Neuroscience Trials Newsletter

From the Birmingham Clinical Trials Unit

October 2011

New Look Newsletter

Collaborative group form this year's meeting at the Birmingham Botanical Gardens.

Welcome to the new look newsletter from the BCTU Neuroscience trials team (formerly the PD Trials team). With a new look comes a new logo and a change in format.

We'll be trying to send out a quarterly newsletter to all of our collaborators, we expect to have a few teething problems to start with but we are committed to trying to keep you up to date as well as giving interesting information to digest and discuss with your colleagues, although to do this we need your help. We want to be more inclusive with our collaborators and we can't do that alone. Are you a Principal Investigator, Research Nurse, Therapist or any person involved with one of the studies form our current portfolio of trials? Do you have anything you want to share with our collaborators? Then please contact us as we are looking for contributions to our quarterly newsletter. We only need short articles of approximately three to four hundred words on anything from the realm of neurosciences, experiences or just something you want to share with the community. We're kicking off with an article from our PD MED Chief Investigator Prof. Carl Clarke (see page 2).

A New Trial "PD COMM Pilot" – Dr Cally Rick

I'm happy to announce that the Dunhill Medical Trust has funded a pilot study into the effectiveness and cost-effectiveness of speech and language therapy (SLT) for people with Parkinson's disease. Professor Cath Sackley is our lead Investigator and Professor Carl Clarke is the clinical lead; rounding out the team leads are Dr Marian Brady and Dr Christina Smith as our lead speech and language therapists. The trial will be run within the Neuroscience trial team here at the BCTU.

Currently in the UK, there is no national standard provision of SLT to people with PD who report speech or vocal difficulties. An alternative to the local standard NHS SLT is Lee Silverman Voice Training (LSVT) – an intensive 4 week programme of impairment based therapy. However, there is very little evidence to show the effectiveness of SLT and access to speech and language services varies across the country.

The pilot study aims to recruit at least 60 participants from 4 centres (City Hospital, Birmingham; Fairfield Hospital, Bury; Royal Devon and Exeter Hospital; and Southern General Hospital, Glasgow) over 18 months. The participants will be randomised between local standard NHS SLT , LSVT & no therapy (where therapy will be deferred for at least 6 months). The pilot will test the feasibility of a full scale clinical trial and inform trial design and the sample size calculation. In this pilot study a battery of participant assessed quality of life and therapist assessed outcome measures will be tested together with participant assessed resource usage questionnaires. Therapist assessed outcomes will be recorded and sent to blinded assessors. Carers will also be invited to join the trial and will be completing the new Parkinson's disease Carer's Quality of Life Questionnaire. Outcome measures will be recorded at baseline, 3, 6 and 12 months.

The timeline for the pilot study is for the application to be submitted to research ethics committee in October and to start recruitment in the New Year. Recruitment will be completed by June 2013 and follow up will be completed by June 2014. Information from the pilot study will be used in an application to the NIHR HTA (National Institute for Health Research, Health Technology Assessment) to run a full scale phase III clinical trial into the effectiveness and cost-effectiveness of SLT for people with Parkinson's disease.

So, when *are* you going to retire dear? - Professor Carl E Clarke

It sounded such an innocent question when my wife asked me the other month when I really was going to retire. Of course, she has her own agenda which includes early retirement, if we can afford it!
Work was on the quiet side at the time, as all the statisticians were off sunning themselves, delicate flowers that they are, so the PD MED results papers couldn't progress much further. So, I sat down and worked out the following table:

Time	Event
2011	PD MED EARLY and LATER results papers published
2012	PD MED subgroup analyses published PD SURG health economics analysis published PD COMM pilot recruitment starts (January) PD REHAB recruitment finishes (~ July)
2013	PD REHAB final patient completes follow up (~ October) PD COMM pilot completes
2014	PD REHAB results published PD REHAB 2 application submitted (?Is exercise in PD disease modifying) PD COMM full scale trial recruitment starts (assuming HTA funding)
2015	PD MED second major analysis (final patient followed for 5 years; assuming funding for extension is granted)
2016	PD COMM recruitment finishes
2017	PD COMM final patient completes
2018	PD COMM results published
2019	PD GEN current date ethics application runs out
2020	PD MED third major analysis (final patient followed for 10 years; assuming funding for extension is granted)

There are a lot of uncertainties in this, I acknowledge that. But it gives an overview of where the PD 'stable' of trials is heading over the next decade.

It assumes a grant extension for PD MED will be forthcoming from the HTA Programme. They have just rejected our first application as too expensive, but we are optimistic that a scaled-down version will eventually be accepted (Professor Gray note the 'scaled down').

