHDRS) with a change from baseline of -0.54 points over 2 years in comparison to the cUHDRS decline from a propensity-matched historical control with 2-year data from the TRACK-HD longitudinal observational study of -2.2 points. The second message from the presentation was related to the use of ADMs with pridopidine, indicating that pridopidine can be used, without masking its effects, with lower doses of certain ADMs, while the effect is masked in participants on higher doses of ADMs. Prilenia has submitted a Marketing Authorisation Application to the European Medicines Agency for pridopidine for the treatment of HD, which is currently under review.

Ed Wild (University College London) provided updates on **uniQure**'s AMT-130 (Phase 1/2) programme. This gene therapy candidate may potentially slow the progression of HD in the early to moderate stages of the disease via one-time surgical administration into affected brain areas. He reported 2-year data showing both nominally significant clinical benefits and a reduction in neurodegeneration (based on NfL). Discussions are underway regarding a potentially accelerated approval pathway with the FDA, and updates on the phase 1/2 trials (up to 3 years of data) are anticipated in mid-2025.

Peter McColgan (**Roche**) presented new biomarker data from the GENERATION HD1 phase 3 trial of tominersen, including an overview of biomarkers for neuroinflammation (YKL-40), neuronal loss (NfL, total TAU), and astrocytic reactivity (glial fibrillary acidic protein (GFAP). In the natural course of HD, YKL-40, NfL, total TAU and GFAP increase compared to healthy controls. In GENERATION HD1, no increases were seen for these biomarkers at the lowest exposures of tominersen. These are the exposures targeted with the doses in the ongoing phase 2 GENERATION HD2 trial. In August 2024, the Independent Data Monitoring Committee reviewed unblinded safety, clinical, MRI and plasma NfL data and recommended that GENERATION HD2 continue as planned. This trial is now more than 80% recruited, with plans to complete recruitment by the end of 2024.

Maddie Pantoni (**Sage Therapeutics**) shared updates on the ongoing dalzanemdor programme (SAGE-718) for cognition in HD. The phase 2 12-week DIMENSION study has completed enrollment, with results expected at the end of the year, and the PURVIEW long-term open-label safety study is currently enrolling.

Jane Atkins (**Wave Life Sciences**) updated on SELECT-HD (a phase 1b/2a study of WVE-003, an allele-selective antisense oligonucleotide designed to target SNP3). We heard that 30 mg WVE-003 dosed

every 8 weeks was generally safe and well-tolerated and that the aim of selectively lowering mutant HTT protein by ≥30% was achieved whilst wild-type HTT protein was preserved. This is the first demonstration of allele-selective silencing in a clinical trial. Results from SELECT-HD also showed for the first time an association between mutant HTT lowering and a slowing of degeneration in the brain (as measured by caudate atrophy). Discussions are underway with the FDA, and a path for further development of WVE-003 is expected to be determined by the end of this year.

Scott Schobel (**VICO Therapeutics)** presented interim data on the ongoing phase 1/2a trial of VO659, an allele-preferential antisense oligonucleotide being investigated for HD, spinocerebellar ataxia type 1 (SCA1) and type 3 (SCA3). Treated HD participants had a reduction of mutant huntingtin protein in CSF and no change in NfL in CSF at day 85 compared with baseline. To date, VO659 appears generally safe and well tolerated and due to the long half-life, may have the potential for infrequent dosing (estimated as 1–2 doses per year).

Finally, Amy Lee Bredlau (**PTC Therapeutics**) shared updates on interim data from PIVOT-HD. PTC518, now known by the non-proprietary name of votoplam, is an HTT-lowering small-molecule splicing modifier. She reported that interim data support a dose-dependent and durable lowering of HTT and a trend of dose-dependent delay in clinical progression. PTC518 will continue to be evaluated in PIVOT-HD and the 2-year long-term extension study PIVOT-LTE.

Update on Planned Clinical Trials

Chaired by **Lena Hjermind** (University of Copenhagen) and **Tim McLean** (EHDN).

The session was opened by Kevin Sloane (**Alnylam**), who recapped on the development of RNAi therapeutics. Their investigational compound ALN-HTT02 is an RNAi therapeutic designed to lower all forms of mHTT (including exon 1 fragments). A phase 1A single ascending dose study of ALN-HTT02 in HD is planned to commence in late 2024.

Serena Hung (**Atalanta**) discussed the role of small interfering RNA (siRNA) in silencing specific genes and the development of their compound ATL-101. Pre-clinical work has confirmed ATL-101's potential for disease modification in HD, and clinical trials to test this in human participants are planned for 2025.

