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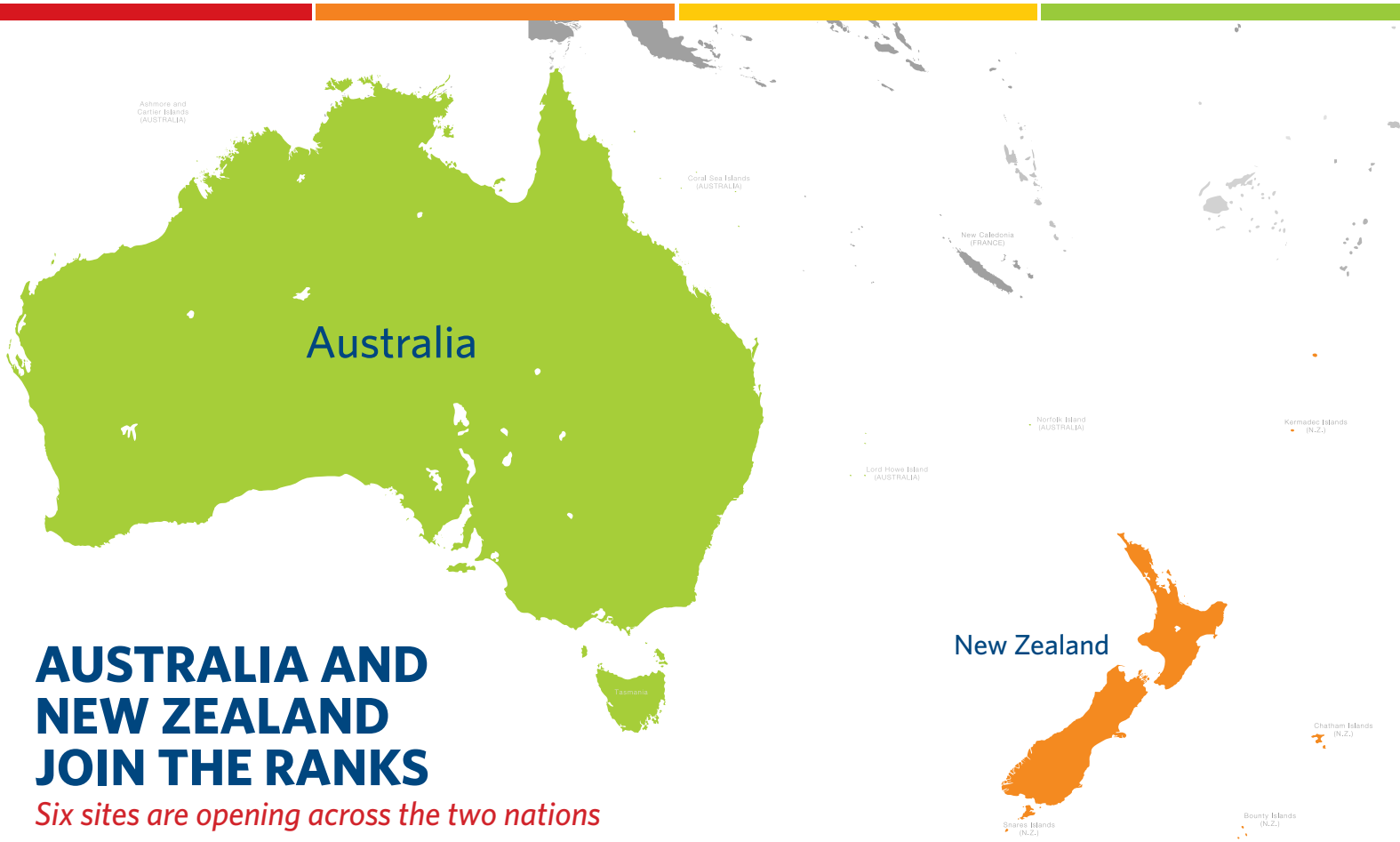
Enroll!

Updates from the Enroll-HD global community

MARCH 2014



AUSTRALIA AND NEW ZEALAND JOIN THE RANKS

Six sites are opening across the two nations

Enroll-HD now spans the Pacific: The first participant in Australia signed up for the study in Melbourne in August. The study is now underway at two sites in Australia and two in New Zealand. As of March 3, 76 people in the region had signed up.