The PD COMM pilot has just been funded by the Dunhill Charity. This will compare Lee Silverman Voice Training (LSVT) versus NHS speech and language therapy versus no treatment in around 60 PD patients with communication difficulties from four UK centres. We hope we have persuaded the HTA Programme to defer our bid for the full scale PD COMM trial until we have the pilot data available in 2013.

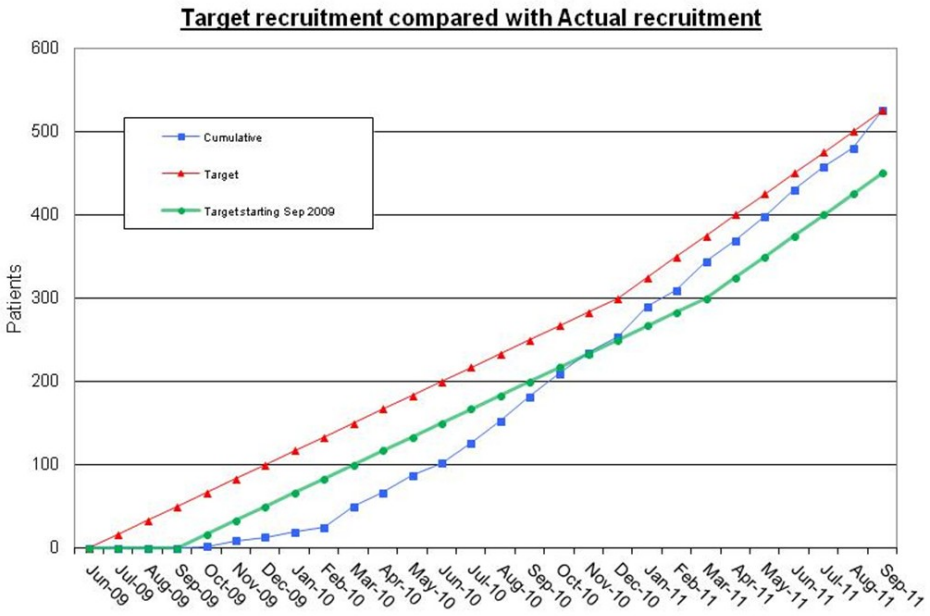
Just yesterday, I received an email from the HTA Programme asking us to consider submitting an outline for another trial, since we had done so well with PD REHAB recruitment! A lot of academics fell off their chairs when that one arrived, I can tell you. So, perhaps PD REHAB 2 could look at a tailored exercise programme from the time of PD diagnosis versus standard care over 5 years. Let me have your ideas.
Throughout this time, there will be spin off papers to work on from all of the trials, including the PD GEN pharmacogenomic work we are planning right now (see page 4 - Ed).

I think you will agree that we have a busy 10 years ahead of us working on all of these trials. The support of all of you patients, doctors, nurses, and therapists, along with the team in the University of Birmingham Clinical Trials Unit, is very much appreciated. We genuinely couldn't do it without you all. But this programme of work will make a fundamental difference to the management of Parkinson's disease, so it will be worthwhile.

So, when *are* you going to retire dear?

Well, you see dear, *it's just not that easy*!

Recruitment and Study Updates



After a poor recruitment month into PD REHAB in August, September took a dramatic upswing with our best recruiting month ever since the PD portfolio of studies started in 2000. With the 40 sites attached to PD REHAB we managed to recruit 45 patients in September alone, bringing the total to 525. This fantastic work has managed to bring us up to our original recruitment target even though we started 3 months late. A big thanks must go to everyone involved in PD REHAB, from the healthcare professionals to the patients who are prepared to join in with research. We can't do this without any of you, but please we can't get complacent as we still need to hit our target of 750 by June 2012, or even better, beat it!

PD GEN is currently our only other study in recruitment, Prof. Karen Morrison will update you on all the work going on in the background (see page 4). As for recruitment, at the moment it stands at 1716 samples taken, with 1130 being Parkinson's disease patient samples and 586 carer samples.

PD MED is no longer recruiting but it is in its 10th year of collecting follow up information. At this point, the most important information to pass on is to please ensure you continue to complete forms for the PD MED study. The study recruited 2120 patients, which is the largest examination into Parkinson's medication so far but that's meaningless without the follow up information to support this large number of recruitments.

