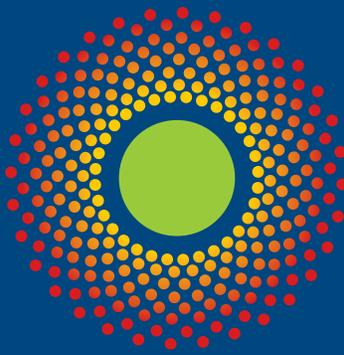


Enroll!

Updates from the Enroll-HD
global community



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THE LATIN AMERICAN CONNECTION

This year, Enroll-HD becomes a truly global effort

By the end of March, Enroll-HD will be officially underway in Latin America. The first five participants are anticipated to join the study during that month, signing up at the Instituto Frenopático in Buenos Aires, Argentina, a clinic focused on the diagnosis and treatment of neurological diseases. About 170 more people are expected to register at the clinic this year, says Federico Micheli, MD, chief of neurology at the Hospital de Clínicas José de San Martín in Buenos Aires, and principal investigator for the site. Eventually, the team hopes to register at least 500 participants. "People come to this hospital from all over the country, and also from Paraguay, Colombia, Venezuela, Bolivia and Peru," says Micheli, who is also head of the movement disorders program and professor of neurology at the University of Buenos Aires.

This site is just the first; by the end of next year, Enroll-HD should include 19 sites in eight nations across the Spanish- and Portuguese-speaking nations of the Americas, eventually involving more than 3,000 people affected by HD, their family members and caregivers. With this launch, Enroll-HD now becomes a truly global effort, soon to include participants in five of the world's six inhabited continents.

Launching a multinational study of HD is new for the region, which has not previously had a network of clinical research sites as existed in North America and Europe. For Latin Americans affected by HD, the study offers a route to participation in

international advances in research and clinical care. When new therapies are tested in clinical trials in coming years, study participants are likely to be among the first to have the choice to join. "We want to have the same chances for our patients as the Americans or Europeans," says Micheli. "If we want to be involved, we have to be ready."

A wave of sites

Enroll-HD will expand gradually across Latin America during the course of this year and next. Argentina plans two additional sites, both in Buenos Aires. Chile and Peru are expected to be next to join, followed by Brazil before the end of 2013, then Ecuador and Venezuela. Locations in Colombia and Mexico will be added in the following year.

Brazil alone, with its population of nearly 200 million, aims to recruit as many people to the study as the rest of the Latin American region combined, says Francisco Cardoso, MD, professor of neurology at the Federal University of Minas Gerais of Belo Horizonte, Brazil. At his clinic, which will be an Enroll-HD site, people welcome the idea. "There is enthusiasm that, finally, something coordinated is being done in the quest for a cure for HD," he says. "In the past, by the time these patients received a diagnosis they felt pretty depressed by the realization that they could find almost no information on the condition itself, and even less about investigation." By instituting a clinical network, improving communication, and tracking how well people do in various centers, Enroll-HD also aims to help improve the quality of care across Latin America.



The members of Red Latinoamericana de Huntington, a network of clinicians and scientists, meet in Santiago de Chile in 2010. Photo courtesy Federico Micheli.

The sites for Enroll-HD were established through the Red Latinoamericana de Huntington (RLAH), a multinational network founded in 2010 to link specialists across Latin America to promote research and share expertise. RLAH now includes about 30 clinician-researchers and has additional contacts with about 250 other interested specialists in neurology, genetics and psychiatry. Micheli is currently president of RLAH, and Cardoso is vice president.

In a sense this is a rebirth of HD research in Latin America. It was because of the families in villages around Lake Maracaibo in Venezuela that the gene for the disease was first identified 20 years ago (see sidebar, “Latin Roots”). That part of Venezuela has the highest known concentration of people with HD in the world, and clinical samples from the families there made it possible to find the gene mutation that causes HD.

Many nations, many rules

For a global study like Enroll-HD, data has to be collected and organized in exactly the same way at all sites so that information gathered on one continent can be combined with and compared to that from participants on the other side of the world. Getting a multinational clinical study off the ground also means meeting all the laws and regulations of each country, which is not trivial. Each nation’s regulatory authorities and various bioethics committees must be satisfied that Enroll-HD is appropriately designed and follows strict ethical guidelines. In some countries the governmental ministry of health must directly approve the study protocol. Licenses must be arranged in order to export blood to the central bio-repository lab in Milan, Italy, and to import clinical supplies to researchers. Fulfilling these obligations requires between six and nine months per nation.

