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Commentary

Supporting Huntington's Disease Families Through the Ups and Downs of Clinical Trials

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Abstract. Recent years have been turbulent ones for the Huntington's disease (HD) community. Three clinical trials for HD, including the first Phase 3 trial of a potentially disease modifying genetic therapy for HD, were all brought to a halt in March of 2021. 2022 brought more study roadblocks and an additional trial termination. As HD science progresses and larger scale trials become more frequent in the community, HD families are faced with the difficult reality that clinical research rarely results in a new drug hitting the market. To better understand how the HD community can be prepared for the ups and downs that accompany an expanding clinical research pipeline, the Huntington's Disease Society of America (HDSA) spoke with members of the Huntington's Disease Coalition for Patient Engagement (HD-COPE). This group of global advocates led by HDSA and the Huntington's Society of Canada (HSC) collaborates with pharmaceutical companies to ensure that HD voices are represented in the planning of clinical trials. These conversations allowed HDSA to summarize how the HD community can be best supported through the clinical research process in three key areas: engagement, support, and education.

Keywords: Huntington's disease, clinical trials, HD-COPE, community engagement, trial recruitment, community support

INTRODUCTION

In March of 2021, three clinical trials for Huntington's disease (HD) went from full steam ahead to a standstill. GENERATION HD1 (NCT03761849), conducted by Roche, was the first Phase 3 trial of a potentially disease modifying genetic therapy for HD. It tested the ability of a huntingtin-lowering drug called tominersen to slow the progression of HD symptoms. PRECISION-HD1 (NCT03225833) and PRECISION-HD2 (NCT03225846) were two Phase 1b/2a trials that tested the safety and target engagement of two drugs developed by Wave Life Sciences to lower mutant huntingtin protein. Prior to their closing, these trials represented a historical turning point for the HD community; the possibility that science would deliver an effective treatment rooted in the genetic cause of this devastating condition.

Over the space of a week, dosing in all three trials was halted – GENERATION HD1 was stopped early due to an unfavorable risk-benefit profile, and the PRECISION trials completed their studies as planned, but both drugs failed to lower huntingtin as expected [1, 2]. This news rocked the HD community, and many felt they were left with more questions than answers as to why these promising pharmaceuticals had failed. In the summer of 2022, the HD community once again faced multiple pieces of difficult

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news simultaneously: uniQure's gene therapy trial of AMT-130 (NCT04120493) paused new surgeries due to neurological complications in some participants, and Novartis's VIBRANT-HD (NCT05111249) trial of the oral huntingtin-lowering therapy branaplam suspended dosing because of reported peripheral neuropathy [3, 4]. In December of 2022, Novartis announced it would end development of branaplam for HD [5].

While shocking, these difficult pieces of news also present an opportunistic question: how can the HD community be better supported and prepared for the ups and downs of future clinical trials? The Huntington's Disease Society of America (HDSA), a non-profit dedicated to improving the lives of all people affected by HD, and other community advocacy groups worldwide are at the center of this problem and its solutions.

HD is a fatal, genetic disorder that causes the progressive breakdown of a person's brain. Often, HD is described as having ALS, Parkinson's, and Alzheimer's—simultaneously. Symptoms usually begin between ages 30–50 and are characterized by decline in a person's mental, physical, and emotional health [6]. An HD diagnosis can throw entire families into uncertainty and create challenges that are more easily navigated with a strong network of support.

HDSA provides numerous medical, social, and disability services for people affected by HD, develops educational materials for laypeople and clinicians, advocates for HD families, funds researchers studying the disease, and amplifies community voices in the HD drug development process. Part of this work is HD-COPE, the Huntington's Disease Coalition for Patient Engagement. This group of global advocates led by HDSA and the Huntington Society of Canada (HSC) collaborates with pharmaceutical companies to make sure the voices of people affected by HD are represented in the design of clinical trials and educational materials [7]. HD-COPE was involved in the planning of GENERATION HD1 and has advised numerous pharmaceutical and biotech companies, providing insight on the realities of living with HD, input on patient-facing study materials, and recommendations related to trial design [8]. In the months since GENERATION HD1 and Wave's PRECISION-HD studies drew to a close, members of HD-COPE as well as other community members and healthcare providers participated in a series of interviews with HDSA staff to reflect on their experiences. In these conversations, three major factors emerged as critical components for future HD clinical trials: engagement, support, and education.