Just like PD MED, PD SURG is in its tenth year and no longer recruiting – in fact, the last of the 366 patients will soon have completed their fifth year of follow up. The first results were published last year, and we are currently working on the health economics side of the analysis. The team have been working hard on ensuring that all the data needed for this analysis is received, checked and cleaned, and have been looking at other analyses that can be done. For example, the data from PD SURG is being used for the Stimulus project described on page 4.

Just like PD MED, it is still important for us to get all the follow up information over the rest of the life of the trial, so please be sure to respond to our various requests and reminders if you are working on PD SURG!

Contact Details

If your interested in sharing with our community of Doctors, Nurses, Therapists and Patients, please supply your articles, stories or experiences to:

Newsletter contact - Francis Dowling, BCTU, Robert Aitken Institute, University of Birmingham,
Vincent Drive, Birmingham. B15 2TT.
Email: PD-Trials@bham.ac.uk
Phone: 0121 415 912 5/6/7/9

PD GEN, it's more than just a bank - Prof. Karen Morrison

Many thanks to all of you who have been, and stay, involved in PD GEN. We are excited to announce that we have now more than 1100 samples in the bank, and are particularly pleased by the number of samples from patients recently enrolled into the PD REHAB study. Genetic research worldwide is continuing apace, and we are collaborating with many groups in the UK and internationally to maximise the value of the resource.

As mentioned in our last update, the first key use of the PD GEN samples was as part of the UK Parkinson's Disease Consortium study, the first large scale genetic study of Parkinson's disease within the UK, published in Human Molecular Genetics earlier this year[1]. The data from this study was then combined with that of several other international groups, allowing for a more in depth analysis of the genetic variants that underpin susceptibility to PD[2,3]. As reported in our last newsletter, results from the large meta-analysis suggests that as much as 60% of the risk of an individual developing PD is determined by genetic variation at the genetic sites that have been identified. The real challenge now is to try to determine how genetic variation within these regions actually leads to the development of PD. Several of the key variants identified encode or influence proteins that function in biochemical pathways that have already been implicated in PD. The anticipation is that by further refining knowledge of these key proteins, and their interactions, new insights into disease mechanism will be gained that eventually may lead to the development of new, effective treatments.

Earlier this year the first PD GEN samples were also sent to international collaborators through the GEO-PD consortium, the first UK samples to be included in this large group of researcher collaborators working to determine the genetic and environmental influences in the disease. One of the projects in which the samples are being used now involves study of a variable region in the promoter, or control region, of the alpha synuclein gene, *SCNA*. Previous work has suggested that excess amounts of alpha synuclein are a risk factor for the development of PD, or that higher levels of the protein predispose to an earlier age at onset of disease or more rapid disease progression once symptoms develop. This study is designed to see if the genetic variants in the promoter region that would predict that more of the alpha synuclein protein is produced are indeed associated with an earlier age at disease onset or more rapid disease course. The results should be available by the end of this year and, if they do suggest that variants that are associated with higher levels of alpha synuclein are associated with a more aggressive disease course, therapies that aim to reduce alpha synuclein levels within the cell might be worth pursuing.

Prof Karen Morrison and the rest of the trial team

As always, we continue to try to raise funds to continue expanding PD GEN and for making the resource widely available. Grant applications are currently underway for funding to support the collection through the NIHR PD REHAB stream, and also, and excitingly, to allow us to make progress on the important studies to link genetic variation in key genes with response and/or side effects to the various classes of drug therapy in PD MED. This is an area of research that the PD GEN samples, linked to the PD MED data, is ideally placed to deliver on, and we hope that the various potential grant funders will agree. Watch this space!

References

1. UK Parkinson's Disease Consortium; Wellcome Trust Case Control Consortium. Dissection of the genetics of Parkinson's disease identifies an independent association 5' of SNCA and multiple associated haplotypes at 17q21. *Human Molecular Genetics* **20**: 345-353. **2011.**
2. International Parkinson Disease Genomics Consortium (IPDGC); Wellcome Trust Case Control Consortium (WTCCC2). A two-stage meta-analysis identifies several new loci for Parkinson's disease. *PLoS Genet* **7**(6):e1002142. **2011.**
3. International Parkinson Disease Genomics Consortium. Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet* **377**:641-9. **2011**.

Support the Spooky Sprint - Neurology Team Leader Cally Rick and BCTU Assistant Director and Head Statistician Natalie Ives are running the Parkinson's 10km Spooky Sprint on the 29th October to raise money for Parkinson's UK, if you'd like to sponsor them (the more encouragement they have the better) you can go to www.justgiving.com/CallyandNatalie and for more information on this event you can go to www.parkinsons.org.uk/support_us/events/running_events/pds_10k.aspx