This wing of Enroll-HD covers a vast geographic area. It includes people on Australia's west coast; participants in Melbourne, 2,200 miles (3,500 km) away on the continent's south coast; people who live on the island of Tasmania 400 more miles (600 km) to the south; and stretches all the way to New Zealand, another 1,500 miles (2,500 km) to the southeast.

In Australia, a huge continental landmass with a population of only 26 million, one of the challenges is reaching everyone who requires HD services, says neurologist Andrew Churchyard, MD, who runs the Enroll-HD study site at Calvary Health Care Bethlehem in Melbourne: "The smaller states have a very sparse population, and there are issues about rural access to services."

Tasmania, the island just south of the Australian mainland, is one of the world's HD hotspots. Churchyard says the disease is two to three times more common there than anywhere in the US or Europe. But while Tasmanians have access to local social workers and psychiatric help there is no HD specialist neurologist on the island. Instead, Churchyard flies down to two Tasmanian towns, Launceston and Devenport, once every three months to hold HD clinics. He expects to begin enrolling people there into the study some time later this year.

New Zealanders have been involved in smaller-scale studies before, but Enroll-HD offers a unique opportunity for international collaboration, says Richard Roxburgh, FRACP, a neurologist and

HD specialist at Auckland City Hospital. "What we do gets magnified, because we're partaking in an international project," he says. "It provides a fantastic way of collaborating in the future."

Getting involved in research is an "incredible opportunity" to reduce feelings of isolation and hopelessness, says Australian Tony Mims.

"Engaging and participating in research gives me an opportunity to link in with people that are in the forefront of knowledge about HD," says Tony Mims, a gene-positive Australian based in Melbourne who has signed up for Enroll-HD. "It also gives me a chance to feel like I'm contributing to the overall effort." Mims helped launch a youth support group called the Australian HD Youth Alliance, and has been involved in publicizing Enroll-HD. "It's not advertising," he says. "It's helping people be knowledgeable about it—and getting the word out that there's an important study out there if you do want to get involved."

"The major value of the study is to get a really good idea about how the disease evolves over time, and getting a lot of information about many people over time is the best way to do that," says Churchyard. "This is going to be a long-term project." He expects to recruit several hundred people, but for now his team is moving cautiously: As of early February, 26 people had signed up in Melbourne. "We want to get the systems running and have the proper human resources so that when the study starts it starts smoothly, with high quality data collection," he says. "In the end the quality of research depends on the quality of the data." Additional sites are planned for Sydney, the nation's capital, and in the small city of Brisbane.

Families are embracing Enroll-HD, says Monash University scientist Nellie Georgiou-Karistianis. She expects the study to be a "fabulous platform" for research.

Enroll-HD and research in Australia

"From what I've seen, families are embracing Enroll-HD," says Nellie Georgiou-Karistianis, PhD, a cognitive neuroscientist at Monash University, also in Melbourne. Georgiou-Karistianis conducts brain imaging studies in HD and other movement disorders, and is working on new ways to track the changes to the brain during the course of the disease. She says that the study offers "a fabulous platform" for new opportunities in research: "We're hopeful that it will facilitate the research we do."

In one of her projects, she measures people's walking speed and coordination with an electronic floor mat that records the length and speed of the stride, and how they deal with obstacles. "We try to understand how patients with HD walk, and what might characterize their walking pattern," she says, as well as how distractions such as carrying on a conversation affect walking. The idea is to find a sensitive way to identify subtle changes in movement. But the research should also provide recommendations about how people might better cope with physical changes and be able to walk and move around more easily. "We're hoping to be better equipped to inform families in the everyday home about what things to do or what not to do" so that HD-affected people can walk stably and safely, says Georgiou-Karistianis.

She predicts that Enroll-HD will make it easier and faster to do studies like these because it will attract more people who may not have previously been aware of the research. That in turn will help her group attract new participants to their studies. She hopes to launch another study to investigate cognitive and emotional training for people with HD—programs that help people learn mental skills to improve memory and information processing, manage strong emotions like anger and frustration, or even slow the changes in brain tissue that happen over time in HD.

One of the major goals of Enroll-HD is to improve care for everyone with HD, not just those who participate in the study. "One problem worldwide is that HD clinics are poorly funded, and these are patients with complicated problems who need resources," says Churchyard. "With a big study, people can employ new staff and develop their skills, upgrading the general quality of care."

