White paper

Neuroscience clinical research

Huntington's disease: Turning fragmented effort into unified progress

Aligning clinical, scientific and community systems to accelerate therapeutic development

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Including feedback from European Huntington Association patient advocacy group (PAG) panel, with contributions from Astri Arnesen, president and CEO, European Huntington Association

By synthesizing insights from clinicians, researchers, global advocacy leaders, individuals with Huntington's disease (HD), and caregivers, this article examines why progress in HD research remains slower than families can afford and outlines the structural, scientific, and systemic strategies needed to accelerate therapeutic development

A field full of promise–and friction

Huntington's disease (HD) research is more active than ever. Longitudinal observational cohorts—such as **ENROLL-HD**—alongside advances in imaging, digital tools, and development of disease-modifying strategies—such as Huntingtin (Htt)-lowering and somatic instability-targeting therapies—are reshaping the landscape.

ENROLL-HD is the largest global observational study and research platform in HD. This long-term, multinational registry serves both as a longitudinal study and as the operational backbone many HD trials rely on for data, site readiness, and identification of individuals with HD.

Yet for families, progress still feels too slow.

Insights from key opinion leader (KOL) interviews, a patient-caregiver spotlight, and discussions at a recent European Huntington Association (EHA) meeting in Bucharest point to a consistent theme: the science is moving forward, but the ecosystem around it remains fragmented. Trial design, site readiness, regional inequities, and communication gaps continue to limit the full impact of scientific progress and diluting the value of today's scientific advances.

As one participant at the advocacy panel in Bucharest put it, "Huntington has no borders."

The response to it shouldn't have borders either.

Trial readiness starts long before a trial exists

Dr. Ralf Reilmann, founding director and CEO, **George-Huntington-Institute**, highlighted a foundational issue: access to ENROLL-HD and other observational cohorts is still uneven across regions. When longitudinal data are patchy, modelling progression becomes harder, powering trials is more uncertain, and recruitment slows. However, access problems start much earlier than the research registry.

Dr. Saul Martinez Horta, neuropsychologist, Movement Disorders Unit, Department of Neurology, Hospital de la Santa Creu i Sant Pau, emphasized broader systemic issues, including significant variability in the standard of care and a lack of clear referral pathways to HD centers of excellence. As a result, many families never reach specialized units where multidisciplinary care and research opportunities are concentrated. Those who do often face long travel distances with significant financial cost and emotional burden. With this context, clinical trial readiness is downstream of system readiness. Without robust accessible pathways into expert care, even the most well-designed trials cannot recruit equitably, or at scale.

Community is ready–if clinical trials fit into their real lives

Across key opinion leader interviews and the EHA, there was a clear consensus: willingness to participate in a clinical trial is not the limiting factor. When given the opportunity to take part in clinical trials, individuals with HD and their families show exceptionally high participation and adherence rates. What they need are trials that respect how complex their lives already are. Key elements include:

- Flexible study visit scheduling, including evenings and occasional weekends)
- Practical support such as reimbursement of travel costs, assistance with transport and accommodation, coverage or compensation for overnight stays, and support for childcare where appropriate
- Clear, honest communication about procedures, expectations, and commitments
- A strong, trusted relationship with the investigator and his/her team

As Martinez Horta emphasized, effective trial design is not only about biology—designing a strong HD trial is not just about targeting a mechanism or measuring biological impact—it is about designing something that is scientifically valid and realistically workable and meaningful for individuals with HD.

Trials must use robust tools to assess cognition, behavior, and motor function, and recognize that different HD clinical subtypes progress differently.

"We cannot consider all individuals with HD to be the same," he noted. Designing for this heterogeneity, while reducing unnecessary burden, makes clinical trials more meaningful and more sustainable.

Regional inequities and untapped populations

During the EHA meeting, patient advocacy leaders emphasized a persistent structural challenge: regions with substantial HD populations remain underrepresented in clinical research.

