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EHDN News

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

The SPC and guest Cristina Sampaio (far right), January 2014

Progress at the Scientific Planning Committee

By Mette Gilling Nielsen, Associated Language Area Coordinator, and Gillian Bates, SPC Chair

Established in 2011 as a key pillar of the EHDN's strategic plan to improve its scientific governance and output, the Scientific Planning Committee (SPC) has since developed clear goals and diverse competences.

The committee's first members were appointed by the EHDN's Executive Committee (EC), and at their initial meeting in Edinburgh in May 2012, they took the first steps towards defining the SPC's remit, scope and responsibilities, and to ensuring that, between them, they could offer the necessary expertise. Since then, their work has progressed through monthly teleconferences and triannual face-to-face meetings.

The SPC currently comprises eight members who—as scientists, clinicians and representatives of industry and/or CHDI—all have in-depth knowledge of HD. They are: Gillian Bates (King's College London, UK), Jang Ho Cha (Merck & Co, USA), Alexandra Dürr (Hôpital de la Salpêtrière, France), Cheryl Fitzer-Attas (CHDI's vice president of clinical research), Rainer Kuhn (cofounder of IRBM Promidis, Italy), Eldad Melamed (Sackler School of Medicine, Israel), Ignacio Muños-Sanjuan (CHDI's vice president of translational biology) and Sarah Tabrizi (University College London, UK) (more information about the members is available on the SPC website). The committee is supported by the EHDN's intrinsic scientific framework, in particular by Bernhard Landwehrmeyer, Michael Orth and Juliana Bronzova of its Central Coordination, all of whom sit on the SPC, and by Danish Language Area Coordinator Mette Gilling Nielsen. >>

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Message from the Editor:

In this issue we're introducing a new regular section to the newsletter, a ROUNDUP OF FUNDING NEWS.

Look out for what's new in terms of grant opportunities.

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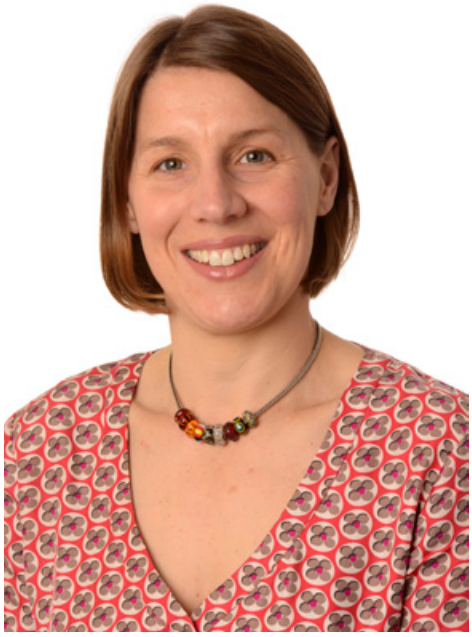
The SPC's remit is to identify and initiate human studies that will improve our understanding of the pathogenic basis of HD, and/or enable high-quality clinical trials to be conducted. It will recommend projects that can be undertaken within the EHDN, but will not limit itself to the EHDN, taking into consideration the global HD community when preparing projects for recommendation. It will engage with experts worldwide as needed, identifying individuals who are willing to take a lead on high-priority projects. Project implementation will be supported by EHDN/CHDI staff, with the SPC providing executive oversight and reporting to the EC.

At its inception the SPC compiled an internal, 13-page working paper listing human studies that would address unanswered questions. These were then prioritised, mainly according to urgency. The project identified as having the highest priority was the collection of cerebrospinal fluid (CSF) for HD biomarker identification. CSF is a peripheral, accessible fluid that is in direct contact with the central nervous system and should therefore provide a good source of relevant biomarkers. These may track disease progression and so be useful in assessing the efficacy of a disease-modifying treatment in a clinical trial, or they may act as pharmacodynamic readouts showing whether a specific treatment is affecting its biological target as intended. The goal of this project is to establish, in close collaboration with CHDI, a worldwide CSF consortium comprising Registry/Enroll-HD sites that will be able to collect CSF in accordance with analyte-specific protocols and train new centres in the associated procedures. Initially, six European centres with the relevant expertise have been asked to participate in the development of CSF collection protocols, quality control and the first sample collections, but in time other centres will be invited to join the consortium. The first protocols are currently being developed, as is the consortium infrastructure.