Ultimately, the decision to participate in studies like Enroll-HD is a personal one, says Mims: "I try to explain both ends of the story." On the one hand, dealing with emotions that may come up during the research visit can be difficult. Mims advises people who do volunteer for the study to make sure they have someone to turn to before and after the visit, whether it's a professional or a trusted friend or family member. On the other hand, joining up with a study is also a concrete contribution toward the effort to find effective treatments. "One of the things that's pervasive in the HD experience is the feeling of helplessness and isolation," he says. "Participating in research is an incredible opportunity to reduce those feelings."

REGISTRY BECOMES ENROLL-HD

The European transition is underway

The most complicated phase of Enroll-HD is just beginning. The European sites that are taking part in REGISTRY began transitioning into Enroll-HD at the end of 2013, after more than a year of preparation. The first European participant to officially become part of Enroll-HD signed up in Ulm, Germany on December 6.

Transforming one study into another is tricky since everything has to be planned in advance. The goal is for nothing to be disrupted. Anyone who was part of REGISTRY should be able to walk into the clinic, provide their HDID number (or the information that can recreate it) and pick up where they left off, without any break. But that requires careful coordination. "Finishing a study means you have to tidy up and make sure you cross your T's and dot your I's," says Michael Orth, MD, PhD, the principal investigator at the site in Ulm. "It's a lot of work to make sure the data you have in there is as good as it gets."

The transition began after more than a year of preparation

The old database from REGISTRY needs to synch up perfectly with the new "Electronic Data Capture" system (the computer system that holds and organizes Enroll-HD data, which is slightly different from the previous database). Even after all the technical work is completed to make that happen, the data doesn't actually get moved into the new system until each participant officially agrees to become part of the new study. The data "is moved into a holding area," explains Jenny Townhill, PhD, who oversees the finalization and transfer of the REGISTRY database as migration manager for Enroll-HD. "The participant then has to show up at the Enroll-HD site and sign a new consent form. Otherwise, their old data never goes into the Enroll-HD database." When the participant signs the new consent form, their data is now live, and is transferred electronically to a central database in the UK.

REGISTRY, which began collecting data in 2004, included 17 nations and more than 12,000 participants at about 150 sites across Europe. Much like Enroll-HD, the study required yearly exams and cognitive tests to monitor any progression of the disease in participants. Enroll-HD uses similar methods, and relies on the same site staff. But because the data collection and storage technology for Enroll-HD is all new, and some of the tests that are part of the study are slightly different, merging the two studies is not simple.

Getting ready for the switch

Each study site must be switched over individually, because all the procedures to move the electronic data from one system to another must be done at the site itself, and there are a number of technical checks. But before that happens, all the paperwork for the study must be agreed upon and finalized, including approval from local or national ethics committees, official agreements between the site and the study organizers, and policies that maintain the privacy of participants. Enroll-HD also involves a few new tests, so the site staff who work with study participants learn how to give these new tests, and how to use the new Electronic Data Capture system.

Next comes the technical part of the transition: Making sure all of the data collected during the last decade in REGISTRY is ready to flow smoothly into the new computer system. Each of the old database records must be 'clean,' with no blanks and no mistakes. The staff at Ulm began combing through their com-

The team at Ulm, Germany, the first site to officially switch from REGISTRY to Enroll-HD

puter records in 2012 to correct oversights and errors by hand, says Katrin Barth, an information specialist who coordinated the transition team at the Ulm site. "It sounds easy, to move it from one database to the next," she says. But making sure that every drug and every diagnosis has the right code number associated with it is time-consuming. "It's a lot of work—you enter a term, the system comes up with several available codes, and you decide which ones are correct." Computers can't do this job, says Barth—only humans.

At the site in Ulm, the REGISTRY database was officially frozen on November 25, 2013, meaning that no new information from study participants could be added to it. Specialists from 2MT, the small German software company that built the Enroll-HD Electronic Data Capture system, converted all the old data into the new format and spent two weeks testing it alongside the team at Ulm. Once they were sure there were no major problems the first participant was officially added to the Enroll-HD database.

So far, says Barth, everything has gone smoothly at Ulm. Following that success, the first UK site transitioned in mid-February in Manchester, and by early spring, three more in Germany and one more in the UK were expected to have switched over. Although the first transition went quickly, it's not clear how long it will take for the rest of the sites to become part of Enroll-HD. "We're feeling our way through for the first few transitions," says Townhill. Sites in Germany, the UK, the Netherlands, Denmark, as well as Italy and Poland are expected to make the shift in 2014, around four per month. Townhill hopes that all the sites will be part of Enroll-HD by the end of 2015.