- **Sweden** is a clear example of how structural rules can limit research readiness even in countries with strong health care systems. Ethical and regulatory constraints make it very difficult for centers to participate in large observational platforms such as ENROLL-HD. This limits longitudinal data collection and "trial-readiness" infrastructure, even though the country has a substantial HD population. The result is an underused community of potential participants and fewer structured opportunities for Swedish families to access research compared with other European countries.
- **India** represents a major untapped opportunity for HD clinical research, with a large population with HD but very few research sites or structured trial programs. This creates a gap between where patients live and where clinical trials are conducted. HD advocacy leaders stressed that countries like India should not be seen primarily as operational headaches; distant, complex, or difficult to set up—but as critical expansions of the global HD community. Bringing trials to India, and to similar under-represented regions, would expand recruitment capacity and make research more inclusive and reflective of the true diversity of HD worldwide.
- **Arabic-speaking countries** are described as having younger, highly engaged HD families, with many individuals still in active working and parenting roles. This demographic profile is particularly relevant for preventive and early-intervention studies, which increasingly target people at risk or in premanifest and prodromal stages. At the EHA meeting, Advocacy representatives noted that families in this region often show strong motivation to participate in research when given the opportunity and clear information. However, the limited number of specialized HD centers and trial sites means this potential is largely underused. Bringing more structured research programs and partnerships to Arabic-speaking countries could significantly accelerate recruitment into early-intervention trials, while also ensuring that the global HD evidence base better reflects the diversity of the community. The disconnect between the geographic distribution of individuals with HD and the locations where trials are conducted remains one of the most significant structural inefficiencies in HD research today.

Clinical sites: The operational bottlenecks in trial participation

A recurring theme was that while people with HD demonstrate a strong willingness to participate in clinical trials, many clinical sites lack the infrastructure or capacity necessary to adequately support their involvement.

Capabilities beyond basic infrastructure

A trial-ready HD site requires far more than clinic space. Depending on the study, sites may need:

- MRI scanners capable of advanced longitudinal imaging
- Lumbar puncture facilities with experienced clinicians
- Strict investigational product (ip) storage at temperatures as low as –17°c
- Staff knowledgeable about hd-specific assessments
- Reliable scheduling, follow-up, and communication processes

Patient advocates pointed to the clinic in Taufkirchen, Germany, as a model of proactive outreach, consistency, and reliability; illustrating how even smaller centers can become high-performing sites with the right commitment.

The doctor–patient relationship: A determinant of retention

Dr. Filipa Júlio, board member and project manager, EHA, emphasized a factor often underestimated in operational planning: clinical trials succeed when families impacted by HD trust their investigator. Recruitment may bring participants into a study, but retention—the patient's willingness to stay engaged throughout the trial—is what ultimately determines whether a study yields high-quality, analyzable data.

Patient advocates also reinforced this point at EHA, noting that retention is shaped by the fundamentals of the doctor–patient relationship, including:

- Transparent communication
- Respect for families' time and commitments
- Clarity about trial expectations
- Continuity and consistency of care

As more HD studies advance into Phase II and Phase III, the demand for an engaged, research-ready community continues to grow. However, as Júlio noted, this expanding pipeline also brings significant challenges. Choosing the right clinical sites, identifying eligible participants, and ensuring efficient recruitment and sustained retention remain critical bottlenecks—ones that can jeopardize timelines, reduce data quality, and undermine trust within the HD community.

As she summarized: "Retention and clinical trial engagement depend on care, communication, and clarity."

An individual with HD and caregiver spotlight: Hope, exclusion, and the need for clarity

For Michaela Wacker, who is HD-positive, and her daughter Katharina, participation in research is more than a clinical opportunity. Under the care of the HD specialist center in Ulm, Germany, it has become a source of hope and a meaningful way to contribute to the future of treatment.

"Studies were and still are significant activities to find the necessary hope for Michaela, who trusts the medical staff in Ulm 100% and is grateful for every visit," Katharina shared.

Their deep trust in the specialist center in Ulm reflects the strength of their local care. Precisely because that foundation is so strong, their experience also helps bring broader gaps across the HD community into focus—gaps that can be addressed through shared commitment and action.

- **Public awareness is low.** Many people in their environment had never heard of HD, reinforcing stigma and leaving families to explain—and often defend—their situation repeatedly.
- **Information is either too technical or too limited.** They want simple, regular updates on research progress and practical topics such as allowances and insurance, ideally summarized for non-experts and shared via trusted channels like patient organizations.
- **Digital tools help, but only when supported.** An HD app with daily tasks kept Michaela motivated—until the device failed and there was no replacement process.
- **Past participation can unintentionally exclude people.** After completing one clinical trial, Michaela discovered she was ineligible for subsequent studies. For families who see participation as a meaningful contribution, this exclusion feels like a closed door.

