



Gateway

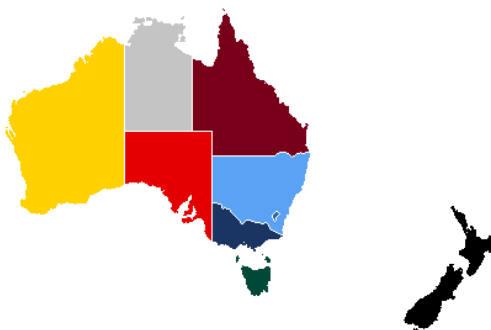
News from Huntington's New South Wales

Volume 17 No 1

Autumn 2014

Australia & NZ Join the Ranks of Enroll-HD

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 3rd, 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, 3,500 km away on the continent's south coast; people who live on the island of Tasmania 600 km to the south; and stretches all the way to New Zealand, another 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 Devonport, 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."

"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

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National Huntington's Conference 2014

"Embracing Opportunities with HD"

Perth, Western Australia 11th - 12th September

University of Western Australia, UWA Club

Save the Date!!

Huntington's WA invites you to the National Huntington's Conference in Perth, bringing together family members, researchers, allied health professionals, care workers and members and supporters of all Huntington's Disease Associations across Australia.

An exciting line up of keynote speakers includes

- Richard Faull
- Nellie Georgiou-Karistianis
- Tony Mims

as well as presentations around living well with HD, sharing best practice and translational research, engaging youth and exploring new boundaries.

Full Program and registration including links to accommodation and popular tourist activities available shortly from www.huntingtonswa.org.au.

Camp Breakaway

Our annual camp on the Central Coast is fast approaching. Interest is high! But we are still inviting members with HD



who might be interested in joining us for five days at Camp Breakaway, San Remo on the Central Coast, Monday 5th May to Friday 9th May inclusive to apply to come to Camp.

The Camp is an excellent opportunity for our members with HD to connect with people who are in a similar situation to themselves, to talk, share experiences, participate in organised activities, indulge in great food, and be with friends.

All participants need to be independently mobile and able to dress, toilet, and shower with NO assistance. Planned activities include walks by the lake, a modified version of lawn bowls, time to relax, and craft. Preference will be given to people who have not previously attended one of our camps.

For a camp application form, please call us at the Association on 9874 9777 or email Karen on karen@huntingtonsnsw.org.au

A Day at HWH Stables

HWH Stables is owned and operated by Chris Fenech, a member of Huntington's NSW. Chris' family is impacted by HD and he would like to give other HD families the opportunity to spend time at his stables, located at 267 Dairyville Road, Upper Orara (approximately 20 minutes drive from Coffs Harbour).

You and your family are invited to have a fun-filled day at the property, participating in various activities— a nature trail, swimming pool and horse riding lessons. You will receive a very warm welcome from Chris and his staff, use of all the facilities and morning and afternoon tea and lunch at no charge.

So if you live nearby or are holidaying in the area why not take advantage of Chris' very generous offer. Please note that he does require 24hrs notice.



For more information, you can visit his website at www.idservices.com.au or ring him on 0419 977 542

Support Groups

Our West Ryde Carers Support Group meets on **Wednesdays** each month at **10.30am**, at the Association's office,
21 Chatham Rd West Ryde,

It's a great time to get together with other carers who, like yourself, are caring for a partner, a family member or a friend with HD. The group is facilitated by Jet Aserios and Cecelia Lincoln from the HD Service.

Come along and join us as we share our chatter, laughter, tears and experiences.

2014 Sessions

23rd April	28th May
18th June	9th July
13th August	24th September
15th October	12th November

A combined Christmas Dinner will be held on either Friday 5th or 12th December (tbc).

We are delighted to announce that a second group is starting in 2014 and these meetings will commence at **2pm** and will be held at the **South Penrith Neighbourhood Centre**
3 Trent St, South Penrith.