BUILDING ON ENROLL-HD

The study is called a "clinical research platform." What does that mean?

In some ways, Enroll-HD is not so unusual. Like other observational or "natural history" studies, it monitors symptoms and underlying changes caused by disease over time. Information is collected every year, from the same people, for a long time. The information can be a major help in the search for treatments because it provides reliable measurements of what is happening inside the brain and rest of the body. And it's essential for testing new drugs that are intended to prevent disease; the only way to tell if a treatment is really working is to have an accurate record of what usually happens as the disease progresses. Then in clinical trials volunteers can be given the drug and the results compared with the predicted course of disease. For all these reasons, Enroll-HD is a lot like other observational studies of diseases like Parkinson's and Alzheimer's.

In the average drug study, **two-thirds of the sites** *don't enroll enough patients.*

But in other ways Enroll-HD is unique since, unlike most studies, it combines observations with opportunities for researchers to conduct sub-studies that ask specific scientific questions, says Bernhard Landwehrmeyer, MD, the principal investigator for Enroll-HD. "The idea is that you combine the collection of some standard data sets with targeted hypothesis-driven data collection," he says. "By combining this in one platform, you take away some of the burden from the patients and from the study site and make it much more efficient."

Enroll-HD also has a practical goal: to make all HD research easier, speeding up the process of finding drugs and other approaches that really work. Rather than being limited to use by a select group of researchers it is designed as a public resource that makes it faster and more efficient for other researchers to do their projects. This is why it's called a platform—it's a structure that supports other work. Basically, it lays out a "Welcome" mat for researchers and pharmaceutical companies to study HD, supplying many of the essential ingredients for a clinical trial, such as a global network of research sites, a carefully maintained database that tracks people's health over time, and, most importantly, an up-to-date anonymized database of people who have HD or the gene mutation who might want to volunteer for a new study. "You can home in on the group of people who are likely to be eligible for a study or trial," says Landwehrmeyer, and these individuals can then be invited to join by their own doctor (see box, "How will I be invited to join a clinical trial?"). "You make the work much more efficient." It's a foundation for all other HD researchers to build upon.

The needle in the haystack

Finding enough of the right people to join up is the biggest challenge of any clinical study or trial. According to one estimate, 40 percent of the cost of testing new drugs for all conditions goes toward finding the right participants—about US $1.9 billion a year in total. Enrolling enough people generally requires twice as long as it is supposed to, and the result is that 80

percent of all clinical trials don't finish on time. The difficulty of finding participants "makes trials longer than they should be," says Cristina Sampaio, MD, PhD, CHDI's chief clinical officer. "And sometimes trials just fail, because people are not able to recruit the patients that they need."

1723 PEOPLE CURRENTLY SIGNED UP FOR ENROLL-HD IN 8 NATIONS AS OF MAR 3, 2014

By having a complete, well-documented and up-to-date secure database of potential volunteers (all anonymized so that privacy is protected; see box), a drug company or other scientists can find out quickly whether or not the study they want to do is even feasible—whether enough people with the HD gene who are at the appropriate stage of their disease are in the right location to take part in the study. "This is all about time," says CHDI president Robi Blumenstein. "Anytime someone says, 'We'd like to study this type of patient, with this combination of age and [HD gene] CAG repeats,' we can look in the database and get the right study up and running as quickly as possible." The idea is that because this knowledge makes it easier for drug companies to get studies underway, it will help move HD higher on their priority lists.

The average drug takes more than ***8 years*** *to test*

Enroll-HD acts like a platform for other studies in other ways. A lot of the paperwork required to conduct these additional projects is already in place because detailed agreements are hammered out when Enroll-HD is launched at each site. The site staff is well-trained in the best ways to measure HD symptoms. And the medical history of the potential volunteers—how they've been doing recently, what medications they've been taking, as well as their family history—is already documented, with multiple quality control checks to make sure that it's all accurate. "It saves time and money to take advantage of the information already available," says Landwehrmeyer.

This research platform will also be available to people studying other aspects of HD. For example, if researchers want to work on better ways to measure changes in motor control and involuntary movement in HD, knowing how many people might volunteer will help them plan where and how to do the study, and how long it will take. "It really helps when planning a study, and it helps you execute the study in a time-efficient way," says Michael Orth of the University of Ulm. "For researchers this is really attractive. You are saving yourself a lot of hassle."