Their experience points directly to several design principles for future HD research: develop clear re-enrolment pathways from the outset, ensure digital tools have reliable technical support and easy replacement, and invest in plain-language, continuous communication co-created with patient groups. Katharina summarizes their message simply: "Keep us informed in simple terms—and help with practical topics like allowances and insurance."

Ultimately, Michaela and Katharina highlight what HD families need most: broader public awareness so they are not constantly explaining the disease; accessible, understandable communication; reliable digital engagement tools; and trial frameworks that allow participants to continue contributing. Equally essential is that trials remain practically accessible—with travel support or decentralized options for people balancing work and caregiving. Together, these elements create a research environment that is both scientifically robust and genuinely aligned with the daily realities of HD families.

Lessons learned from recent trials

Recent HD programs have made it increasingly clear not only what is progressing well in the HD field, but also what must evolve. On the positive side, Dr. Yury Seliverstov, neurologist and researcher, University Hospital of Ulm, highlighted the remarkable expansion of HD clinical research, including new mechanisms of action and a growing emphasis on somatic instability and allele-selective Htt lowering. First-in-human studies aimed specifically at modifying CAG-repeat instability are expected soon. At the same time, emerging tools—such as patient-derived 3D cellular models, AI-enabled simulations, and more refined biomarkers—are transforming how candidate therapies are evaluated and de-risked before reaching patients.

But there are important lessons as well. Martinez-Horta underscored the need for far greater caution in how expectations are communicated. HD still has no approved disease-modifying therapy, and overly optimistic narratives can create hopes that current science cannot yet fulfill. When studies are halted or yield negative results, this misalignment can erode community trust and slow progress. Scientifically, recent trials also suggest that targeting a single pathway may be insufficient: focusing exclusively on mutant Htt-lowering is unlikely to produce the meaningful, disease-wide changes that families are seeking—particularly if clinical designs fail to capture the true heterogeneity of HD.

Moving forward, he argued that success will depend on rigorous, multidimensional trial designs that integrate biological, functional, and patient-centered outcomes, alongside communication that remains transparent, measured, and honest. Only through this combination of scientific depth and responsible messaging can the field sustain momentum and maintain the trust of the HD community.

What must change in the trial ecosystem

Conversations with KOLs, patient advocates, and families reveal several priorities for HD clinical research.

Co-design with the community

Trials should be built with HD families, not around them. This means getting individuals with HD, caregivers, and associations involved early in protocol design, burden testing, and feasibility reviews—and maintaining an advisory structure throughout the study.

Smarter support for sites

Many HD clinics are highly motivated but overstretched. Sponsor-funded coordinators or dedicated trial staff can relieve pressure, keep protocols on track, and ensure high-quality data without eroding standard care.

Regulatory flexibility

Broader acceptance of biomarkers as endpoints, use of external controls from robust observational datasets, and openness to adaptive and decentralized designs have the potential to shorten timelines and reduce burden, without compromising scientific rigor.

Stronger community education

As Filipa Júlio and EHA's work shows, health literacy is not a given. Families need information that is realistic, timely, and in their own language—about both science and practical support. When education is continuous and rooted in lived experience, engagement becomes more equitable and sustainable.

A shared responsibility: "We're not competing"

HD advocates repeatedly emphasize that the community is small and that fragmentation is a luxury it cannot afford. Organizations such as EHA, Huntington's Disease Youth Organization (HDYO), Huntington's Disease Society of America (HDSA), along with clinical investigators, sponsors, and regulators each hold part of the solution and must work in concert rather than in parallel.

As one advocate said during the discussion at EHA:

"We're not competing. We're collectively fighting the same disease."

The message from families, KOLs, and advocates is clear:

- Invest in site and system readiness
- Design trials that reflect both biological complexity and daily reality
- Communicate with honesty
- Involve the community from the start

Unified action is essential. It is the clearest path to ensuring that people with HD can access the treatments, care and support they deserve.

For families living with HD, every year matters—every year without progress is a year they cannot get back.

Learn more at **ppd.com/therapeutic-expertise/neuroscience**