The dates for these sessions are

26th March	30th April
11th June	23rd July
27th August	1st October
5th November	

To RSVP for either group and for further information, please contact:

Jet Aserios or Cecelia Lincoln 9845 6699, Social Work Department, Westmead Hospital or Robyn Kapp, Huntington's NSW, 9874 9777

Raising Funds for Huntington's NSW

*11th Annual Rotary Club of Concord
Charity Golf Day and Dinner
will be held on Thursday 19th June 2014 at
Concord Golf Club, Majors Bay Road, Concord.*



*All proceeds will assist Concord Rotary Club to support
Huntington's NSW and the Colorectal Unit at Concord Hospital*

Registration: 11am

Hit-Off: 12noon

Dinner: 5.45pm

Golf & Dinner Package: \$170 pp

Golf Only (incl lunch): \$130 pp

Dinner Only: \$65 pp



Corporate Sponsorship is available:

\$800 for four players, dinner for four and naming rights and signage for one hole.

Applications close on 5th June and forms are available from Huntington's NSW.

Meet the Staff Team ...

Executive Officer: Robyn Kapp

Robyn joined the Association in 1976, serving as President from 1978 to 1983 when she was appointed Executive Officer until her retirement in 2006.

Throughout this period she worked to develop appropriate state, national and international approaches and programs for the care of people with HD and their families. She has also served as National President and President of the IHA. Robyn, who has a BA, returned in 2011 and is committed to providing and enhancing quality services for people impacted by HD. Robyn has a daughter and enjoys reading, gardening and travelling.

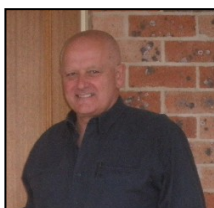


Activities Co-ordinator: Karen Bevan

Karen is from an HD family, her father having been diagnosed with HD in the late 1970s. Since that time, she has had a strong connection with the Association as a family member, an employee and board member. Karen previously worked for HNSW as the Activities Co-ordinator and Clerical Assistant from 2001 until 2007. She has returned to the role of Activities Co-ordinator which she loves and counts it a privilege to be able to work with families impacted by Huntington's. Karen is married to Mark and they have two children and ten grandchildren.



Family Support Worker: Mark Bevan



Mark has been working with HNSW in this position nearly four years. His previous working history includes IT, the NSW Police Force and a Pastor. He loves his current role and enjoys meeting families around the state. Mark continues to be

inspired by the resilience they show under pressure. "It is wonderful to be able to journey with them as they deal with Huntington's." He has been involved with HNSW since the 1970s when his father-in-law was diagnosed with HD. Mark is married to Karen and they have two children and ten grandchildren.

Activities Volunteer: Stewart Swales



Stewart is the volunteer for the Tuesday Lunch Club. He has had an association with HD for as long as he can remember as his father was diagnosed in the late 1960s. Stewart served for a short time on the board during the mid 1990s. Late last year he

accepted a redundancy from his employer and when the vacancy at Lunch Club arose, he suggested to Robyn that he might be a good fit. Stewart is married to Minette and they have two children. He is a passionate Bulldogs supporter, which creates interesting discussion at the Tuesday get together.

Administration Co-ordinator: Margaret Lind

Margaret joined the Association in February. Previously, she has worked in a variety of organisations including not-for-profits in both paid and voluntary capacities in the areas of accounting, administration and providing services to clients. Semi-retired she enjoys time with her family and two grandchildren, meeting with friends, cake decorating, teaching English to migrants, with a child in a literacy program for foster children and getting back to regular exercise. Margaret is looking forward to working with the team at HNSW.



Goodbye & Good Luck...

In December we said goodbye to Lily Ma, our Activities Co-ordinator and Admin Assistant. After more than six years with HNSW, Lily has decided to widen her experience and is currently undertaking a TAFE course in Aged Care. We thank Lily most sincerely for her commitment to and enthusiasm for the work of the Association and our best wishes go with her for her future endeavours.

Meet the Board ...



President : Brian Rumbold joined the Board in 2011. He is a management consultant working with organisations that include not-for-profits in the health and aged care sectors. His work encompasses business strategy, facilitation, project design, information

management, and electronic publishing. Brian has a primary degree in Electrical Engineering and a Master of Business Administration. He and his wife Margaret have two married sons and four grandchildren.