COMMUNITY ENGAGEMENT: COLLABORATION FOR OPTIMAL TRIAL DESIGN AND EFFICIENT RECRUITMENT

Clinical trials are planned to answer specific questions: "Does x drug change y symptoms in z population?" Individual medical conditions come with distinct needs that create unique conditions around how these questions can be answered, and these needs may be addressed through careful trial design. HD is a slow-progressing neurodegenerative disease; realistically, in a multi-year trial, participants' symptoms are likely to progress. How will the progression of symptoms affect their ability to travel to a study site, move independently around a hospital campus or doctor's office, or sit for long periods of time over the course of a study? These questions are key not only to maximizing participant comfort and retention during a trial, but also for ensuring that the clinical endpoints studied are aligned with the priorities of HD families.

HD-COPE is tasked with communicating the needs of people with HD and their care partners to the people who design clinical trials. In the planning process, numerous companies have consulted with HD-COPE to make sure their study protocols are as participant-friendly as possible [7]. The effects of these partnerships are overwhelmingly positive. For example, community representatives that partook in conversations about GENERATION HD1 described the outcome as a genuine sense of trust. "It felt like Roche really put in the effort to make the HD community more than just a cog in the wheel—it was like we were all playing on the same team."

Whether in the form of intensive advisory boards and 1-on-1 interviews, or community letters, webinars, and presence at HD educational and fundraising events, community engagement efforts from companies in the HD space can have a profound impact not only on awareness and trust, but also on quantitative measures like recruitment. For GENERATION HD1, this was very much the case. Almost 800 people with early manifest HD were enrolled to participate in GENERATION HD1 between January 2019 and April 2020—a recruitment rate nearly twice as fast as the average speed of large-scale clinical trials, and four times faster than Roche's average recruitment rates for rare disease trials in the ten years preceding tominersen [8]. Additionally, increased site traffic

was observed around major GENERATION HD1 study announcements on HDSA's HD Trialfinder platform, a clinical trials matching service and educational resource for people affected by HD [9]. This further affirms that the unique level of engagement Roche had with the HD community around GENERATION HD1 contributed to the study's rapid enrollment.

Despite the heartbreak brought on by its end, in many ways, GENERATION HD1 is a success story of community engagement. The rate at which participants were recruited to this trial was unprecedented, and trust in HD families was fundamental to that achievement. HD advocates said it best; "In inviting the HD community into conversations to fine-tune the details of the study protocol, Roche made the HD community their partners in planning this trial." The result was not only a study that was as sensitive to the needs of the HD community as possible, but also carried an added layer of community investment in its outcomes.

Perhaps this harshened the blow of GENERATION HD1's demise, but it also opened doors for honest dialogue between Roche and the HD community in the trial's wake. "Families give a piece of themselves [when they participate in clinical trials]; they are investors in and beneficiaries of their outcomes." Strengthening the relationships between pharmaceutical companies and the communities at which their efforts are aimed is paramount in developing cures for HD. "There will be no therapies without clinical trials, but there are no clinical trials without participants," said one member of HD-COPE. "The community must be engaged and empowered in order for the process to move forward."

SUPPORT FOR A VULNERABLE COMMUNITY

There are no known disease-modifying treatments for HD, and its heritable nature inflicts a distinct devastation on the families it affects. In the absence of effective therapeutics to slow or stop the inevitable progression of cognitive, psychiatric, and motor symptoms, HD families are uniquely invested in clinical research, and, as one advocate put it, they "hope for their success from a vulnerable place." Although only a small portion of the HD community is directly involved in clinical trials, the weight of their outcomes is wider than most recognize. Clinical trials are a source of optimism in a desolate situation, with participants not only searching for options to alter the course of their HD, but also to prevent the next generation from developing symptoms altogether.

These generational circumstances draw a fine line for the HD community; they are a group that will always be willing to participate in clinical trials, but also one likely to have a strong emotional response to their outcomes and roadblocks that may arise in the research process. For this reason, support is imperative at every step of clinical development—for the HD community at large, and especially for those who make the heroic choice to participate in clinical research.