Argentina also has a special requirement: review by the government’s National Directorate for the Protection of Personal Data. In the past, some clinical studies have recruited rural indigenous people without adequate privacy protection and without ensuring that participants truly understood what they were agreeing to. In Argentina, the protection of personal data is now a constitutional right. A law passed in 2000 also protects confidentiality and requires that people enrolling in a clinical study receive information appropriate to their level of education.

Despite these tough regulations, the directorate officially approved Enroll-HD at the end of 2012 without any objections. “We’re proud of that,” says Claudia Perandones, MD, PhD, a clinical geneticist with the National Administration of Laboratories and Institutes of Health in Argentina who is also the scientific director of RLAH, and sits on the scientific and publication review committee for Enroll-HD.

Launching Enroll-HD in Latin America involves some practical hurdles. Argentina is dealing with a prolonged economic and social crisis. Sites like the one in Buenos Aires draw many different types of people with different needs, from wealthy city dwellers to poor rural people with limited education. But Latin America also offers unique opportunities. Echoing Cardoso’s sense of optimism, Perandones points out that at a scientific conference about movement disorders last fall in central Argentina some people traveled all the way from Venezuela, more than 4,000 km (2,500 miles) away, to hear about Enroll-HD. “We have a lot of excitement here about the start of Enroll-HD,” she says. “It means that there’s hope.” 

Latin Roots

Starting in the 1970s, researchers interested in HD traveled to the towns around Lake Maracaibo in Venezuela. In some towns in this poor region, where fishing supports many local families, people with obvious signs of HD are part of everyday street life. A team lead by Nancy Wexler, PhD collected blood samples and clinical data from many people in the area. These samples made it possible to identify in 1993 the genetic mutation that causes HD.

THE STARTUP AT ROCKFORD, ILLINOIS

A unique project brings big-city resources to a small community

When people in the small US manufacturing city of Rockford, Illinois began discussing what help they most needed in dealing with Huntington’s disease, a few themes became obvious. Even though social services were available, it wasn’t always easy to access them. Also, there was a desperate need for a local medical specialist. It was just too difficult to regularly drive an hour and a half to the nearest HD treatment center at Rush University Medical Center in Chicago. Faced with this journey, some local people just weren’t being treated at all.

The solution turned out to be building community expertise in HD. Members of the Rockford support group of the Illinois chapter of the Huntington’s Disease Society of America, in partnership with the local medical college, found a doctor who could provide essential medical services nearby. They also recruited a part-time social worker devoted exclusively to the needs of HD families. Soon, with financial support from Enroll-HD, the group plans to add a telemedicine service that will make it possible for people in Rockford to consult with a movement disorders specialist without leaving town. The result is an innovative combination of community-based support and expert world-class care, plus a connection, through Enroll-HD, to a global network. “We need to give better care and greater assistance at the local level to families dealing



Ted Ross (left), Sadie Foster, MA (center) and Mitch King, MD (right) are working to improve HD care in Rockford, Illinois. Photo courtesy Brian Thomas.

with HD,” says support group member Ted Ross, who led the effort. “Enroll-HD is helping.”

Although the number of people affected by HD in Rockford is relatively small, the strength of the local network makes the city a natural study site for Enroll-HD. Rockford’s first participant was registered at the end of 2012 (see sidebar, “Enroll-HD in North America”). “If we help families with the many issues they deal with, there will be greater participation in clinical trials,” says Ross. “In the future, we’ll have the proof of this here.”

Bringing the doctor to town

At first, the Rockford group explored the idea of bringing a doctor who specializes in movement disorders to the city, but the logistics and the cost were overwhelming, says Ross. There just weren’t enough patients to keep a specialty clinic afloat. So Ross approached a local institution, the University of Illinois College of Medicine at Rockford, where he was introduced to Mitchell King, MD. King is a general practitioner and did not have specific expertise in HD, but since part of the medical college’s mandate is to address local medical needs he began working on ways to help. “As we learned more and more, it was clear there was a need,” says King. “The HD population in Rockford will sometimes not seek care, because there are no movement disorder specialists in the community, and travel is a major obstacle.”

One idea was telemedicine, a system that could allow people in the area to consult with an expert in Chicago via a high-definition video link. It is powerful enough to allow the doctor and patient to see each other clearly and have a face-to-face conversation. It’s a bit like a souped-up version of Skype, explains King. “It’s higher-resolution, so patients can actually be examined,”

he says. “A lot of the physical exam in HD is observational—you have to be able to observe movements, and talk.” If the HD group in Rockford couldn’t bring an expert to the city in the flesh, this virtual visit seemed like the next best option. The challenge was finding a way to pay for this technology.