Vice President: Deborah Cockrell

Deb is a registered Oral Surgeon who currently practices and lives on the Central Coast. She moved from the UK in 1996 and since that time she has held senior academic appointments in dentistry and oral health, at the University of Sydney and the University of Newcastle. Deb has a PhD in dentistry and an MBA and is President of the Dental Council of NSW. Her mum, Pat, was affected by HD, hence Deb's willingness to use her skills, expertise and personal family experience on the Board.



Secretary: Don Ayres



Don has been a member of Huntington's NSW for ten years and on the Board for four years. Don is married to Terry and they have three children and one grandson. Both boys are gene positive and like everyone in the organisation and many others throughout the world, they are

looking forward to a cure for HD.

Don's background is in real estate spanning some 40 years and operating in vast areas across NSW. His hobbies include golf, tennis, music, reading non-fiction, motor racing, both cars and bikes. Don is a committed Christian.

Treasurer: Richard Bobbitt first joined the Board in 1994 and has also served as Vice President. He is married to Helen and he has a degree in Chemical Engineering. Richard is a Supply Chain Manager for a chemical company. He is a keen farmer, camper, 4wdriver and enjoys travelling overseas.



Board Member: Amanda Dickey

Amanda was first elected to the Board in October 2012. and has been an active member of the HD Central Coast Support Group since 2010. She is a Technical Business Analyst, within the finance industry, and is experienced in many technologies, process improvement and relationship building. For 25 years she has witnessed how HD has affected close family members. Inspired by their strength and sacrifice Amanda is a committed HD advocate. Amanda believes that the aims and objectives of HNSW align with her will to challenge the status quo to clear pathways through bureaucracy toward customer-oriented outcomes.



Board Member: Jenny Coutts



Jenny first became acquainted with HNSW when she was the Director of Nursing at Lottie Stewart Hospital in Dundas and the transfer of the inpatient unit from Lidcombe Hospital to Lottie Stewart Hospital was being planned in 1995. When the Unit was established at Lottie Stewart

Hospital she employed Angela Lownie to establish the Outreach Service from Lottie Stewart Hospital. Jenny worked closely with the staff in the unit and enjoyed watching the outreach service expand to support people affected by HD throughout NSW. Jenny continues to have an interest in supporting staff in the community and in residential aged care facilities to provide the best care and advice to individuals and families in their care.

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data." **Additional sites are planned for Sydney and Brisbane.**

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."



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

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."

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.

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

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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 hone 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. "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."

By having a complete, well-documented and up-to-date secure database of potential volunteers (all anonymized so that privacy is protected), 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.

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. 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

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Prana announces results of Reach2HD trial of PBT2 for Huntington's disease

Results are in for a clinical trial testing the drug PBT2 for HD. Are the claims in the announcement justified? By Dr Jeff Carroll on February 20, 2014 Edited by Dr Ed Wild

The results are in from the Reach2HD study, which was designed to test the experimental drug PBT2 for early and mid-stage Huntington's disease. The drug seems safe and well-tolerated at the doses that were tested, but we have major concerns about the way the results have been reported.

What is PBT2?

Prana Biotechnology, an Australian drug development company, is working to develop a drug called **PBT2** for use in Huntington's Disease and Alzheimer's Disease (AD). The company has previously reported that the drug has positive effects in animal models of HD, and that it is well-tolerated when given to human research participants.

The drug works in an unusual way, which is to reduce interaction between the HD-causing **huntingtin** protein and the metal **copper** in the brain. Copper, in small and well-regulated amounts, is critical for the normal function of cells. In fact, copper is important for our cells to produce energy, so without it we'd have a hard time!

But in diseases like HD and AD, metals like copper can start to have harmful as well as useful properties. Some scientists think this may contribute to the early death of cells in the brains of patients with these diseases.

Prana tested PBT2 in mouse and worm models of HD, and found that it led to improvements in some signs of disease in these animals.

What is Reach2HD?