Community advocacy organizations like HDSA play a key role here, providing community services like support groups, as well as facilitating community education. Several have taken steps to rapidly amplify sponsor messaging, whether hopeful or disappointing, and, where necessary, to create forums for collective grieving and healing. Following the close of GENERATION HD1 and the PRECISION studies, HDSA and groups like it across the globe held webinars and virtual gatherings to discuss news and provide space to process it [10]. HDSA, the Huntington's Disease Youth Organization (HDYO), HD Reach, the European Huntington Association (EHA), and HSC all hosted online events of this nature. Despite the already isolating nature of a global pandemic, these virtual, community-wide assemblies were a place for geographically diverse groups to unpack headlines and seek understanding of complicated science in lay-friendly terms.

The power of these gatherings to spread factual information, encourage support, and provide a safe space for expression of difficult emotions led HDSA to respond similarly following the news shared by uniQure and Novartis in August 2022 around their trials of AMT-130 and branaplam, respectively. No matter the news, the stage within the therapeutic pipeline, or the number of individuals directly affected by a decision, the global HD community responds positively to clarity and to direct messaging from companies and trial sponsors. When interfacing is not feasible, a family-centered gesture of support in parallel with investor-facing materials, such as a lay-language community letter, can promote trust, understanding, and continued faith in the clinical research process.

While the outcomes of clinical research have implications for the HD community at large, there is also a demand for support specific to trial participants. As an HDSA social worker described, "There needs

to be a structured safe space for participants to talk about their trial participation in the wake of its conclusion." Clinicians, social workers, and mental health professionals are a critical part of strengthening services for this population, and advocacy groups are important for educating providers to be a part of that network. Effective clinical trial sites should have the infrastructure and multidisciplinary staff necessary to support and communicate efficiently with trial participants in the event of a major pivot in study plans. "Research participation is already emotionally distressing, and failure can magnify that effect. The differences between [members of the community] and study participants must be understood in the follow-up of a clinical trial."

Additionally, outside of western countries where HD clinical trials are rarely or have never been conducted, community members are not as much affected by trial closures as they are by the fact that there is still no cure for their condition. Symptomatic treatments commonly prescribed in Europe and North America may be difficult or impossible to access in these areas where direct participation in clinical trials is not an option. Advocates in China and Africa expressed a need for more resources in their communities to help them cope in the present, as well as understand ongoing global research efforts to engender optimism for the future. "Research creates options, and without them, we need other sources of support to keep living our lives and planning for the day this cycle can end." Industry engagement across the globe could help build and fortify educational resources in places where the HD community copes with their condition in more isolating circumstances, as well as create opportunities for more global diversity in future clinical trials.

EDUCATION: BUILDING COMMUNITY KNOWLEDGE AND SETTING EXPECTATIONS

The harsh reality is that most drugs tested in clinical trials for brain diseases never make it to market. Excitement around clinical trials and disappointment surrounding their failures are common and valid responses in the HD and other disease communities. However, expectation management around this anticipation can help prevent highs and lows like the ones felt by the unexpected ends of recent trials. To do this, a broader understanding of the clinical trial process must be made accessible to the HD community.

Amongst individuals interviewed for this article, who are highly educated about the process of drug development, a common concern was public misconception that participating in a clinical trial means being treated for a disease. Even in the case of a Phase 3 trial of a compound that has strong supporting evidence of safety and target engagement, a clinical trial is not a guarantee. As one advocate put it, "[The HD community] can be excited about [the possibility of] a treatment for this horrible disease, but that needs to be balanced with the fact that [a trial] is a science project." At their core, clinical trials are experiments with uncertain outcomes. "[Clinical trials] might make things better, they may make things worse, or they could do nothing at all—but we won't know unless we try."

Community advocacy organizations, including HDSA, are key players here as well. One HD-COPE member suggested that drug discovery education be incorporated into community-oriented meetings that highlight research. "We need to make sure the HD community understands how drug development works and the timeline it follows. [HD] is a slow progressing disease, which means we need to wait a long time to see the effects [of a clinical intervention]."

Unlike other conditions like cancer or diabetes where clinical outcomes of an experimental drug can be evaluated relatively quickly, it can take many years from when a drug is first tested in someone with HD for it to reach the market. For many research participants in the HD community, this means they join studies for the benefit of their children or grandchildren, not for themselves. "The time is the issue; we will have something eventually, but it might not come fast enough for our loved ones who need treatment now."