It's like a smartphone

Sampaio suggests that another way to think about the study is like a smartphone; just like the phone provides hardware that programmers can build apps for, Enroll-HD provides a basic system that gets everyone working with the same basic protocols and procedures. From that starting point, all the studies that other researchers will invent and carry out can be thought of like the apps that programmers build and add to the phone.

HOW WILL I BE INVITED TO JOIN A CLINICAL TRIAL?

If you are part of Enroll-HD, you may have the chance to join other clinical studies and clinical trials. The words mean slightly different things (and not everyone uses the words in the same way.) Trials usually test either a new drug or a non-drug therapy such as exercise or diet for HD. Studies, on the other hand, don't test a treatment. They might investigate a better way to measure the changes caused by the disease or explore factors that influence the health of people with HD.

If a scientist or drug company researcher has a new idea or a new drug to test in HD, the investigators at each local site can help, by looking through the Enroll-HD database for people who have already said they are willing to be contacted for an outside study. If you have agreed in your consent form to be contacted, and you have the right characteristics for the study, your neurologist or another person at the site where you get care will contact you with a description of the research project to see if you are interested in joining. Nobody outside your local site, where you go for Enroll-HD visits, will be able to see any identifying information such as a name, address or birth date. Volunteering is completely up to you and is always your choice. Whatever choice you make, it won't affect your care—you can still be part of Enroll-HD even if you don't want to join other studies or trials.

$20,000: *Average cost for one patient in the first phase of a clinical trial*

Just as the phone inspires software programmers to come up with all kinds of new and creative apps, the idea is that Enroll-HD will spark innovative ideas to test about treating HD.

Maybe one of the most unusual things about Enroll-HD, in comparison to other observational studies, is that it is also designed to improve the quality of care. Because so many people who are already being treated for HD will be involved in the study, and because ways of treating HD symptoms (such as physical therapy or drugs for psychiatric problems) vary a lot from region to region, it should be possible to compare treatment regimens around the world and identify the best ones. Enroll-HD makes it possible to carefully compare how HD is managed in Australia, Argentina, and Austria, and figure out what works best. That information can then be shared worldwide. "The idea is, let's capture this information in an appropriately confidential way, and put it in a database so it has extra utility," says Blumenstein. "Then, you can see which approaches work out better and share best practices across all regions."

Because Enroll-HD is such a large study—bigger than any other similar study for other neurodegenerative diseases—that will last a long time, the hope is that it will also be a beacon for young researchers to bring their talents and energy to fighting HD. Having such a big collaborative study for a relatively rare disease is unique, and it creates an important resource and new research possibilities that will encourage young researchers to view HD as a promising field where they can make a difference.

The study also creates a permanent global community of scientists, health professionals, patients and families, says Sampaio. "The health professionals are getting training and education, and being made aware of the needs of the community, and simultaneously patients and families are getting educated with more awareness about what's going on in research and why it's important," she says. "This is an extremely positive process."

By providing a common set of tools and common goals, the study has the potential to unify the HD research community worldwide. Launching and maintaining it is a big effort, but the rewards will come fairly quickly, predicts Orth. "The real purpose is treating people, and Enroll-HD has the power to serve that purpose really well, do away with the red tape and hassle, with results that are likely to be robust and reliable," he says. "That's the overall goal—we want to treat people."

ENROLL-HD AS A PUBLIC RESOURCE

Another way that Enroll-HD is unique is that it is designed to be a public resource shared by the whole HD research community. Most studies are restricted, so that only the researchers who collect the information can get access to it to learn about the disease. Enroll-HD uses high standards to protect the privacy of participants, so that anyone with a valid research project can get access to de-identified data with all potentially identifying information removed. The work of granting permission falls to the Scientific Publication Review Committee, which is now developing ways to connect with researchers. The committee also will review suggestions to collect new types of information that Enroll-HD currently doesn't ask about. Data from Enroll-HD should become available for researchers within the next six to 12 months.

Sources for statistics about clinical trials: Tufts Center for the Study of Drug Development, the Center for Information and Study on Clinical Research Participation, RDP Clinical Outsourcing

Enroll! is a publication of CHDI Foundation, Inc., a not-for-profit biomedical research organization that is exclusively dedicated to rapidly developing therapies that slow the progression of Huntington's disease (HD). As part of that mission, CHDI Foundation sponsors and manages Enroll-HD. More information can be found at: www.chdifoundation.org

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