Zhong Pei (**exoRNA**) presented an *in vivo* self-assembled exosome-based therapy known as ER2001. This compound delivers RNAi with application across diseases including HD. Phase 1 studies are planned to start in China in late 2024 and in the USA in early 2025.

Gerard Griffioen (**reMYND**) discussed the development of their small molecule drug REM0049949, which aims to target and mediate mHTT neurotoxicity. Phase 1 and proof of concept trials in individuals with HD are planned to start in 2025.

Donna Finch (**Alchemab Therapeutics**) presented the novel approach of analysing antibodies from resilient individuals (i.e., those who are susceptible to neurodegenerative diseases such as HD but who progress more slowly than expected). Clinical trial planning is focused on ATLX-1095, an HTT-binding antibody, for 2025 onwards.

Travis Wager (**Rgenta**) presented on the development of small molecule drugs to target RNA, and specifically, the development of PMS1 to enhance RNA–RNA-binding protein interactions. Clinical decision-making will include single and multiple ascending dose studies, which will include various biomarkers.

Keynote Lecture: Huntington's Disease Now – Mechanisms and Therapeutics

Chaired by **Alexandra Durr** (Paris Brain Institute).

Sarah Tabrizi (University College London) discussed mechanisms of pathogenesis, current therapies under development, 'hot off the press' data from HD-YAS (longitudinal study of young adult HD gene expansion carriers) and promising feedback from the FDA on biomarker integration into the drug development process.

Special Sessions

Jenna Heilman (Huntington's Disease Youth Organization) presented on genetic testing and participation in research. At the same time, a meeting was held on the EHDN MDS HD Fellowship programme, chaired by **Juliana Bronzova** (EHDN), and 'Implication des Associations de Patients dans le Parcours de Soins des Patients HD' was chaired by **Christine Tranchant** ((Strasbourg University Hospitals).

Parallel Sessions III

A. Genetic Modifiers and Somatic Mosaicism

Chaired by **Hoa Nguyen** (Ruhr-Universität Bochum) and **Mahmoud Pouladi** (University of British Columbia).

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. He was followed by **Davina Hensman Moss** (University College London), who discussed recent work looking at the CAG repeat size in DNA from sperm and blood of men with HD (Sperm-CAG), and the expansion of this project. In addition, **Nathan Heintz** (The Rockefeller University) presented 'Mechanisms of Molecular Pathogenesis in HD', and **Verónica Inés Brito** (University of Barcelona) presented 'A Novel Molecular Assay to Quantify DNA Repair Synthesis in the HTT Exon 1 as a readout of somatic instability in HD'.

B. Global Impact of HD

Chaired by **Jean-Marc Burgunder** (University of Bern) and **Claudia Perandones** (National Administration of Laboratories and Institutes of Health).

Alex Medina Escobar (Moncton Interdisciplinary Neurodegenerative Diseases Clinic) presented on the clinical epidemiology of HD, and examined the barriers and limitations associated with this research. He also emphasised the challenges from a research perspective in resource-limited settings. **Ahmad Aziz** (German Center for Neurodegenerative Diseases) presented on molecular HD epidemiology, including an evaluation of strategies to measure the prevalence of HD. **Anne-Catherine Bachoud** (Paris Est University) discussed the worldwide data on the disease burden in relation to costs but also to the social and familial implications. **Cao Xi** [Chinese Huntington's Disease Association (CHDA)] and **Feng Luyang** [Chinese Huntington's Disease Network (CHDN)] introduced their organisations, and explained how they collaborate closely while maintaining their own distinct focus (CHDA on patient support and CHDN on research) to achieve the shared goal of assisting the HD community in China.

C. Occupational Therapy: Lessons Learned from Other Clinical Conditions

Chaired by **Astri Arnesen** (European Huntington Association) and **Dina De Sousa** (HD representative).

Hortensia Gimeno (Queen Mary University of London) presented new insights into paediatric movement disorder and implications for client-centred occupational therapy. **Fernando Aguzzoli** (Walking the Talk for Dementia) discussed the walking initiative – an immersive experience that challenges conventional power dynamics and hierarchies in healthcare by using shared vulnerability as a catalyst for transformation. The session concluded with a panel discussion followed by questions and answers facilitated by **Alexandra Fisher** (Birmingham and Solihull Mental Health NHS Foundation Trust).

Parallel Sessions IV

A. Development and Ageing in HD

Chaired by **Anne Rosser** (Cardiff University) and **Christian Neri** (French Institute of Health and Medical Research).