Additionally, the education efforts following clinical trials are equally as important as those preceding them. One HD-COPE member noted that "The data [that is announced following a clinical trial] affects its participants and the community at large. They need to be prioritized in the communication of its analysis and any conclusions that are drawn from it." This is in part the responsibility of pharmaceutical companies. While data analysis can be a slow and cumbersome process, findings from any study should be shared directly with the communities they affect in a timely fashion and in terms they can understand. "[After a presentation of data from a big clinical trial], I should walk away feeling empowered and ready to share what I've learned with other members of my community."

This is especially important when sharing with HD families. "[The HD community] has cognitive issues, processing difficulties, and delays in understanding complex concepts among us." Advocacy groups play an important role here as well to act in a translational capacity between pharmaceutical companies and patient communities. "For scientific conferences, you have to give all of the data and details. But for patient groups, how can you paint a complete picture while also communicating in the simplest terms possible?"

Companies that strive to meet these needs know that education is a two-way street; industry representatives can learn from opportunities to interface with families in both formal and casual settings. From Q&A sessions to conversations at an event table, these interactions identify gaps in knowledge, reveal HD-specific communication challenges, underscore families' urgency as day-to-day abilities slip away, and showcase their readiness to embrace hope.

MOVING FORWARD: CONSIDERATIONS FOR THE FUTURE

Trial failures like the ones that the HD community has seen with the first experimental genetic therapies for HD are unfortunately a norm of clinical research. Whether due to adverse side effects like we saw in Novartis' VIBRANT-HD study of branaplam, or because a drug just doesn't work, like Wave's PRECISION HD1 and PRECISION HD2 studies, unfavorable outcomes frequently send researchers back to the drawing board [2, 5].

In some cases, when a company abandons one drug, they recalibrate their efforts to target resources where they are most likely to have a positive outcome. Wave discontinued its development of two experimental compounds that failed to engage the target (mutant huntingtin) in early trials, and pivoted to focus on a third, similar drug in their pipeline which had been redesigned with improved chemistry [2]. Early data from their Phase 1b/2a trial of WVE-003 appears positive, with target engagement following a single dose [11].

In other instances, the emergence of new data from a trial that fails to meet its outcomes can make the case for continued development. Prilenia's small molecule drug, pridopidine, is an example of this: promising secondary outcomes and novel findings related to the drug's mechanism led to its continued development in the Phase 3 PROOF-HD trial, for which results are expected in 2023 [12]. And though GENERATION HD1 didn't meet its objectives, in January of 2022, Roche announced it would plan a new Phase 2 trial for tominersen (GENERATION HD2) based on *post hoc* analysis that suggested the drug may benefit younger individuals with lower disease burden [13, 14]. Recruitment for this trial began in January of 2023 [15].

Occasionally, a bump in the road is just that. In August 2022, uniQure paused enrollment in the high-dose cohort of its study of AMT-130, an experimental gene therapy for HD, due to serious neurological side effects in some participants [3]. After extensive review from the data safety monitoring board, the study was deemed safe to resume in October 2022, and adverse side effects observed in participants have resolved [16].

Cases like tominersen's are exciting, but new trials can also open up new concerns. When discussing the new target population for GENERATION HD2, one advocate said, "Younger participants mean more variables. These people are in the prime of their life—making advances in their careers, possibly having children, while also caring for the older HD generations in their families and dealing with the emotional burden of their deterioration."

The hope is that experimental treatments will be tested earlier and earlier in an individual's course of disease, thanks to better biomarkers, a novel staging system, and a highly engaged population of youth at risk for HD. Careful considerations around community input, support, and education at all stages of the drug development process will be even more critical for any company that aims to engage the HD community or re-engage a new subset for the purposes of building trust and achieving recruitment goals. This community's faith is staked in research to bring about an alternate ending to their HD stories, and all its stakeholders must make efforts to better prepare for the ups and downs of future clinical trials.

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CONFLICT OF INTEREST

The authors are employees of HDSA, which has relationships and nondisclosure agreements with a variety of pharmaceutical companies, including those mentioned in the article.

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