The project the SPC identified as having the next highest priority is the development of new imaging techniques to identify biomarkers, in collaboration with CHDI's biomarker task force. There is an urgent need to identify biomarkers that will be useful in assessing the efficacy of huntingtin-lowering strategies in clinical trials. Key to measuring the pharmacoodynamics of these treatments will be robust measures of the presence of huntingtin protein in CSF, however it would also be very useful to have biomarkers that reflect improvement in different aspects of HD pathology. PET ligands are currently under review for this purpose.

In recent years, HD models have taught us a great deal about the pathogenic mechanisms that are triggered by the HD mutation. We desperately need to validate these mechanisms in HD patients, in order to ensure that our drug development programmes are on track. We also need to ensure that all future trials are optimally designed, and that the techniques are in place to determine that our new therapeutic agents are hitting the right targets. Going forward, the SPC will help facilitate these crucial human studies.



Multidisciplinary rehabilitation: what future?

By Monica Busse, Lead Facilitator, Physiotherapy Working Group

Ever since a landmark study published in 2007 by Zinzi et al (*Clin Rehab,* vol 21, p 603), in which they reported objective and perceived benefits of a periodic, multidisciplinary inpatient intervention delivered over a two-year period, the potential benefits of rehabilitation in HD have been recognised increasingly in the scientific literature.

Since 2007, at least two replicative studies have confirmed the association between complex multidisciplinary rehabilitation and benefits in terms of physical function and quality of life. Piira et al (*PLoS Curr* 2013 September 20; 5: ecurrents.hd.9504af71e0d1f87830c25c394be47027) conducted a prospective study at two Norwegian inpatient rehabilitation centres, in which 37 patients with early to mid-stage HD were followed over a year. As in the original Zinzi protocol, patients were admitted three times in that period, for three weeks each time. The intervention focused on physical exercise, social activities and group sessions for up to eight hours a day, five days a week. Of the original 37 patients recruited, 31 completed all admissions (83.8%). Participation in the rehabilitation programme was associated with improvements in measures of gait and balance, physical functioning and quality of life. Cognitive decline was apparent, however, as reflected by symbol digit modality test scores.

Also in 2013, Ciancarelli et al (*Eur J Phys Rehabil Med*, vol 49, p 189) published a replication study in support of the model of intensive rehabilitation provided by inpatient admissions. In their study, 34 HD patients were admitted for three weeks, during which time interventions were provided for at least four hours a day, six days a week. The researchers reported significant improvement on all measures. Another study conducted last year by Mel Ziman and colleagues reported positive outcomes as a result of a multidisciplinary, combined outpatient physical and occupational therapy intervention in nine people with HD compared to 11 matched controls (see for example *Eur J Neurol*, vol 20, p 1325). As in the three studies mentioned previously, the intervention resulted in improvements in cognition and quality of life, as well as reduction in depression and postural instability—this time over an 18-month period.

While these proof-of-principle studies are exciting, the challenges of evaluating rehabilitation interventions should not be underestimated. For one thing, our understanding of the complex interactions between the "active components" of interventions is poor. Increased social interaction could be an important mediator of outcome associated with the intervention, for example. Every effort should therefore be made to quantify intervention components, interactions and environments, so that we can improve our interpretation of outcomes.

Typically, the rehabilitation interventions described here address generic impairments in physical fitness, strength, balance and walking. Interventions tailored to HD might place more emphasis on monitored, intensive aerobic exercise, or striatally-directed training activities—for example, training in complex tasks with appropriate intensity and specificity, in line with theories of motor learning and skill acquisition. It will therefore be important, in future rehabilitation trials, to consider that the environment should be conducive to optimising the target, modality, intensity and specificity of the intervention. It will also be crucial to relate any measured benefit to an evaluation of mechanism. Those designing future trials should pay attention to controlling

for bias, reporting confidence intervals and effect sizes rather than p-values, and using predetermined statistical analysis in line with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Innovative study designs such as stepped wedge designs or cluster randomised trials, that practically accommodate the need for a control condition, may become routine in this area.