Given favorable results in the lab with animal models of Huntington's disease, Prana Biotechnology decided to test PBT2 in people with HD. They worked with clinical centers under the direction of the Huntington Study Group in the US and Australia to run a trial they called **Reach2HD**.

The Reach2HD trial involved 109 Huntington's disease patients with early or mid-stage disease who participated for about 6 months. During that time, they were randomly assigned to one of three groups: a low dose of PBT2, a higher dose of PBT2 or a 'placebo' group, who received dummy pills containing no drug. Neither the patients, nor the

researchers running the study, knew who was receiving active drug and who was assigned to the placebo group.

This kind of trial — called by researchers a randomized, double-blinded, placebo-controlled trial — is the gold standard for testing new drugs. At two timepoints — 3 and 6 months — all of the participants were given a battery of tests,

including brain scans and blood sampling.



The Reach2HD study was sponsored by Prana Biotechnology and conducted by the Huntington Study Group at sites in the United States and Australia.

Prana's announcement

In a press release, Prana announced what sound like very impressive results from the study. They say PBT2 was "safe and well-tolerated", "met its primary endpoint", produced a "significant benefit on cognition" and brain scan changes "suggestive of a beneficial effect".

That sounds amazing... almost too good to be true, in fact.

First let's remind ourselves that the claims were made in a press release, not in a peer-reviewed scientific publication. That means the company's claims have not yet been subject to the level of scrutiny needed to be accepted by the scientific community.

Now let's look at what each of the claims means in practise. First we need to learn a bit about clinical trials.

A Phase 2 trial

Regulatory agencies like the FDA need various kinds of evidence in favor of a new therapy, before they can approve it for patients. First, they need to ensure the drug is generally **safe** in people, having been tested previously in animal models. This is established in what's called a **phase 1** study, in which a few volunteers take doses of the drug under close supervision, to make sure there aren't unexpected side effects.

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Once we've established that the drug isn't highly toxic, we're interested in whether the drug is safe for patients, and whether it works. So-called **phase 2** studies are designed to further establish whether a drug is safe — that it doesn't make the disease worse, for example. They also aim to get an idea of whether a drug might be effective.

Finally, a drug with a successful phase 2 study can be tested in a larger group of patients to confirm the beneficial effects seen in the smaller phase 2 study. These **phase 3** studies are usually the basis of an application to have a drug approved and sold to patients.

Reach2HD was a **phase 2** trial — intended to establish the drug was safe, and to get an early idea of whether it might have some benefits. So Prana's statement that PBT2 "met its primary endpoint" simply means the drug was safe and well-tolerated.

Why we need endpoints

Testing whether a drug is 'effective' or not can be challenging. In Huntington's disease, lots of things go wrong. Patients experience movement problems, thinking and memory problems, depression, apathy, brain shrinkage, and a whole host of difficulties with the activities of daily life. Which of these symptoms should we target if we want to fight HD?

Complicating things further, there are often dozens of different ways of measuring a particular feature. For instance, there are many ways of testing thinking skills or 'cognition' in HD. Which measurement should be the one we use to decide whether the drug is working?

The goals that a drug has to meet in a trial are called **endpoints**. A very important feature of Phase 2 and 3 studies is that the endpoints need to be established in advance. The goalposts mustn't move after the trial begins. Otherwise, nobody will be able to agree on whether the trial was a success.

Reach2HD had **safety and tolerability** as its **primary endpoint**. And indeed, the drug didn't cause too many side effects, and not too many people stopped taking the drug.

One patient who took the higher dose experienced a **worsening** of their HD symptoms after finishing the study. Though this happened after the patient stopped taking the drug, the investigators decided that the effect was due to PBT2, which raises an important caution for future studies.

But overall, the safety and tolerability news is good

for PBT2.

Secondary endpoints

In a phase 2 clinical trial, many different things will be measured, to give a broad picture of what aspects of the disease are affected by the drug. The measurements the trial designers think are important, are called **secondary endpoints**. Again, these are set in advance to avoid confusion later.

Reach2HD had **seven** secondary endpoints: cognition; motor function; functional ability; behavior; global assessments (whether people are feeling better overall); blood and urine tests; and brain scans.