Sandrine Humbert (Paris Brain Institute) opened by taking a neurodevelopmental approach in tracing a path from embryonic and post-natal development to before and after clinical motor diagnosis in adulthood. **Oliver Bartley** (Cardiff University) described work comparing authentic human medium spiny neurons to those derived from human pluripotent stem cells and reminded us of the need to understand the advantages and disadvantages of different experimental models. In addition, Juan Botas (**Baylor College of Medicine**) presented on supercentenarian genes and HD pathogenesis.

B. Observational Study Highlights

Chaired by **Robert Doot** (CHDI) and **Swati Sathe** (CHDI).

Stephen Smith (University of York) presented the Tap-HD study, a pop-up study at an HD family convention. Findings demonstrated the utility of obtaining data on fine motor and eye movements in informal settings. **Gabe Phelan** (Prioris.ai) presented on SHIELD-HD, providing context for this longitudinal natural history study and exploring ways in which it may guide future research. First, he demonstrated that SHIELD''s cohorts (as determined by CAP score) did not correlate well with disease stages assigned retrospectively via the HD-ISS, and recommended that HD-ISS staging be applied prospectively during recruitment. Next, longitudinal rates of change were estimated for a variety of endpoints, of which only a limited subset showed robust changes over time. Finally, rates of change were compared to those observed in a one-to-one matched sample from the TRACK-HD study; the rates differed significantly between the two studies in one of nine variables. Lastly, **Daniel van Wamelen** (King's College London) presented updates on iMarkHD, a longitudinal study aiming to identify biomarkers for HD progression by linking neuroimaging changes to clinical data.

C. The Importance of Psychological Support in HD

Chaired by **Rob Haselberg** (European Huntington Association) and **Saija Ristolainen-Kotimäki** (European Huntington Association)

Siri Hagen Kjølaas (Centre for Rare Disorders, Oslo University Hospital) presented her PhD research on the lived experiences of individuals who grew up or are currently growing up in families where a parent has or had HD. **Filipa Júlio** (European Huntington Association) presented 'I understand we are not alone', which highlighted the positive results of an online psychological support service offered by the European Huntington Association to the Spanish HD community. This presentation emphasised the importance of providing psychological support to the younger generations of families impacted by HD. The session concluded with a panel discussion facilitated by **Jane Simpson** (Lancaster University) and **Maria Dale** (Leicestershire Partnership NHS Trust)

Keynote Lecture: CAG Triplet Repeat Disorders

Chaired by **Åsa Petersén** (Lund University).

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.

Short Communications

Chaired by **Flaviano Giorgini** (University of Leicester) and **Davina Hensman Moss** (University College London).

Ella Mathews (University of Washington) opened with data on how HTT-lowering therapies affect instability – a key driver of age at clinical motor diagnosis. **Jasmine Donaldson** (University College London) discussed insights into FAN1 (a DNA repair enzyme) in protecting against repeat expansions. **Anat Bahat** (Weizmann Institute of Science) discussed the relief of HD symptoms and progression via the lowering of mHTT by selective Spt5-Pol II inhibitors. Finally, **Faravareh Khordadpour Deilamania** (University of Glasgow) discussed longitudinal somatic expansion of the CAG repeat in blood DNA as a potential biomarker.

Poster awards were presented by **Flaviano Giorgini** (University of Leicester) to:

Baptiste Brulé (University of Strasbourg)

Clément Le Moine-Veillon (École normale supérieure)

Dorine Boersema-Wijma (Leiden University Medical Center)

The day concluded with a talk by **Charles Sabine** (Hidden No More) chaired by **Filipa Júlio** (European Huntington Association) and a movie night.

Saturday 14 September

The final day of the meeting was opened by **Bernhard Landwehrmeyer** (University of Ulm), **Eileen Neacy** (CHDI), and **Cristina Sampaio** (CHDI).

Practical Deployment of HD-ISS in Clinical Research

Chaired by **Chris Ross** (Johns Hopkins University) and **Sarah Tabrizi** (University College London).

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

Parallel Sessions V

A. Advances Obtained Through Enroll-HD Part 1: Biomarkers and Modelling

Chaired by **Irina Antonijevic** (Trace Neuroscience) and **Hilary Wilkinson** (CHDI).

Katrin Barth (EHDN) opened the session with a detailed overview of the Enroll-HD platform and the associated biosamples and clinical datasets that are available to researchers and advertised their use, in addition to providing examples of how Enroll-HD data have been used to date. **Jong-Min Lee** (Harvard Medical School) provided further illustration of the utility of Enroll-HD data in the context of genome-wide association studies and the identification of genetic modifiers of HD. **Douglas Langbehn** (University of Iowa) discussed the potential prognostic significance of neurofilament light serum data based on research using Enroll-HD samples. Finally, **James Mills** (University of Iowa) explained how Enroll-HD data has informed clinical research with a particular focus on the prognostic index normed (PIN), a score that combines clinical measures with age and CAG to predict HD progression.