It is becoming increasingly clear that rehabilitation may represent, if not a cure, then a powerful tool in the lifelong management of HD. The benefits of physical activity are now accepted in many other chronic conditions, as highlighted by a 2013 meta-epidemiological study which found exercise to be more beneficial than most medications with respect to mortality outcomes (*BMJ*, vol 347, p f5577). Whether these kinds of interventions become a reality will depend on the economic situation and the healthcare infrastructure in different countries, but given the promise they have shown to date, they require further investigation.

I would like to thank Lori Quinn and the Cardiff Physiotherapy Group for their contributions to this article.

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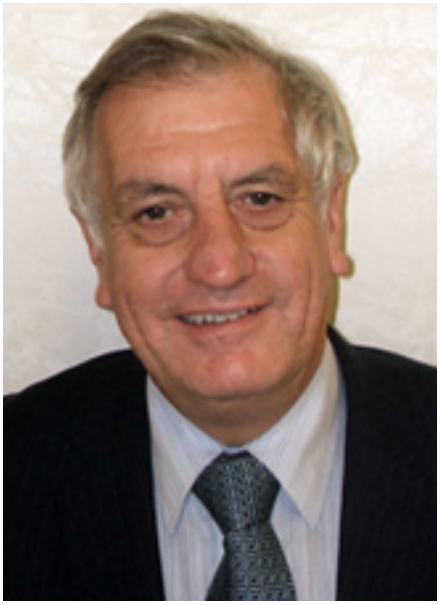
Rating scales for JHD come a step closer

By Oliver Quarrell, Lead Facilitator, Juvenile Huntington's Disease Working Group

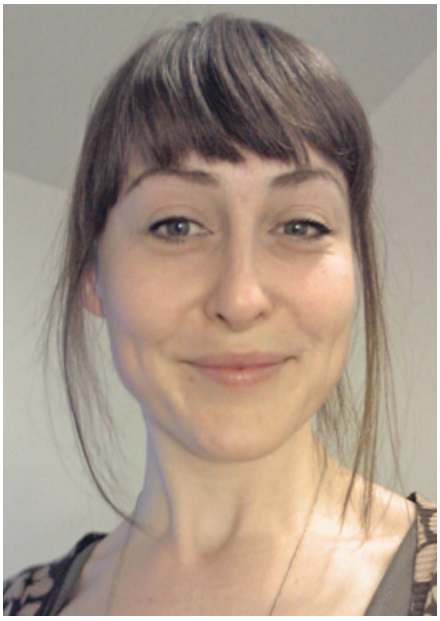
The first stage of a project to devise modified rating scales for younger patients has been completed.



Juvenile Huntington's disease (JHD), the onset of which occurs before the age of 20, accounts for 5% of HD. Some evidence suggests that JHD is associated with a more rapid disease progression than the adult form of the disease, meaning that clinical trials involving younger patients could provide a means of testing interventions more quickly than is possible in the adult patient population. For that to happen, however, rating scales tailored to JHD need to be developed to allow for accurate assessment of those interventions.

The JHD working group has been collecting information from younger patients enrolled in the Registry/Enroll-HD observational study, using modified versions of the motor and functional subscales of the Unified Huntington's Disease Rating Scale. The first analysis of these data has now been completed using a statistical technique called Rasch analysis, and the results will be discussed at a meeting in Princeton, New Jersey, in April.

The process of adapting the scales to JHD is iterative: a modified scale is proposed and tested, and the results of the testing are then analysed. On the basis of that analysis, further modifications are then proposed. Ultimately, we hope that a rating scale will emerge that will meet researchers' needs.