What's more, each of these endpoints was based on many different individual tests. For example, the cognitive endpoint contained **eight different thinking tests**.

So when the press release claims success in meeting the cognitive endpoint, you might think that drug-treated patients had improved on all eight tests... or maybe four out of eight?

Unfortunately that's not what happened. There was only a 'significant' difference on **one of the eight tests** - called 'trail making B'. That involves connecting letters and numbers with a pencil against the clock. None of the other tests was better in drug-treated volunteers.

So, while it may be technically correct for Prana to claim that a cognitive endpoint was met, cooler minds will want to look behind the headline, and consider the **seven tests that did not improve**.

Multiple comparisons

Humans are optimistic by nature — and HD family members are desperate for good news. But it's generally frowned upon in the scientific community to report only positive findings, or to give them undue prominence. That's because of what we call the **problem of multiple comparisons**.

To understand this, think about flipping a coin. If you flipped a coin ten times and got ten heads, you'd wonder how honest that coin was! But, if you flipped a coin a million times, you'd expect to get ten heads in a row several times, somewhere in the million flips.

Put simply: the more things you test, the more likely one will show positive results, simply by chance. That's why we're skeptical about the single cognitive test that improved among the eight that were tested.

In the Reach2HD study, the investigators cast a

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very wide net — measuring 7 different categories of HD problems, each measured with multiple different tests, ultimately measuring dozens of different things in all 3 groups of people.

In fact, almost all of the tests for the secondary endpoints were not improved by the drug.

From the limited data released by Prana so far, it's not clear how they dealt with the problem of multiple comparisons. Remember, so far we only have a press release: the full results haven't been peer-reviewed and published.

There are well-established mathematical techniques for dealing with the problem, but they're not always used correctly, and it's not clear exactly how Prana dealt with this problem in their clinical trial analysis. The press release doesn't say — **but this is really important stuff.**

What about the functional improvement?

Prana's press release claims PBT2 was "associated with a favourable signal in functional capacity." Surely that's good news?

Doctors use the word 'function' to refer to how people are getting on in their everyday lives. Things like working, household chores, finance and so on. This is different from the cognitive testing we've already mentioned. Huntington's disease causes a steady decline in function, and there are a number of well-established ways to measure this, turning function into a number that can be compared across groups.

Reach2HD used two different measures of function, as well as two measures of 'global' wellbeing which are closely related to function.

So what was this "favorable signal in functional capacity"?

What was actually seen was a small difference in one score — the **total functional capacity** — in patients receiving the higher dose of drug, compared to placebo-treated volunteers.

Scientists use statistical tests to help decide whether a difference like this is real or arose by chance. If the difference is big enough, it passes the test. If it's not, it fails and the scientists are not allowed to say there was a 'significant' difference.

The difference in functional capacity scores in Reach2HD came close, but **did not pass the statistical test.** That's why the phrase "favorable signal" was used instead of "significant difference".

That turn of phrase might be technically correct, but we don't think it's helpful in conveying results

accurately to HD patients and families.

What's more, the other function score, and the two scores reflecting global wellbeing, **didn't differ between groups.**

It could be argued that the responsible thing to do here, given the desperation of HD families for good news, would be to say "no overall functional improvement was seen".

Instead Prana chose to trumpet the borderline positives while playing down the negatives.

But the brain scans!

The final claim we want to look at is that PBT2 "reduced atrophy of brain tissue in areas affected in Huntington disease".

Some Reach2HD volunteers had two brain scans to measure the brain shrinkage, or 'atrophy', that HD patients experience. Reduced atrophy sounds great! But what did they actually show?

Believe it or not, the atrophy results described in the press release are only based on the brain scans of **two patients from each group!**

We're genuinely amazed that this analysis was done in such a small number of volunteers. And we're even more amazed that Prana has chosen to report this as a positive finding from the study.

Two people from each group is **nowhere near enough people** to even begin to understand what's happening with atrophy. It typically takes dozens of volunteers to be able to even **detect** brain shrinkage due to HD over six months, let alone measure the tiny difference a drug might be making.