Making the local link

Meanwhile, Ross and his collaborators were developing additional resources. In October 2009, the college of medicine hired social worker/counselor Sadie Foster, MA part-time to specialize in HD. She now makes regular home visits with about 10 families, helping them tackle logistical issues such as life insurance, home health care and disability, and cope with day-to-day problems like personal conflicts, diet and medication. Because HD affects the whole family, visiting people at home is crucial, she says. “You get to know the other family members, and they know you’re available if someone else should develop the disease, or if a child has a question,” she says. “You become part of their world.”

In addition to her direct work with those families, Foster hosts a monthly call-in support group discussing HD-specific issues. Callers can ask questions anonymously via email or over the phone—an alternative for people who can’t or don’t want to go to a public support group.

King also now sees a few HD patients regularly at his practice, providing primary care and making referrals to neurologists and other specialists. The idea is that once the telemedicine component is underway, patients will see him for their basic needs, and from his office consult remotely with an HD specialist.

What Enroll-HD can offer

The Rockford group recently formed a nonprofit organization, Huntington’s Disease Rockford Support Inc., to raise money in the community to improve the quality of care over the long haul. With those funds and revenue generated from participating in Enroll-HD they hope to expand in-home social work

Enroll-HD in North America

The clinic in Rockford is one of the first study sites officially launched in North America as part of Enroll-HD. As of February 8, 269 participants were registered for the study at 15 study sites in Canada and the US. In these two nations, about 2,000 are expected to sign up by the end of the year. Some sites, like the one in Rockford, are new, but others were previously part of COHORT, the observational study launched in 2006 that included roughly 3,000 people in the US, Canada, and Australia.

services and make remote video link consults available some time this year. Ross also plans to export this micro-network approach to other parts of Illinois and beyond.

King and Ross expect that as many as 50 people may participate in Enroll-HD from the region. People don't have to enroll in the study to be King's patients, and people who aren't his patients can get involved in the study. But the two projects

reinforce each other. On the one hand, people in Rockford now have more resources and more options that don't require leaving town. They will be seen regularly by medical professionals who know about HD. On the other, the strong network and improved services in the community have built local interest in Enroll-HD. This kind of mutual support is what will ultimately attract people to the study, says Ross: "If we're going to make Enroll-HD successful, that's just going to be required." 

G. BERNHARD LANDWEHRMEYER

The principal investigator of Enroll-HD on how the study will work, and what we can learn from it



Enroll-HD will encourage collaboration, improve local health care and accelerate new research, says Landwehrmeyer. Photo courtesy Laura Spinney.

Clinical trials that test new therapies usually get all the attention because they can have a fast payoff if the drug being tested actually works. But an observational study like Enroll-HD, which tracks how people affected by HD change over time, has a potentially transformative impact that goes far beyond one new drug or treatment, argues neurologist G. Bernhard Landwehrmeyer, MD, FRCP, the principal investigator of the study. Enroll-HD will make it easier to understand the biology of HD, more quickly identify physical signs and symptoms that accurately reflect the stage of the disease and, ultimately, enable the trials that will demonstrate effective therapies. It will act like a booster rocket, lifting future clinical HD research into a new realm so that studies are better, faster, and more economical (in terms of burden on participants and research staff alike).

Enroll-HD will create the world's largest database for clinical research on HD, eventually including information from as many as 20,000 people in around 33 countries. Landwehrmeyer, who is a professor of neurology at the University of Ulm in Germany and chair of the executive committee of the European Huntington's Disease Network, explains why this type of study is so rare—and why it is so important.

Q: What is Enroll-HD, and why do we need it?

A: Enroll-HD is a platform that allows health care professionals, scientists, and families affected by HD to work together towards a better understanding of HD and identify effective treatments. Despite the fact we have more than 100 years of clinical observation of HD, our understanding of the biological effects of the mutations and the mutant protein is still far from complete. We'd like to come up with reference values, like physicians do for many other things, such as knowing the number of red blood cells you'd normally have in your blood. In HD, we'd like to understand far better what you'd expect in someone at any given age, gender and CAG-repeat length [the gene mutation that predicts when disease onset is likely to occur].

Since the identification of the HD mutation and gene in 1993, we've gained a lot of insights by studying model systems of HD, such as mice with copies of the mutant gene. What we don't know is whether the mechanisms we've identified in model systems are drivers for the real thing in real people. Enroll-HD will help us understand that.

Q: In the past, many studies of HD failed to prove anything one way or the other. Why did that happen, and will Enroll-HD fix that problem?