Update: Enroll-HD

By Ruth Fullam, European Manager, Enroll-HD

In the 17 months since it recruited its first participant, Enroll-HD has continued to grow steadily. Participation now stands at over 1,500 individuals with 55 sites recruiting in North and South America, Australasia and, most recently, Europe.

Congratulations to Ulm in Germany which recruited its first participant on 6 December 2013 and has since added another 22. Of those 23 recruits, 14 are returning Registry participants. Following Ulm's example, the other German sites of Aachen, Taufkirchen, Erlangen, Münster and Lübeck received site initiation visits in the first two months of 2014. In the UK, Birmingham was the first site to be initiated in January, followed by Manchester and London's National Hospital for Neurology and Neurosurgery. Language area coordinator (LanCo) teams for Italy, Denmark, the Netherlands and Poland have submitted requests for ethical approval, while French, Belgian and Spanish LanCos will do so soon.

The Enroll-HD team is working hard on the scheduling of the transition of the European sites, however due to the sheer number of them the transition is not likely to be complete until well into 2015. Transition is being staggered by country to ensure that the workload remains manageable and sites make the transition smoothly and with the minimum of disruption to their activities. The success of Registry means that there is a considerable volume of data to transfer in Europe, and this alone will take time. However, by incorporating these data into the Enroll-HD electronic data capture system, not only do we increase the longitudinal data collected for returning Registry participants, we also save site staff time because much of the information they are required to provide will already be in the system.

We are just at the beginning of the transition in Europe, and the coming months will produce an exponential rise in participation as Registry makes its mark on its successor. We look forward to a new chapter of international collaboration for Enroll-HD. These are exciting times!

For further information, please contact EnrollHD@quintiles.com or visit www.enroll-hd.org

Roundup: funding news

By Fionnuala Margreiter, Grant Manager

Lend your expertise

The European Union's new research and innovation funding programme, Horizon 2020 (H2020), has launched its first calls for proposals, and it's looking for independent experts to review them. If you would like to know more about how projects are evaluated, why not join their ranks? It's a great way to find out what's really expected from a grant application and to maximise your own chances of funding success.

Experts are mainly involved in the evaluation of proposals and the monitoring of actions, but they may also have the opportunity to assist in the preparation, implementation or evaluation of programmes, and in designing policies.

To take part in the scheme, you need to demonstrate a high level of expertise in fields of research and innovation relevant to the calls, as well as availability for occasional, short-term assignments. To apply via the online registration process takes about 20 minutes.

Fit for Health 2.0 open for business

Fit for Health 2.0 is a four-year project that aims to promote and enhance a sustainable participation of European industry in the health-related sector of H2020, by offering support to H2020-funded research projects throughout their innovation cycle.

It offers expert advice and training free of charge, including mentoring, coaching and SME-academia matchmaking. SMEs and researchers will be supported during all phases of their research projects, including first orientation, consortium-building, proposal-writing, project management and efficient exploitation of results.

For further information or advice on how to make the most of funding opportunities, please contact Fionnuala: fionnuala.margreiter@euro-hd.net

Living life to the full, with HD

By Jamie Levey, Chief Operating Officer,
Central Coordination

I was born into an HD family. When I was a child, we did not know what HD was. Nor did many other HD families. It was the '60s, and the lay associations had yet to organise themselves and bring awareness to the community.

My grandmother, Belle, had been in and out of psychiatric hospitals for several years, but I have fond memories of sleeping over at her apartment in Rego Park and laughing hysterically as we watched the Jackie Gleason show on TV. I can still smell the brisket in the hallways! Belle was a woman ahead of her time. She worked as a stenographer at the Queens County Court during the Depression, which is where she met my grandfather. He was preaching—excuse me, litigating—New York State penal law (Grandpa liked to have the floor).