The claim that brain atrophy was reduced by PBT2 is **clearly unsupported by the described data.** We'll have to wait for an analysis of the entire data set before seeing whether this claim is actually true.

This bold claim is another reason why we view the press release with skepticism and some disappointment.

Take home and next steps

We think two conclusions can safely be drawn from the Reach2HD press release.

First, that the drug is safe enough to proceed to larger trials.

Second, that the claims of cognitive, functional and imaging benefits are not supported by enough evidence to place much confidence in them.

We're as enthusiastic as anyone for drugs to benefit

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HD patients. ***Your humble author, for instance, is an HD researcher and research volunteer who happens to carry the HD mutation himself.***

To be clear: we're **not** saying the Reach2HD press release contains untruths. But, in our opinion, it does contain statements that overemphasise the positives in the trial's results, play down the negatives, and are likely cause false hope in HD families.

We're all for hope, but we'd rather have cautious optimism than hype and false hope.

We're also keen to see a larger, phase 3 trial of PBT2. But first, we call on Prana and the HSG to submit the trial results to the proper scientific scrutiny of a peer-reviewed publication so that researchers and HD family members can see and evaluate the full data set.

Acknowledgement:
www.hdbuzz.org



(Continued from page 7)

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."

Acknowledgement: *Enroll!! Newsletter March, 2014*
www.enroll-hd.org

***Westmead Hospital is the planned site for the Enroll-HD Study in Sydney.
The study is currently in the final stages of establishment.
We'll keep you posted in "Gateway" and on our website.***



Huntington's New South Wales

PO Box 178, West Ryde, NSW 1685

21 Chatham Road, West Ryde, NSW 2114

Telephone: (02) 9874 9777 Facsimile: (02) 9874 9177

STD Free Call: 1800 244 735 (Country NSW only)

Email: info@huntingtonsnsw.org.au

Web Site: www.huntingtonsnsw.org.au

AHDA (NSW) Inc

The Australian Huntington's Disease Association (NSW) Inc is a not-for-profit organisation established in 1975.

Our Mission

The energies and resources of the Australian Huntington's Disease Association (NSW) Inc are directed towards satisfying the needs of people with or at risk for Huntington's Disease and their families in NSW and the ACT by providing and/or facilitating delivery of a range of quality services.

Our Philosophy

People with Huntington's Disease and their families are individuals with equal value to all other members of Australian society, with the right to treatment and care by knowledgeable professionals and care givers, the right to appropriate support services and the right to have the best quality of life possible.

Our Services

These include education and information; advocacy; counselling and referral; holiday programs; family support; rural outreach and client services.

Our Board

President: Brian Rumbold

Vice President: Deb Cockrell

Treasurer: Richard Bobbitt

Secretary: Don Ayres

Member: Jenny Coutts

Member: Amanda Dickey

Association and Other Useful Contacts

Association Staff

Robyn Kapp OAM
Executive Officer

Mark Bevan

Regional Family Support
Worker

Margaret Lind
Administration Co-ordinator

Karen Bevan
Activities Co-ordinator

Huntington Disease Service

Dr Clement Loy
Director
Westmead Hospital
(02) 9845 6793

Dr Sam Kim
Neurologist
Westmead Hospital
(02) 9845 6793

Research Queries
Dr Elizabeth McCusker
(02) 9845 6793

HD Clinic Appointments
Outpatients Department
Westmead Hospital
(02) 9845 6544

Jet Aserios
Social Worker
Westmead Hospital
(02) 9845 6699

Cecelia Lincoln
Social Worker
Westmead Hospital
(02) 9845 6699

Outreach Service
Colleen McKinnon & Mark Cirillo
Westmead Hospital
(02) 9845 9960

Huntington's Unit
St Joseph's Hospital
(02) 9749 0215

Predictive Testing

Fiona Richards
Social Worker
The Children's Hospital
Westmead
(02) 9845 3273

Hunter HD Service

John Conaghan
Social Worker
Hunter Genetics
(02) 4985 3100