B. Advantages and Disadvantages of Decentralised Visits

Chaired by **Selene Capodarca** (EHDN) and **Gail Owen** (University College London).

Sam Frank (Beth Israel Deaconess Medical Center/Harvard Medical School) presented on a remote version of the Unified Huntington's Disease Rating Scale. **Matthew Roché** (CHDI) discussed the development of the HD Structured Interview of Function (part of the Later Stage HD Assessments study). **Erin Caruso** (Georgetown University) presented on the advantages and challenges of remote visits, and **Lauren Byrne** (University College London) presented on remote blood collection. The session concluded with a panel discussion.

Flash poster presentations were chaired by **Christine Capper-Loup** (EHDN) and **Joel Perlmutter** (Washington University School of Medicine).

Parallel Sessions VI

A. Advances in Enroll-HD Part 2: Clinical Trial and Clinical Study Support

Chaired by **Yuan Huang** (Yale University) and **Jennifer Ware** (CHDI).

Jenny Townhill (EHDN) recapped on the Enroll-HD study and platform and described the scientific and operational support that is offered to clinical trial sponsors. **Marcelo Boareto** (Roche) discussed insights from Enroll-HD on natural history progression, the placebo response, and the consequences for clinical trial design. **Jamie Hamilton** (CHDI) took a health economics perspective in explaining the indirect and out-of-pocket costs for individuals with HD and their caregivers based on the HD-Charge study. **Joaquim Ferreira** (University of Lisbon) presented an insightful vision of the potential of Enroll-HD 2.0 to facilitate the development of efficacious therapeutics, the qualification of novel assessment tools and biomarkers, and the design and implementation of innovative clinical trials.

B. Best Practices in Study Coordination – Part of Something Bigger

Chaired by **Ruth Fullam** (EHDN) and **Noopur Modi** (CHDI).

Selene Capodarca (EHDN) and **Jenny Callaghan** (EHDN) opened with a discussion on Enroll-HD best practices, followed by **Bonnie Hennig-Trestman** (Carilion Clinic), who presented strategies for attracting, recruiting, and maintaining younger populations in HD research. **Katie Andresen** (Cambridge University) shared insights into scheduling and managing Enroll-HD with other studies. **Monika Hartmann** (King's College London) concluded the session with a consideration of parallel studies using Enroll-HD sites and the iMARK-HD study.

Keynote Lecture: Use of Innovative Trial Designs to Accelerate Drug Development in HD

Chaired by **Rebecca Fuller** (CHDI) and **Lauren Byrne** (University College London).

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.

The Next Frontier of Enroll-HD

Chaired by **Lexi Mansbach** (CHDI) and **Jenne Coler-Dark** (Huntington's Disease Society of America).

Swati Sathe (CHDI) explained the key changes arising from Enroll-HD 2.0 (specifically discussing enrollment, recruitment, cohorts, and assessments) and the rationale for these. She also introduced a new biobanking protocol which will enable CHDI to store and distribute vital data as well as collect additional biosamples.

Matthew Roche (CHDI) introduced selfEnroll-HD, a smartphone-based study and research platform. The technology is expected to be available in late 2025–early 2026, and roll-out is planned to begin in the USA shortly after. Participants will be able to able to take part in both Enroll-HD or selfEnroll-HD, or either alone, and the data can be linked between the two platforms.

Advances in Enroll-HD Part 3: Novel Clinical Trial Design

Chaired by **Brian Beers** (PTC Therapeutics) and **Juliana Bronzova** (EHDN).

Priyantha Herath (Alnylam) opened the session with insights into the best time to start treatment in HD, given the importance of taking into account the perspectives of affected individuals, regulators, and ethicists, and what can be gleaned from research in different medical fields, such as cardiology.

Andrew Wood (CHDI) discussed the development of an early phase biomarker strategy, noting the importance of imaging data in supporting early intervention and the implications of this for Enroll-HD 2.0.

Tiago Mestre (University of Ottawa) proposed a 'bridge model' to move more readily between phase 2 and phase 3 studies, with the aim of streamlining the discovery of effective treatments. He considered the operational requirements and logistics as well as the advantages of such an approach.

Patrick Weydt (Bonn University and EHDN) concluded the session with an insightful discussion on the next steps toward achieving clinical benefit from clinical research. This session concluded with a short panel discussion between the presenters.

EHDN & Enroll-HD 2024: Wrap Up

The conclusion to the meeting was chaired by **Eileen Neacy** (CHDI) and **Cristina Sampaio** (CHDI).