My mother, Nancy, did not become aware of her risk of inheriting the mutation until my grandmother's death, when the doctor explained the underlying cause of the pneumonia that took Belle's life. My mother turned to her elder sister on the spot and said, "I have that." Thirty-two years old at the time, she had three kids aged between five and 11. She didn't inform anyone else of her suspicions, but slowly prepared herself for the same demise as her mother. An educated person who had studied ballet and read voraciously, she came of age in the '50s (think Sandra Dee) but by the '60s had transformed herself into an anti-war housewife, embracing freedom, equal rights, her family, Saturday nights out and psychotherapy.

Hannah and Jamie's brother Greg in Central Park

Jamie with daughter Hannah

With hindsight, I realise that by the time my mother was diagnosed with HD at the age of 42, she was well-prepared to confront her condition. We were fortunate enough to live close to the soon-to-be Huntington's Disease Society of America Center of Excellence at Columbia University in New York City, where pioneers of the budding movement disorder field were available to provide clinical care, support and advice (God bless Carol Moskowitz!). Life went on as normal for several more years, and it is only now, in retrospect, that I recognise how HD changed my mother prior to her diagnosis. Once, on vacation in San Francisco, we were waiting to take the trolley up California Street. There was no space for us on the first trolley that pulled up so we resigned ourselves to wait for the next one. All of us except my mother, that is. Breaking away from the family group, she ran after the crowded trolley, stepped onto its platform as it started up the hill, fell off and tumbled backwards down California Street. At the bottom of the hill she picked herself up. Her handbag was still on her shoulder and her sandals were still on her feet, and all she had to show for her stunt was a sprained finger. My little brother, however, was traumatised by the incident and didn't speak for the rest of the vacation.

The occasional incident of odd behaviour or outburst apart, my mother was usually very good at explaining and accepting what was happening to her. We met family therapists to discuss problems and concerns related to my mother's illness. Her biggest fear was that she would be abandoned by her family, which is

Jamie with her father and daughter

not surprising since her father abandoned her mother. Therapy, communication, understanding and love helped assuage her fear. When it was time for her to move to the Terence Cardinal Cooke Health Care Facility (TCC) in 1988, not long after they had allocated the first beds to residents with HD, she packed her bags enthusiastically and marched into the facility like a true camper, ready for the next phase of her life. She was finally getting her studio on Fifth Avenue overlooking Central Park!

We kids knew that we would undergo predictive testing when we were ready. We wanted to know in order to plan our lives for the best. Our mother had taught us how to do that. She approached most moments with grace and dignity.

Today I'm the only sibling without HD. There but for the grace of god and natural selection go I. My brother Greg resides at TCC where he is cared for by many of the same staff who looked after my mother. TCC feels like home. There are daily activities, various therapies, exceptional clinical and custodial care and plenty of entertainment, including some provided by my daughter, Hannah, who is starting her community service there. When the weather is good, we stroll in the park; when it's bad, we visit one of the many museums along Fifth Avenue, all of which are handicapped-accessible. My sister Randi lives at home in Bellmore, a suburb of Long Island, with her saint of a husband and son. They have 12-to-24-hour homecare, depending on the day of the week and availability. My sister is lovingly referred to at home as "the Queen". Most of the time they are happy. I am happy too.

> *"HD has always been a part of my life, teaching me to appreciate the simple things, to live each day to the full and to find the humour in even the worst situations."*

In the summer of 2011, for example, Hurricane Irene left my sister's home without electricity in hot, humid weather. She was irritated, agitated and unable to sleep, so at 1am I picked her up in an air-conditioned car and drove her up and down Sunrise Highway for three hours, my nephew David joining us for the ride. Cruising in the dark, we listened to music and counted Dunkin' Donuts and 7-Elevens. And since we were in the city that never sleeps, and they were all open, we also ate a lot of donuts. Now that was fun!

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Photo: Gabriele Stautner, artfox.com

Dates for your diary

Save the dates for

- The European Conference on Rare Diseases & Orphan Products in Berlin, Germany, 8-10 May 2014
- 18th International Congress of Parkinson's Disease and Movement Disorders in Stockholm, Sweden, 8-12 June 2014
- EHDN2014 in Barcelona, Spain, 19-21 September 2014