A: From the 1950s through the 1980s, most HD studies were performed with less than 100 participants. They were convenience samples. That means that if you, the researcher, had an idea for a study, you might talk to your colleague, who referred the patients he or she happened to have. That results in a cohort of patients that are not systematically collected. So it's unlikely you'll end up with a conclusive study. To be conclusive, you have a range of people with different CAG repeats, at different ages and stages of disease. That's why Enroll-HD needs to be so big, and why it needs to include people in such different circumstances. Enroll-HD helps us to do conclusive studies, ones large enough to provide an answer. We cannot guarantee that the answers will be as we hope they will be. But we can guarantee that the studies will give us answers.

269
PEOPLE
CURRENTLY
SIGNED UP
FOR ENROLL-HD
AS OF FEB 8, 2013

Q: How does Enroll-HD accelerate research into new treatments?

A: We can work together with partners in pharmaceutical companies, for example, to find out whether a planned drug trial is feasible, and can help study sites by flagging participants who might be suitable for a particular trial. Enroll-HD sites see participants on a regular basis, at least once a year, and are more acutely aware of who is interested and who might fit the study requirements. Of course, it's still the decision of the individuals whether or not they want to participate. But in our experience, having a database with participants who have volunteered for an observational study will tremendously speed up recruitment into clinical trials of potential therapeutics. We were able to recruit 150 participants in four months for the last study we did. That's pretty good.

Also, Enroll-HD provides tools to foster collaboration and stimulate local center-based HD research. All clinical data from all participants at a given study site will be available for HD research at this center in real time, with no strings attached. We'd like to encourage people to do their own research, or team up with like-minded people, so that progress in research is not bottlenecked by a central planning committee. Instead, we'll have local initiatives that are quick and competent.

“You personally may not benefit... but you're making a great contribution... you're doing it to speed up the process”

since it will already be available on the Enroll-HD database. That means it's less time and effort for participants and less burdensome documentation for study sites.

Lastly, we would like to make sure that the experience for people who volunteer for HD research is further improved. Nothing is more annoying for patients and families than to have to engage with yet another health care provider every year anew. Enroll-HD should help to build stable HD centers. Also, the burden that comes with additional HD studies should be reduced; you don't have to go over your medical history and explain your medications yet again,

Q: Why does Enroll-HD need to be global?

A: One main reason is that we need both genetic and environmental diversity. For example, in the New World you have people who are genetically very close to people in the Old World, but they live in quite different environments. We are doing extensive genetic studies. If we also do a good job capturing environmental differences, we can contribute to understanding how the environment modifies disease progression.

Also, from the patient perspective, it makes sense. Otherwise, just because you were French, let's say, you might be denied the opportunity to contribute to clinical trials. Where's the justice in that? That's not fair.

Q: There's no immediate benefit for people who join the study. Why should they do it?

A: You personally may not benefit—you may even have to accept some risk—but you're making a great contribution that changes the landscape for you and your own kids. You're doing it to speed up the process of getting to solid results, as part of a larger community that is striving toward the same aim. Progress depends on the coming together of science, industry, clinicians and people affected by HD.

Because Enroll-HD is a long-term, open-ended study, there's the potential for HD centers to have long-term stability. That perspective is good for everyone. It's also important that young physicians and scientists see that HD research is an exciting field where things are really moving, where cutting edge therapies are being developed. The smart young people will get drawn to it—it's working, it's collaborative. That's how you'll get the best people.

Enroll-HD is also designed to improve clinical care, which will improve in part because people will talk to each other about intelligent approaches to problems. Also, we'll have records of the therapies people are receiving, and we can identify centers that have particularly beneficial outcomes, and ask: Why is that? This will help all the centers start to do it better. Through Enroll-HD we want to foster a culture of exchange between health care professionals and families, so that we can talk about a standard of care that truly deserves that name. 

THE GLOBAL VIEW

Enrolling the world

19
Number of nations
anticipated to be
involved in Enroll-HD
by year's end

33
Number of nations
currently scheduled
to eventually be in
Enroll-HD

Countries in green show where Enroll-HD is underway or will soon launch; nations in orange are candidates to join later. Enroll-HD will unify the COHORT study in North America and Australia with REGISTRY in Europe. Organizing a global study is challenging—it must meet all the scientific and legal requirements of each nation, and be translated into at least 16 languages. But only such a massive study with so many diverse participants can answer the most fundamental questions about HD.



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ONLINE RESOURCES



For updates in HD research and clinical news, check out **HDBuzz** at www.hdbuzz.net where Jeff Carroll, PhD, and Ed Wild, FRCP, PhD, describe the latest discoveries and explain what they mean for patients, families, doctors and scientists.

The **Huntington's Disease Youth Organization** (HDYO), www.hdyo.org provides support and education to young people impacted by Huntington's disease worldwide. The HDYO website has educational content for kids, teens, young adults, parents and professionals available in several languages. Get understandable information, ask questions, chat on forums with other young people, or learn what opportunities are available in your region.